

Insights into the Role of Oxalamide Ligands in the Ullmann C-N Cross- Coupling Reaction

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Degree for Doctor of Philosophy

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Declaration of Originality

The work in this thesis was carried out between September 2019 and December 2023 at the Department of Chemistry, Imperial College London and Jealott's Jill International Research Centre, Syngenta. The work reported in this thesis is my own, unless stated otherwise through cited references, and has not been submitted for another degree at this or any other university.

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Abstract

Since their discovery in the early 1900s by Fritz Ullmann, copper-catalysed C-N cross-coupling reactions have been widely investigated in both academic and industrial settings. While the discovery of oxalamide ligands by Ma *et al.* has advanced the Ullmann reaction by increasing the substrate scope and improving reaction conditions, greater advancement has been stunted by limited understanding of the reaction mechanism. The work in this thesis attempts to clarify the mechanism of the Ullmann C-N cross-coupling reaction.

In Chapter 2, kinetic studies were performed on a successful Cu/oxalamide-catalysed C-N cross-coupling reaction. It was found that catalyst deactivation occurred at low loadings of copper, while increased loadings of ligand prevented deactivation. This led to improved reaction conditions whereby the ligand was employed in large excess while copper loadings could be decreased to as low as 5 ppm for a range of substrates. TONs of 6.88×10^4 and 1.9×10^5 were achieved with an aryl bromide and iodide substrate respectively. The reaction was first order in [aryl bromide], zero order in [amine] and [base], and first order in [copper] and [ligand].

In Chapter 3, the role of the oxalamide ligand was investigated. The ligand did not show evidence of inducing formation of the active Cu^{I} species, but the base, KOH, was able to reduce Cu^{II} species, indicating its role in the formation or recycling of the active catalytic species. A multiple addition experiment with the ligand proved the ligand is being consumed during the reaction, but the nature of this process could not be determined.

In Chapter 4, alternative ligands were investigated in the reaction conditions employed in Chapters 2 and 3. The ligands employed were not as effective as the asymmetric oxalamide ligands, since the yields obtained were much lower, and, generally, higher copper and ligand loadings were required.

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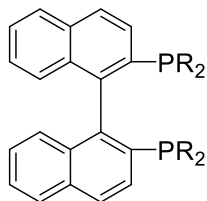
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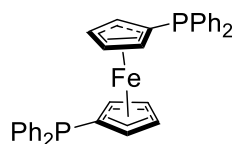
List of Numbered Compounds: Ligands

v

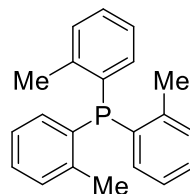


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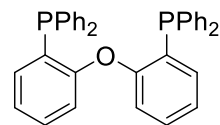
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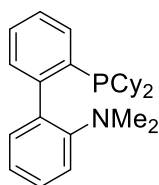
L3



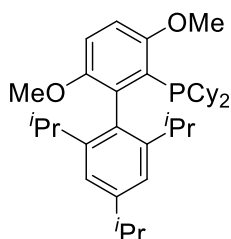
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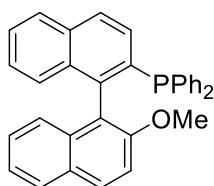
L5



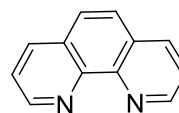
L6



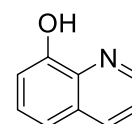
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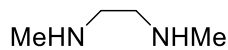
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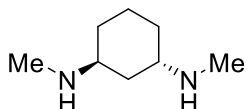
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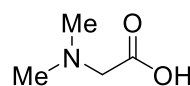
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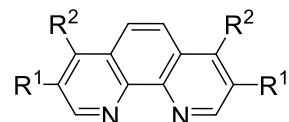
L11



L12

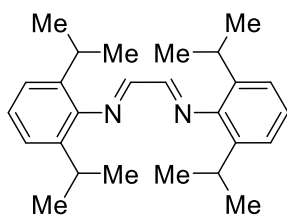


L13

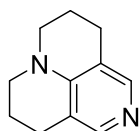


L14a: R¹ = Me, R² = H

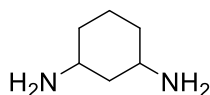
L14b: R²=R³= Me



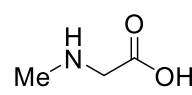
L15



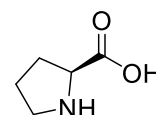
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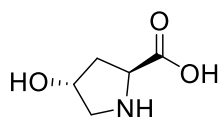
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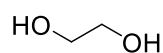
L18



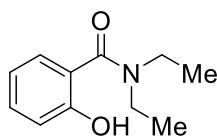
L19



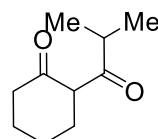
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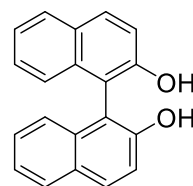
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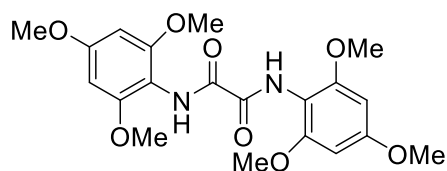
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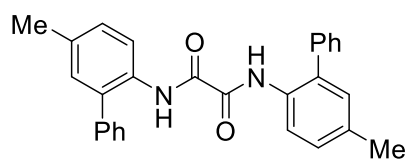
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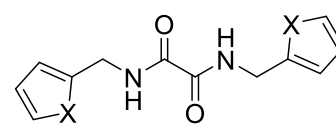
L24



L25

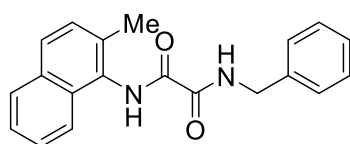


L26

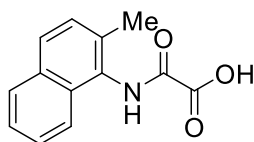


L27: X = O

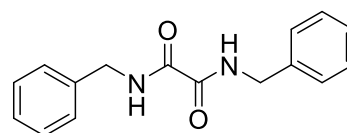
L28: X = S



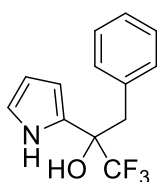
L29



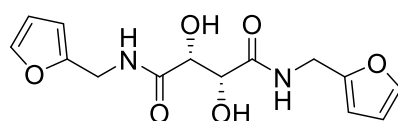
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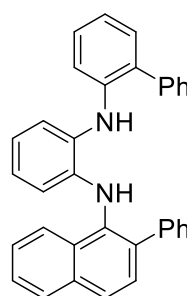
L31



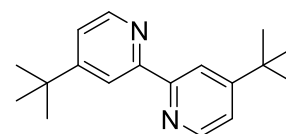
L32



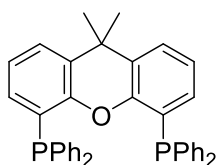
L33



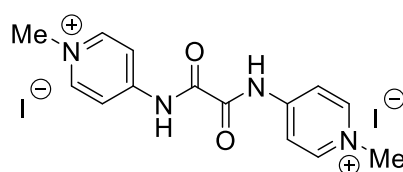
L34



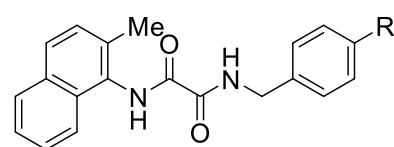
L35



L36



L37

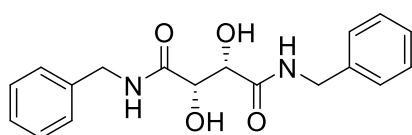


L38: R = OMe

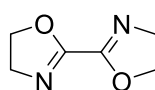
L39: R = F

L40: R = CF₃

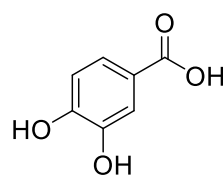
L41: R = Me



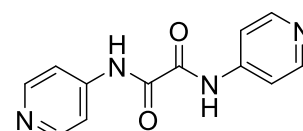
L42



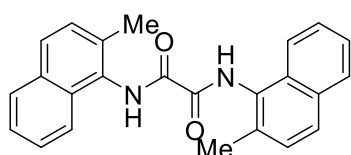
L43



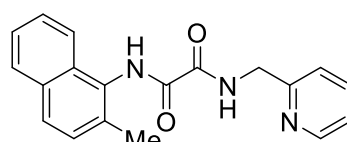
L44



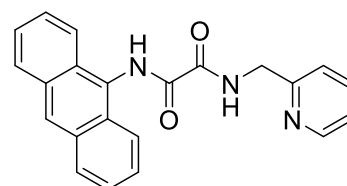
L45



L46

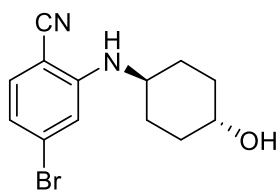


L47

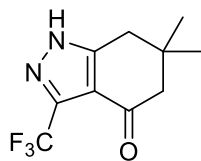


L48

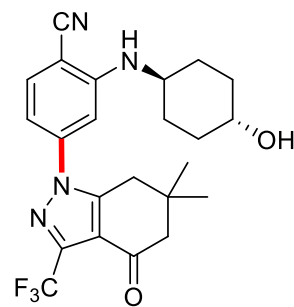
List of Numbered Compounds: Chapter 1



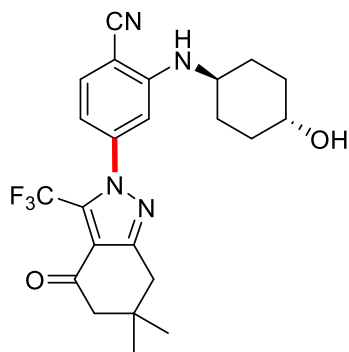
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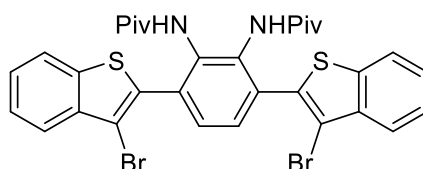
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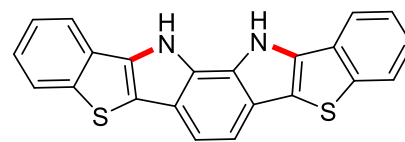
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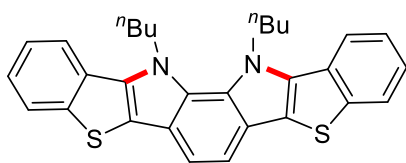
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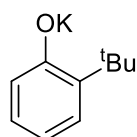
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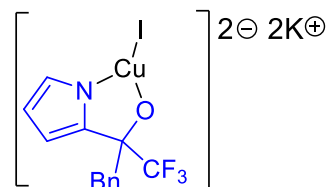
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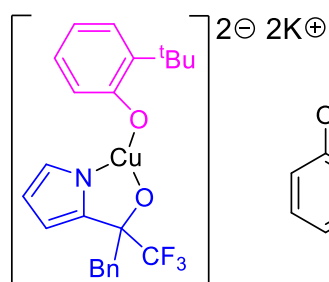
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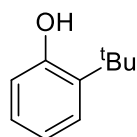
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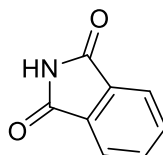
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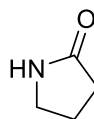
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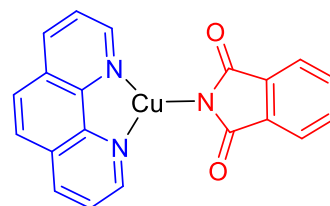
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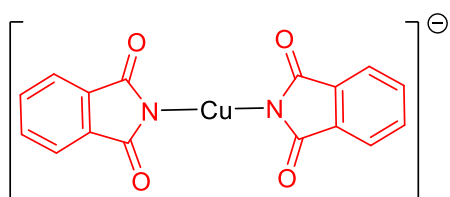
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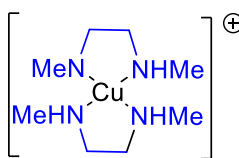
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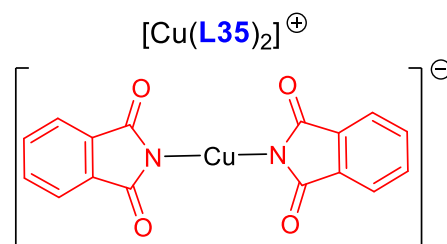
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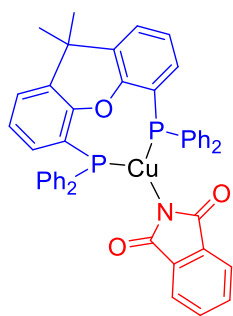


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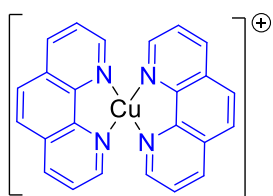


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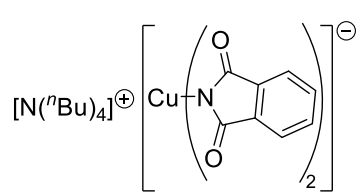
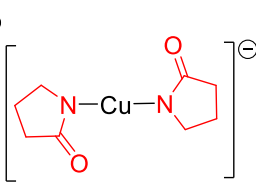




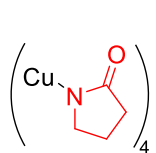
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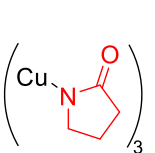
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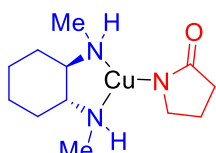
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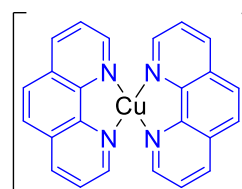
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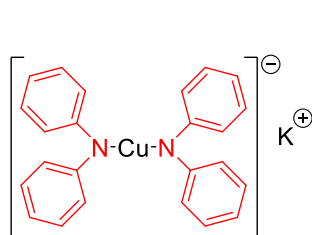
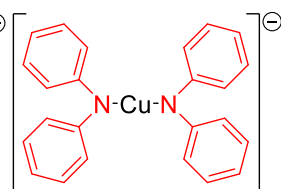
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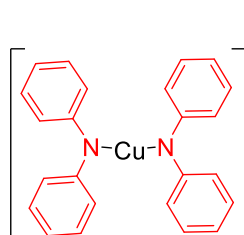
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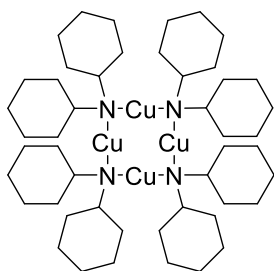
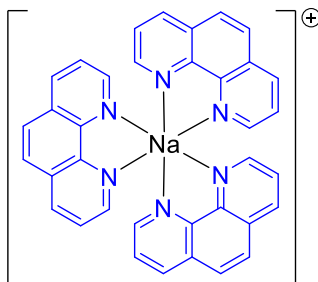
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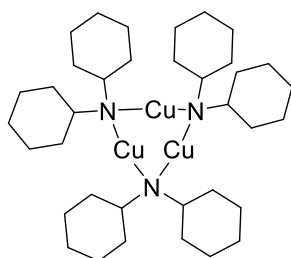
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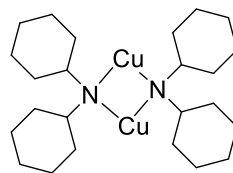
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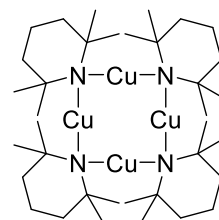
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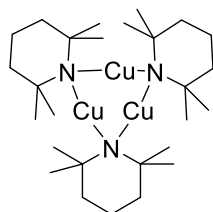
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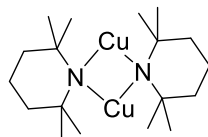
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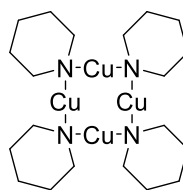
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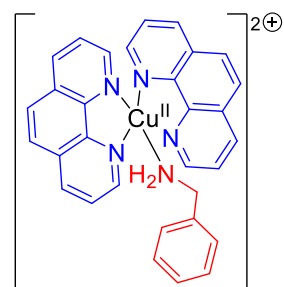
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1.27b



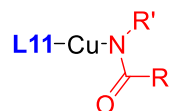
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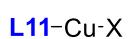
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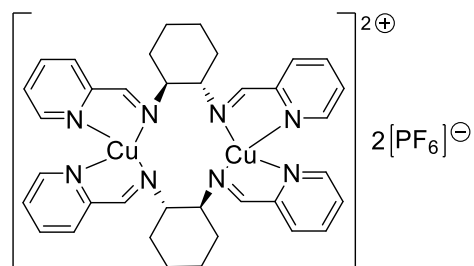
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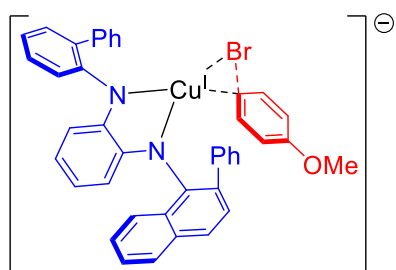
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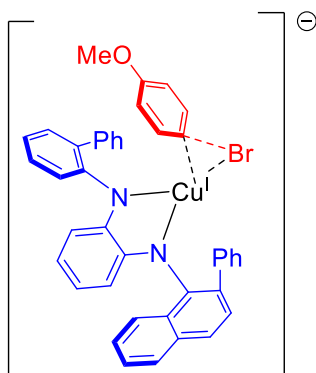
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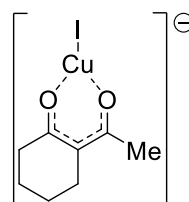
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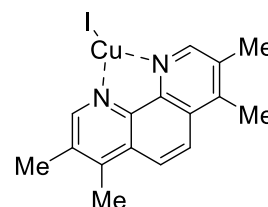
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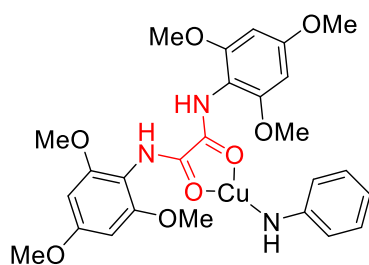
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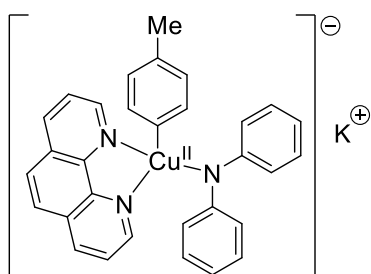
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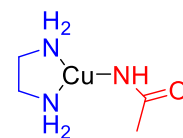
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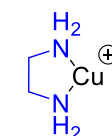
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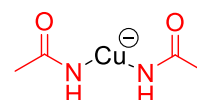
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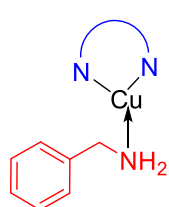
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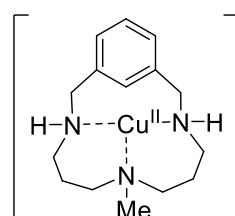
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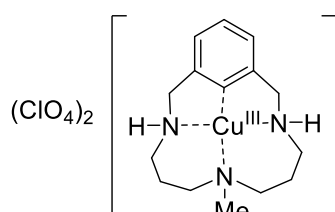
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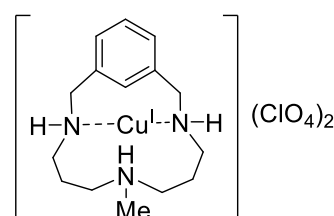
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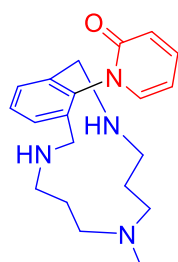
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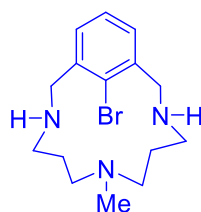
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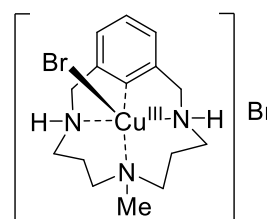
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1.47

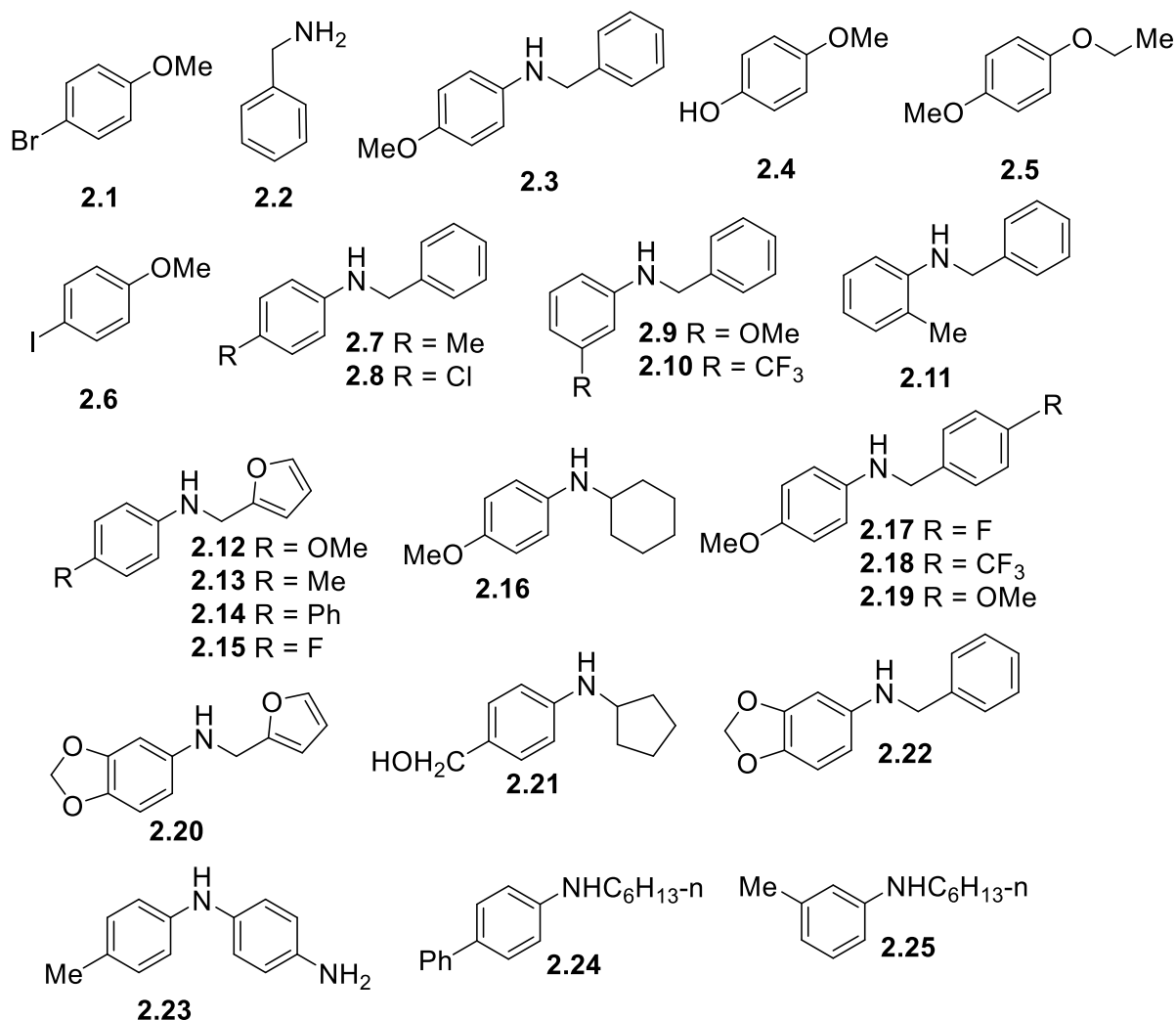


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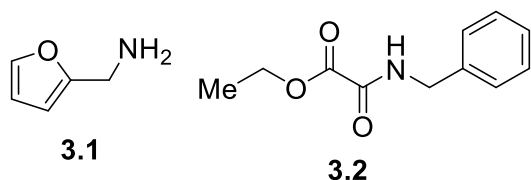


1.49

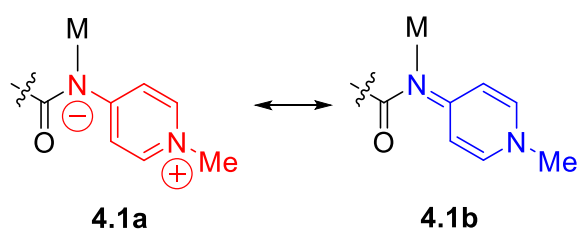
List of Numbered Compounds: Chapter 2



List of Numbered Compounds: Chapter 3



List of Numbered Compounds: Chapter 4



Acknowledgements

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Abbreviations

AMRI	Albany Molecular Research Inc.
Ar	Aryl
B	Base
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
BPPO	<i>N,N'</i> -Bis(2-phenylphenyl) oxalamide
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
BTMPO	<i>N,N'</i> -bis(2,4,6-trimethoxyphenyl) oxalamide
Cat	Catalyst
CFSE	Crystal field stabilization energy
COSY	Correlated spectroscopy
CV	Cyclic voltammetry
d	Doublet
DavePhos	2-Dicyclohexylphosphino-2'-(<i>N,N</i> -dimethylamino)biphenyl
DEG	Diethylene glycol
DEGEE	Diethylene glycol monoethyl ether
DFT	Density functional theory
DMAc	<i>N,N</i> -Dimethylacetamide
DMDETA	<i>N,N''</i> -Dimethyldiethylenetriamine
DMEDA	<i>N,N'</i> -Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DOSY	Diffusion-ordered spectroscopy
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
DPPF	1,1'-Ferrocenediyl-bis(diphenylphosphine)
Eq	Equivalent
EI	Electron ionization
EPR	Electron paramagnetic resonance
ESI	Electrospray ionization
Et	Ethyl
EDG	Electron donating group
EWG	Electron withdrawing group
FT	Fourier-transform
FTIR	Fourier-transform infrared spectroscopy

GC	Gas chromatography
h	Hour
h	Planck constant
<i>H</i>	Enthalpy
HAT	Halogen atom transfer
HMBC	Heteronuclear multiple bond correlation
HPLC	High-performance liquid chromatography
Hz	Hertz
IR	Infrared
<i>J</i>	Spin-spin coupling constant
<i>K</i>	Rate constant
KHMDS	Potassium bis(trimethylsilyl)amide
L	Ligand
m	Multiplet
M	Molar
Mal	Malonate
Max	maximum
Me	Methyl
MeCN	Acetonitrile
Mol	Mole
m.p.	Melting point
MS	Mass spectrometry
MW	Molecular weight
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser spectroscopy
ⁿ Bu	<i>n</i> -Butyl
Nm	Nanometers
Nu	Nucleophile
OA	Oxidative addition
OAc	Acetate
obs	Observed
OMe-MOP	(2'-Methoxy-[1,1'-binaphthalen]-2-yl)diphenylphosphane
OTf	Trifluoromethanesulfonate
Ph	Phenyl
ppm	Parts per million
<i>p</i> XRD	Powder X-ray diffraction

PYA	Pyridylidene amide
q	Heat flow
Rac-BINOL	Racemic-1,1'-bi-2-naphthol
RE	Reductive elimination
RPKA	Reaction progress kinetic analysis
r.t.	Room temperature
s	Singlet
SET	Single electron transfer
S _N Ar	Nucleophilic Aromatic Substitution
t	Triplet
T	Tesla
TBPM	Tetrabutylphosphonium malonate
^t Bu	<i>Tertiary</i> -butyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TOCSY	Total correlation spectroscopy
TOF	Time of flight
ToIBINAP	2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl
TOF	Turnover frequency
TON	Turnover number
UV-Vis	Ultraviolet-visible
VTNA	Variable time normalization analysis
X	Halide
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
[e]	Excess
Å	Angstrom
η	Hapticity
σ	Substituent constant
ρ	Proportionality Constant
μ	Micro
ν	Frequency of a photon
ΔG	Gibbs Free energy
ΔH_{rxn}	Enthalpy of reaction
δ	Chemical shift
°	Degree

1 Introduction

1.1 Importance of C-N Bond Formation

Carbon-nitrogen bonds are abundant in agrochemicals,¹ pharmaceuticals,² natural products³ and the materials industry,⁴⁻⁶ hence their formation is an incredibly important process (see **Figure 1.1** for some examples). Various methods have been developed to aid in the formation of sp^2 C – sp^3 N bonds, some of which are shown in **Scheme 1.1**.

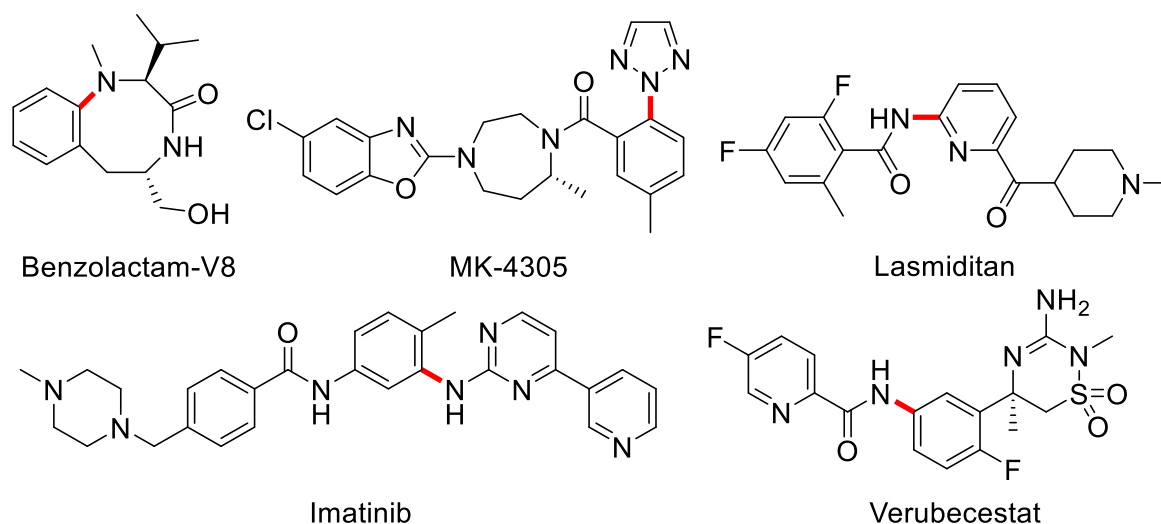
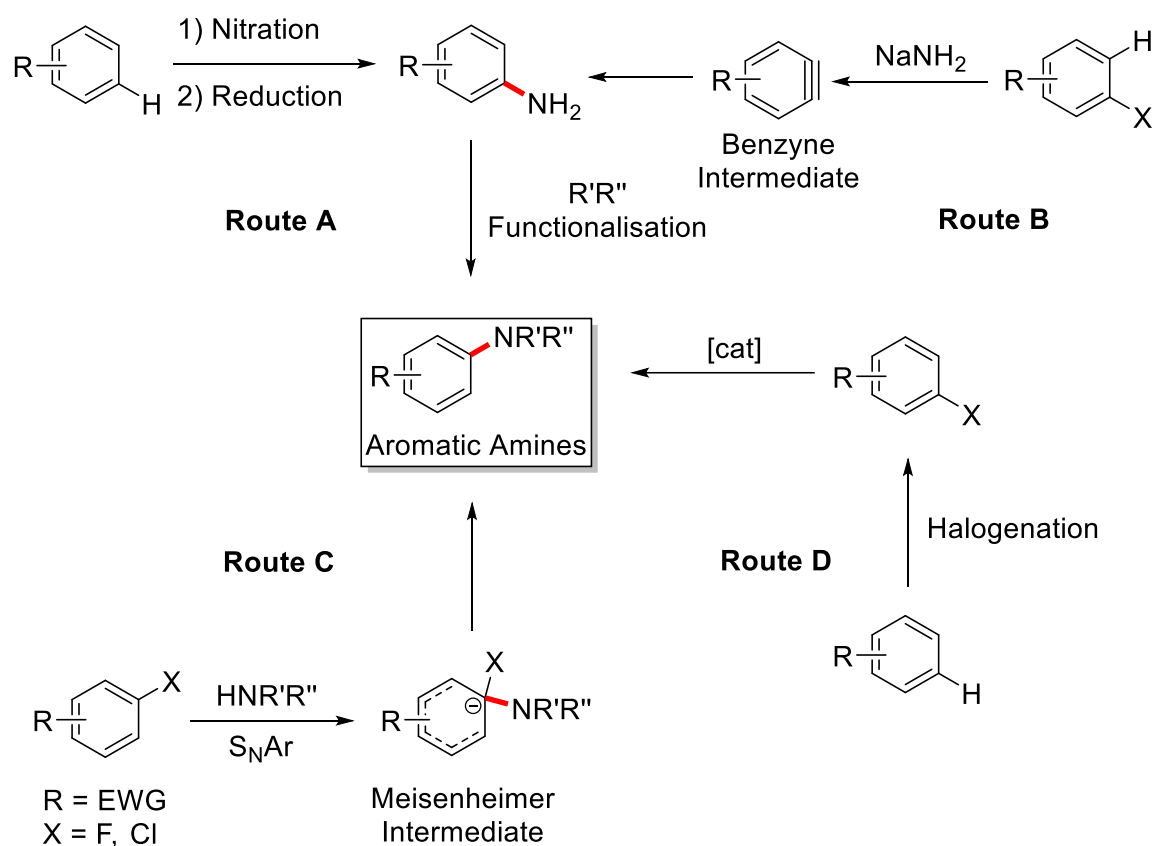


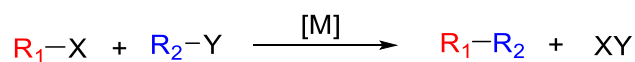
Figure 1.1 Examples of compounds containing $C(sp^2)$ -N bonds.^{2,7-9}

A classical method for preparations of arylamines is outlined in **Route A** of **Scheme 1.1**. It involves the nitration of benzene with concentrated nitric and sulfuric acid, followed by reduction of the $-NO_2$ group. Due to the harsh acidic conditions required, this route is not successful with compounds containing sensitive functional groups and the scope of amines that can be used is limited.³ **Route B** outlines the use of a strong base such as $NaNH_2$ to form a benzyne intermediate which can undergo amination by attack from a N -nucleophile, but this latter step is not selective and can form regioisomeric mixtures.³ Formation of arylamines can also occur from nucleophilic aromatic substitution (S_NAr) via a Meisenheimer complex (**Route C**), but drawbacks include the need for high temperatures or the requirement for strongly electron withdrawing groups in the para or ortho position to stabilise the intermediate which reduces the substrate scope.³ The process outlined in **Route D**, whereby halogenation is followed by transition-metal catalysed amination, is an improved route which can lead to arylamines under milder reaction conditions and with a larger substrate scope.

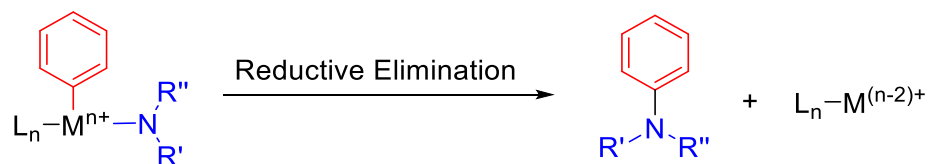


Scheme 1.1 Synthetic routes to sp^2 C – sp^3 N bond formation.^{3,10}

The transition metal-catalysed cross-coupling reaction can be defined as the linking of two distinct molecular entities in a covalent-bond-forming process (**Scheme 1.2**).¹¹ In the case of sp^2 C – sp^3 N coupling, reductive elimination of an intermediate containing the aryl and amide substrates σ -bound to the metal centre occurs to give the desired product (**Scheme 1.3**).¹²



Scheme 1.2 General scheme for the cross-coupling process.¹¹



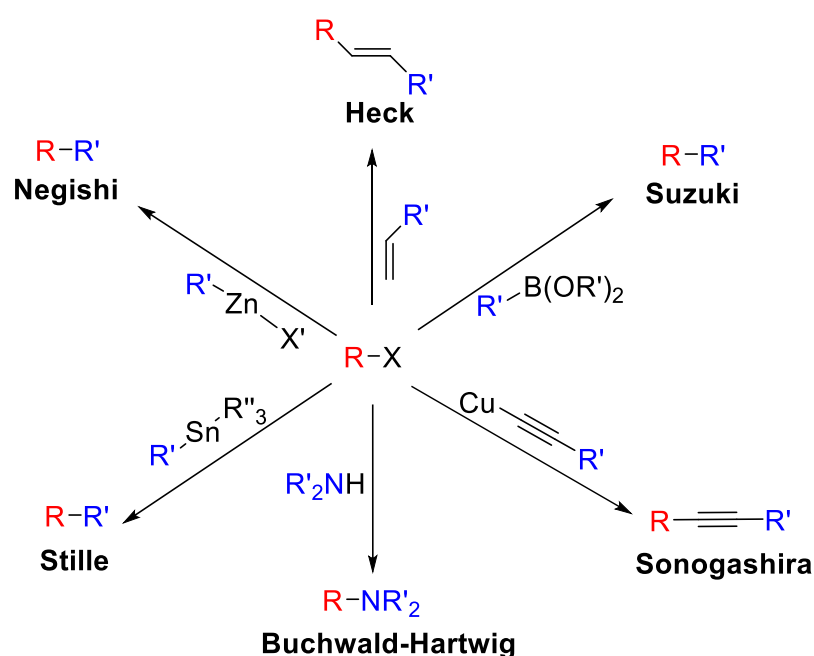
Scheme 1.3 Final step in C-N bond formation following the transition metal-catalysed pathway.¹²

Since the 1970s, transition metals have been used to catalyse C-N cross-coupling reactions,⁹ and a large library of reactions has been investigated, including metal catalysts based on Pd, Cu, Ni, Ru and other d-block metals. This has allowed for milder reaction conditions and wider reaction scope compared to the classical methods mentioned above. In section 1.2, the investigations into Pd- and Cu-catalysed reactions will be highlighted and contrasted.

1.2 Transition Metal Catalysed Cross-Coupling for C-N Bond Formation

1.2.1 Pd-Catalysed Cross Coupling

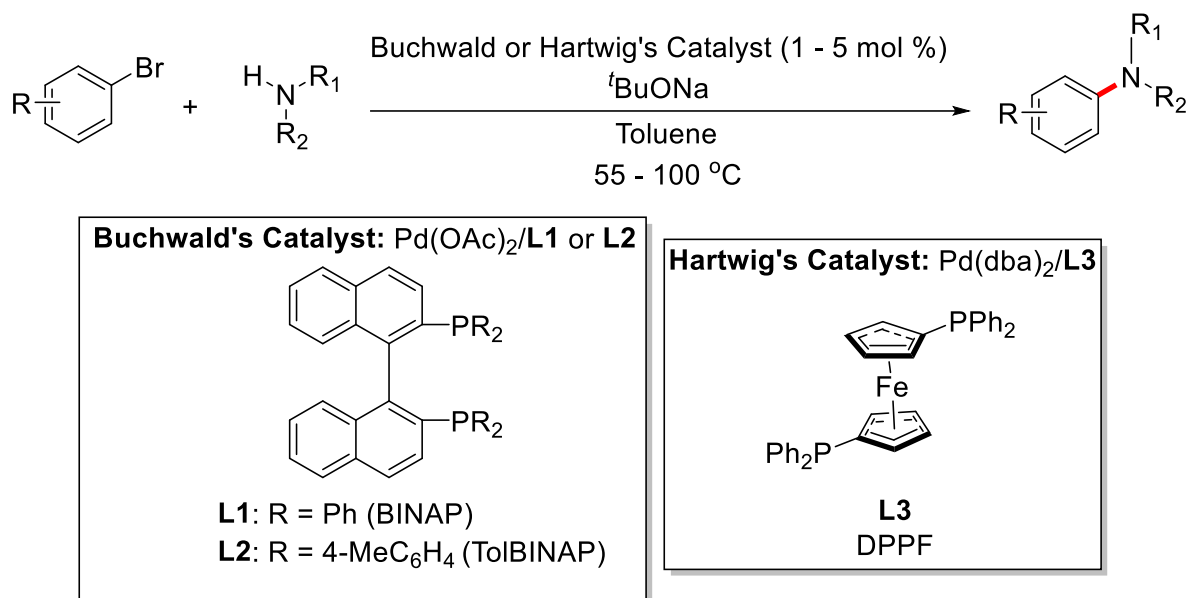
While the initial research in Pd-catalysed cross-coupling reactions was slow-moving, a great surge in research in the area has occurred over the last few decades. Notable figures in the development of this technology include Sonogashira, Stille, Buchwald, Hartwig, Heck, Negishi and Suzuki, and examples of their work are shown in **Scheme 1.4**.⁹ The latter three scientists were presented with the Nobel Prize in Chemistry in 2010 for their extensive work on developing palladium-catalysed cross-couplings in organic synthesis.¹³



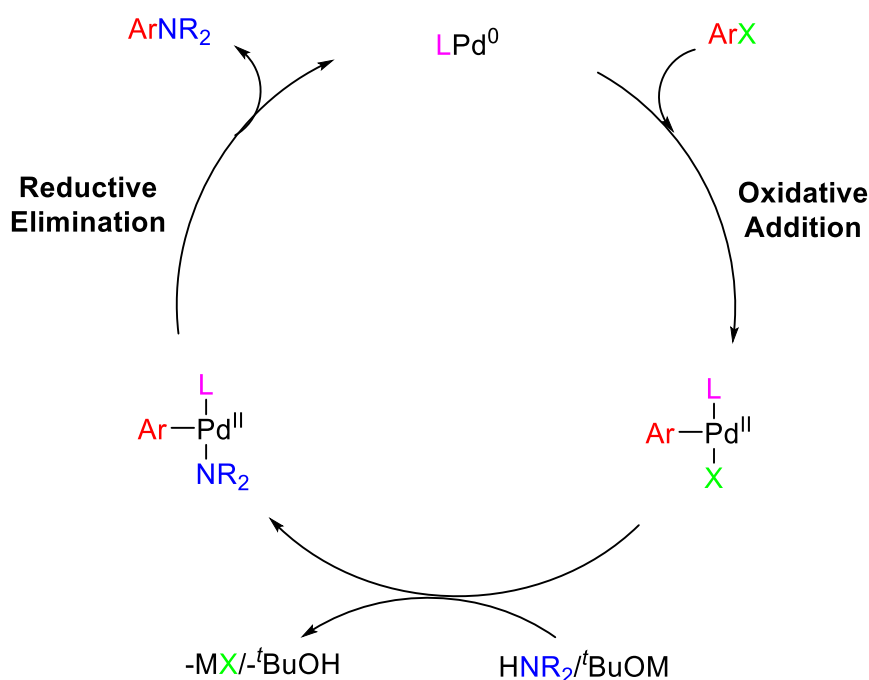
Scheme 1.4 Key palladium-catalysed processes.¹³

Of particular interest here is the Buchwald-Hartwig amination which employs Pd as a catalyst in the cross-coupling of amines and aryl (pseudo)halides. Seminal reports from the two scientists Buchwald and Hartwig in 1995 cemented the prototypical conditions for the coupling (**Scheme 1.5**)^{14,15} and later Hartwig consolidated the general

mechanism for Pd-catalysed reactions with $P(Ar)_3$ -type ligands. This catalysed the expansion of research in this field and led to an in-depth understanding of the reaction. **Scheme 1.6** highlights the now widely accepted mechanism for the Buchwald-Hartwig amination process. From this, a huge library of reactions and conditions were explored and expanded into various applications.¹⁰



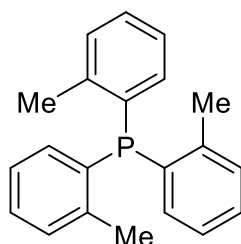
Scheme 1.5 Initial protocols reported by Buchwald and Hartwig.^{14,15}



Scheme 1.6 Simplified mechanism of the Buchwald-Hartwig amination reaction.¹⁶

It is known that the success of Pd-catalysed processes relies heavily on the type of ligands used. Well-defined complexes form whereby the coordination sphere of the transition metal is easily controlled depending on the ligand and conditions used, mitigating the formation of undesirable coordination events.¹² First generation ligands in the Buchwald-Hartwig reaction include bulky tris(*o*-tolyl)phosphine (**L4**, **Figure 1.2**) which did not allow for a good level of control of Pd-coordination, which in turn led to a low reaction scope and the need for harsh conditions. Chelating bis-phosphines were then employed such as BINAP and DPPF (**L1-L3**).^{17,18} These second generation ligands are able to control two coordination sites which suppresses side reactions, but they are only successful at higher temperatures and have limited selectivity and scope. Finally, third generation ligands drew on the understanding that cross-coupling reactions require electron-rich and bulky monodentate ligands to succeed (**L6-L8**).¹² Thus, a large library of ligands which possess steric bulk, strong electron donating ability and the ability to bind spontaneously as a monodentate ligand in reaction conditions was formed.

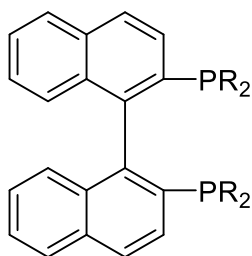
First Generation:



L4

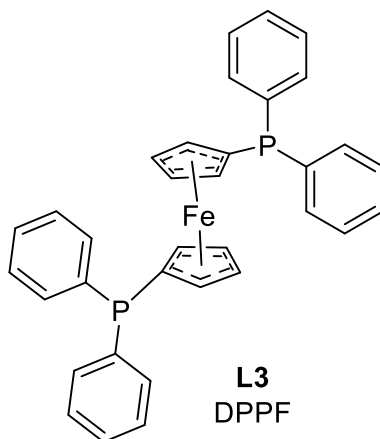
Tris(o-tolyl)phosphine

Second Generation:

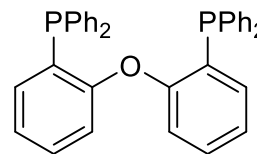


L1: BINAP (R = Ph)

L2: TolBINAP (R = 4-MeC₆H₄)

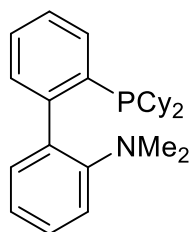


L3
DPPF

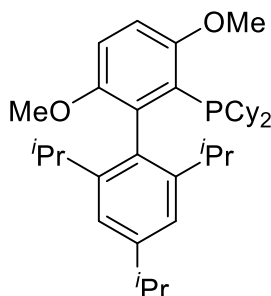


L5
DPEPhos

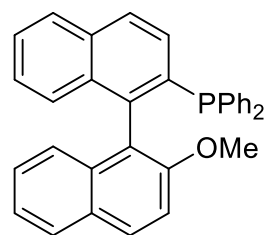
Third Generation:



L6
DavePhos



L7
BrettPhos



L8
OMe-MOP

Figure 1.2 A selection of ligands used in Pd-catalysed cross-coupling reactions.¹²

In addition to the high activity of palladium as a catalyst, one reason for the success of Pd-catalysed C-N bond forming reactions is the ease at which Pd complexes can be isolated and analysed and the stability of the intermediate complexes within the Pd(0)/Pd(II) cycle. This has allowed for an in-depth understanding of the role of ligands in the reaction and in turn the reaction mechanism.

However, there are several drawbacks to the system which need to be addressed. As a precious metal, Pd is limited in supply and is becoming increasingly expensive, so as a catalyst it is becoming less economical.¹⁹ In terms of the ligands used, they are often expensive, complex and high molecular weight molecules which are toxic and reduce the atom economy of the reaction. The ligands also inhibit the recycling of Pd. Thus, in spite of the great advancements and optimisation in the field, the C-N cross-coupling reaction must look to alternative metal/ligand systems in order to have sustained success in industrial applications.

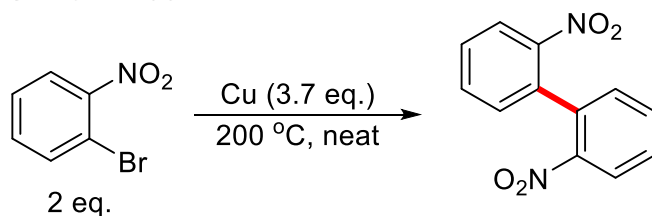
1.2.2 Cu-Catalysed Cross Coupling

Cu is a promising alternative to Pd in C-N cross-coupling reactions since it is cheaper (Pd is 3000 times more expensive than Cu)²⁰ and is not in limited supply.²¹ Its use in a cross-coupling reaction was first reported in 1901 by Fritz Ullmann, who noted that stoichiometric amounts of Cu could aid in the binding of two aryl halides to form biaryl moieties.²² In 1903, the same protocol was utilised to form C-N bonds, while in 1905 and 1906, catalytic amounts of Cu were used successfully for the formation of both C-O and C-N bonds.²³ These are regarded as 'classical' Ullmann reactions. At a similar time, Goldberg and Hurtley reported catalytic amounts of copper could aid in the cross-coupling of aryl halides with amides and β -dicarbonyls.^{24,25} Examples of these early reactions can be seen in **Scheme 1.7**.

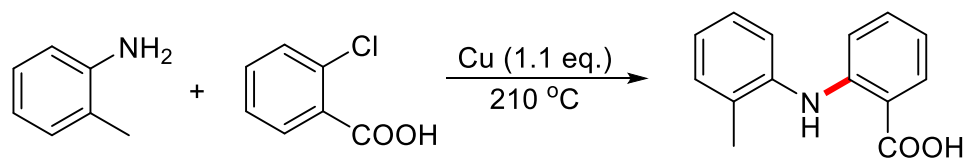
While these reactions highlighted the potential use of Cu in cross-coupling reactions, their many drawbacks including the need for harsh conditions (strong base, temperatures > 200 °C), limited substrate scope and the need for high amounts of Cu rendered them unfavourable for potential applications.²⁶

Despite this early research, there was a lull during the 20th century in the study of Cu for C-N bond formation, until the late 1990s when a series of reports allowed the research area to gain momentum. Research from Ma,⁷ Hauptman,²⁷ Goodbrand²⁸ and Buchwald²⁹ introduced the use of auxiliary ligands in copper-catalysed cross-couplings which aided in both the stability and solubility of the catalyst, hence enhancing the efficiency and success of the reaction (**Scheme 1.8**). These structurally simple and cheaper ligands allowed the reaction to proceed under much milder conditions.

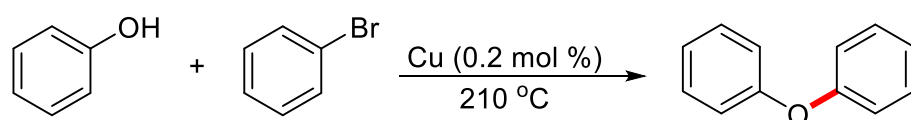
Ullmann 1901:



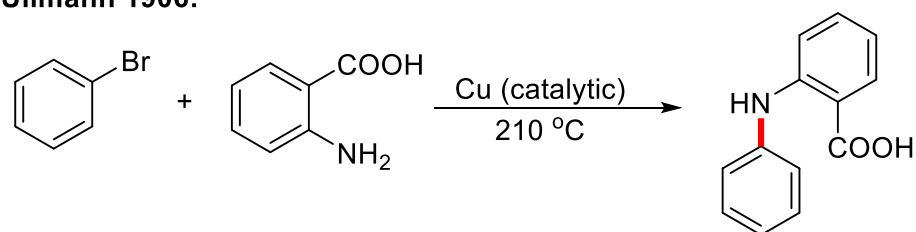
Ullmann 1903:



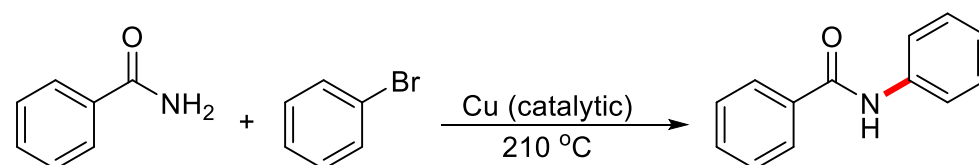
Ullmann 1905:



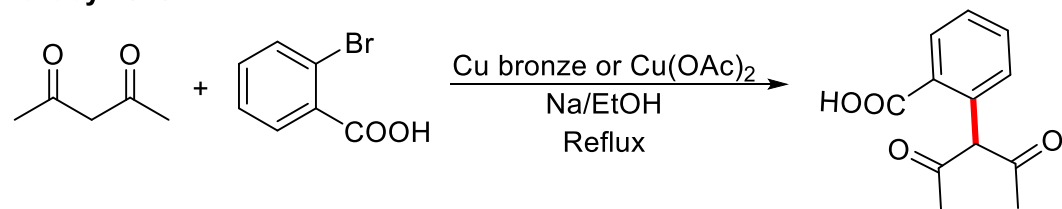
Ullmann 1906:



Goldberg 1906:

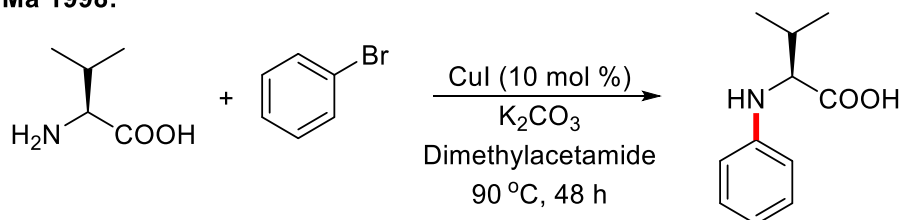


Hurtley 1929:

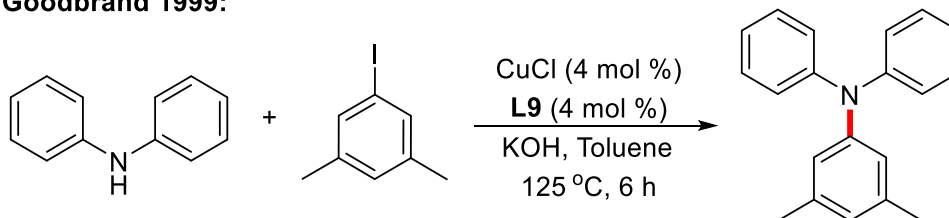


Scheme 1.7 Initial cross-coupling reactions involving Cu.^{21–25}

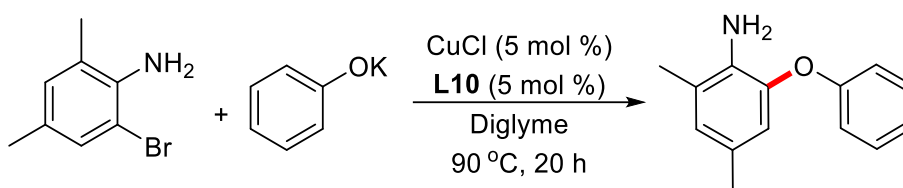
Ma 1998:



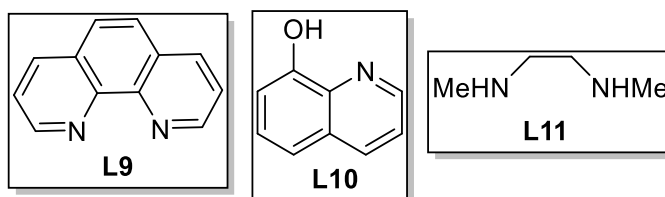
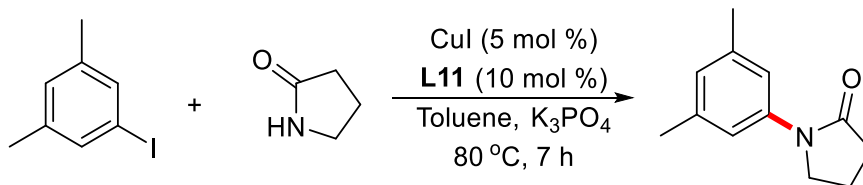
Goodbrand 1999:



Hauptman 2000:



Buchwald 2002:



Scheme 1.8 Initial uses of auxiliary ligands in the Ullmann cross-coupling reaction.^{7,27–29} Note that L-valine in the entry from Ma is thought to act as both a ligand and nucleophile.

From these initial reports, extensive optimisation of ligands and reaction conditions have been performed – these will be highlighted in section 1.3. The compatibility of copper with cheap, simple and low toxicity ligands is a major advantage compared to Pd, but the exact interaction between the copper and the ligand is still unclear. In the ligands reported so far there are no common trends in their properties so the reason for their enhanced effect on the reaction is not immediately clear. Mechanistically, it has proven difficult to consolidate a single mechanism for the Ullmann reaction. Compared to Pd, Cu-catalysed reactions do not proceed via well-defined complexes and the mechanism likely involves an interplay of complex equilibria¹², making it

difficult to follow the reaction progress experimentally. This can be attributed to the smaller size of the Cu centre, which is not compatible with large ligands, and therefore there is less control over the coordination sphere through ligand design.¹² Additionally, since Cu^I complexes have a d¹⁰ configuration, and thereby zero crystal field stabilisation energy (CFSE), they are more labile than Pd^{II} complexes and their geometry is more defined by steric effects, again limiting control of ligand design. In turn, this means the optimisation of the Ullmann reaction cannot be rationally performed, which has greatly hindered its progress.

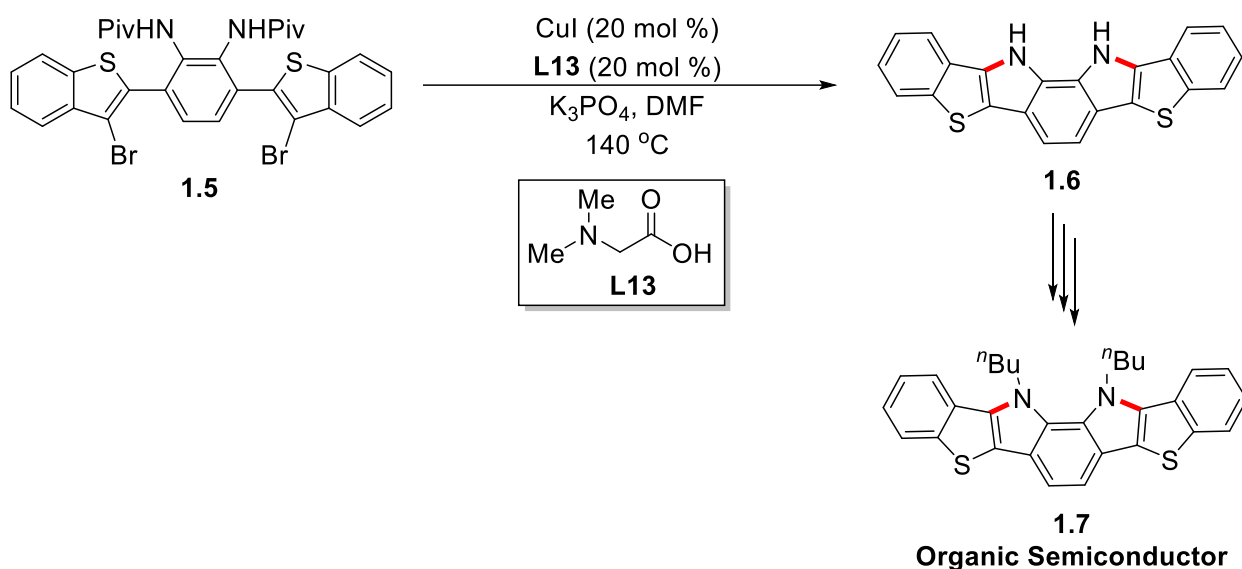
Despite the advancements with the introduction of auxiliary ligands there are still major drawbacks to the copper-catalysed Ullmann reaction which prevents it from being as widely used as Pd-catalysed processes. Due to limited reaction and ligand development, the loading of copper and ligand required for successful reactions are much higher than those for Pd, and the activation of more challenging substrates is limited or requires much higher loadings. Most notably, the reports of copper-catalysed processes involving activation of less reactive but cheaper aryl chloride substrates is rare.²⁶

1.2.3 Applications of Cu-Catalysed C-N Cross-Coupling Reactions

While optimisation of the Ullmann C-N cross-coupling reaction is still ongoing, there have been some examples of its use in industrial settings. This section will highlight a select few examples of its success in the synthesis of agrochemicals, pharmaceuticals and materials, to show the potential of the utility of this process with further advancement.

Duan *et al.* utilised the Ullmann C-N cross coupling process in the synthesis of Hsp90 inhibitor SNX-5422 for Curia (formally AMRI).³⁰ It was employed in the conjoining of aryl bromide **1.1** (**Scheme 1.9**) and the pyrazole moiety **1.2**, and after optimisation the desired product **1.3** was formed with complete conversion of **1.1** and only 2-4 % of the undesired regioisomer **1.4**. Scaling to 3.5 kg was successful, and a key aspect is that after purification and isolation of the final product, only 14 ppm of residual Cu remained.⁸

Syngenta have employed Ullmann coupling in the final synthesis step of the fungicide Isopyrazam (**Scheme 1.10**). Pre-complexation of the CuBr/**L12** catalyst system was effective in facilitating the reaction. Low loadings of the catalyst system were employed to achieve the target compound, and the optimised conditions were effective for a range of substrates including less-reactive aryl chlorides to form other structurally similar fungicides.⁸



Scheme 1.11 Ullmann cross-coupling reaction for the synthesis of an organic semiconductor.⁶

These examples show the versatility of the Ullmann C-N cross-coupling reaction and how it can be applied to a wide variety of applications. With further optimisation of the reaction conditions the Ullmann reaction may become one of the most economical and sustainable routes to forming C-N bonds in synthetic chemistry.

1.3 Modified Ullmann Reaction

1.3.1 First Generation Ligands

Cu-catalysed C-N cross-coupling reactions which involve the addition of an auxiliary ligand are often referred to as the 'Modified Ullmann Reaction'. While ligands do not have a defined influence on the Ullmann reaction and their exact role is unclear, their importance in the success and efficiency of the reaction is evident. In initial works, first generation ligands are reported which are generally low molecular weight, low toxicity, affordable compounds. These properties give them major advantages compared to the complex ligands required in Pd-based C-N couplings. The bidentate ligands often fall into three categories: *N,N*-, *N,O*- and *O,O*-, and some examples have been highlighted in **Figure 1.3**.³¹ The Cu metal centre is able to retain greater Lewis acidity compared to Pd due to its smaller size, thus it has a greater affinity for *O*- and *N*-based ligands rather than phosphorus-based ligands.¹²

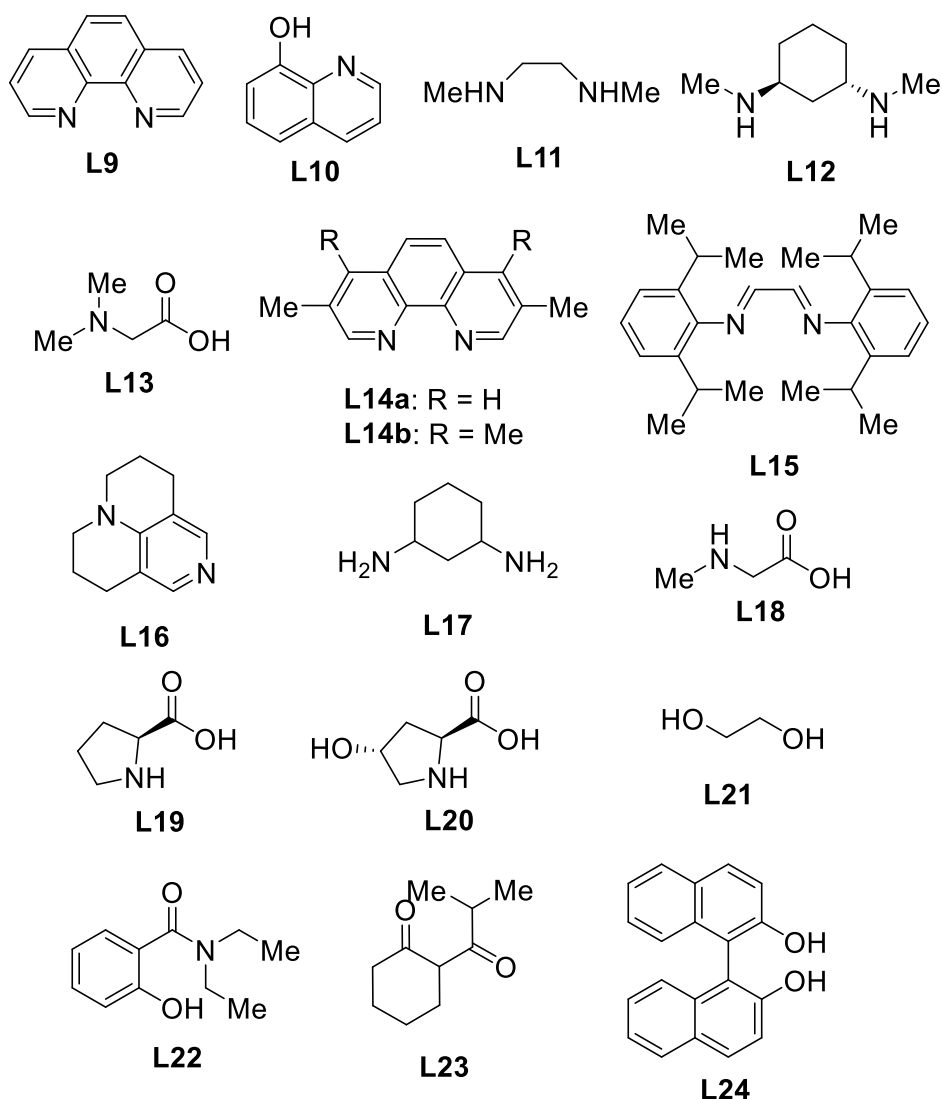
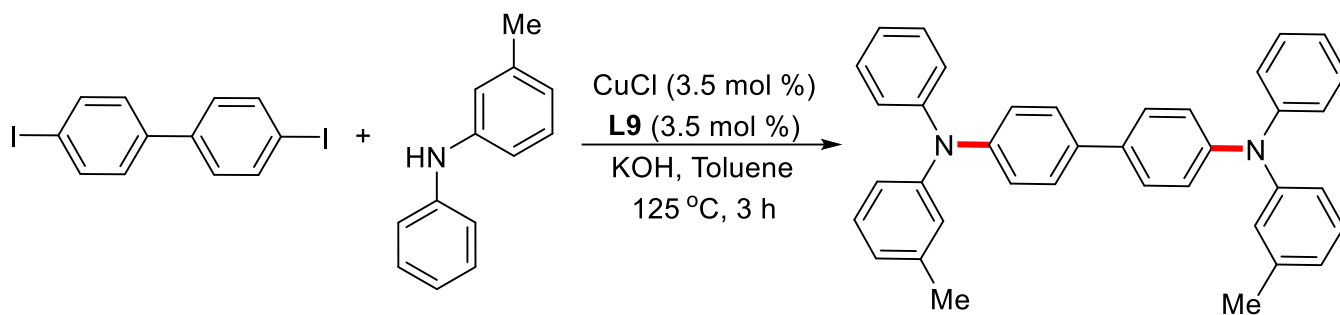


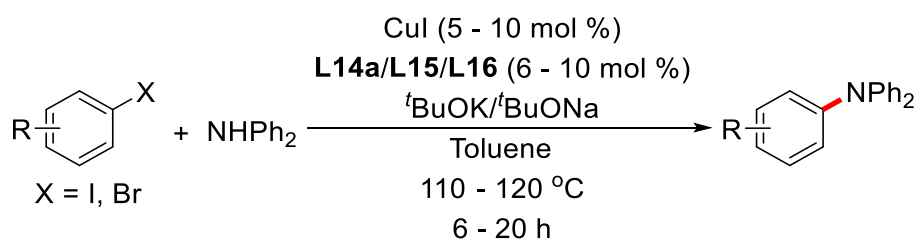
Figure 1.3 A selection of first generation bidentate ligands used in Ullmann C-N coupling.³¹

Goodbrand *et al.* initiated the use of 1,10-phenanthroline (**L9**) as a simple but effective ligand in C-N cross-couplings by noticing its accelerating effect in the reaction in **Scheme 1.12**.²⁸ The rate acceleration was clearly due to the addition of **L9**, since without it reaction completion was only reached with a reaction time of 6 h at 160 °C. With **L9**, conditions of 3 h and 125 °C were sufficient. The conditions were extended to other substrates, but the reaction scope was limited to arylation of secondary aryl amines only.



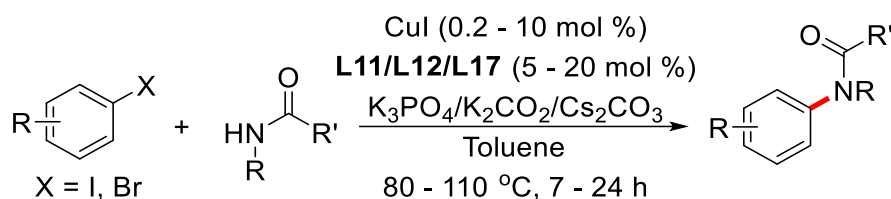
Scheme 1.12 Initial reaction conditions employed by Goodbrand *et al.*²⁸

Later, ligands **L14a**, **L15** and **L16** were successful in the arylations of diarylamines with the presence of a strong base (**Scheme 1.13**).^{32–34} Ligands such as 1,10-phenanthroline are now accepted as a widely applicable ligand in Ullmann couplings and can be applied to a large scope of aryl halides and amines.^{35–40}

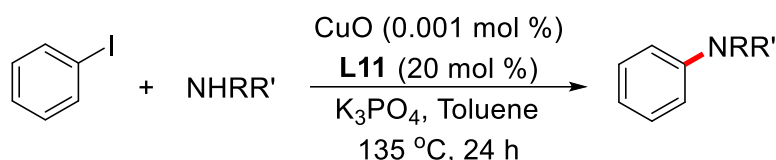


Scheme 1.13 General scheme for reactions with ligands **L14a**, **L15** and **L16**.^{32–34}

Other diamine ligands followed a few years later with reports from Buchwald *et al.* highlighting the efficiency of **L11**, **L12**, **L17** and their derivatives (**Scheme 1.14**). These ligands were found to be even more effective in *N*-arylations of heteroaryl amines due to their success with a wider substrate scope, but higher loadings of 20 mol % ligand were required.^{29,41} The utility of these simple diamines was extended by Larsson *et al.* in 2009 when copper loadings were dropped to ppm levels in the coupling of pyrazole and phenyliodide.⁴² A large excess of 1,2-dimethylethylenediamine (DMEDA, **L11**) was required for reaction success, and this protocol has only been applied to reactive nucleophiles, but with copper loadings as low as 0.001 mol %, a turnover number (TON) of 8.6×10^4 and turnover frequency (TOF) of 3583 h^{-1} , this is still one of the most active catalytic systems reported for a copper-catalysed cross-coupling reaction (**Scheme 1.15**).

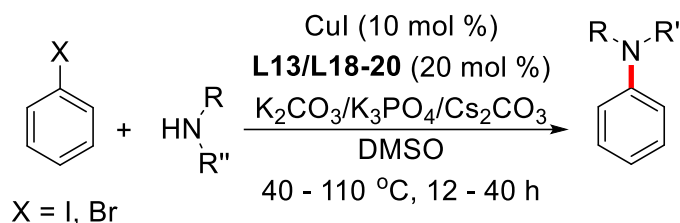


Scheme 1.14 General conditions for diamine ligands.^{29,41}



Scheme 1.15 General conditions to achieve high TONs with **L11** as a ligand.^{42,43}

Amino acid type ligands were discovered by Ma *et al.* in 2003 and were found to accelerate the Ullmann C-N cross-coupling reaction under relatively mild conditions (**Scheme 1.16**). Simple and commercially available compounds such as *N,N*-dimethylglycine (**L13**), *N*-methylglycine (**L18**), *L*-proline (**L19**) and 4-hydroxy-*L*-proline (**L20**) were successful in promoting a range of reactions.⁴⁴⁻⁴⁷ **L18** allowed C-N cross-coupling to occur at 40 °C but the scope of aryl halide substrates was limited to electron-deficient aryl iodides. **L19** was only used successfully at slightly higher temperatures of 60 – 90 °C, but a much wider scope of amines and aryl halides could be employed. It is thought that the success of **L19** is due to its strong coordination ability as a bidentate ligand, and its limited reactivity to compete as a nucleophile. At higher temperatures **L19** can couple to the aryl bromide substrate, but **L13** can be used to prevent this. It is still unclear why these ligands are so successful but their suggested affinity to bind to copper as bidentate ligands is highlighted in **Figure 1.4**.



Scheme 1.16 Summary of reaction conditions used for Ullmann coupling with amino acid type ligands.⁴⁴⁻⁴⁶

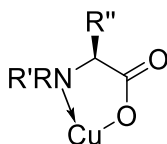
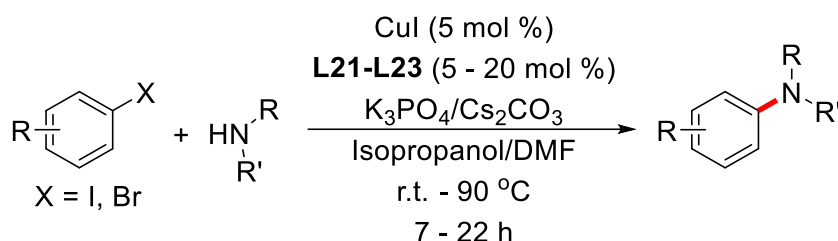
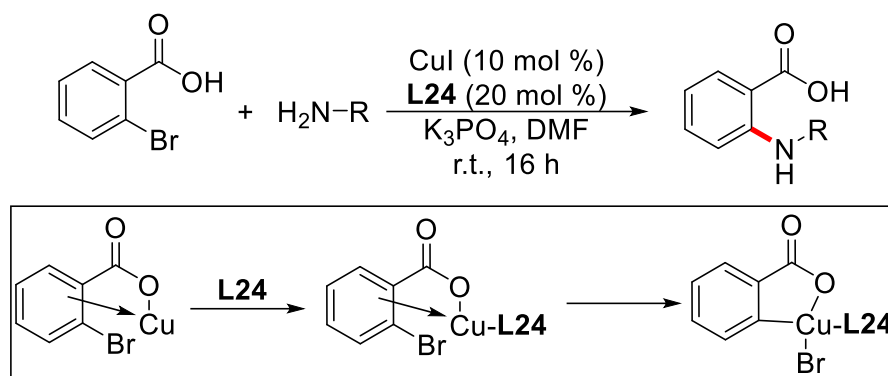


Figure 1.4 Suggested binding mode of amino acid type ligands.⁷

In the case of O,O- ligands, ethylene glycol (**L21**) was employed as a successful ligand in the arylation of aliphatic amines by Buchwald, but it was only successful for aryl iodide substrates which greatly limited the reaction scope.⁴⁸ **L22** was found to be more active and was able also to activate aryl bromides.⁴⁹ Following this, 2-isobutyrylcyclohexanone (**L23**) was found to be an excellent ligand and could even allow cross-coupling reactions with aryl iodide substrates at room temperature, which were extremely rare at the time (**Scheme 1.17**).⁵⁰ Astoundingly, Zhao *et al.* reported that *rac*-BINOL (**L24**) could also facilitate cross-couplings at room temperature with both aryl iodide and bromide substrates, although the latter required the presence of *ortho*-carboxylic acid group to aid this, which has previously been known to accelerate homogeneous copper-catalysed reactions (**Scheme 1.18**).⁵¹ The authors suggest that after deprotonation of the -OH from the base to form a potassium benzoate, coordination of copper occurs to form a Cu^I complex. Coordination of **L24** follows, which facilitates oxidative addition to form a Cu^{III} complex. Amine coordination can then occur, followed by reductive elimination of the product.



Scheme 1.17 Summary of conditions reported for O,O-bidentate ligands.^{48–50}

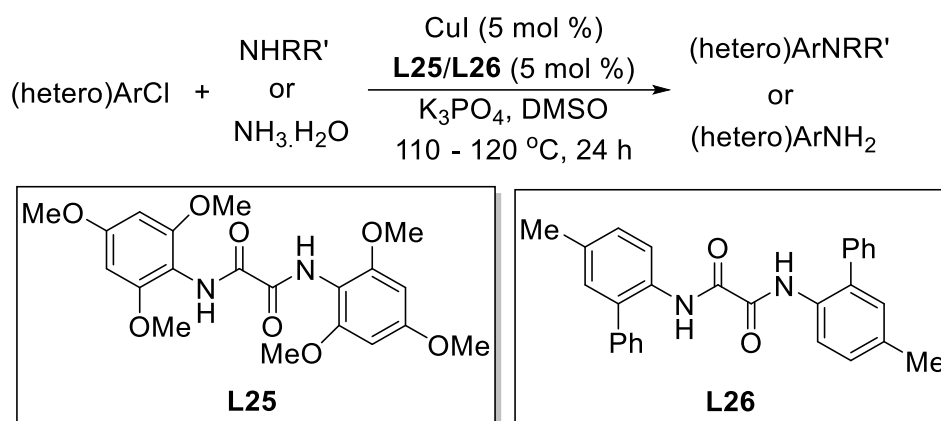


Scheme 1.18 Optimised reaction conditions for aryl bromide coupling with aliphatic amines, and suggested mechanism of oxidative addition for reactions containing an ortho-carboxylic acid group.⁵¹

1.3.2 Second Generation Ligands

While the first generation ligands reported in **Figure 1.3** helped advance the field of C-N cross-coupling reactions greatly through allowing for milder reaction conditions and a wider scope of products, there are two aspects which had still not been addressed which prevented the Ullmann coupling reaction becoming widely applicable. Firstly, the loading of copper and ligand required was still high – the loading of copper was rarely below 5 mol % particularly for more challenging substrates, and the ligand is generally required in excess. Secondly, the activation of aryl chloride substrates had not been successful with the ligands shown thus far. Both of these issues were addressed when Ma *et al.* introduced oxalic diamides as a successful class of ligands in the Ullmann reaction.

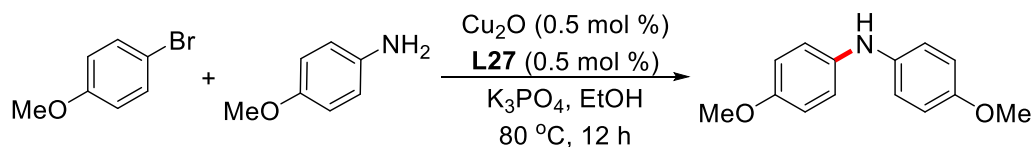
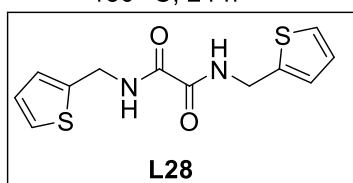
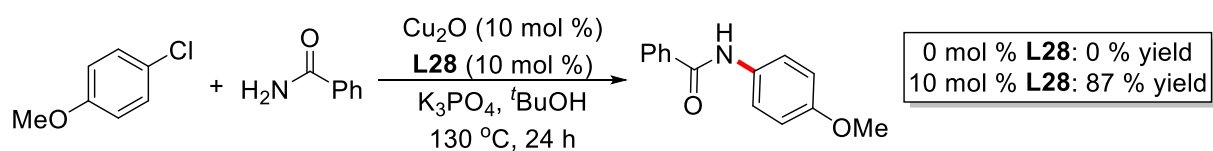
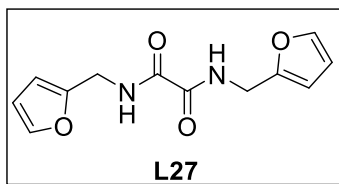
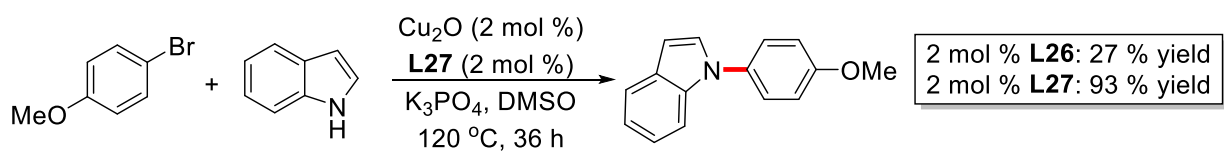
An initial report in 2015 showed the use of oxalic diamide ligands in the copper catalysed coupling of aryl chlorides and amines (**Scheme 1.19**).⁵² A wide range of oxalic diamide ligands were tested and while many of them were successful, obtaining yields of 60 – 92 % product, it was clear that the ligand structure was key to its success. Both sterically hindered and electron-rich oxalamide ligands were most successful. In the same year a second report was released which highlighted successful oxalamide ligands in aryl chloride coupling with ammonia.⁵³ While the results from this report also showed that the electronic nature of the oxalamide ligand was important in its success, the structure-activity relationships deviated from the trends seen in the previous report.



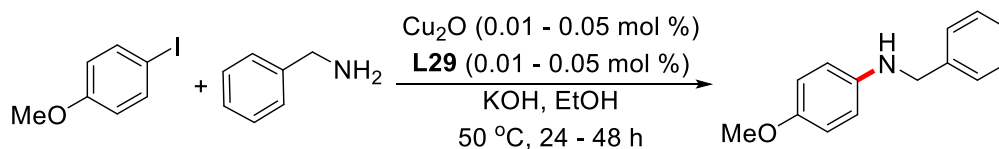
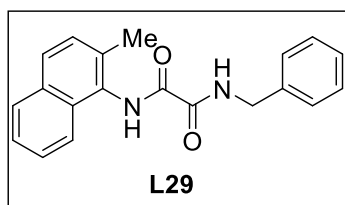
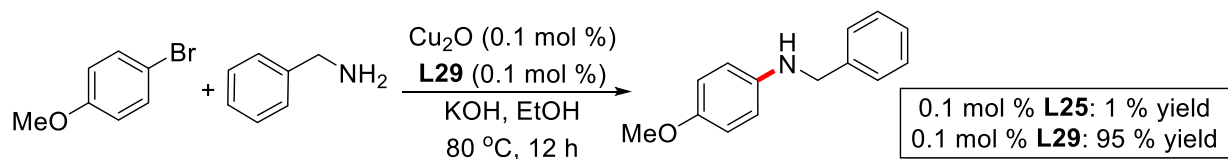
Scheme 1.19 General conditions for the cross-coupling of aryl chlorides and amines/ammonia with oxalamide ligands.^{52,53}

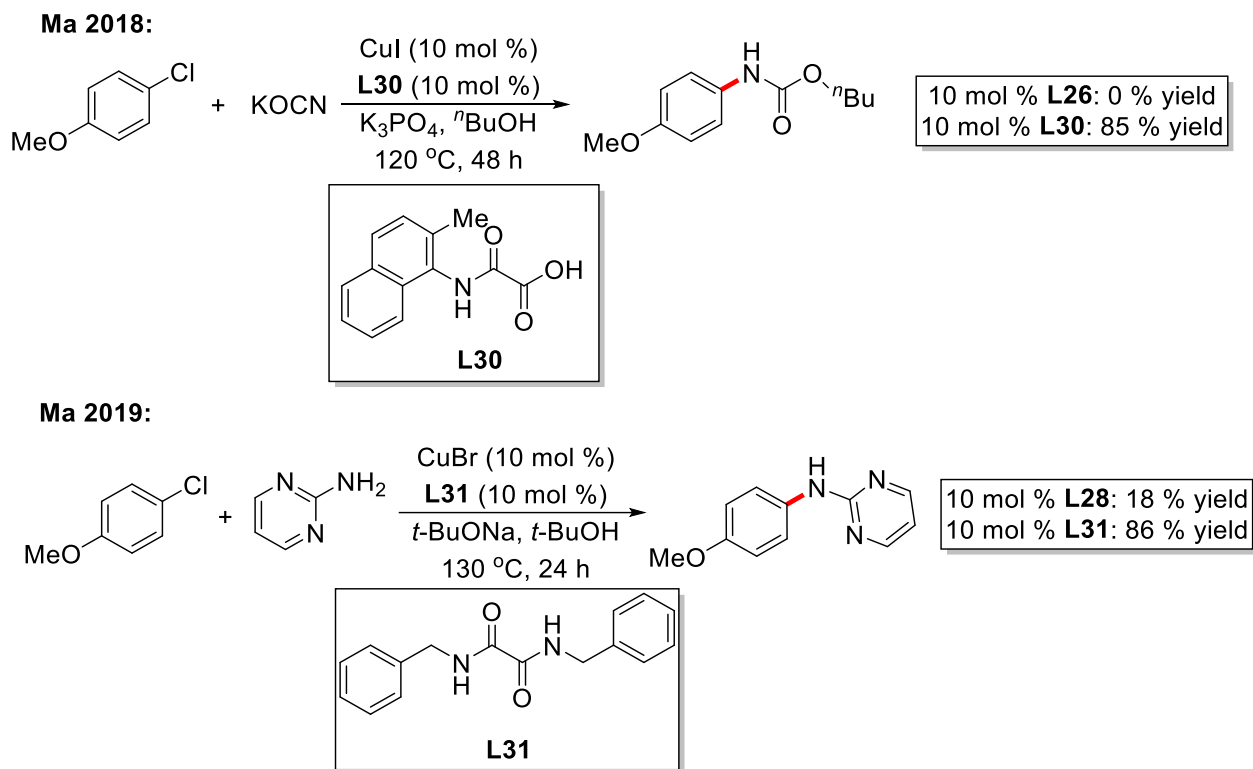
Following this breakthrough, Ma *et al.* continued to broaden the scope of substrates which could be activated with oxalic diamides (**Scheme 1.20**). They continually developed new oxalamide ligands to guide this, and they also applied the ligands to aryl iodide and bromide cross-coupling which was very effective in allowing the copper and ligand loading to be dropped below 5 mol %.^{54–60} Notably, results using **L29** show that the reaction could proceed with as little as 0.1 mol % copper/**L29** for aryl bromide substrates and 0.001 mol % for aryl iodide substrates which is some of the lowest loadings for both copper and ligand seen in C-N cross-coupling reactions.⁵⁴

Ma 2017:



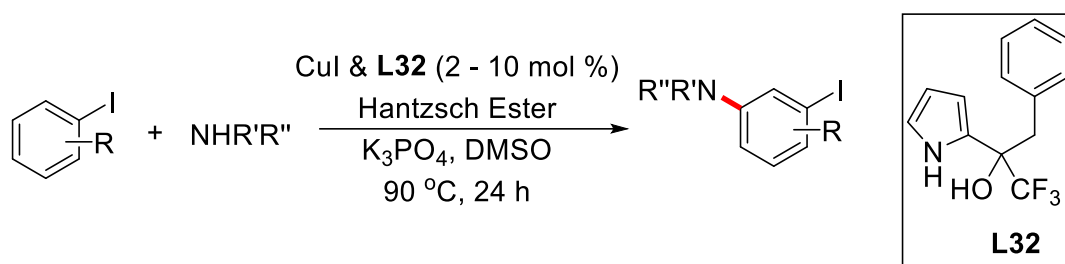
0.5 mol % **L29**: 30 % yield
0.5 mol % **L27**: 95 % yield





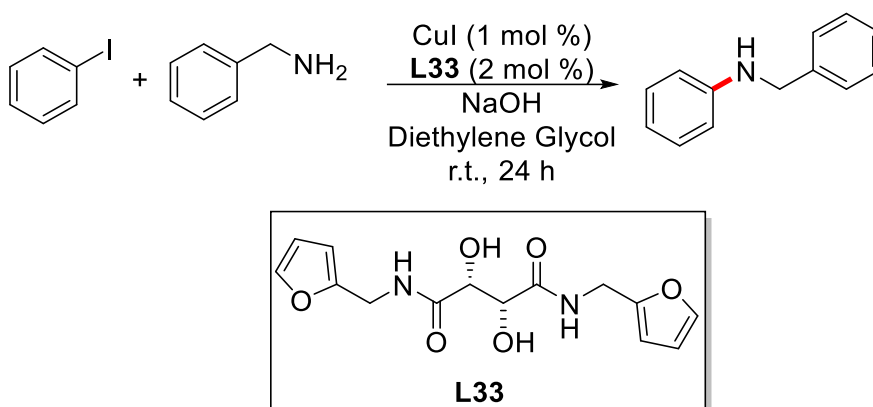
Scheme 1.20 Examples of C-N cross-coupling reactions reported by Ma *et al.* between 2015 – 2019.^{54,55,57–59}

Much of the development of oxalic diamide ligands, and in fact first generation ligands, was performed using an empirical trial-and-error method which involves performing a huge number of experiments to test different ligands, solvents, bases and copper sources. This is a very time-consuming and inefficient process, so researchers are keen to find a rational understanding of the mechanism of the reaction to determine what structural properties are required for their success. An alternative approach from Modak *et al.* in 2020 sought to utilise a library of compounds to quickly screen potential ligands for Ullmann C-N coupling and efficiently find a new ligand.⁶¹ Their method was successful: **L32** was effective in the coupling of substituted aryl iodides with sterically hindered *N*-nucleophiles (**Scheme 1.21**). This research demonstrates that compounds which are not typically known as a ‘good’ ligand can in fact be found to accelerate the reaction, which highlights the importance in determining the key role of the ligand so that more rational ligand design can take place in future.



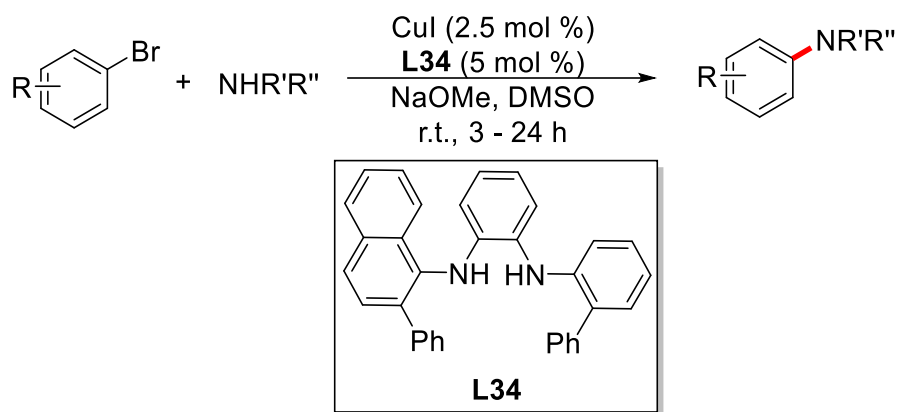
Scheme 1.21 General conditions of coupling with sterically hindered nucleophile with pyrrole-ol-based ligand.⁶¹

A new class of ligand inspired by oxalic diamides was reported by Davies *et al.* in 2022. Tartaric diamides have a similar backbone structure but with added hydroxyl groups which can help introduce flexibility into the structure.⁶² A range of tartaric diamide ligands showed superior performance to first generation ligands in the cross-coupling with an aryl iodide, with low catalyst loadings of 1 mol %. **L33** proved to be the most efficient (**Scheme 1.22**). The reaction could also be carried out at room temperature and it utilised a simple and cheap solvent and base. A wide substrate scope was achieved with various aryl halides and secondary amines. Despite their efficacy, there is limited understanding surrounding the mechanistic effect of tartaric diamide ligands on the reaction.



Scheme 1.22 Tartaric diamide ligand in C-N cross-coupling reaction.⁶²

Buchwald *et al.* attempted to utilise a DFT-guided approach to ligand design. They envisioned that the ligand should be able to increase the electron density on the copper centre to enhance the rate of oxidative addition, and also stabilise the anionic copper intermediate. This led them to develop **L34** which proved to be a successful ligand in aryl bromide cross-coupling and could activate a large number of substrates at room temperature (**Scheme 1.23**).⁶³



Scheme 1.23 General scheme for reaction with new class of ligand developed by Buchwald *et al.*⁶³

It is clear that there are distinct structural differences between all second generation ligands highlighted in this chapter and thus there is still no clear determining factor as to why certain ligands are more successful than others.

1.3.3 Copper Source, Solvent, Base and Amine Effects

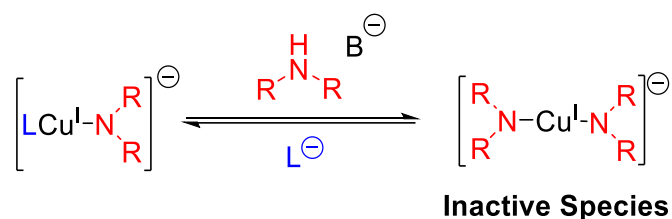
Many different copper salts have been tested in C-N cross-coupling reactions, but it is generally accepted that the initial oxidation state of copper source does not have a significant effect on reaction success. Sources can be Cu⁰, Cu^I or Cu^{II} with marginal difference in yield of product observed.²¹ However, in general, Cu^I sources give a slightly better performance, and it is widely accepted based on experimental evidence that the active catalytic species in the Ullmann reaction is a Cu^I complex. Thus copper compounds with other oxidation states are presumed to convert to Cu^I in situ. This will be discussed further in section 1.4.1.

The solvent chosen for the reaction depends greatly on the polarity of the substrates and the desired reaction temperature, and thus both polar and non-polar solvents have been used successfully.²¹ There have not been any experimental reports examining the mechanistic effect of the solvent, so is still unclear exactly what role the solvent plays in the catalytic cycle, if any, and whether it has any influence in the success or detriment of the reaction.

The choice of base has similarly not been thoroughly investigated, but it is thought to play a more significant role in the reaction compared to the solvent, as it allows for deprotonation of amine substrate and ligand before or after coordination to the copper centre. While weaker inorganic bases are often chosen, such as K₃PO₄, K₂CO₃ and Cs₂CO₃, they are often not soluble in the reaction medium. More recently, examples

from Ma *et al.* and Davies *et al.* have utilised stronger metal hydroxide bases such as NaOH and KOH which have better solubility in some organic solvents.^{54,62}

The use of heterogeneous bases can introduce undesired issues in the reaction – differences in the solid form of the base can lead to negative effects on the reaction. For example Nguyen *et al.* noticed that induction periods and reproducibility issues arose from the inorganic base used in their reactions. They demonstrated that more finely milled inorganic bases may not improve the reaction. Using finely milled Cs₂CO₃ caused an induction period due to faster dissolution of base which in turn led to a larger amount of amine being initially deprotonated.⁶⁴ This causes the majority of the Cu^I catalyst to exist in an inactive Cu-bisamido complex (**Scheme 1.24**). The inhibitive effect is attributed to the amount and basicity of the base, which can shift the equilibrium towards off-cycle inactive species.

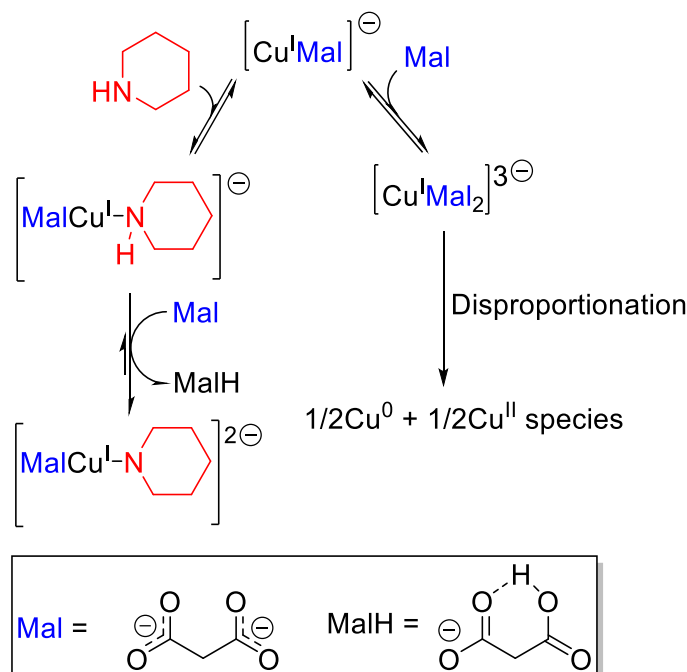


Scheme 1.24 Bases can affect the equilibrium between Cu^I, nucleophile and ligand.⁶⁴

This work is closely aligned with that of Buchwald *et al.* who investigated the effect of rate of addition of base in the Goldberg amidation reaction.²⁹ By adding the strong base potassium bis(trimethylsilyl)amide (KHMDs) slowly, complete conversion of starting material led to 92 % yield of product. However, when adding the base in a single portion, only 1 % conversion of starting material was observed. They concluded that the rate of deprotonation of amide must match the rate of the amidation reaction, otherwise an unreactive Cu-bisamido complex will form, as seen in **Scheme 1.24**. They also showed that the pK_a of the base employed should be lower than the pK_a of the amide substrate, unless the base is added slowly.

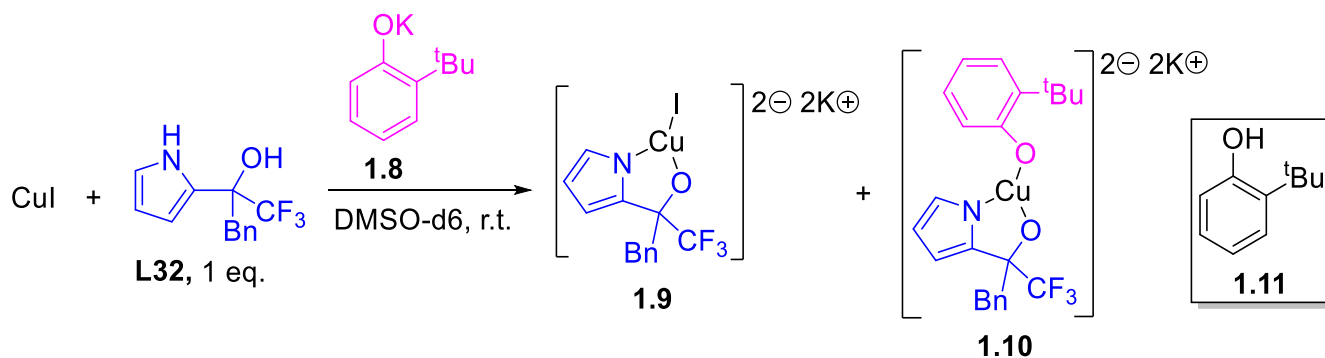
Organic ionic bases have also been investigated as these have high solubility in a range of polar solvents and have been shown to be highly reactive in Ullmann couplings.⁶⁵ However, they are more expensive and not readily available like most inorganic bases, and they cannot be applied to moisture sensitive reactions easily due to their high hygroscopicity. In addition, they have been shown to competitively bind to the Cu^I-centre and cause catalyst deactivation. Work by Davies *et al.* demonstrated that using tetrabutylphosphonium malonate (TBPM) as a base led to the malonate

anion causing disproportionation of copper (**Scheme 1.25**). Adding an excess of amine was shown to shift the equilibrium towards the active piperidine-ligated species.



Scheme 1.25 Deprotonation pathway when TBPM is employed as a base.⁶⁶

More recently, Blackmond *et al.* reported the use of inexpensive phenolate bases which have high solubility in organic solvents. The use of potassium 2-*tert*-butylphenoxide (**1.8**, **Scheme 1.26**) was successful in the cross-coupling of sterically-hindered nucleophiles, but it was demonstrated that the quantity of base used was key to the success of the reaction.⁶⁷ More than one equivalent of **1.8** will lead to the formation of inactive complex **1.10** (**Table 1.1**). Optimal conditions were obtained when addition of an equimolar amount of reaction by-product **1.11** (0.2 eq.) helped to promote higher concentrations of complex **1.9**. Slow addition of **1.8** also helped mitigate formation of complex **1.10**.



Scheme 1.26 Possible complex formation when using phenolate base **1.8**. Complex **1.10** only forms when equivalents of **1.8** exceeds 1.⁶⁷

Equivalent of 1.8	Ratio of Complex Quantified by NMR		
	L32	1.9	1.10
1	48	52	0
3	19	26	55

Table 1.1 Different ratios of compounds that form based on different quantities of **1.8**.⁶⁷

Inevitably, different amines exhibit different pK_a values and nucleophilicity, and can be expected to react differently under different reaction conditions, as well as exhibiting different effects on the copper centre. **Figure 1.5** summarises the key amines reported in this chapter, and the pK_a values associated with their conjugate acids (pK_{aH}).

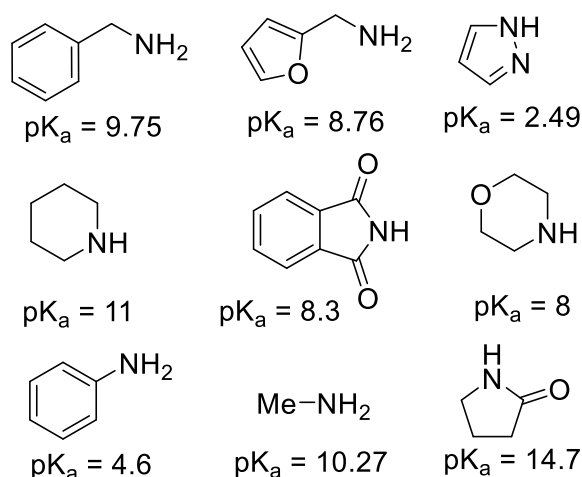


Figure 1.5 Summary of the key amines used in Ullmann reactions and their pK_{aH} values.

Secondary amines are more nucleophilic than primary amines, due to the inductive effect of the alkyl groups which can stabilise the conjugate acid. Amines that can form resonance structures, such as phenylamine and pyrazole, have a much lower pK_{aH} (4.6 and 2.49 respectively), since delocalisation of the lone pair reduces electron density on the amine nitrogen. Thus they would be expected to be less reactive in the Ullmann reaction.

1.4 Mechanistic Studies

The research reported thus far indicates that the ligand, base and solvent have important roles to play in the success of the Ullmann cross-coupling reaction, but the exact nature of their roles and interactions with substrates is still unclear. It is evident from the evolution of Pd-catalysed reactions such as the Buchwald-Hartwig amination that thorough understanding of the reaction mechanism will greatly aid in the optimisation of

the Ullmann reaction. While many reports seem to agree that the reaction follows an oxidative addition/reductive elimination pathway, there is still dispute over whether other pathways are followed such as radical-based mechanisms, and the exact nature of the aryl halide activation step is still unclear. This section will endeavour to summarise the key reports which have investigated the Ullmann reaction to date, and attempt to address any disparities.

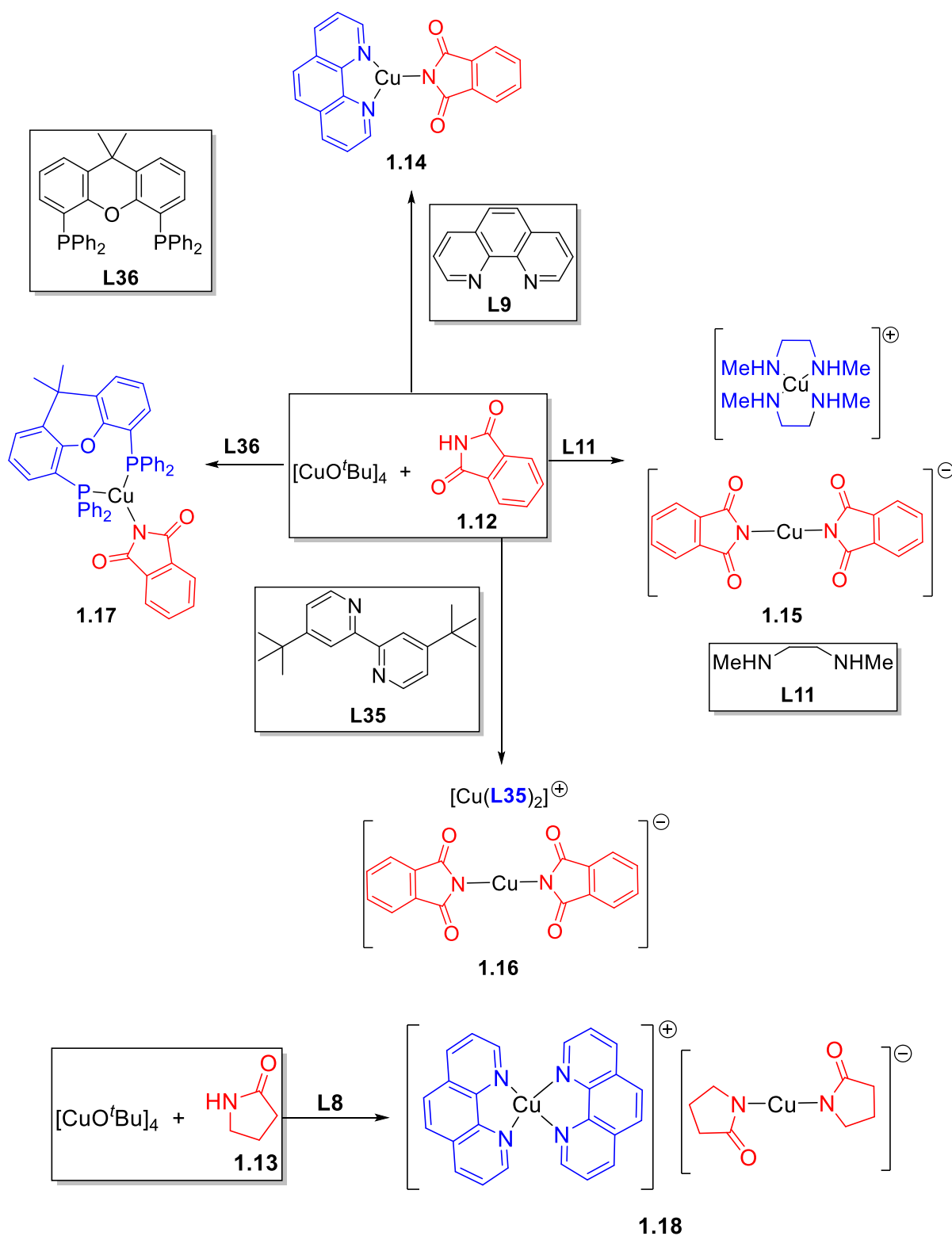
1.4.1 Active Catalytic Species

It is widely accepted that the active catalytic species in Ullmann couplings is a Cu^I centre bound to the nucleophile and ligand. Even if Cu⁰ or Cu^{II} sources are used, Cu^I is thought to form in situ (this is discussed further later in the section). Some Cu^I complexes have been synthesised and characterised in the literature, and their use in the Ullmann reaction confirmed their likelihood as species on the catalytic cycle.

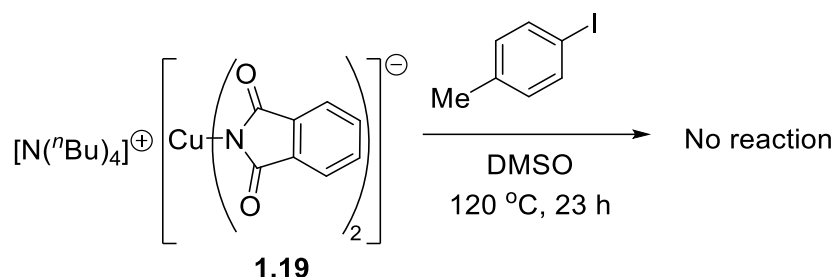
One of the first reported studies of Cu^I complexes in the Ullmann reaction was from Hartwig *et al.* in 2008.⁶⁸ They synthesised and characterised a range of amidate and imidate-ligated Cu^I complexes and determined their role as intermediates in the Ullmann reaction. The complexes were formed by reaction of copper *tert*-butoxide with either phthalimide (complexes **1.14** – **1.17**, **Scheme 1.27**) or pyrrolidinonate (complexes **1.18** and **1.19**) and the desired ligand, and were characterised by ¹H NMR, XRD and solution-phase methods. Solid-state analysis revealed that complexes **1.14** and **1.17** formed 3-coordinated monomers with a trigonal planar Cu^I centre, while complexes **1.15**, **1.16** and **1.18** formed an ionic structure with formula [L₂Cu]⁺[CuX₂]⁻ where X = phthalimide or pyrrolidinonate, and the anionic portion was linear. These complexes were shown to be plausible intermediate species in the cross-coupling reaction with aryl halides. For complexes **1.14** – **1.17** it was shown that solvent polarity affected the rate significantly – using DMSO gave much faster reaction rates compared to THF. On the other hand, reactions with complexes **1.18** and **1.19** were not significantly influenced by solvent polarity, which was suggested to be due to a different rate-determining step in both cases as a result of the different electronic properties arising from the different anionic ligands, although this was not proven experimentally.

Reaction of complexes **1.14** – **1.19** with *p*-iodotoluene was used to obtain kinetic data on the reaction. It was seen that the reaction showed first order kinetics in the copper complex in all cases, and this was observed whether the complex was neutral or ionic, and in either polar or non-polar solvents. This led the authors to conclude that the reactive neutral complex is formed in situ in small equilibrium amounts. In addition, there was no reaction of *p*-iodotoluene with ligandless copper complex **1.19** (**Scheme**

1.28) which highlighted that the active catalytic species is the neutral copper complex containing the ligand and amide substrate, rather than the anionic portion of the complex.

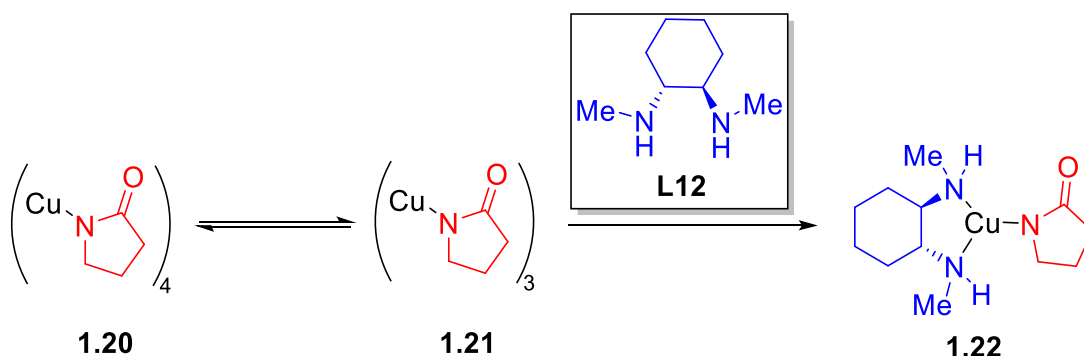


Scheme 1.27 Complexes synthesised by Hartwig *et al.*⁶⁸



Scheme 1.28 Ligandless copper complex which showed the anionic portion is not the active species.⁶⁸

In 2009, Buchwald *et al.* synthesised a Cu^I-pyrrolidinone complex, and their results closely aligned with that of Hartwig *et al.* The structure was identified using ¹H NMR and the Signer method (an equal quantity of the unknown solution and a standard are added to a graduated tube and the heights of the liquid are inversely proportional to the molar mass).⁶⁹ Broad peaks in the ¹H NMR spectrum suggested that the complex exists as oligomeric species which rapidly exchanged at room temperature (complex **1.20** and **1.21**, **Scheme 1.29**), but upon addition of **L12**, the peaks sharpen, suggesting a single species forms. The Signer method supported this finding and confirmed that the solution structure consists of a monomeric Cu^I complex containing **L12** and pyrrolidinone (complex **1.22**).



Scheme 1.29 Cu^I species that forms in the presence of **L12** and pyrrolidinone.⁶⁹

To confirm whether complex **1.22** was an intermediate in the cross-coupling reaction, the authors performed a series of experiments to obtain kinetic data on its reaction with 3,5-dimethyliodobenzene. These confirmed the reaction was first order in [aryl halide] and [complex **1.22**]. Hammett analysis with a series of aryl halides confirmed electron-deficient aryl halides enhanced the reaction rate. These data, along with comparison of reaction activation energies using Eyring analysis, was consistent with their kinetic studies on the *N*-arylation reaction between 2-pyrrolidinone and 3,5-dimethyliodide in

the presence of Cu^I and **L12**, which strongly suggests that complex **1.22** is a likely intermediate in the reaction.

Following on from their previous work, Hartwig *et al.* further investigated the presence of Cu^I intermediates in the Ullmann reaction by synthesis of Cu^I-amido complexes both with 1,10-phenanthroline as a ligand (complex **1.23**) and without (**L9**, complex **1.24**) (Figure 1.6).³⁸ Complex **1.23** has a tetrahedral cationic copper portion ligated by **L9** and an anionic portion which contains two linearly bound amides. Upon reaction of complex **1.23** with p-iodotoluene, the cross-coupled product 4-methyltriphenylamine formed in 95 % yield after 1.5 hours at 80 °C. Reaction of the non-ligated complex **1.24** with p-iodotoluene led to only 44 % yield after 3 hours at 110 °C, which indicated that the dative ligand **L9** may help to form the active catalytic species.

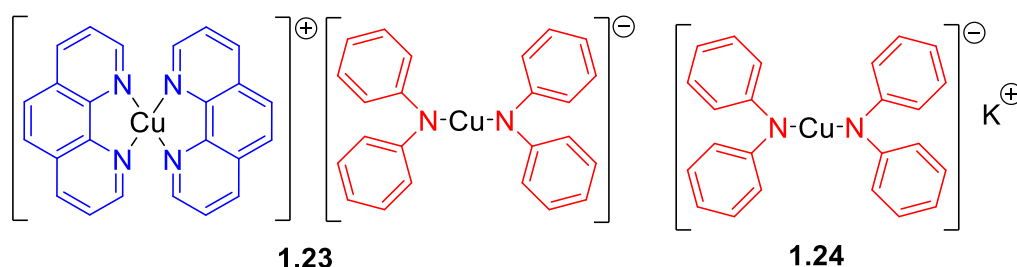


Figure 1.6 Complexes synthesised by Hartwig *et al.*³⁸

Similar work has been reported by Shyu *et al.* whereby they attempted to synthesise Cu^I complexes with **L9** as an auxiliary ligand.⁷⁰ However, in their case, they reported a linear Cu^I-bisamido anion complex and a tris(1,10-phenanthroline)sodium counter ion (**1.25**, Figure 1.7) which has a distorted octahedral structure. 10 mol % of the complex successfully reacted with 4-iodotoluene to achieve the cross-coupled product in 99 % yield which confirmed that it is likely to be an intermediate in the reaction. Through in situ ESI-MS, the anionic portion of the complex was confirmed to be the active catalytic species. Despite this, the coupling of 4-iodotoluene and *N*-phenylaniline was compromised when **L9** was not present in the reaction medium, only forming the coupled product in 22 % yield, which suggests the presence of **L9** enhances catalytic activity. The authors suggest this may be due to its stabilising effect of the Cu-bisamido cation. The presence of **L9** may also influence the equilibrium position and promote the formation of the active species.

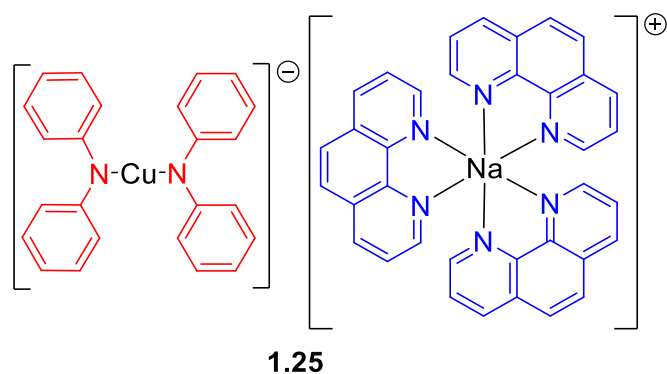


Figure 1.7 Cu^I-bisamido complex with octahedral cation proposed by Shyu *et al.*⁷⁰

More recently, a series of Cu^I alkylamide complexes were synthesised and characterised by Davies *et al.*³⁵ Structures **1.26** – **1.28** (**Figure 1.8**) were characterised by single-crystal XRD and were found to exist as tetramers in the solid state, forming 8-membered Cu₄N₄ rings.

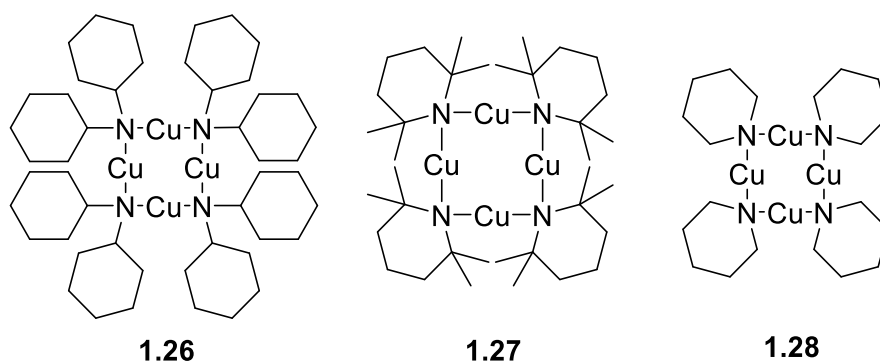
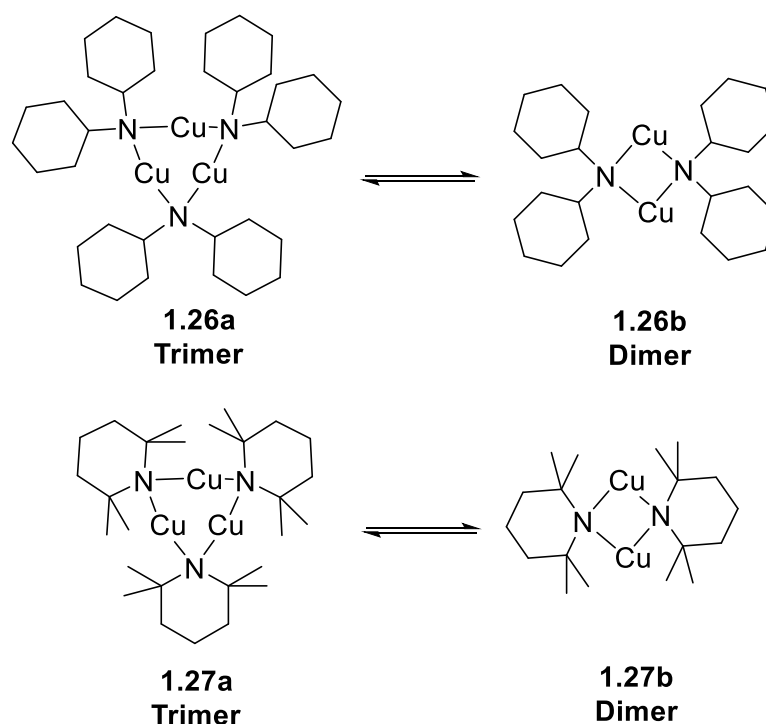


Figure 1.8 Complexes synthesised by Davies *et al.*³⁵

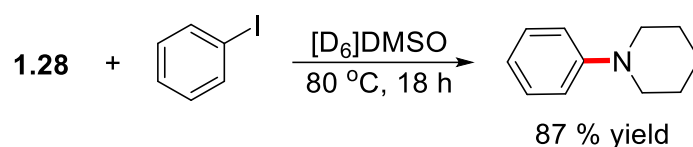
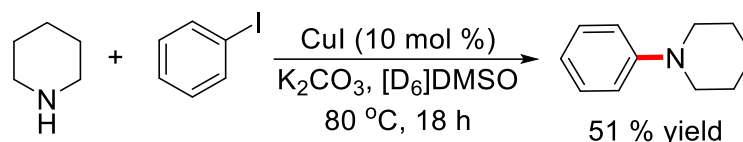
Their structures in solution were also investigated by using ¹H diffusion-ordered NMR spectroscopy (DOSY) by using diffusion coefficients to determine the radii of the structures and comparing this to DFT-optimised values. Although the solid-state structures are present as tetramers, in solution the complexes adopt different aggregation states, which are determined by the steric bulk of the amide group (**Scheme 1.30**).



Scheme 1.30 Aggregates formed from Cu^I-amide complexes in solution.³⁵

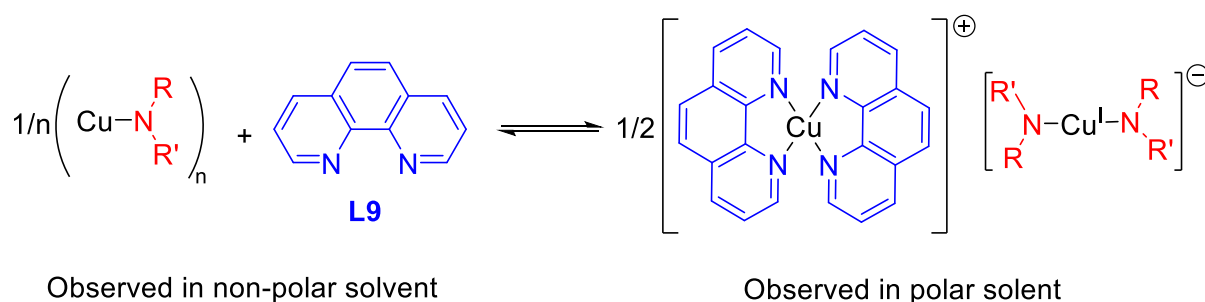
The synthesised complexes were then tested as intermediates in the Ullmann reaction by reaction with iodobenzene in DMSO and benzene solvents. Complexes **1.26** and **1.27** were too sterically bulky to undergo coupling in either solvent. **1.28** was more successful: when used stoichiometrically, high yields of the cross-coupled product formed (75 %) in DMSO. It was compared to the catalytic reaction with CuI, iodobenzene and piperidine, which yielded 51 % of cross-coupled product, which thus confirmed the likelihood of complex **1.28** as an intermediate in the reaction (**Scheme 1.31**). It also highlighted that the reaction can occur with Cu^I-amide aggregates without the need for an additional ligand.

Given that bulkier complexes **1.26** and **1.27** were not compatible in the cross-coupling reaction, this indicated that steric bulk had a detrimental effect on the reactivity of the Cu^I-amide complex. This indicated that cross-coupling reactions with bulky amines that result in low yields are inhibited at the aryl halide oxidative addition step and not during the formation of the Cu^I-amide catalyst resting state.

Stoichiometric Reaction:**Catalytic Reaction:**

Scheme 1.31 Stoichiometric and catalytic reactions carried out to consolidate the viability of **1.28** as a reaction intermediate.³⁵

Next, Davies *et al.* investigated the solution structure of complex **1.28** in the presence of 1,10-phenanthroline (**L9**) in a polar (DMSO) and non-polar (benzene) solvent (**Scheme 1.32**).³⁵ They observed that in benzene, a ligand-free Cu^I -amide complex was present, along with **L9** which was not bound to the Cu centre since there was no evidence from 1H NMR that a ligated complex was present, and the observed radii from 1H DOSY NMR were not consistent with a ligated complex. In DMSO, 1H NMR resonance displayed a large shift compared to that of free **L9** which indicated that coordination of **L9** had occurred.

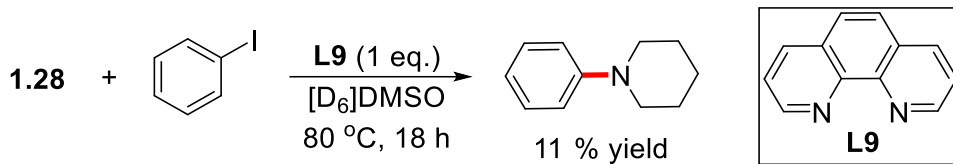


Scheme 1.32 Solution structure of **L9**-ligated complex.³⁵

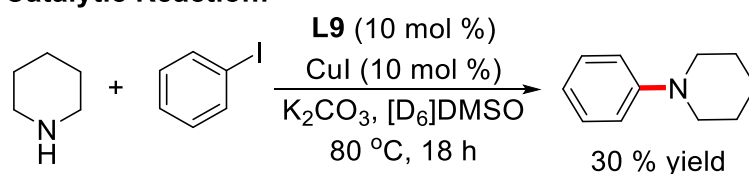
The reactivity of the Cu^I complexes was evaluated in the presence of **L9** as a ligand. It was interesting that in both DMSO and benzene solvents, the yield of reaction where **L9** was present was drastically reduced. As can be seen from **Scheme 1.33**, the yield of cross-coupled product reduced from 87 % to 11 % in the stoichiometric reaction, and from 51 % to 30 % yield in the catalytic reaction, which indicated that additional **L9** was detrimental to the reaction. It was concluded that additional **L9** shifted the solution equilibrium towards the unreactive ionic bisamidocuprate species and away from the reactive ligand-free Cu^I -amide species. The authors highlight the contradiction

of these findings to previous reports; however, they highlight that the reactivity of solution species is likely affected by many factors in the reaction such as pK_a of the amine, solvent and temperature.

Stoichiometric Reaction:

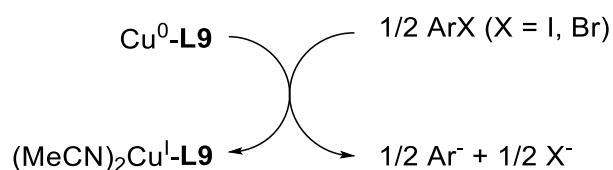


Catalytic Reaction:



Scheme 1.33 Stoichiometric and catalytic reactions with addition of **L9** to determine its effect on the reaction.³⁵

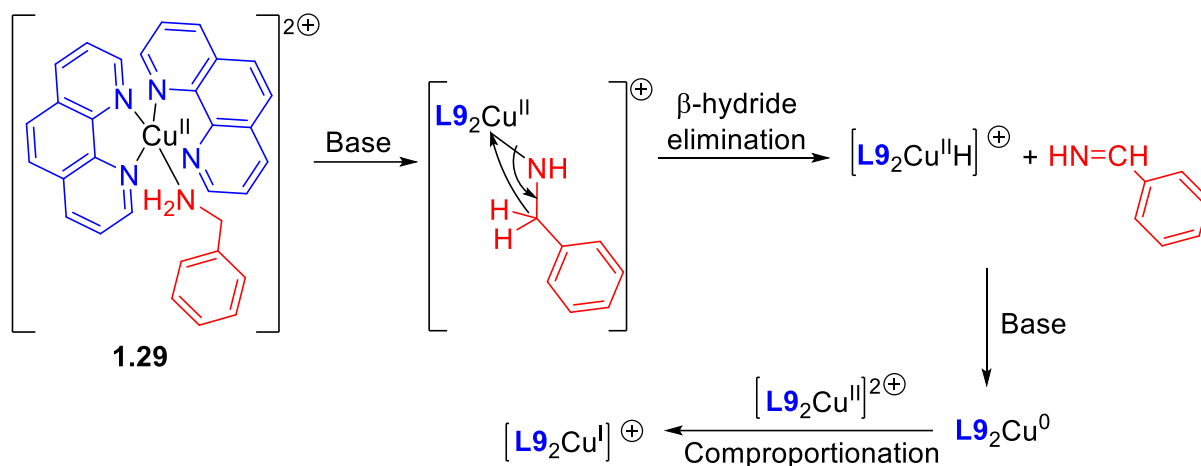
Characterisation techniques such as cyclic voltammetry (CV), ultraviolet-visible spectroscopy (UV-Vis) and electron paramagnetic resonance spectroscopy (EPR) have also been used to determine the oxidation state of copper intermediates throughout the reaction. Jutand *et al.* used CV to determine the copper species present during the Ullmann reaction.³⁹ They clarified that Cu^0 precursors can be oxidised to Cu^I complexes in situ by reaction with the aryl halide (**Scheme 1.34**).



Scheme 1.34 The reduction of Cu^0 precursor to Cu^I complex in the presence of acetonitrile solvent.³⁹

Utilising the differing colours obtained with Cu^I and Cu^{II} complexes, UV-vis was found to aid in the understanding of the formation of the active catalytic species in the Ullmann reaction.⁷¹ Addition of **L9** to CuI or $CuBr$ led to the formation of a deep red solution which is indicative of a Cu^I complex, and displayed an absorption band of $\lambda_{max} = 445\text{ nm}$. A mixture of $CuBr_2$ and **L9** showed an absorption band of $\lambda_{max} = 746\text{ nm}$ suggesting a Cu^{II} complex formed. With addition of amine to the Cu^{II} complex, a stable penta-coordinated Cu^{II} complex is thought to form as shown by a hypochromic shift of λ_{max} from 746 to 690 nm (**1.29**, **Scheme 1.35**).

The addition of **L9** to this mixture led to the absorption band for Cu^{II} disappearing while the band at 445 nm increased, and the authors suggested β -hydride elimination would then occur in the presence of a base (based on comparison to the activity of Pd^{II} salts), and the Cu^I active complex can be generated. However, the authors were not able to provide experimental evidence for the exact pathway of Cu^I formation from Cu^{II} precursors.



Scheme 1.35 Proposed scheme for formation of Cu^I complexes from Cu^{II} precursors.⁷¹

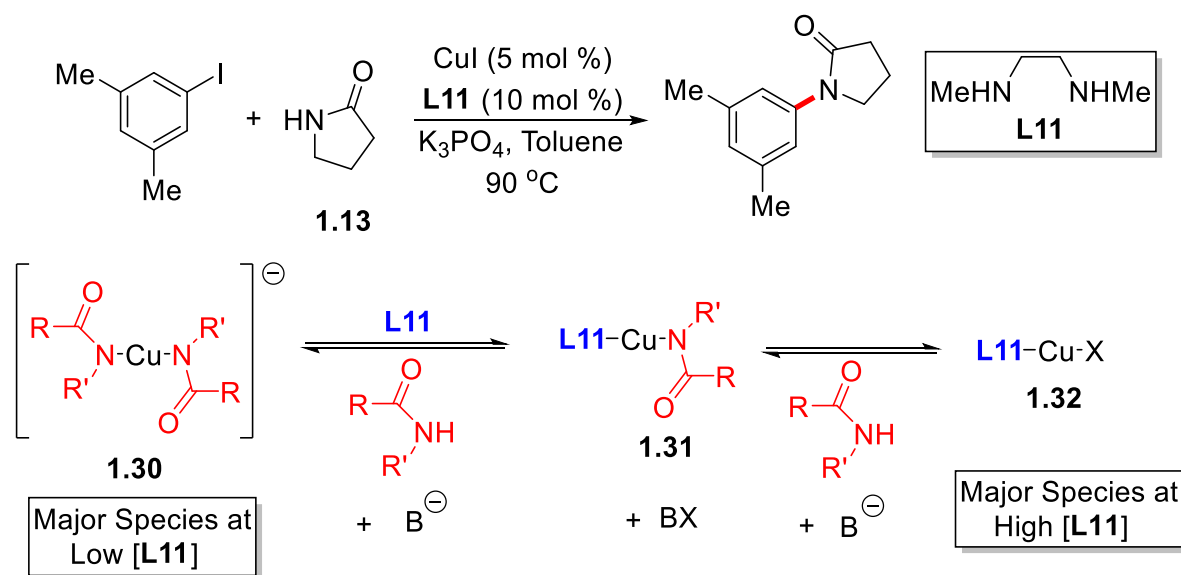
More recently in 2017, Nguyen *et al.* studied an Ullmann cross-coupling reaction using CuI as a copper source.⁶⁴ While investigating possible reasons for an induction period in their reaction, they theorised that it may be due to rapid formation of a Cu^{II} species when initiating the reaction, which slowly gets reduced to the active Cu^I species. In situ EPR data clearly showed the presence of a Cu^{II} species when CuI was added to the mixture at room temperature. Upon heating to 90 °C, the Cu^{II} peak disappears and no EPR signal is detected for the remainder of the reaction. While they concluded that the Cu^{II} species was not responsible for the induction period due to its fast disappearance, it still highlights the likelihood that Cu^I species are the active catalytic species in the reaction and can be formed in situ from Cu^{II} precursors.

1.4.2 The Role of the Ligand

While there is still limited understanding of the exact role of the ligand in Ullmann cross-coupling reactions, fragments of understanding have been gained by various studies of individual systems which may allude to the general role ligands can exhibit.

It has been reported that a key role of ligands is that it prevents multiple binding of the *N*-nucleophile to the copper centre. While both the nucleophile, solvent and base can compete with the ligand, it is clear from previous work reported in section 1.3.3 and

1.4.1 that multiple ligation of the nucleophile leads to inactive species which hinders the reaction progress.¹² Indeed, this was further explored by Buchwald *et al.*, where they showed that a higher concentration of ligand prevented multiple ligation of the amide nucleophile.^{69,72} This was proven by performing kinetic studies on the reaction in **Scheme 1.36**, which showed that at low concentrations of **L11**, the resting state of the catalyst is a multiply amide-ligated species (**1.30**). This was proven since increasing the concentration of amide **1.13** lowered the reaction rate. Inversely, at high concentration of **L11**, the reaction rate increased and they suggested this was due to the equilibrium shifting to complex **1.31** which is in equilibrium with **1.32**.



Scheme 1.36 The equilibrium shifts which occur with different concentrations of **L11**.⁷²

Taillefer *et al.* have suggested that the ligand may be responsible for making the copper centre more electron rich.⁷³ This was highlighted in their CV studies of precatalytic species with copper complex **1.33** (**Figure 1.9**) which was compared to acetonitrile-ligated complex $[\text{Cu}(\text{MeCN})_4]^+$ which was inactive in the cross-coupling reaction. While the CV of complex **1.33** showed oxidation at $+0.44\text{ V}$ and reduction at -1.35 V , $[\text{Cu}(\text{MeCN})_4]^+$ showed oxidation at $+1.10\text{ V}$ and reduction at -0.80 V . The oxidation potential of the copper centre in $[\text{Cu}(\text{MeCN})_4]^+$ is significantly higher than the ligated complex which suggests the ligand makes the copper centre more electron rich.

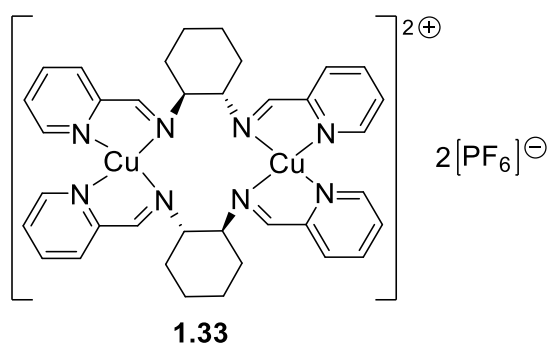


Figure 1.9 Ligated complex studied by CV.⁷³

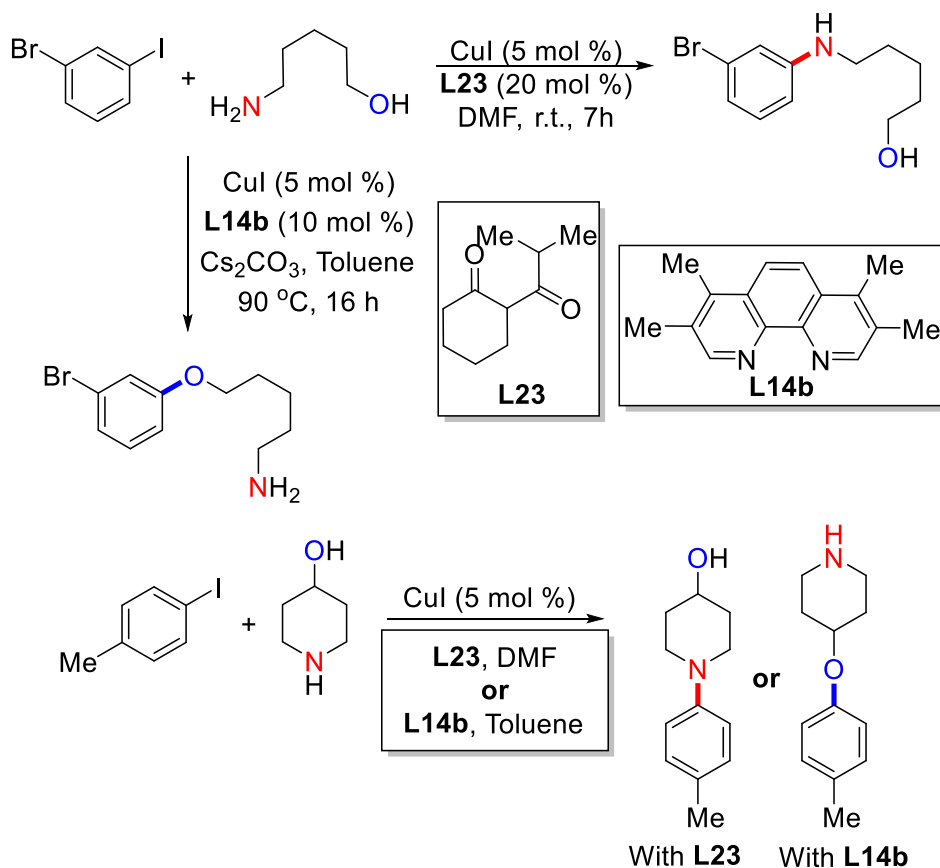
Similarly, when Hartwig *et al.* studied complexes **1.14** – **1.17** in **Scheme 1.27** above, they observed that the complexes containing more electron donating dative ligands had superior rates to those with less electron donating ligands.⁶⁸ Additionally, comparing complexes **1.14** and **1.18** which both contain a cationic portion ligated to 1,10-phenanthroline, **1.18** reacted faster which confirms the anionic portion with a more electron donating amide can enhance the yield.

In the same work, the authors observed that the cross-coupling reaction between complex **1.15** and 4-iodotoluene led to the formation of a Cu^{II} species [Cu(**L11**)₂]₂ in 43 % yield. They suggested that disproportionation occurs from [Cu(**L11**)] to form the Cu^{II} complex and Cu⁰.⁶⁸ This highlights that sometimes ligands have a detrimental effect on the reaction and can negatively influence the copper species which form.

DMEDA (**L11**) has been studied widely in the Ullmann reaction, and in 2010, Larsson *et al.* utilised a large excess of **L11** (1000x Cu) to achieve high yielding cross-coupling reactions. They could not kinetically rationalise the rate enhancement that **L11** provided, but they suggested that it could help to solubilise the heterogeneous inorganic base, K₃PO₄, or it could act as a reducing agent to form the active Cu^I species. They did not provide experimental evidence for this, but in the same year Jutand *et al.* were able to show via UV-vis investigations that **L11** does not reduce Cu^{II} species to Cu^I at room temperature.⁷¹

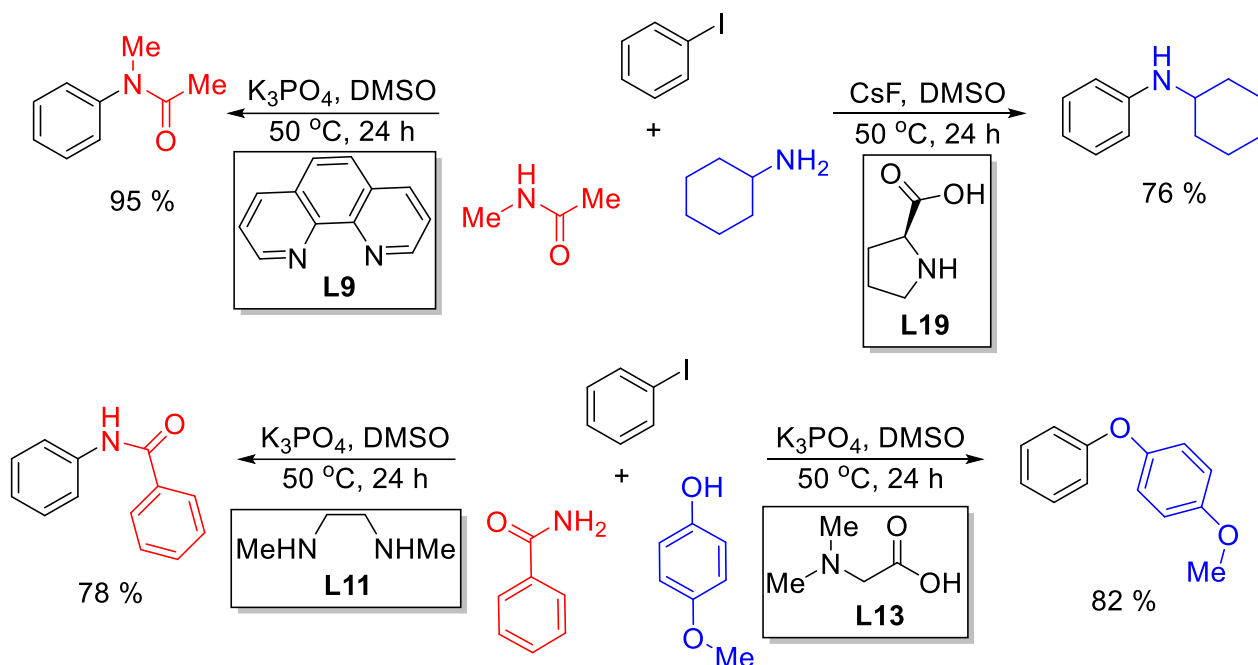
Some studies have also explored the influence that ligands can have on the selectivity of the reaction. In 2007, Buchwald *et al.* utilised ligand **L23** and 1,10-phenanthroline derivative **L14b**, **Scheme 1.37**, in the arylation of 5-amino-1-pentanol.⁵⁰ It was observed that with **L23**, the *N*-arylated product formed, while with **L14b** the *O*-arylated product was synthesised. The authors suggest that binding of **L23** lowers the electrophilicity of the Cu^I centre which would disfavour binding of the alcohol. Since **L14b** is more Lewis acidic, the Cu^I complex which forms would enhance binding of the

alcohol and favour O-arylation. This study highlights the impact the ligand can play in changing the electronic properties of the copper centre.



Scheme 1.37 Selective coupling achieved with different ligands.⁵⁰

More recent work by Ribas *et al.* broadened the scope of cross-coupling reactions which could show different selectivity with different ligands.⁷⁴ They showed that careful selection of ligand can allow orthogonal discrimination with amines, amides and alcohols. General, mild conditions with either K₃PO₄ or CsF as a base and 50 °C temperature allows a range of cross-coupled products to form. A selection of examples for conditions and ligands are shown in **Scheme 1.38**. It is clear that the ligand plays a key role in controlling selectivity between nucleophiles, but there is no clear trend as to what causes the selectivity, and there is still limited mechanistic understanding behind these behaviours, so further work is required to delve deeper into the different reactivity.



Scheme 1.38 Selectivity of different nucleophiles can be achieved with different ligands.⁷⁴

Recent DFT studies from Buchwald *et al.* highlight the role that **L34** (**Figure 1.10**, blue) plays in lowering the energy barrier for oxidative addition of the aryl halide to occur.⁶³ It was shown that the ligand is able to control the π - π interaction between the naphthyl portion of **L34** and the aryl halide. It can position itself so that the aryl halide is parallel to the naphthyl group (complex **1.34**) or the biphenyl arm of **L34** (complex **1.35**). When the ligand is positioned so that the aryl halide is over the naphthyl ring, a lower energy barrier is observed ($13.9 \text{ kcal mol}^{-1}$ compared to $18.3 \text{ kcal mol}^{-1}$) and this difference was proven to occur primarily from a difference in interaction energies. This confirmed that **L34** is able to facilitate oxidative addition of the aryl halide to the metal centre, and demonstrates that non-covalent interactions between the ligand and reaction substrates can have a large influence on the success of the reaction.

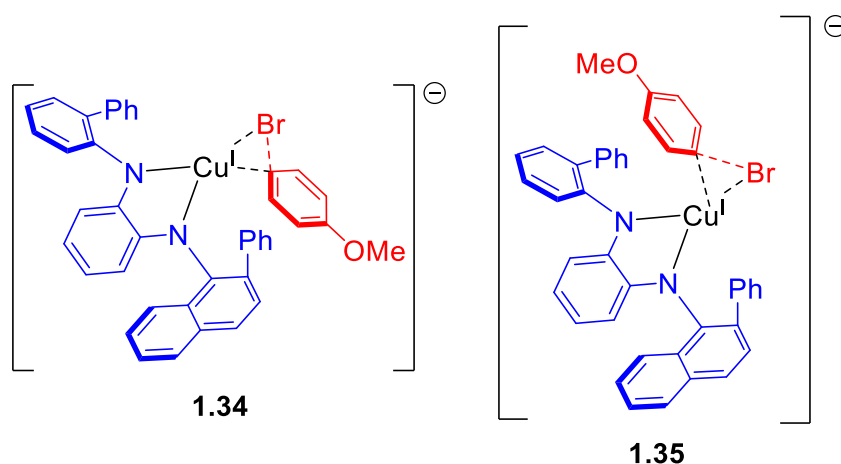


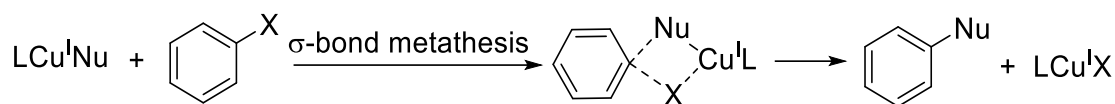
Figure 1.10 The orientation of aryl halide allows interaction with **L34** (blue).⁶³

1.4.3 Proposed Mechanistic Pathways

As discussed in the previous sections, a definitive mechanism for the Ullmann reaction is yet to be determined. Although it is generally agreed that the mechanism follows pathways involving either σ -bond metathesis, π -complexation, radical intermediates or $\text{Cu}^{\text{I}}/\text{Cu}^{\text{III}}$ intermediates in oxidative addition/reductive elimination steps, there are many conflicting findings which continually raise questions about what the aryl halide activation step entails. The reactivity of aryl halides in the Ullmann reaction is such that aryl iodide substrates are the most reactive ($\text{I} > \text{Br} > \text{Cl}$). It is likely that the influence of the leaving halide ion is much higher in the Ullmann reaction than it is in Pd-based couplings, since Cu is smaller and less electron-rich, and thus attachment of Cl^- would decrease the electron density of the copper centre more than I^- would.¹² This suggests that copper-based mechanisms are certainly involved, and understanding the aryl halide activation step is key to advancement and optimisation of the Ullmann reaction. The next sections will highlight key works which show evidence for each type of mechanistic pathway.

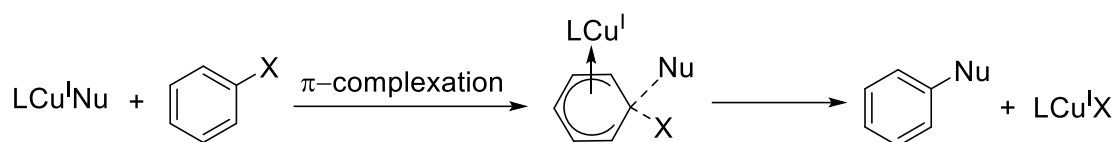
1.4.3.1 σ -Bond Metathesis and π -Complexation

σ -bond metathesis involves the activation of the aryl halide through a four-centred Cu^{I} -nucleophile intermediate whereby the metal centre forms a σ -bond with the halogen atom. A partial positive charge is generated on the carbon atom bound to the halogen atom which allows attack by the nucleophile to form the cross-coupled product (**Scheme 1.39**).²⁶



Scheme 1.39 General mechanism for σ -bond metathesis.²⁶

The π -complexation process involves the Cu^{I} -nucleophile species interacting with the π -electrons of the aromatic ring of the aryl halide substrate. This allows for polarisation of the C-X bond, and the resulting complex allows the nucleophile to substitute the halide ion (**Scheme 1.40**).²⁶

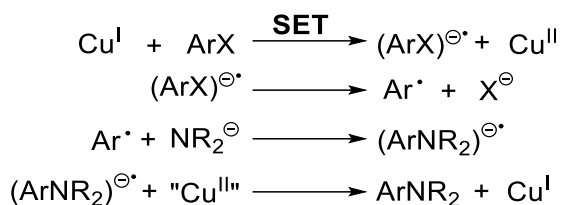


Scheme 1.40 General mechanism for π -complexation.²⁶

In both σ -bond metathesis and π -complexation pathways, the copper oxidation state remains at +1. There remains very limited experimental evidence of these two pathways, and thus the likelihood of their presence in the Ullmann reaction is low. In 1964, Weingarten proposed that the cross-coupling between bromobenzene and potassium phenoxide followed the π -complexation pathway. Their experimental evidence was limited, but they suggested it was due to the relative reactivity order in the aryl halides they studied, whereby aryl iodides were faster than -bromides and -chlorides.⁷⁵ In the same year, the reaction between aryl halide and cuprous salts was studied by Bacon *et al.*, and these reactions were suggested to follow the σ -bond metathesis process, but again experimental evidence is sparse.⁷⁶ To date, no further examples have been proposed for these mechanisms.

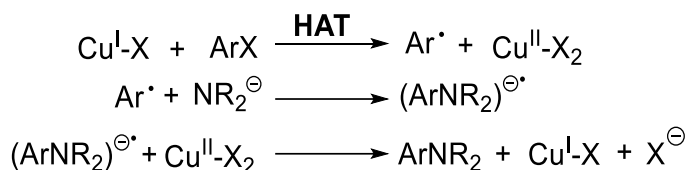
1.4.3.2 Aryl Radical Intermediates

Radical-based pathways can occur via single-electron transfer (SET) or halogen atom transfer (HAT). In SET, an electron is transferred to the aryl halide from the Cu^{I} complex which is oxidised to form an aryl halide radical anion and Cu^{II} intermediate. The radical then couples to the nucleophile and the Cu^{II} complex is reduced back to Cu^{I} which regenerates the active catalyst (**Scheme 1.41**). This process is also known as 'outer-sphere' electron transfer whereby the initiator does not coordinate to the aryl halide, and only the electron is transferred.^{21,26}



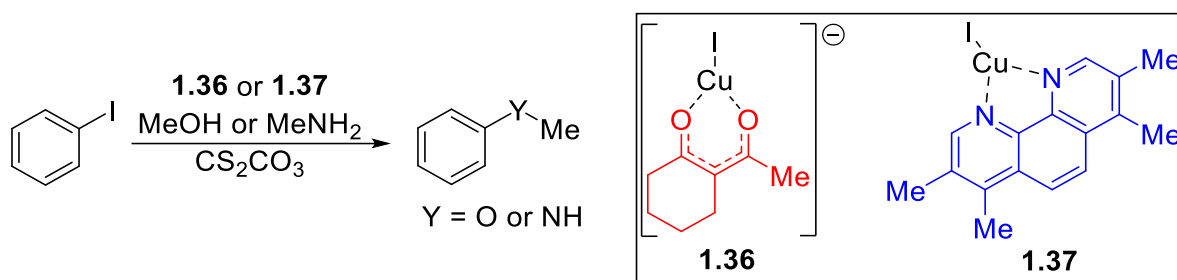
Scheme 1.41 General mechanism for SET.^{26,77}

In HAT, the halogen anion is transferred to the Cu^I centre which in turn produces a Cu^{II} intermediate and an aryl radical. The nucleophile can then react with the radical to form the desired product (**Scheme 1.42**). This process is known as ‘inner-sphere’ electron transfer and involves the simultaneous transfer of electrons and C-X bond cleavage.²⁶

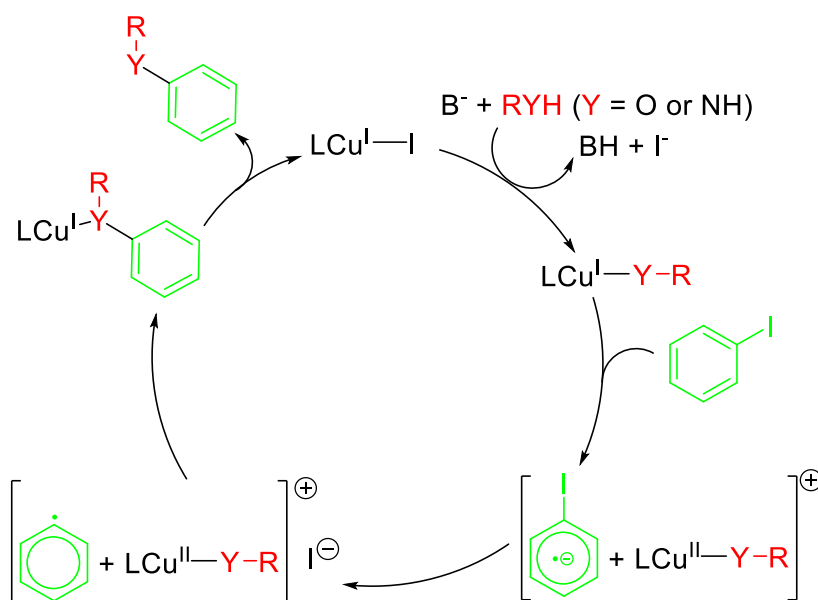


Scheme 1.42 General mechanism for HAT.⁷⁷

In 2010, Buchwald *et al.* reported a theoretical study into the mechanism behind the ligand-selective reactions which were discussed in section 1.4.2 (**Scheme 1.37**).^{50,78} DFT studies on the reaction shown in **Scheme 1.43** suggest that activation energies for radical-based SET or HAT pathways are much lower than those for oxidative addition or σ -bond metathesis. Their findings also demonstrate that the selectivity that arises with different ligands occurs in the aryl halide activation step rather than the nucleophile formation step. The electron rich ligand in complex **1.36** promotes SET in reactions with both *N*- and *O*-nucleophiles, but SET is faster in reactions with Cu^I-amido complexes rather than Cu^I-methoxide complexes which leads to selective formation of the *N*-arylated product. The less electron-rich complex **1.37** promotes SET in the Cu^I-amido reaction but promotes HAT in the reaction with Cu^I-methoxide. The rate of HAT is faster than SET in this case, thus leading to *O*-arylation. The proposed general mechanism is shown in **Scheme 1.44**.

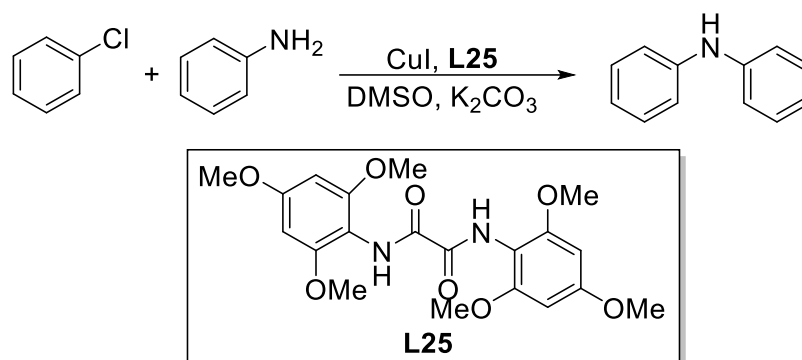


Scheme 1.43 The reaction studied computationally by Buchwald *et al.* to determine the mechanism of selective O- and N-arylation.⁷⁸



Scheme 1.44 Radical-based mechanistic pathway proposed by Buchwald *et al.*^{26,78}

More recently, Morarji *et al.* suggested a SET pathway for the cross-coupling involving oxalamide ligands.⁷⁹ They studied the mechanism of the reaction between aniline and chlorobenzene using DFT (**Scheme 1.45**), thus investigating the mechanism with the rarely studied aryl chloride substrate. They suggest that aryl chlorides are more likely to follow the free-radical pathway.



Scheme 1.45 Reaction chosen by Morarji *et al.* for computational analysis of the mechanism.⁷⁹

To support the theoretical investigation, in situ FTIR and ¹H NMR were utilised to determine the binding mode of **L25** to the copper centre. FTIR revealed that there was no shift in the N-H peak when comparing the spectra of **L25** and **L25** + CuI, but a shift in peaks corresponding to C=O occurred (**L25** = 1680 cm⁻¹, **L25** + CuI = 1664 cm⁻¹) which indicates a C=O-Cu bond may have formed. An IR spectrum with addition of base could not be determined due to low solubility in THF solvent, so the authors conducted ¹H NMR studies in DMSO-*d*₆ which allows solvation of base. Again they did not observe a shift in the N-H peak even after addition of base which suggests deprotonation of ligand does not occur. DFT studies also showed that binding to Cu through C=O was favoured over N-H by 10 kcal mol⁻¹. Assuming therefore that the ligand binds to the Cu centre through C=O, the structure **1.38** was proposed as the most probable species in the reaction (**Figure 1.11**). The likelihood of the reaction proceeding by oxidative addition/reductive elimination, HAT, SET, σ-bond metathesis or π-complexation was determined by comparing the calculated free energy barriers, ΔG, for these processes. A summary of the findings can be seen in **Table 1.2** where it is clear that the SET pathway has the lowest calculated activation energy.

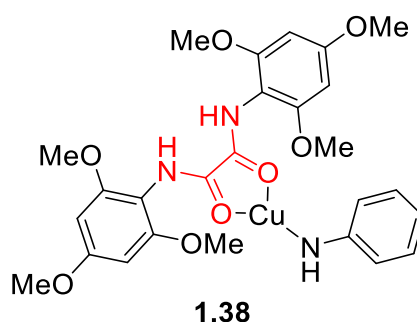


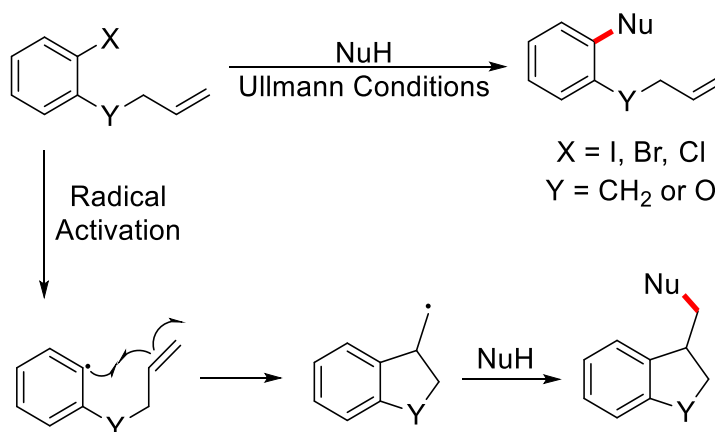
Figure 1.11 Proposed active Cu^I catalytic species.⁷⁹

Aryl Chloride Activation Pathway	Free Energy Barrier, ΔG (kcal mol ⁻¹)
Oxidative Addition/Reductive Elimination	OA = 85.3, RE = 70.9
HAT	78.8
SET	41.0
σ -bond metathesis	98.0
π -complexation	103.7

Table 1.2 Summary of the free-energy barriers calculated by DFT.⁷⁹

The values of free energy reported seem to be extremely high. Given these values rely on the fact that the active Cu^I species is complex **1.38**, further experimental evidence would be required to validate the exact active species, such as single-crystal XRD of the copper complex. Then, more accurate mechanistic insights can be extracted from the theoretical calculations.

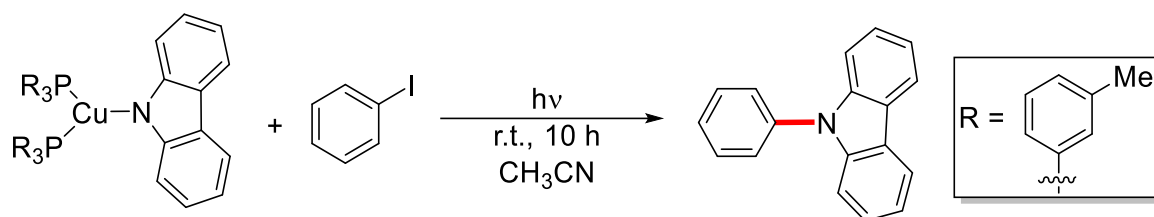
While these select few theoretical examples suggest a radical-based mechanism may lead to the activation of aryl halides, various reports have utilised radical clock experiments to experimentally determine whether radical-based mechanisms are present in the Ullmann reaction.^{37,66–68,74} As seen in **Scheme 1.46**, under radical conditions the most kinetically favoured product is a methylcyclopentane moiety which would occur via 5-exo-trig closure, since the ring-closure reaction would occur much faster than nucleophile coupling.²¹



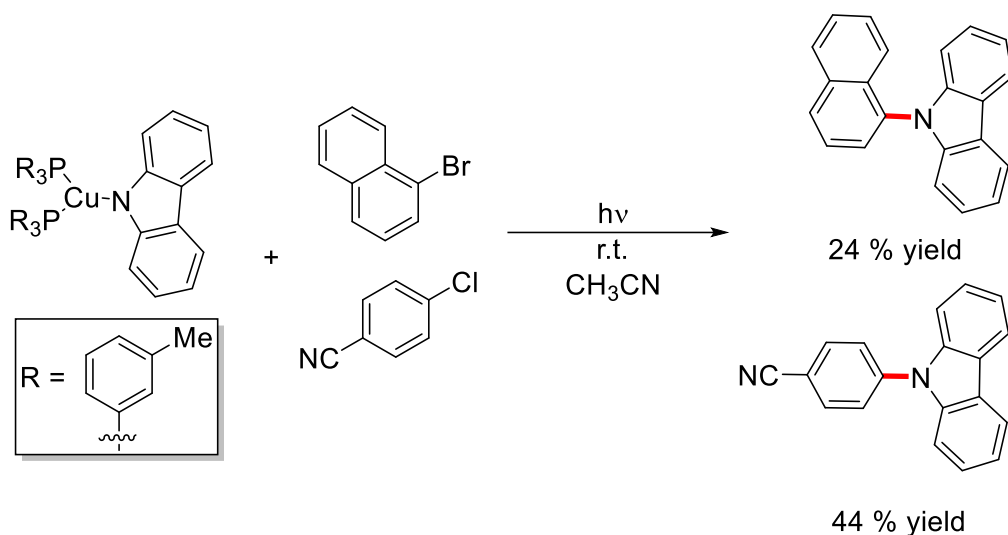
Scheme 1.46 General scheme for radical clock experiments.²¹

In most cases, radical clock experiments can discount any radical-based pathways. However, one report by Peters *et al.* demonstrated experimentally that a radical-based mechanism was active in the coupling between a Cu^I-carbazolide complex and iodobenzene (**Scheme 1.47**).⁸⁰ Indications included the side-products that formed (benzene, deuterated arene and succinonitrile when CD₃CN was used,

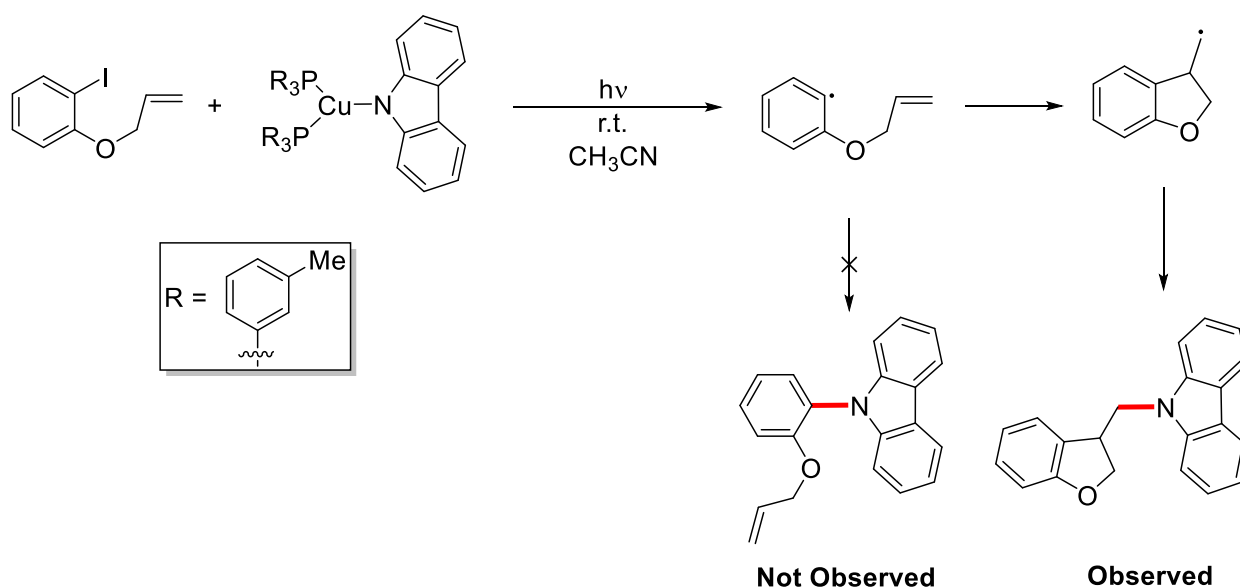
iodobiphenyls when iodobenzene was in large excess), EPR spectra (evidence of Cu^{II} -radical), a competition reaction between 1-bromonaphthalene and 4-chlorobenzonitrile (**Scheme 1.48**) and a radical clock experiment (**Scheme 1.49**).



Scheme 1.47 Photo-induced reaction studied by Peters *et al.*⁸⁰



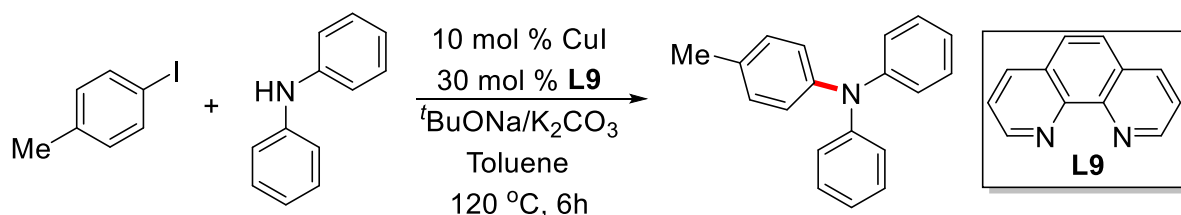
Scheme 1.48 Competition experiment which supported the SET pathway.⁸⁰



Scheme 1.49 Radical clock experiment which supported the SET pathway.⁸⁰

While there is sufficient experimental evidence to support an SET pathway, the authors acknowledge that the pathway cannot be universally applied to all Ullmann reactions, since they reiterate that the reaction requires a carbon-centred radical to be generated which is likely formed due to photochemical activation, and would not be as likely to form under thermal Ullmann reaction conditions.⁸⁰ Generally, this section shows that a radical-based pathway may be followed in exceptional circumstances but it is not the mechanism followed in the majority of cases.

Shyu *et al.* experimentally investigated the coupling between 4-iodotoluene and *N*-phenylaniline using ESI-MS to decipher the intermediates in the reaction (**Scheme 1.50**).⁸¹ A *m/z* peak at 541.1 corresponded to a Cu^{II} complex (**1.39**, **Figure 1.12**) which implied that a radical-based pathway was followed. The authors suggest that the base, sodium *tert*-butoxide, can transfer a single electron to 4-iodotoluene, thus forming a free-radical [CH₃C₆H₄][•] which can go on to react with the **L9**-Cu^I-amido complex to form the observed species. To further validate this, the use of a radical scavenger was employed, which would be expected to transfer its electron to any radicals present and terminate the radical-based process. 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added at 20 and 100 mol % to determine its effect on the reaction. At 20 mol %, the yield of the reaction reduced from 93 % to 85 %. At 100 mol %, the yield was reduced to 64 %. The slight reduction in yield suggests there may be some radical-based pathways occurring in the reaction – the authors suggest it accounts for a third of the catalytic system and that a dual mechanism could be occurring.



Scheme 1.50 The reaction studied by Shyu *et al.*⁸¹

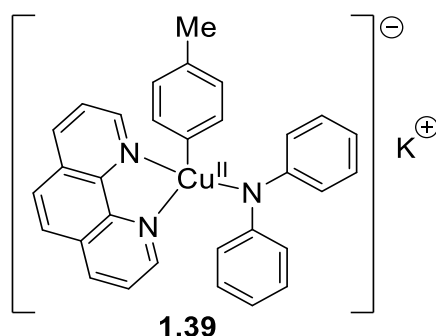
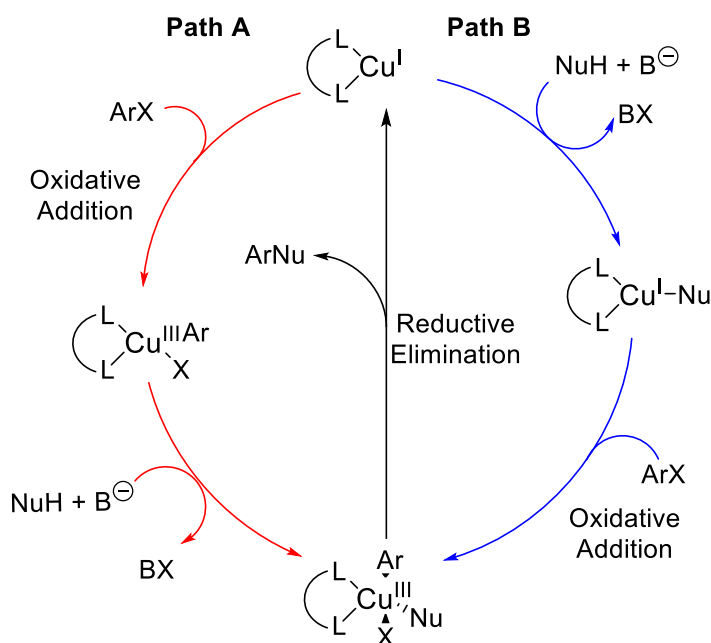


Figure 1.12 Intermediate which corresponds to a m/z peak of 541.1 which was observed in ESI-MS.⁸¹

1.4.3.3 Oxidative Addition and Reductive Elimination Pathways

A Cu^I/Cu^{III} catalytic cycle arising from an oxidative addition/reductive elimination (OA/RE) pathway is the most commonly accepted mechanism for the Ullmann reaction. It involves oxidative addition at the Cu^I centre to form an aryl Cu^{III} intermediate. A reductive elimination step then follows to form the coupled product.²⁶ There are two possible pathways for the OA/RE process – the base-deprotonated nucleophile can bind to the copper centre after oxidative addition of the aryl halide (Path A, **Scheme 1.51**), or the nucleophile can coordinate before activation of the aryl halide (Path B). Generally, path B is accepted as the most likely route since the coordinated nucleophile aids in the stability of the Cu^I intermediate.²⁶

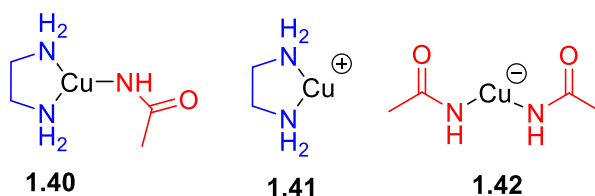


Scheme 1.51 General mechanism of the oxidative addition/reductive elimination pathway.^{26,77}

Due to the high oxidation state, Cu^{III} species are highly unstable and thus they are difficult to isolate and detect, which means intermediates of the OA/RE pathway cannot be easily observed. In addition, since they are thought to form after the rate-determining step, their short-lived presence makes them difficult to observe through experimental methods. To overcome this, DFT studies have been performed to probe the mechanism theoretically.

Hartwig *et al.* utilised kinetic and DFT studies to determine the mechanism of various Ullmann-type reactions.⁶⁸ For reactions with the copper complexes **1.14** – **1.18** discussed in section **1.4.1**, they were able to rule out radical-based pathways by competition experiments between 4-chlorobenzonitrile and 2-bromonaphthalene, whereby no reaction was seen with 4-chlorobenzonitrile which has a more favourable reduction potential and thus would be more likely to undergo SET or HAT. Radical clock experiments also showed the Ullmann product was obtained in > 95 % yield while the cyclised product formed in low yield (see **Scheme 1.46** above). DFT calculations allude to the possibility that aryl Cu^{III} intermediates containing dative nitrogen ligands are kinetically plausible which highlights the possibility of an oxidative addition/reductive elimination reaction pathway.

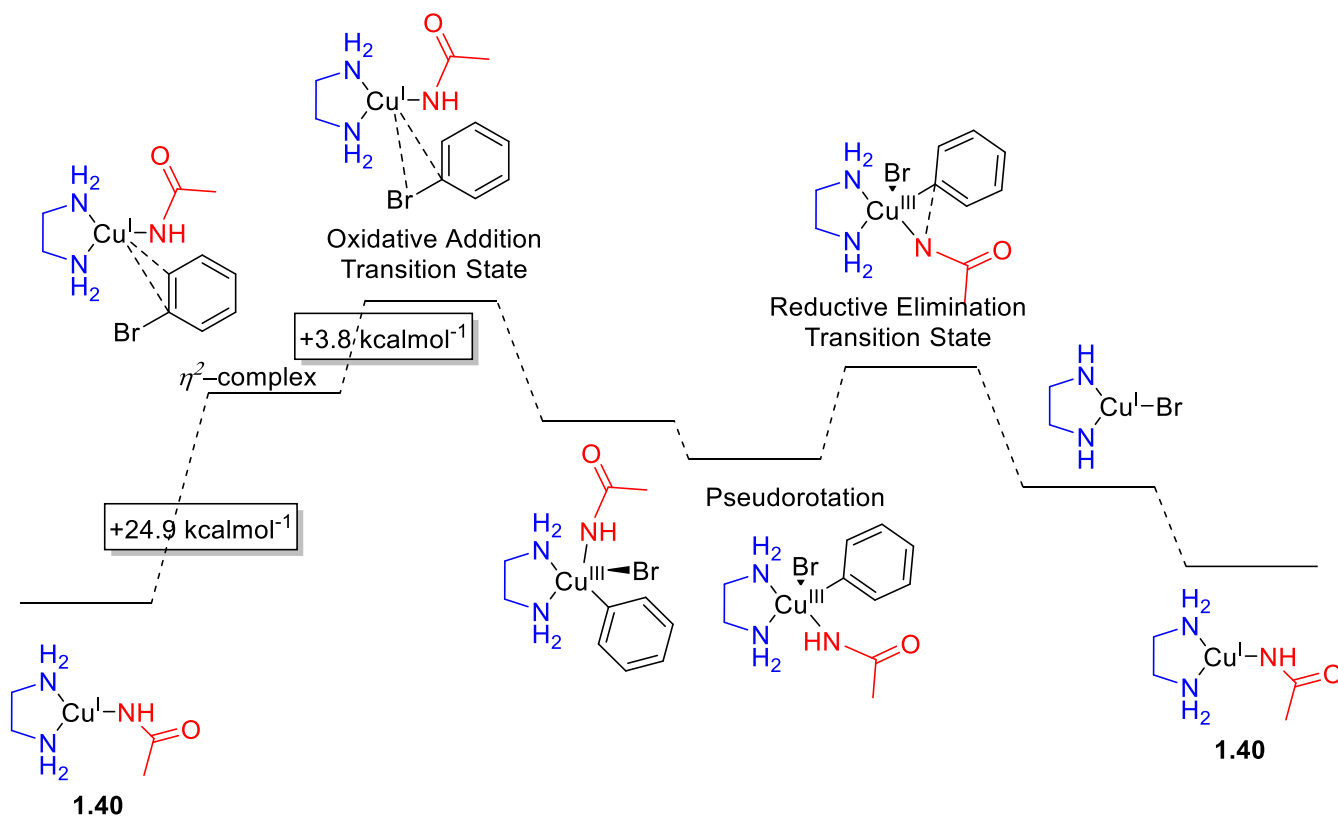
Guo *et al.* employed DFT to study the cross-coupling reaction between bromobenzene and acetamide, with ethylenediamine as a ligand.⁸² Their calculations determined that complex **1.40** (**Figure 1.13**) is the major species in the reaction mixture. They then determined that the most favourable reaction route is via an η^2 -complex. Calculating the overall free energy barrier for the studied complexes (sum of the free energy for η^2 -complex formation and subsequent conversion from the η^2 -complex to the transition state), complex **1.41** was seen to have the lowest barrier for oxidative addition. However, these findings do not reflect the overall reactivity due to different concentrations in reaction solution. By calculating the relative reactivity, complex **1.40** is found to be the most reactive intermediate in oxidative addition. Multiple ligation of the amide to the Cu^I centre leads to the least reactive intermediate (**1.42**), which is in line with previous reports outlined in section **1.4.1**.



Complex	Free Energy for Formation of η^2 -Complex (kcalmol ⁻¹)	Free Energy from η^2 -Complex to Transition State (kcalmol ⁻¹)	Overall Free Energy Barrier (kcalmol ⁻¹)	Relative Reactivity
1.40	+24.9	+3.8	+28.7	1.0
1.41	-6.0	+9.0	+3.0	1.7×10^{-6}
1.42	+36.6	+7.7	+44.3	1.1×10^{-21}

Figure 1.13 Intermediate complexes and their overall free energy barrier for oxidative addition.⁸²

Investigating the reductive elimination step, it was found that a pentacoordinated Cu^{III} intermediate is most likely to form. The corresponding free energy barrier to this complex is +2.6 kcal mol⁻¹ while the barrier for oxidative addition is +8.7 kcal mol⁻¹, which indicates that the oxidative addition is the rate-determining step in the reaction. They propose the mechanism outlined in **Scheme 1.52** based on these findings.



Scheme 1.52 Suggested mechanism by Guo *et al.*⁸²

In section **1.4.3.2** above, work by Buchwald *et al.* to decipher the mechanism of the ligand-dependent selective cross-coupling reaction was presented; they suggested an SET pathway was followed. A report from Liu *et al.* contradicted those findings to suggest that an oxidative addition/reductive elimination pathway was followed in this reaction (**Scheme 1.37**).^{78,83} In this case, 5-aminopentanol was used as the model amine rather than the simplified methylamine or methanol used by Buchwald. The difference in observed mechanisms can be attributed to the fact that Liu *et al.* found different complexes to be the most stable species with the lowest free energy transition states (**Figure 1.14**). They also found the oxidative addition transition states to be most favourable – while Buchwald *et al.* had a barrier of +43.2 kcal mol⁻¹, Liu *et al.* calculated values of +13.8 and 26.5 kcal mol⁻¹ for complexes with **L22** and **L9** respectively. These values were considerably lower than those for SET and HAT (+53.1 and +42.7 kcal mol⁻¹ respectively).

Their calculations allowed them to determine the reasons for different reaction selectivity with different ligands. They suggest *N*-arylation is favoured with **L22** because coordination of the nucleophile happens after oxidative addition of the aryl halide to the copper centre, due to the presence of the negatively charged ligand.

With neutral ligand **L9**, a positive Cu^I complex forms, and oxidative addition of the aryl halide occurs after coordination of the nucleophile.

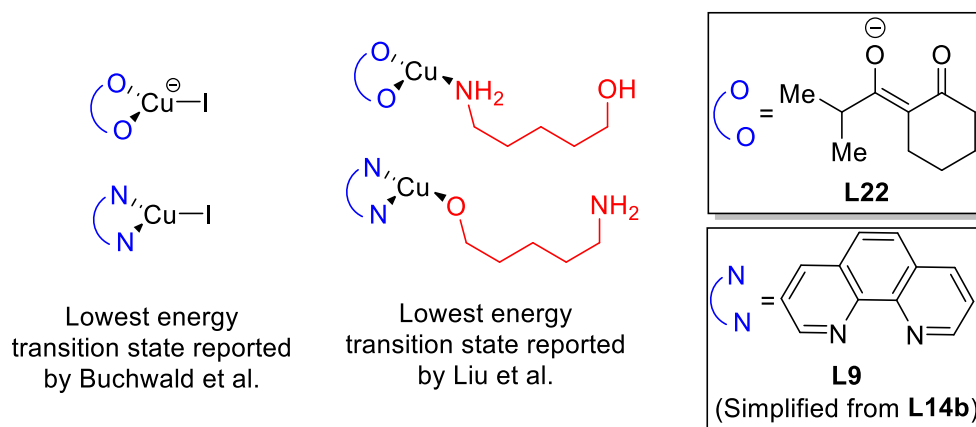
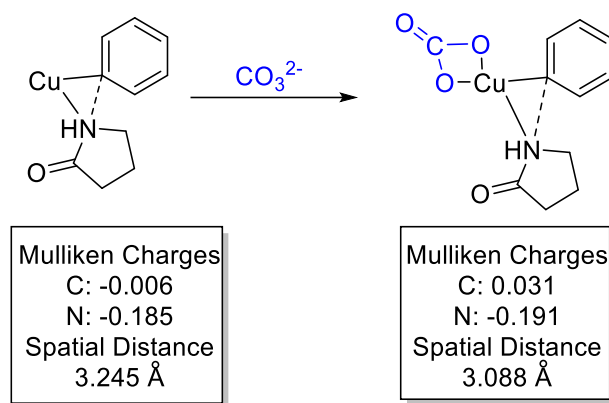


Figure 1.14 Transition states with the lowest calculated free energy.^{78,83}

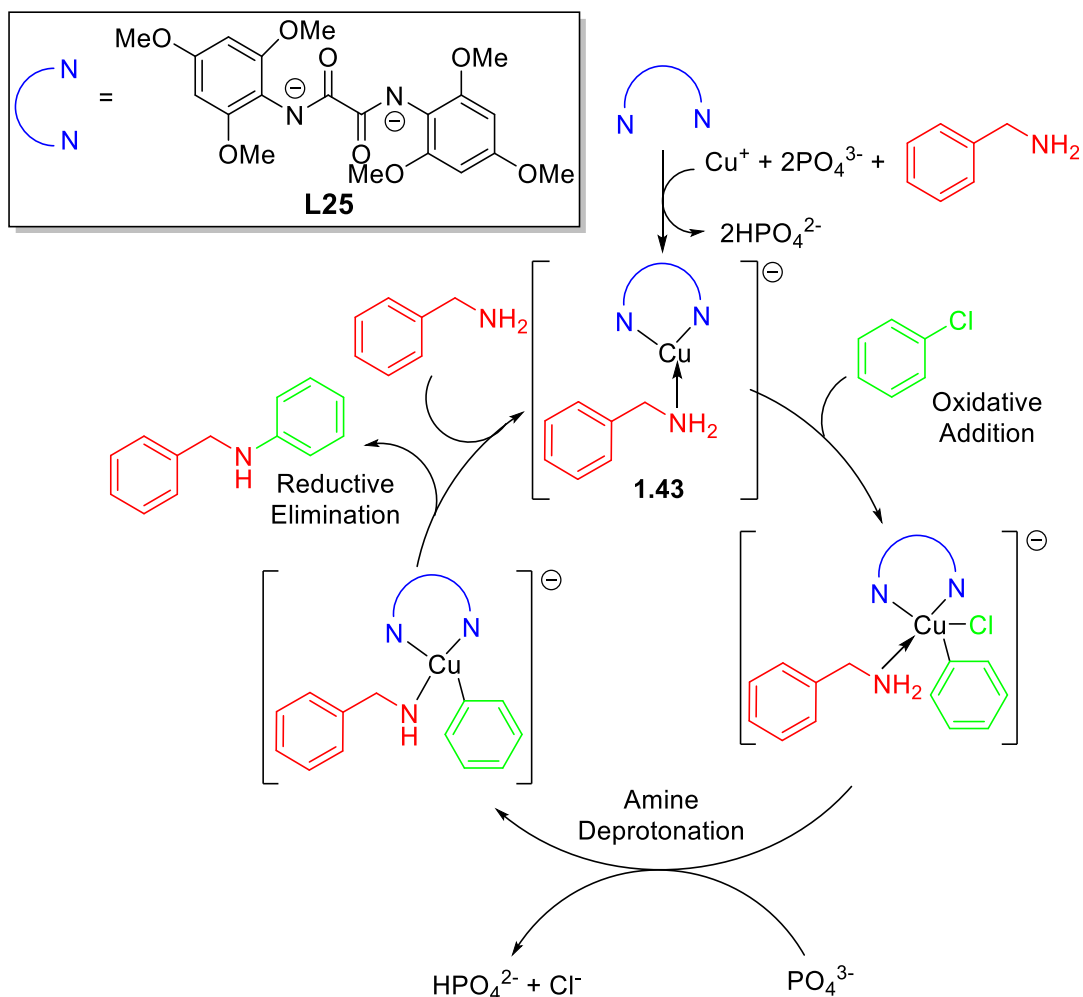
Sharma *et al.* investigated whether the anionic portion of inorganic bases can act as a chelating ligand by experimental and DFT studies on a range of amides and aryl iodide substrates.⁸⁴ First, it was shown that Cu^{III} intermediates form in the reaction since the electronic absorption spectrum indicated the presence of a pentacoordinated Cu^{III} species. This species was able to form without the presence of base. After addition of the base, an octahedral Cu^{III} intermediate containing a carbonate ligand was observed by CO₃²⁻ peaks in the FTIR spectrum and a shift in the λ_{max} of the absorption spectrum upon addition of the base. It is suggested that the carbonate is able to reduce the spatial distance and increase the charge on the coupling atoms (the C atom of the aryl halide substrate gains a positive charge while the N atom of the nucleophile becomes more negative) (**Scheme 1.53**). The authors also suggest that the reductive elimination step can occur without deprotonation of the nucleophile – according to their DFT calculations, the free energy barrier for the transition state for reductive elimination is +1.07 kcal mol⁻¹ which is lower than that reported by Guo *et al.* as previously discussed.⁸² Thus, the addition of carbonate facilitates reductive elimination by lowering the activation energy of the transition state.



Scheme 1.53 The effect on Mulliken charges and spatial distance between C and N atoms when CO_3^{2-} anion acts as a ligand.⁸⁴

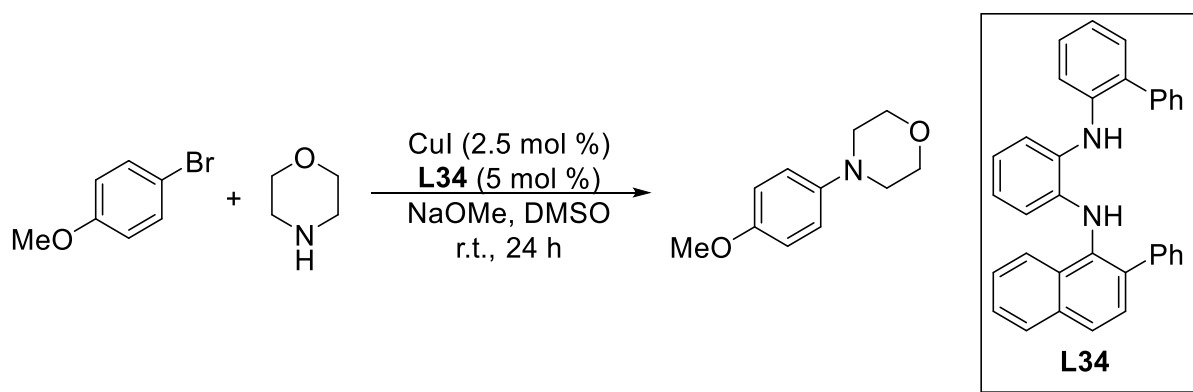
Later work by Sharma *et al.* suggests that, although aryl chloride substrates are more susceptible to SET, the reaction between chlorobenzene and phthalimide follows an OA/RE pathway, which was shown through DFT studies.⁸⁵

A study of the mechanism of the cross-coupling reaction with chlorobenzene and benzylamine with oxalic diamide ligand **L25** was recently reported by Roy *et al.*⁸⁶ Complex **1.43** was shown to be the most stable copper intermediate complex after reaction with **L25**, and it had the lowest activation energy for the oxidative addition step. This was also lower than an SET pathway so the reaction is suggested to follow the OA/RE pathway. The proposed pathway is outlined in **Scheme 1.54**.



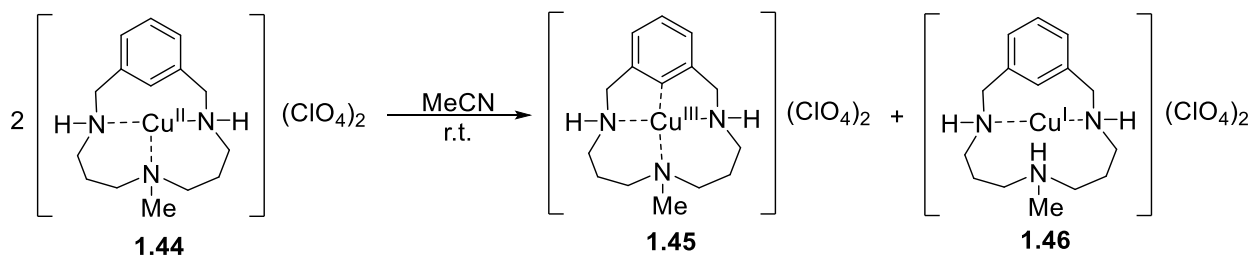
Scheme 1.54 Proposed mechanistic pathway for aryl chloride cross-coupling reaction.⁸⁶

A report from Buchwald *et al.* explored the efficacy of novel ligand **L34** and sought to gain deeper insights into the reaction mechanism. Through DFT studies, they confirmed that the reaction follows an OA/RE pathway whereby the oxidative addition of the aryl halide is the rate-limiting step (**Scheme 1.55**).⁶³ Initial rates were used to determine that the reaction had an order of one in [4-bromoanisole] and [Cu/**L34** complex], again consistent with a rate-limiting oxidative addition event occurring.



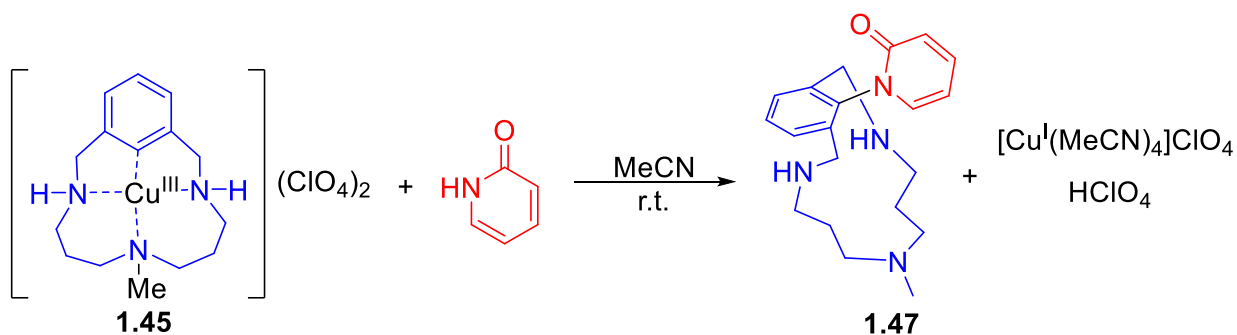
Scheme 1.55 Reaction for DFT kinetic study performed by Buchwald *et al.*⁶³

In recent times, researchers have successfully isolated Cu^{III} intermediate species through the addition of bulky or macrocyclic ligands to add stability. One of the first reported Cu^{III} complexes was presented by Stack *et al.* in 2002, whereby the use of triazamacrocyclic ligands allowed for stable copper complexes to form.⁸⁷ The formation is outlined in **Scheme 1.56** and is due to disproportionation of the Cu^{II} complex **1.44** to form two diamagnetic products, **1.45** and **1.46**. Compound **1.45** was analysed by ^1H NMR, ESI-MS and single crystal XRD and it was confirmed that the copper atom is coordinated by six groups (three nitrogen atoms of the triazamacrocycle and one aryl carbon donor, plus two perchlorate anions which are weakly bound).



Scheme 1.56 Synthesis of Cu^{III} complex.⁸⁷

Stahl *et al.* were inspired by this work to test compound **1.44** as a possible intermediate in the C-N bond formation reaction.⁸⁸ When reacted with pyridone, the cross-coupled product **1.47** was successfully observed along with a Cu^{I} by-product (**Scheme 1.57**). They further determined that more electrophilic Cu^{III} complexes would react faster with nitrogen nucleophiles (**Figure 1.15**), and that deprotonation of the nucleophile likely occurs before or in the rate-limiting step since more acidic nucleophiles react faster. These findings consolidate the fact that Cu^{III} species are likely intermediates in the Ullmann C-N cross-coupling reaction.



Scheme 1.57 Cross-coupling reaction with Cu^{III} intermediate.⁸⁸

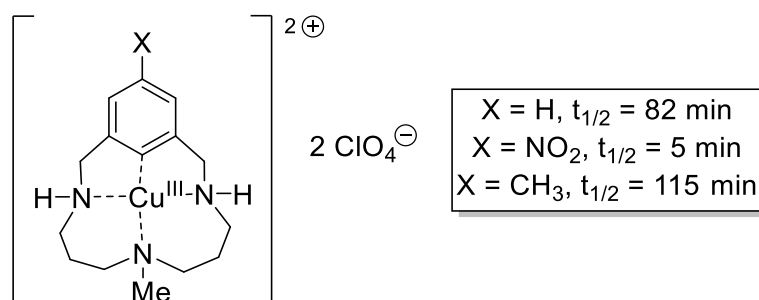
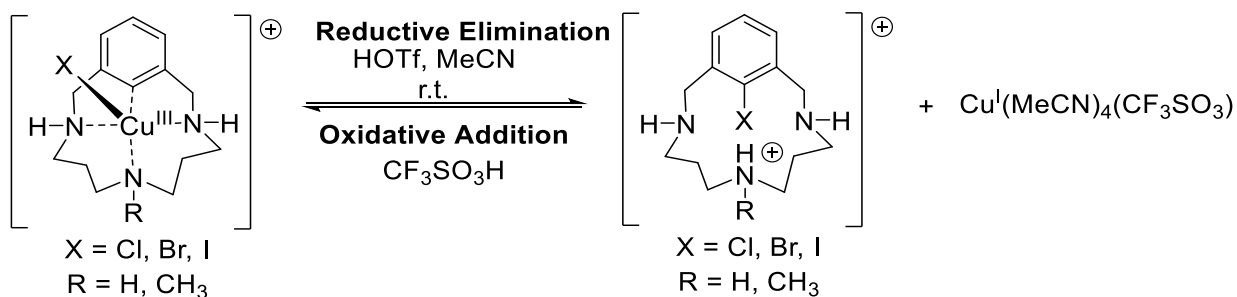
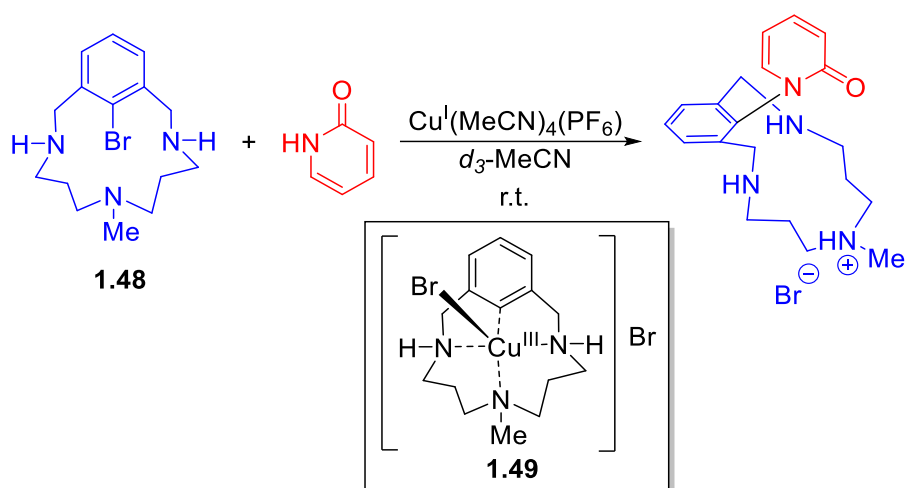


Figure 1.15 Reaction rate with different substituents on the aryl- Cu^{III} species.⁸⁸

In 2010, Ribas *et al.* synthesised a series of aryl- Cu^{III} -X (X = Cl, Br, I) complexes also containing triazamacrocyclic ligands, which undergo acid-triggered reductive elimination to form aryl-X products.⁸⁹ The reverse reaction of oxidative addition to Cu^{I} -complexes occurs readily without acid to regenerate the Cu^{III} complex (**Scheme 1.58**). The presence of Cu^{III} -X intermediate **1.49** was successfully observed by in situ ^1H NMR and UV-vis during a reaction between complex **1.48** and pyridone (**Scheme 1.59**).



Scheme 1.58 Reversible OA/RE with Cu^{III} complexes.⁸⁹



Scheme 1.59 Reaction between macrocyclic ligand and pyridone which allowed a Cu^{III} intermediate complex to be observed.⁸⁹

The use of Hammett plots can also indicate whether a reaction follows an oxidative addition/reductive elimination pathway. The Hammett equation describes the linear free energy relationship between para- or meta-substituted aromatics and the hydrolysis of benzoic acids with the same substituents (**Equation 1**).⁹⁰ It is the log of the ratio of the acid constants which is equal to the reaction (proportionality) constant (ρ) times the substituent constant (σ) which is a measure of the total polar effect exerted by a substituent on the reaction centre (relative to no substituent, **Equation 1.2**).

$$\log \left(\frac{k_X}{k_H} \right) = \rho \cdot \sigma$$

Equation 1.1 The Hammett Equation.⁹⁰

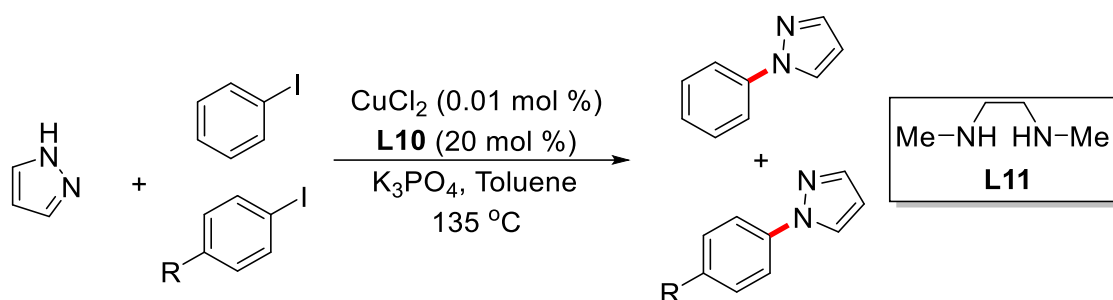
$$\sigma = -(pK_a - pK_a(H))$$

Equation 1.2 Hammett constant.⁹⁰

The sign and value of ρ gives information on whether the reaction rate is accelerated or suppressed by electron donating or withdrawing substituents. If ρ is negative, it suggests the reaction rate will be slower with electron withdrawing substituents. If ρ is positive, the rate is reduced with electron donating groups. A higher value of ρ means the reaction is more influenced by the electronic effects of the substituent. A ρ value of 0 indicates a radical-based pathway is followed.

In 2014, Norrby *et al.* reported kinetic studies of the copper catalysed C-N cross-coupling with ultra-low loadings of copper (0.01 mol %) and DMEDA (**L11**) as a ligand

(as discussed in section 1.3.1, **Scheme 1.15**).^{42,91} They performed a competitive Hammett study (**Scheme 1.60**, **Table 1.3**) which allowed for unknown influences from the heterogeneous base to be omitted. A ρ value of 0.3234 was obtained, and the positive correlation suggests that electron withdrawing groups increase the reaction rate and that negative charge develops at the centre of the transition state. However, while the authors suggest that a positive ρ value indicates a radical-based pathway is not followed, it could be argued that at a magnitude of ~ 0.3 , the correlation between the substituent and reaction rate is not significantly high. Therefore, there is a possibility that a radical-based pathway is followed, since both electron donating and -withdrawing groups are expected to stabilise radical intermediates. Similar results were also observed by Buchwald *et al.* in the Cu-catalysed cross-coupling with amides.⁶⁹



Scheme 1.60 Competitive conditions for Hammett study.⁹¹

R	k	σ
OMe	0.8291	-0.27
^t Bu	0.8235	-0.20
Me	0.8857	-0.17
Cl	1.1802	0.23
CF ₃	1.4862	0.54

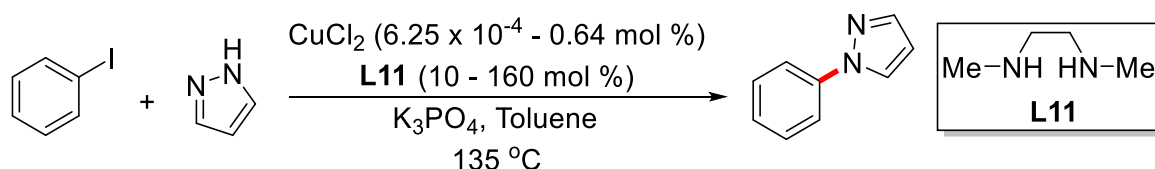
Table 1.3 Results from a Hammett study performed by Norrby *et al.*⁹¹

1.4.4 Kinetic Studies on Ullmann C-N Cross-Coupling Reactions

As discussed in section 1.4.3, isolating the reaction intermediates in order to determine the reaction pathway is difficult due to their instability. An alternative approach to mechanistic elucidation is through kinetic studies, whereby the concentration dependencies of the reaction components are confirmed and rate and equilibrium constants for elementary reaction steps can be explored.⁹² Traditional kinetic studies utilise initial rates to gain mechanistic data on a reaction. While this is a simple method, it requires performing a range of experiments with different substrate concentrations

to determine the order in substrate, which is repetitive and time consuming. It also only considers the first 10 % of the reaction which means catalyst deactivation or product inhibition is not observed since these typically happen later in the reaction. Pseudo first-order reactions are often used which involve keeping one substrate at a large excess so that it appears to stay at a constant concentration during the reaction, allowing the reaction to operate as a first order reaction and the order in the second substrate to be studied. While this is a simple way to investigate 2nd order reactions, it is not representative of the actual reaction conditions and hence the kinetic data obtained may not accurately portray the reaction.

Despite their limitations, initial rate and pseudo-first order methods have been utilised to understand the Ullmann C-N cross-coupling reaction. For example, a range of reports by Norrby *et al.* attempted to address the reasons behind the success of using a large excess of **L11** to obtain high TONs. In the reaction shown in **Scheme 1.61**, they found that the reaction was first order in [CuCl₂] at concentrations below 0.04 mol %, but at concentrations over 0.16 mol % it was zero order in [CuCl₂].⁹³ They concluded that at higher concentrations, inactive dimers formed due to saturation. The reaction was first order in [iodobenzene] which indicates that iodobenzene is present in the rate-determining step. The reaction order in [pyrazole] was variable depending on its concentration – at lower concentrations it was weakly positive, while at higher concentrations it was strongly negative. This indicated that it coordinates to copper in the rate-determining step, but at higher concentrations it can form multiply-ligated species which would block its binding sites and lead to an inactive species. The reaction was first order in [**L11**] although no rational conclusion could be drawn from this.



Scheme 1.61 Kinetic study performed by Norrby *et al.*⁹³

1.4.4.1 RPKA and VTNA

Reaction Progress Kinetic Analysis (RPKA) was described by Blackmond in 2005⁹² when reaction monitoring methods became more sophisticated – it requires in situ monitoring of the reaction for accurate data collection e.g. using calorimetry, FTIR or NMR. Benefits of RPKA include the utilisation of data from the full length of the reaction, so any processes occurring later in the reaction are also accounted for, and

the fact that reactions can be performed at synthetically relevant conditions which means the data obtained is likely a true representation of the reaction. It also has drastically reduced the number of experiments which need to be performed in order to obtain kinetic profiles. However, drawbacks include a high learning curve associated with data processing and data manipulation (the formation of 'graphical rate equations' requires the transformation of data collected in situ into rate data), as well as the need for in situ data acquisition which is not accessible for all reactions and conditions.

In recent years, Variable Time Normalisation Analysis (VTNA) has been developed by Bures *et al.* with the aim to reduce the data processing required with RPKA. VTNA utilises concentration vs time reaction profiles rather than rate vs concentration, so data collected from reaction monitoring techniques such as NMR or FTIR can be used directly without further processing.⁹⁴

Both RPKA and VTNA are visual kinetic analyses whereby visual comparisons are made between reactions with varying conditions (**Figure 1.16**). The overlay of reaction profiles can be compared to determine the effects that different conditions can have on the reaction.⁹⁴ This involves performing time-adjusted analysis or transforming the axes to achieve overlay. Blackmond first introduced the parameter of ['excess'] ([e]) in reactions, whereby [e] is equal to the difference in the initial concentrations of two substrates (**A** and **B**) of a reaction (**Equation 1.3**).

$$[B] = [B]_0 - [A]_0 + [A] \Rightarrow [B] = ['excess'] + [A]$$

Equation 1.3 Definition of 'excess'.⁹²

The parameter [e] allows for the change in concentration of both substrates to be investigated without the need for a large excess of one substrate. It can be a small value so that the concentrations of both substrates are kept within synthetically relevant conditions. Same excess experiments can be conducted to determine whether catalyst deactivation or product inhibition is occurring. They involve reactions where [e] is the same as the original reaction, but the starting concentration of **A** and **B** is different. This means the reaction is effectively started at a different point, and will have a different number of turnovers completed, so any catalyst effects can be observed. In RPKA, rate against concentration is plotted. If the curves overlay, no catalyst deactivation or product inhibition is occurring. If they do not overlay, there may be catalyst deactivation or product inhibition. To decipher between the two, a second same excess reaction is performed whereby the major products of the

reaction are added at an amount that would be generated under the same excess conditions. If this reaction overlays with the original reaction, product inhibition is occurring. If it does not overlay then catalyst deactivation occurs.⁹⁴ With VTNA, for visual comparison to be made, the reaction with a lower starting concentration of **A** and **B** must be time-adjusted so that the first point of the profile overlays with the second reaction profile (**Figure 1.17**).⁹⁵ If the curve continues to overlay after the first point, this indicates no catalyst deactivation or product inhibition occurs. If they do not overlay, this indicates the reverse scenario. To discern between the two, the same principles as RPKA can be applied, as mentioned above.

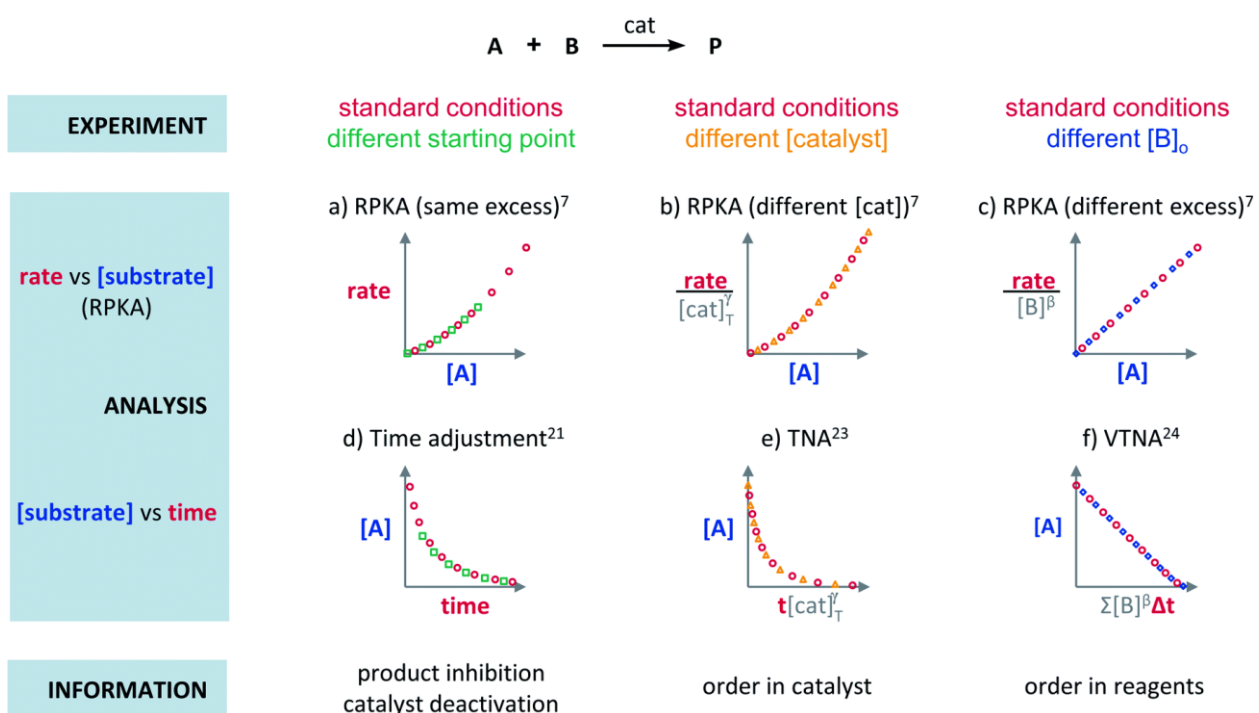


Figure 1.16 A visual comparison between rate vs [substrate] and [substrate] vs time analysis techniques, whereby **A** and **B** are reaction substrates and **P** is the reaction product. The powers of γ and β correspond to the order of the reaction in the substrate studied.⁹⁵

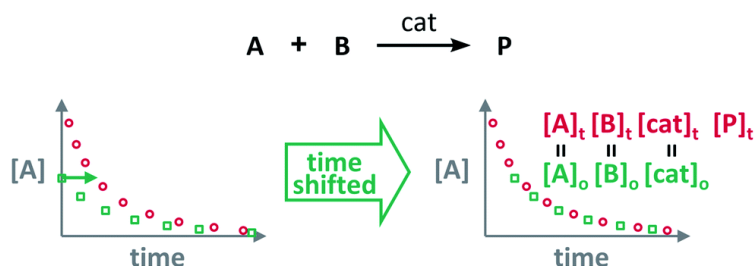


Figure 1.17 Method derived by Bures *et al.* to determine if catalyst deactivation or product inhibition occurs in a reaction.⁹⁵

RPKA and VTNA can also be used to determine the order in catalyst and substrate (**Figure 1.18**). For catalyst order, reactions with different catalyst loadings can be performed and compared. RPKA requires the plotting of $\text{rate}/[\text{cat}]_T^\gamma$ against $[\text{substrate}]$ where ' γ ' corresponds to the order in catalyst when the curves overlay. For VTNA, a plot of $[\text{substrate}]$ vs $\sum [\text{cat}]^\gamma \Delta t$ is made (**Equation 1.4**) and again when the curves overlay for a certain value of ' γ ', this corresponds to the catalyst order.

$$\sum [\text{cat}]^\gamma \Delta t = \sum_{i=1}^n \left(\frac{[\text{cat}]_i + [\text{cat}]_{i-1}}{2} \right)^\gamma (t_i - t_{i-1})$$

Equation 1.4 Catalyst order determination with VTNA.⁹⁴

For substrate order elucidation, a 'different excess' reaction is performed, whereby the difference between the initial concentration of substrates **A** and **B** is different (the concentration of only one is changed). For RPKA, the different excess experiment can be compared to the original reaction by plotting $\text{rate}/[\text{A}]^\beta$ vs $[\text{B}]$ and changing the value of ' β ' until the curves overlay, to determine the order in **[A]**. For VTNA, the time scale is substituted by $\sum [\text{A}]^\beta \Delta t$ (**Equation 1.5**). Again the value of ' β ' is changed until the curves overlay, and this value corresponds to the order in substrate **[A]**.

$$\sum [\text{A}]^\beta \Delta t = \sum_{i=1}^n \left(\frac{[\text{A}]_i + [\text{A}]_{i-1}}{2} \right)^\beta (t_i - t_{i-1})$$

Equation 1.5 Substrate order determination with VTNA.⁹⁴

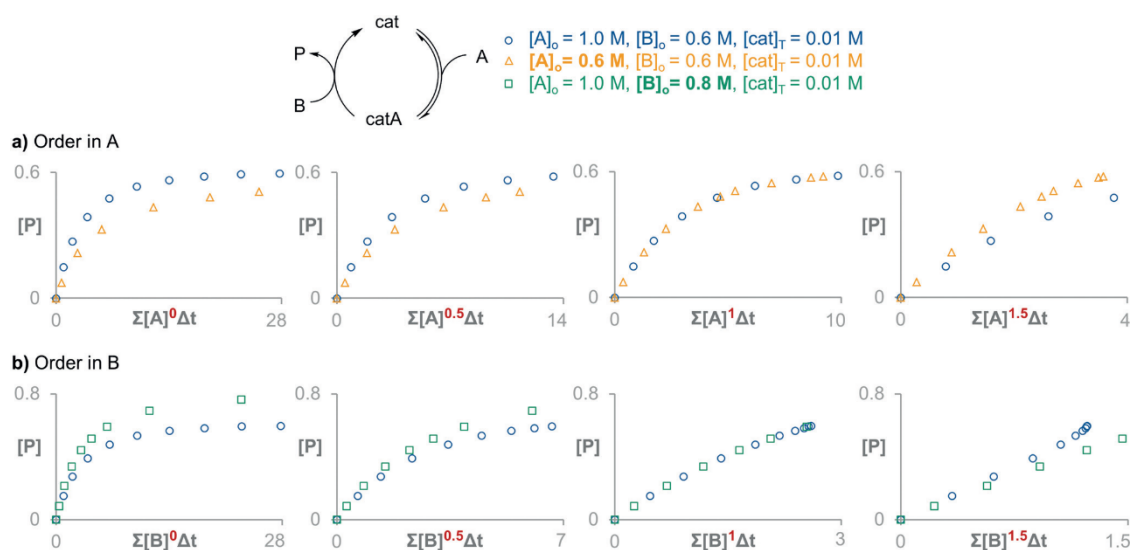


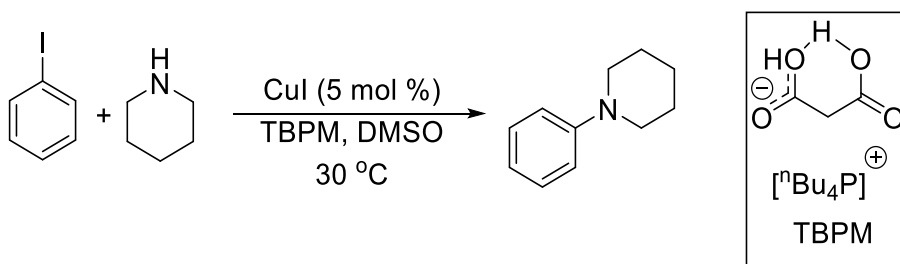
Figure 1.18 Examples of how VTNA can be used to determine the order in **[A]** and **[B]**.⁹⁶

There are no current examples where VTNA has been employed in mechanistic elucidation of Ullmann C-N cross-coupling reactions, but multiple reports have employed RPKA. These will be discussed in section 1.4.4.2.

1.4.4.2 Kinetic Studies on Ullmann Reaction

Kinetic studies by Buchwald *et al.* have been conducted on the cross-coupling reaction with amides.^{69,72} Through in situ calorimetry and RPKA analysis, they determined that the reaction was first order in [aryl iodide] regardless of the concentration of the amide, which suggests the aryl iodide activation step is the rate-limiting step. A positive rate dependence was also observed for the ligand DMEDA; however, the reaction order varied with respect to [amide] depending on the concentration of ligand. This led to the understanding that inactive copper species formed. This has been discussed in section 1.4.2.

Davies *et al.* reported kinetic studies on the reaction between piperidine and iodobenzene by using in situ calorimetry and RPKA (**Scheme 1.62**).⁶⁶ They observed first-order kinetics in [aryl halide], [amine] and [copper]. However, a negative first-order was observed for the organic ionic base, [TBPM]. This is shown by RPKA analysis in **Figure 1.19** whereby reaction profiles for different concentrations of TBPM overlayed with an order of -1.



Scheme 1.62 The reaction studied by Davies *et al.*⁶⁶

Symbol	[PhI] ₀ (M)	[Piperidine] ₀ (M)	[TBPM] ₀ (M)
●	0.1000	0.1500	0.1500
●	0.1000	0.1500	0.2000
●	0.1000	0.1500	0.3000

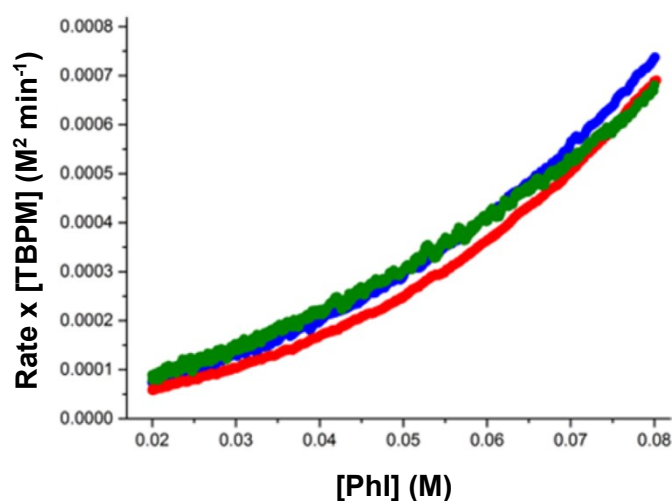


Figure 1.19 Graphical rate equations for reactions with different concentrations of TBPM, normalised by dividing the rate by $[\text{TBPM}]^{-1.65}$

RPKA also highlighted that catalyst deactivation was occurring (**Figure 1.20**) since the same excess experiments did not overlay with the original reaction profile. Further investigations showed that the catalyst is unstable when TBPM is present without piperidine, since, as seen in **Figure 1.21**, when the reaction is initiated with piperidine, the rate and yield is drastically compromised. Thus, the authors conclude that the piperidine has a stabilising effect on the catalyst and can prevent catalyst deactivation. The reason for this is the ability of piperidine to prevent formation of off-cycle inactive species which is discussed further in section 1.3.3. Increasing the concentration of amine can improve catalyst stability and improve the TON.

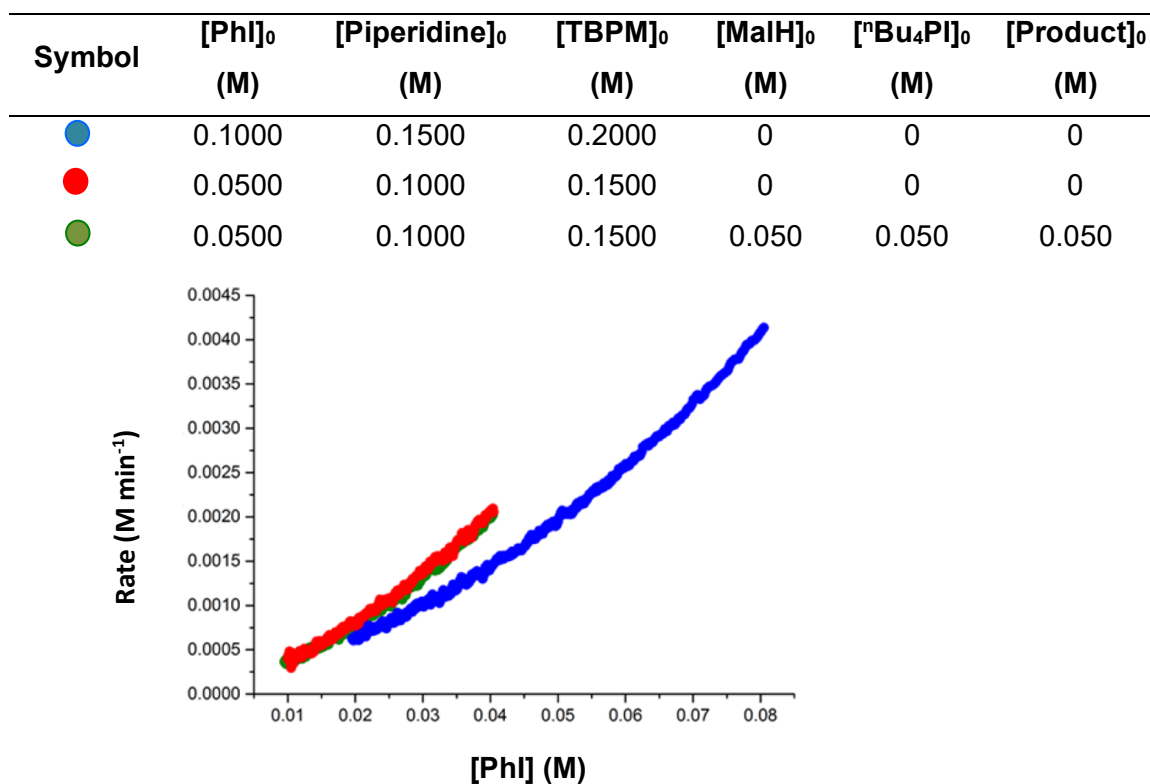


Figure 1.20 Graphical rate equations for the same excess experiments conducted by Davies *et al.*⁶⁶

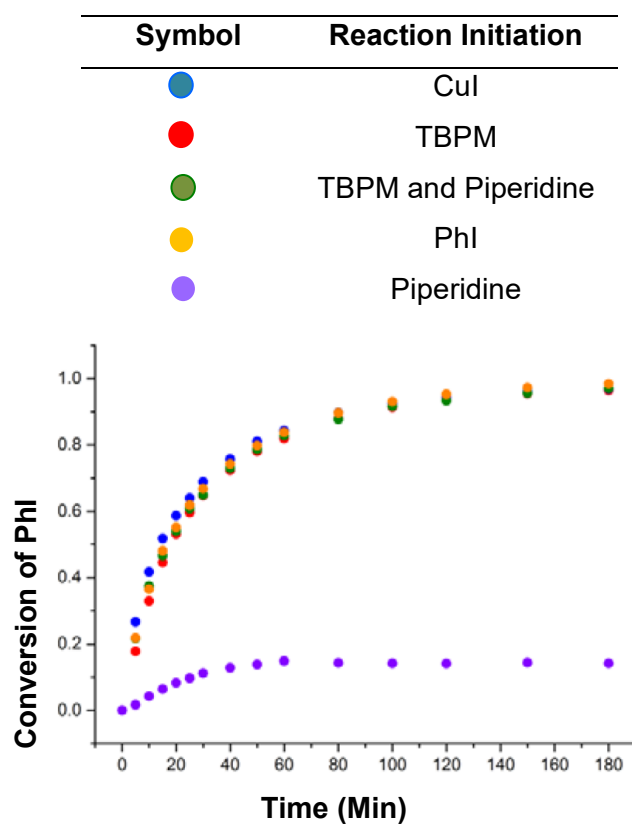
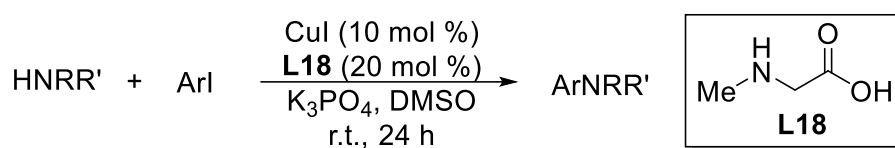


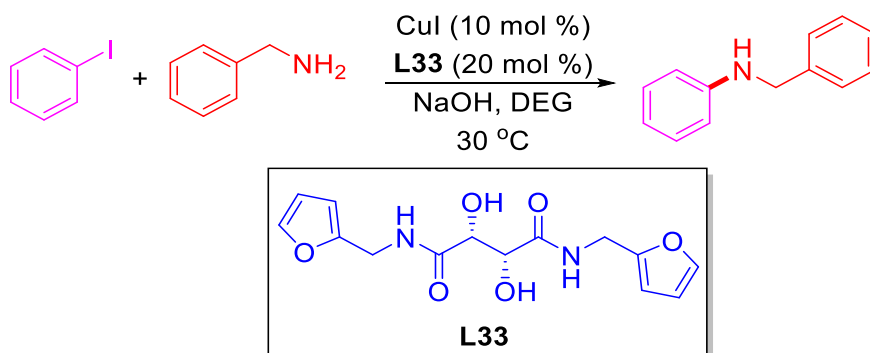
Figure 1.21 Conversion vs time of reactions with different initiations.⁶⁶

This work was continued in 2018 by studying the addition of auxiliary ligands.³⁷ Through same excess experiments and RPKA analysis with different ligands, it was shown that certain ligands were able to decrease the amount of catalyst deactivation occurring. The pathway of decomposition was not experimentally confirmed, but this information allowed the authors to improve the reaction design to increase its efficiency. Firstly, they switched bases to inorganic K_3PO_4 due to it being more commercially available, but a higher CuI loading of 10 mol % was required. *N*-methylglycine (**L18**) proved to achieve the best balance between a fast initial reaction rate and low catalyst deactivation, so it was chosen for reaction optimisation. A wide scope was explored with the conditions reported in **Scheme 1.63** and allowed for a mild, room temperature Ullmann C-N cross-coupling reaction to be successfully applied. This study shows the positive advancements that kinetic studies can have on reaction optimisation.



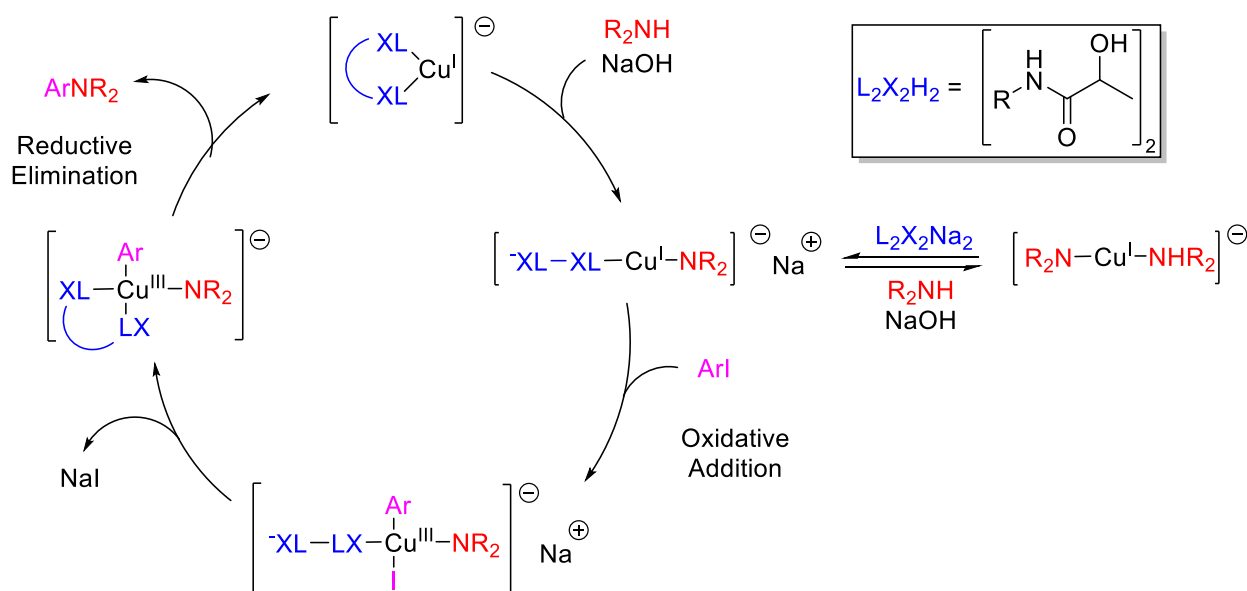
Scheme 1.63 The optimised conditions which produced a wide substrate scope.³⁷

Reaction calorimetry and RPKA were utilised more recently by Davies *et al.* in 2022 to study a class of tartaric diamide ligands which have not previously been used in the Ullmann C-N cross-coupling reaction.⁶² They were envisioned to have similar reactivity to oxalamide ligands due to possessing a similar backbone structure, and they showed excellent reactivity with aryl iodide substrates at room temperature. Kinetic analysis of the reaction in **Scheme 1.64** was achieved through a homogeneous base/solvent system of NaOH and diethylene glycol (DEG).



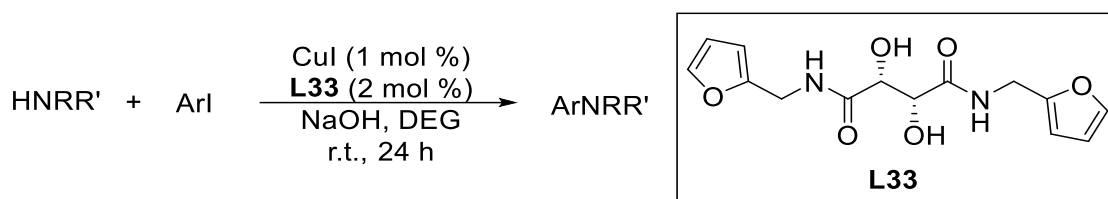
Scheme 1.64 Conditions used by Davies *et al.* in kinetic studies.⁶²

Previous studies in the Davies group use weaker TBPM as a base which led to the formation of off-cycle species, and these events likely masked the true rate dependence in the amine and base. The use of stronger NaOH in this case likely leads to facile deprotonation of the amine substrate and the order of reaction in [amine] and [base] were both found to be zero. The authors conclude that the kinetically meaningful intermediate contains a deprotonated amine and anionic auxiliary ligand bound to the copper centre. As with previous reports, the reaction was first order in [aryl iodide] which suggests oxidative addition of the aryl halide to the copper centre is the rate-limiting step. The reaction had an order of 0.9 in [CuI] which supports their finding that catalyst deactivation is occurring since the order deviates from 1. Through studying the effects of adding a large excess of ligand, it was concluded that the active catalytic species is an $\text{LCu}^{\text{I}}\text{NRR}'$ complex which can form inactive species with lower loadings of **L33**; however, the exact binding mode of the ligand could not be determined. A radical-clock experiment ruled out a radical-based pathway, and thus the authors concluded that an OA/RE pathway is likely followed. They suggest the pathway outlined in **Scheme 1.65**.



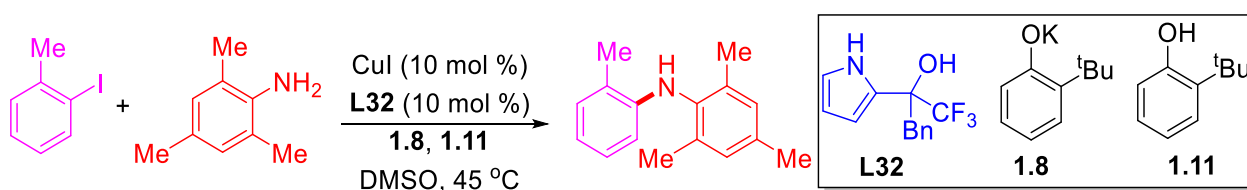
Scheme 1.65 The proposed pathway by Davies *et al.*⁶²

These mechanistic insights allowed the reaction conditions to be improved and optimised. Most notably, due to the discovery that the amine and base do not affect the rate of the reaction, their equivalents can be lowered so they are not in large excess, with little impact on the reaction yield. In addition, the optimum ratio of Cu:**L33** was found to be 1:2. With these findings, a wide substrate scope with very mild reaction conditions could be explored with the conditions reported in **Scheme 1.66**.

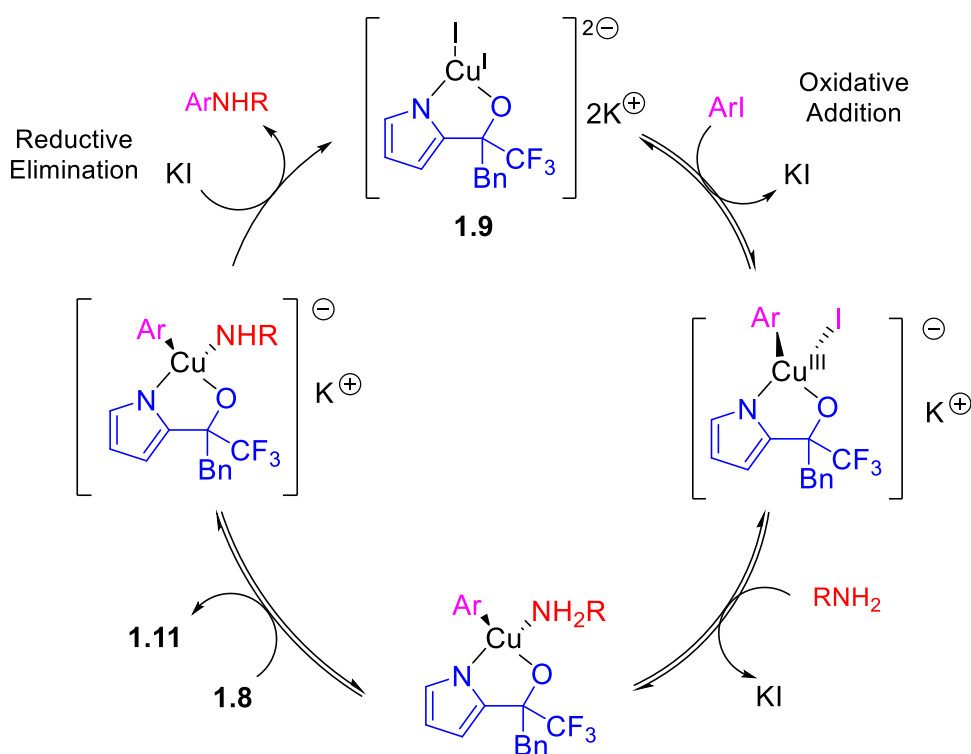


Scheme 1.66 Optimised conditions reported by Davies *et al.*⁶²

RPKA was performed by Blackmond *et al.* to gain further insights into the reaction with **L32** which was highlighted in section 1.3.3.⁶⁷ For the reaction in **Scheme 1.67**, first order in [catalyst] and [aryl halide] was observed, but there was no rate dependence on [amine]. The authors conclude that the oxidative addition of the aryl halide is rate-determining and this step precedes the addition of amine to the copper centre. This finding contradicts previous findings from Davies *et al.* which suggest that the amine coordinates first to the copper centre in order to stabilise the Cu^{III} intermediate which forms upon oxidative addition of the aryl halide. The reaction by Blackmond *et al.* differs in that it employs different, sterically hindered nucleophiles, which have not successfully undergone cross-coupling with previously reported conditions. It is suggested that **L32** increases electron density on intermediate **1.9** (**Scheme 1.68**), and thus it is sufficiently electron-rich to undergo oxidative addition without the presence of amine.



Scheme 1.67 The reaction investigated by Blackmond *et al.*⁶⁷



Scheme 1.68 Proposed catalytic cycle with sterically hindered nucleophiles.⁶⁷

1.5 Summary

This chapter highlights a range of research that has been undertaken to determine the mechanism of the copper-catalysed C-N cross-coupling reaction. It has been found that *N,N*- or *N,O*- bidentate ligands generally work best in these reactions, and their key roles are to prevent multiple ligation of the *N*-nucleophile to form inactive species, and to increase electron density on the copper centre to facilitate oxidative addition.

The oxidative addition/reductive elimination mechanism is thought to be the most likely pathway for Ullmann-type reactions, whereby the copper cycles from a Cu^I species to a Cu^{III} intermediate. This has been investigated through a range of computational and experimental techniques. The synthesis of Cu^{III} intermediates which, when reacted stoichiometrically, form the same yield of cross-coupled product as the catalytic reactions highlights that the reactions are likely to occur via a Cu^{III} intermediate.

Kinetic studies employing RPKA have successfully probed the full mechanism of the reaction and is a useful method to gain insights into the total reaction cycle. They generally indicate that the reaction is first order in [aryl halide] which confirms that the oxidative addition of the aryl halide to the copper centre is the rate determining step. Recent reports suggest that the reaction is zero order in [amine] which may suggest that the amine binds to the copper after the oxidative addition of the aryl halide. Catalyst

deactivation is also observed in most cases, and this is thought to occur via a disproportionation reaction to form Cu^0 and Cu^{II} species.

Figure 1.22 below summarises the key kinetic studies addressed in this chapter.

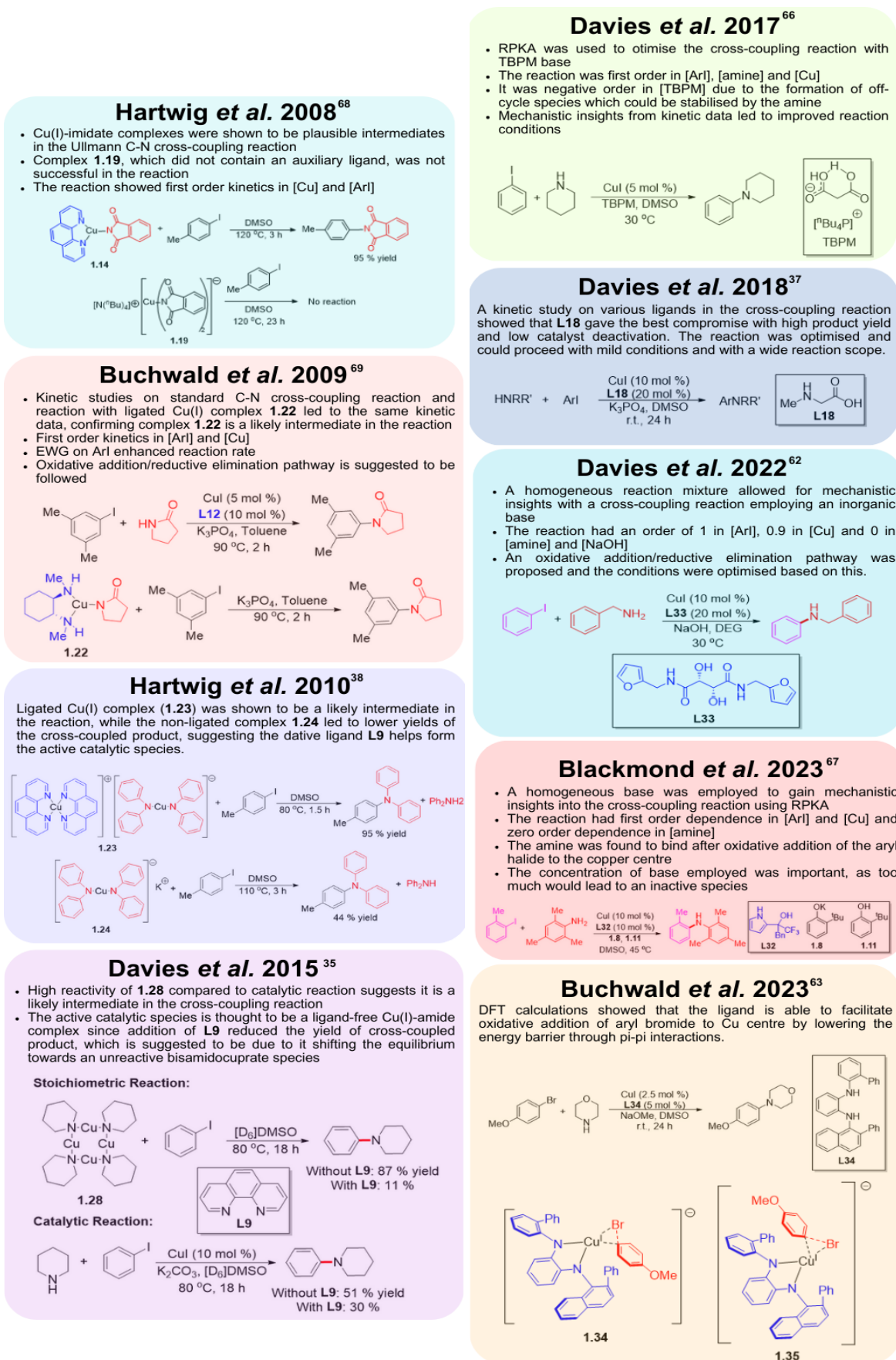


Figure 1.22 Summary of key kinetic studies explored in Chapter 1.

1.6 Aims

Despite recent success in delving deeper into the mechanistic pathways of the Ullmann reaction, uncertainty around the exact pathway of the reaction remains. A key aspect of this uncertainty is due to the unknown role of the ligand. While new ligand systems have been successfully employed to enhance the reaction and to allow copper loading to be lowered significantly (sometimes to below 1 mol %), the exact role the ligand plays is unclear. There is no clear correlation between ligand structure and catalytic performance, but also changing other reaction parameters such as base and solvent can cause the reaction to be less successful. In addition, the discovery of improved reaction conditions is often performed through trial and error which requires a large number of experiments and is very inefficient. Having a greater understanding of the mechanism of the Ullmann reaction will allow for a rational and quality-by-design approach to improving reaction conditions, and will aid in increasing the efficiency of the reaction so that it can become advantageous over the Buchwald-Hartwig amination reaction.

This work aims to investigate the role of ligands in the Ullmann reaction. In particular, oxalamide ligands will be investigated, since they have allowed for a huge improvement in the efficiency of the Ullmann reaction and have even been able to activate aryl chloride substrates, but their success is not well understood. Kinetic studies will be performed to gain mechanistic insights into the reaction – time-adjustment analysis and VTNA will be utilised with the same and different excess protocols. The reaction will look at the activation of aryl bromide substrates which are less studied than aryl iodides. Insights into the rate dependence of substrates and any catalyst deactivation pathways will be explored. Based on these findings, a rational approach to reaction design can be applied to aid in the improvement of current reaction conditions.

In order to clarify what impact oxalamide ligands can have on the copper centre during the reaction, spectroscopic techniques such as NMR, EPR, CV and MS will be utilised to attempt to visualise their binding to the copper centre and any intermediates in the reaction. This will aid in the wider understanding of the role of the ligand in the mechanistic pathway and can aid in the design of new ligands.

Finally, a range of ligands will be tested in the reaction conditions utilised in the kinetic studies to aid in the expansion of the simple and accessible solvent (EtOH), base (KOH) and temperature (80 °C) combinations. Finding alternative ligands to oxalic diamide ligands, particularly asymmetrical ones, is desirable due to their multi-step synthesis procedure. Thus, more structurally simple ligands will be explored, as well as ligands

which are cheaper and easier to synthesise. Catalyst and ligand loadings will also be altered to determine the optimum conditions to obtain high yields of cross-coupled product.

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2 Mechanistic Insights and Reaction Optimisation of Cu/Oxalamide Catalysed Ullmann Reactions

2.1 Introduction

Understanding the mechanistic pathway of the Ullmann reaction is key to developing improved reaction conditions and increasing reaction scope. Insights into the role of the ligand, base and solvent, as well as reaction steps such as aryl halide activation are imperative to allow for more informed approaches to reaction design. Previous research relies on trial-and-error approaches to optimise reaction conditions, with a wide range of ligands, solvents and bases tested, which is laborious and time-consuming. Utilising methods for kinetic study such as RPKA and VTNA can allow for an understanding of the influence of various reaction components on the success of the reaction, and thus can lead to an informed adjustment to reaction conditions.

To perform kinetic studies, homogeneous reaction conditions are usually required. Insoluble inorganic bases such as K_2CO_3 or K_3PO_4 are often employed in Ullmann reactions. In kinetic studies, this would lead to mass-transfer effects such as changes in the rate of deprotonation of amine or ligand, and thus a true representation of the reaction cannot be studied.

Recent examples from Davies *et al.* utilise the soluble organic base tetrabutyl phosphonium malonate (TBPM) to gain insights into the reaction mechanism, and these highlight the importance of mechanistic studies in the development of improved reaction conditions. Employment of RPKA has allowed for the understanding of catalyst deactivation processes which were caused by the organic base TBPM acting competitively as a ligand (**Chapter 1**, section 1.4.4.2, **Figure 1.19 – 1.20**).¹ Increasing the concentration of amine was shown to stabilise the catalyst and prevent deactivation, which leads to improved reaction conditions and higher TONs. Addition of auxiliary ligands to the same reaction led to the discovery that certain ligands can aid in decreasing the extent of catalyst deactivation, and optimum conditions were obtained by switching to inorganic base K_3PO_4 and employing *N*-methylglycine as a ligand which achieved the best balance of rate acceleration and low catalyst deactivation.² Through these improvements, mild, room temperature reaction conditions could be employed to obtain a wide scope of products at high yields (**Chapter 1**, section 1.4.4.2, **Scheme 1.63**). Following this, a more accessible base/solvent combination was employed for

kinetic studies. The use of diethylene glycol (DEG) and NaOH allowed for a homogeneous reaction mixture. Additionally, NaOH is a stronger base than previously used TBPM which allowed for the intrinsic rate dependence of base and amine to be determined.³ Through this the reaction order in [amine] and [base] was determined to be zero which meant they did not need to be added in such a large excess. The authors were able to report mild, room temperature conditions with low loadings of copper and ligand (1 and 2 mole % respectively) based on these findings (**Chapter 1**, section **1.4.4.2**, **Scheme 1.66**).

While the reaction conditions have been successfully optimised in these cases, the loading of ligand and copper are still high compared to palladium-based Buchwald-Hartwig amination reactions, which means the Ullmann reaction cannot compete in industrial and large-scale settings. Previous work by Norrby *et al.* utilised ultra-low loadings of copper (0.001 mol %) which led to a high TON of 8.6×10^4 and TOF of 3583 h⁻¹, but very high loadings of ligand were required (20 mol %) and the conditions were only tested with very reactive nucleophiles such as pyrazole (**Chapter 1**, section **1.3.1**, **Scheme 1.15**).⁴ Reports from Ma *et al.* presented loadings of copper and oxalamide ligand **L29** at 0.1 mol % which led to a TON of 950 and TOF of 79 h⁻¹ with aryl bromide substrates, while with aryl iodide substrates the loading was successfully dropped to 0.01 mol % leading to a TON of 9500 and TOF of 396 h⁻¹ (**Chapter 1**, section **1.3.2**, **Scheme 1.20**).⁵ More recently, Hartwig *et al.* reported loadings of 0.0125 mol % in aryl bromide coupling with phenols which led to TONs of up to 8000.⁶ Linking these works is the fact that the role of the ligand was unidentified, and this will be key to identifying how lower loadings of copper can be achieved. In 2023, Hartwig *et al.* reported new mechanistic insights into copper-catalysed C-O coupling with oxalamide ligands.⁷ In this work, they propose that the ligand exhibits radical character and its redox non-innocence allows the Cu^{II} species, which is the proven resting state of the catalyst, to undergo oxidative addition of the aryl halide species to form a Cu^{III} complex (**Figure 2.1**). This work provides insights into the key role of the ligand in the catalytic cycle.

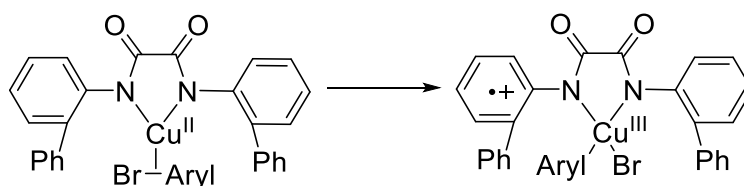
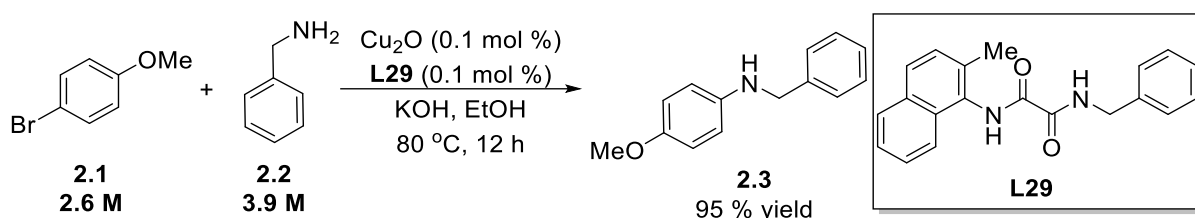


Figure 2.1 Hartwig *et al.* propose that radical character in the ligand facilitates oxidative addition of the aryl halide.

In this chapter, catalyst deactivation and substrate rate dependences in the Ullmann reaction have been explored through kinetic studies using VTNA. The reaction reported by Ma *et al.* in 2017 (**Scheme 2.1**) has been chosen due to the fact that 1) there are not many examples of reactions with such low loadings of copper and ligand being investigated by kinetic analysis, 2) there are limited studies with aryl bromide substrates, 3) the less-studied oxalamide ligands can be investigated, and 4) the reaction conditions of KOH/EtOH/**L29** led to a homogeneous reaction mixture.⁵ Through kinetic studies, the reaction has been optimised and new conditions have been established.

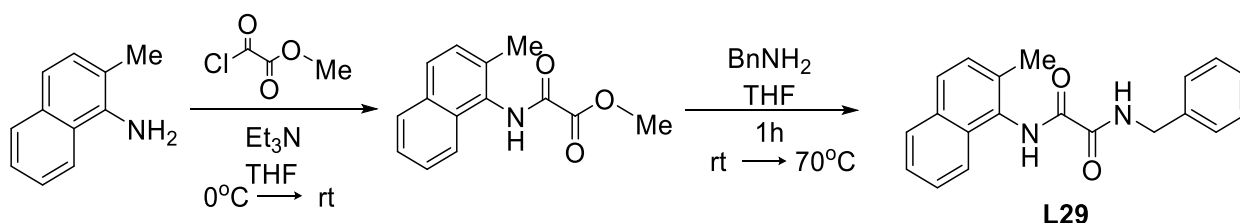


Scheme 2.1 Reaction reported by Ma *et al.* which was chosen for kinetic studies.⁵

2.2 Results and Discussion

2.2.1 Suitability of Reaction for Kinetic Studies

As mentioned above, the reaction reported in **Scheme 2.1** by Ma *et al.* was selected for kinetic studies.⁵ Ligand **L29** was synthesised according to the procedure outlined by Ma *et al.* (**Scheme 2.2**) whereby mono-methyloxalyl chloride was reacted with 2-methylnaphthalenylamine to form methyl-2-(benzylamino)-2-oxoacetate in 59 % yield after purification.⁵ This was then reacted with benzylamine to yield **L29** as a white powder in 40 % yield.

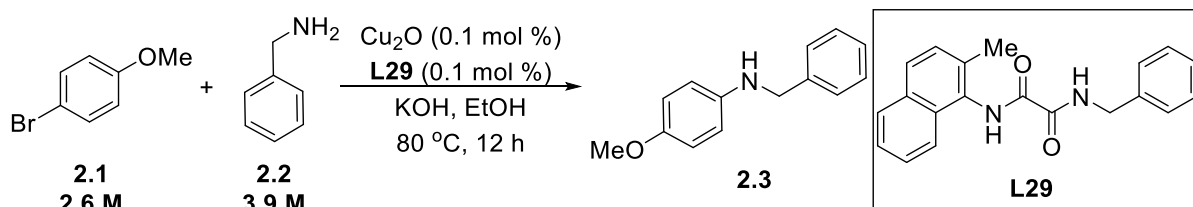


Scheme 2.2 Synthesis of **L29**.

Cross-coupling reactions were initially performed on a 10 mmol scale of aryl bromide under air in a sealed vial. Full experimental details can be found in **Chapter 6**. To confirm if the reaction was suitable for kinetic studies, firstly it was determined that the reaction was reproducible through replicate reactions and similar yields were obtained compared to those reported by Ma *et al.* (**Table 2.1**, entries 1, 2 and 3). Secondly, it

was determined that the reaction yields no product unless there is both copper source and **L29** present (**Table 2.1**, entries 4 and 5).

Additionally, it was confirmed that the success of the reaction was not due to trace amounts of palladium present in the reaction, since the addition of 0.001 mol % Pd(OAc)₂ instead of Cu₂O yielded no product (**Table 2.1**, entry 5). This was also successfully performed by Norrby *et al.* and it indicates that copper-catalysed processes are operating in this reaction.⁸

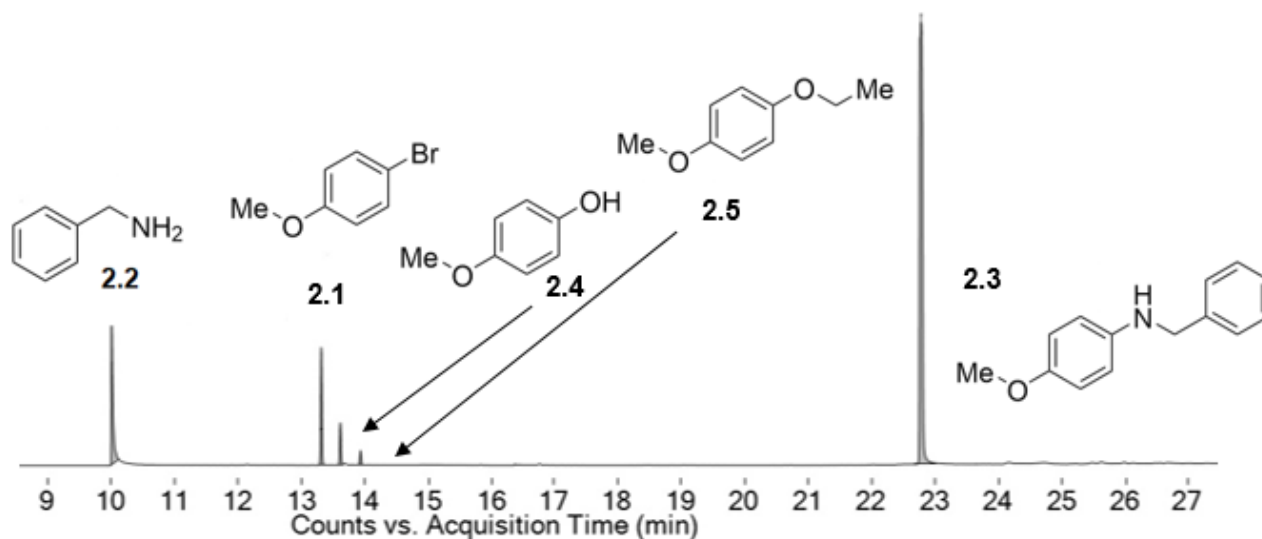


Entry	Cu ₂ O Present (0.1 mol %)	L29 Present (0.1 mol %)	NMR Yield of 2.3 (%)
1 ^a	Yes	Yes	95
2 ^b	Yes	Yes	87
3 ^c	Yes	Yes	87
4	Yes	No	0
5	No	Yes	0
6 ^d	No	Yes	0

Table 2.1 Reproducibility of reaction with Cu₂O and yields obtained without presence of copper source or **L29**. ^aIsolated yield reported by Ma *et al.*⁵ ^b3 replicates achieved 87 % yield. ^cIsolated yield. ^d0.001 mol % Pd(OAc)₂ added instead of 0.1 mol % Cu₂O.

Due to limitations in equipment, in situ reaction monitoring could not be performed under reaction conditions. Therefore, concentration profiles were utilised instead and kinetic analysis can be performed by VTNA as described in section 1.4.4.1. For this reaction, substrate **2.1** and product **2.3** can be identified by ¹H NMR spectroscopy and their concentrations determined by comparison with an internal standard, in this case naphthalene. Naphthalene was chosen as a suitable internal standard since 1) it does not participate in the reaction, 2) its ¹H NMR resonances do not overlay with those in the crude reaction mixture, 3) the reference protons have a similar relaxation time ($T_1 = 4.3 - 4.9$ s)⁹ to the OMe group in **2.1** ($T_1 = 5.3$ s)¹⁰ and the CH₂ peak in **2.3** ($T_1 = 4.7$ s)¹¹. Substrate **2.1** can be identified by the -OMe group in the 3.8 ppm region, although there is some overlay with **2.3** and side-products. The concentration of product **2.3** is more accurately determined, with two unique peaks at ~6.67 (aromatic proton) and

~4.30 ppm (-CH₂ group). The concentration of substrate **2.2** cannot be accurately determined due to its miscibility with brine which is used in the work-up stage prior to ¹H NMR acquisition. Two side-products were observed for this reaction via GC-MS and ¹H NMR (**Figure 2.2**) - 4-methoxyphenol (**2.4**, ~3 % yield) and 1-ethoxy-4-methoxybenzene (**2.5**, ~3 % yield) – both have been previously reported in the literature and form due to reaction of **2.1** with water or potassium ethoxide formed in situ.^{3,12}



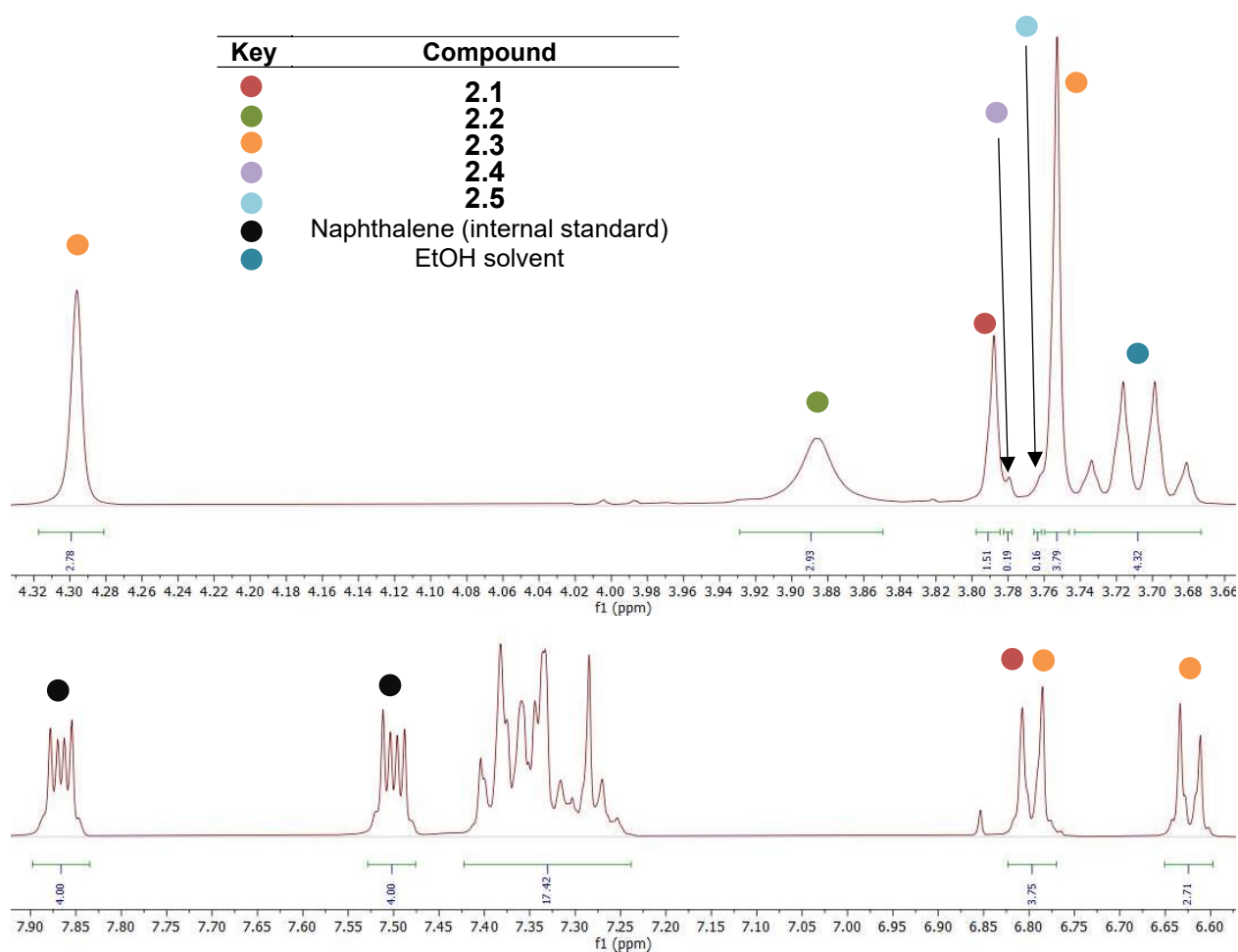


Figure 2.2 GC-MS (in EtOAc) and ^1H NMR (in CDCl_3) analysis of reaction mixture.

A solid by-product forms during the reaction and it was identified to be KBr by pXRD analysis (**Figure 2.3**). Although this leads to a non-homogeneous reaction mixture as the reaction proceeds, KBr is not thought to be kinetically relevant in the reaction and thus its formation is not likely to affect the kinetic studies.

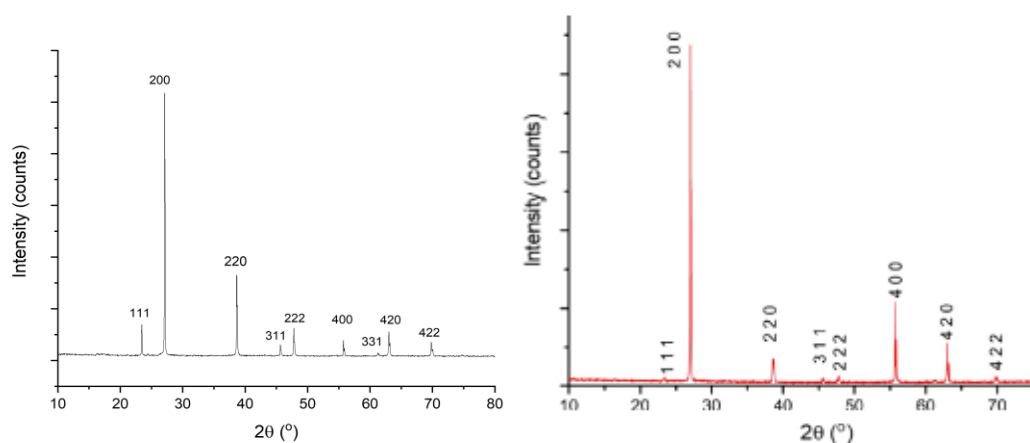


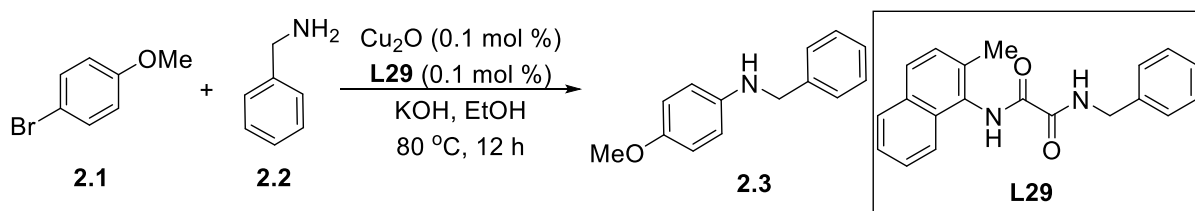
Figure 2.3 Left: Experimental pXRD data for white precipitate formed during reaction.

Right: Literature pXRD data for KBr.¹³

Herein, unless otherwise stated, the NMR yields reported are obtained by quantitative NMR and are relative to the internal standard, naphthalene.

2.2.2 Optimisation for Kinetic Studies

While the reaction in **Scheme 2.1** was reproducible, the reaction was not homogeneous at the reported concentrations, since the base did not dissolve completely. By doubling the volume of EtOH solvent the reaction became homogeneous without any negative effects on the yield of **2.3**. (**Table 2.2**, entries 1 and 2).



Entry	Reaction Scale (mmol)	Volume of EtOH (mL)	[2.1] (M)	[2.2] (M)	NMR Yield of 2.3 (%)
1	10	1	2.6	3.9	87
2	10	2	2.0	3.0	93
3 ^a	50	10	2.0	3.0	33
4	50	10	2.0	3.0	90

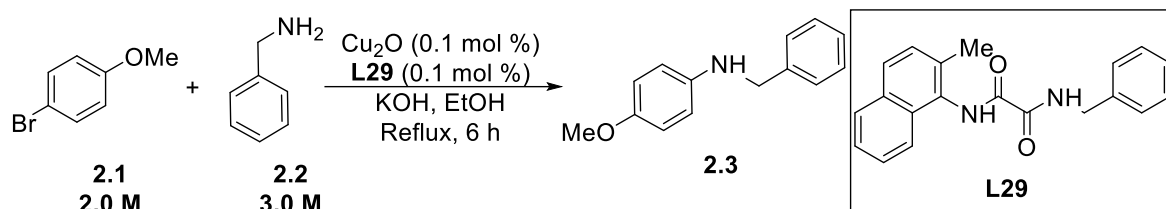
Table 2.2 Yields obtained with Cu_2O with different volumes of EtOH and different reaction scale (based on [**2.1**]). ^aReaction performed in air.

As stated in section **2.2.1**, ^1H NMR has been used to obtain concentration profiles for the reaction, and it was therefore necessary to increase the scale from 10 mmol to 50 mmol to allow for removal of aliquots (~0.1 mL) of the reaction mixture without large changes to the reaction volume. This also aids in increasing the accuracy of the reaction due to measuring larger volumes, particularly with Cu_2O and **L29** present at very low loadings. As seen in **Table 2.2**, entry 4, there was no impact on the yield by scaling up the reaction.

While Ma *et al.* prepared reactions in air and ran reactions under a N_2 atmosphere, it was found that at the smaller scale of 10 mmol, the reaction ran well in a sealed vial in air. However, upon scaling the reaction to 50 mmol and changing the reaction vessel to a round-bottom flask, the reaction performed better under a nitrogen atmosphere, thus all reactions for kinetic studies at a larger scale were performed under nitrogen

(**Table 2.2**, entry 3). Due to time constraints, the reason for the different reaction performance at a larger scale was not investigated.

Addition of Cu_2O as a solid yielded reproducible reaction profiles (**Figure 2.4**, top); however, the use of Cu_2O in kinetic studies is not practical since it tends to adhere readily to surfaces which makes it difficult to weigh out accurately, and it is not very soluble in EtOH which means stock solutions in the reaction solvent cannot be made. Attempts were made to add Cu_2O as a slurry stock solution – these reactions are profiled in **Figure 2.4** (bottom), but the reaction was not reproducible, most likely due to different concentrations of Cu_2O being added from the slurry. It was therefore decided that a more soluble copper source would be identified so that stock solutions can be used for the addition of copper and ligand.



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[Cu_2O] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)	Method of Addition of Cu_2O and L29
● ●	2.0	3.0	0.002	0.002	2.7	Solid
● ●	2.0	3.0	0.002	0.002	2.7	Slurry

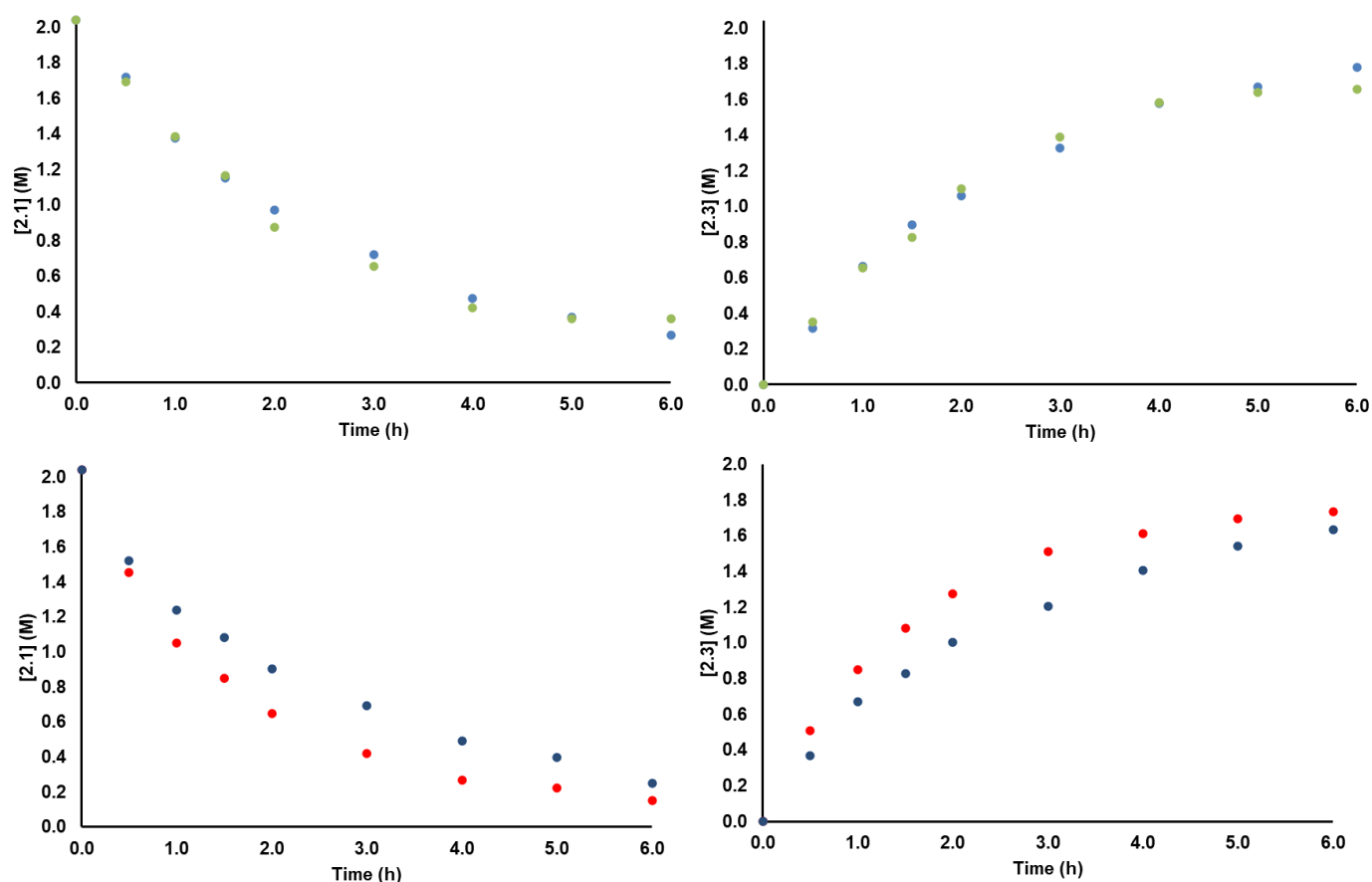
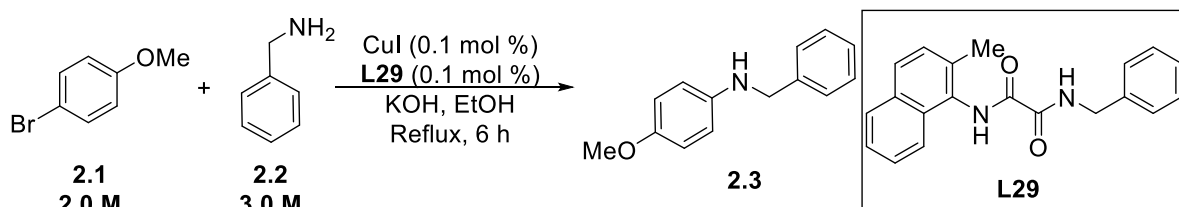


Figure 2.4 Concentration profiles of reactions with addition of Cu_2O via slurry stock solution and as solid.

Given these difficulties, CuI was tested as the precatalyst due to its higher solubility in organic solvents. A stock solution of CuI in acetonitrile was used (since it is not soluble in the reaction solvent EtOH), while **L29** was added as a solid due to its insolubility in acetonitrile. In this case, while the concentration profiles were reproducible (**Figure 2.5**, top) an induction period was seen between 0-1 hours (highlighted in the red box). This is not desirable as it causes complications when performing visual kinetic

analyses such as VTNA. The bottom graph in **Figure 2.5** shows that the induction period does not occur when CuI is added as a solid, which suggests that, as complexation of MeCN to the copper centre occurs, this may delay the formation of the active catalytic species in the reaction mixture. Further investigations would be required to determine the true cause of this induction period, but in this case it was more pressing to select a new copper source which would be suitable for kinetic studies.



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[CuI] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)	Method of Addition of CuI
● ● ●	2.0	3.0	0.002	0.002	2.7	Stock solution in MeCN
●	2.0	3.0	0.002	0.002	2.7	Solid

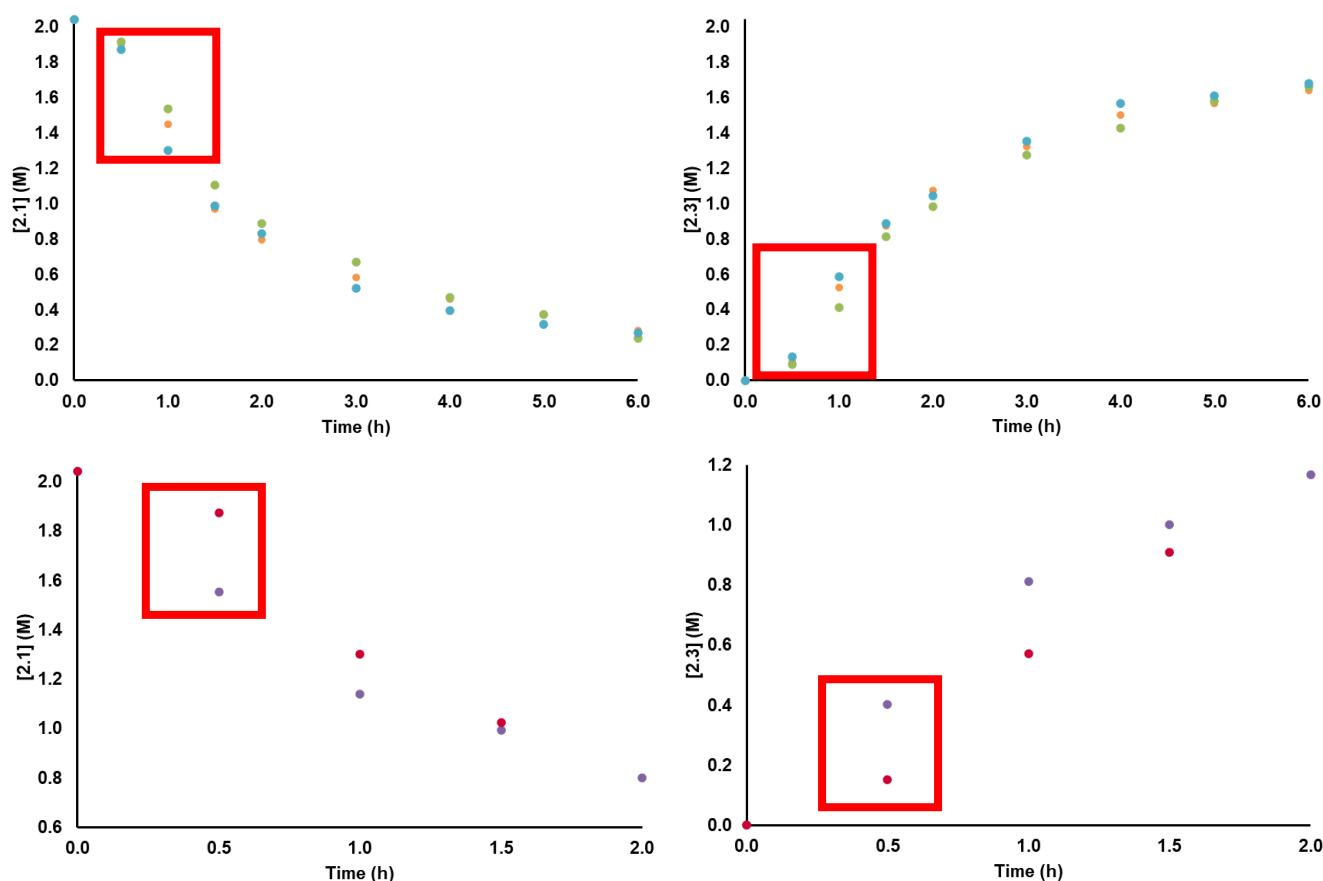
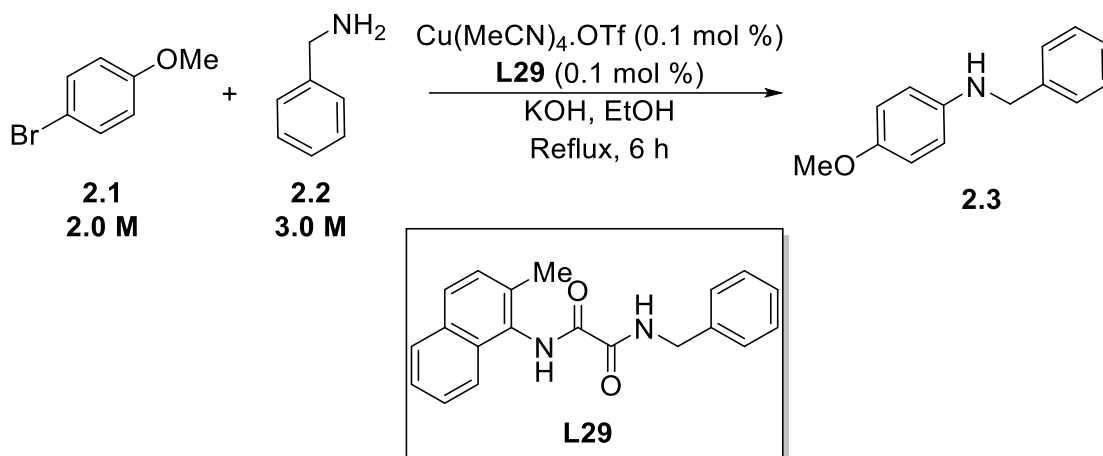


Figure 2.5 Concentration profiles of reactions with CuI added via stock solution in MeCN (top) and comparison of CuI added in MeCN vs as a solid (bottom).

Lastly, $\text{Cu}(\text{MeCN})_4\cdot\text{OTf}$ was found to be a suitable and practical alternative. It is highly soluble in EtOH which allows for improved accuracy by addition via stock solutions in the reaction solvent, for both copper source and **L29**. **Figure 2.6** confirms that the concentration profiles obtained were reproducible and are therefore suitable for kinetic studies. For all further studies in this chapter $\text{Cu}(\text{MeCN})_4\cdot\text{OTf}$ has been used as the copper source unless otherwise stated.



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[Cu(MeCN) ₄ .OTf] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)
● ● ●	2.0	3.0	0.002	0.002	2.7

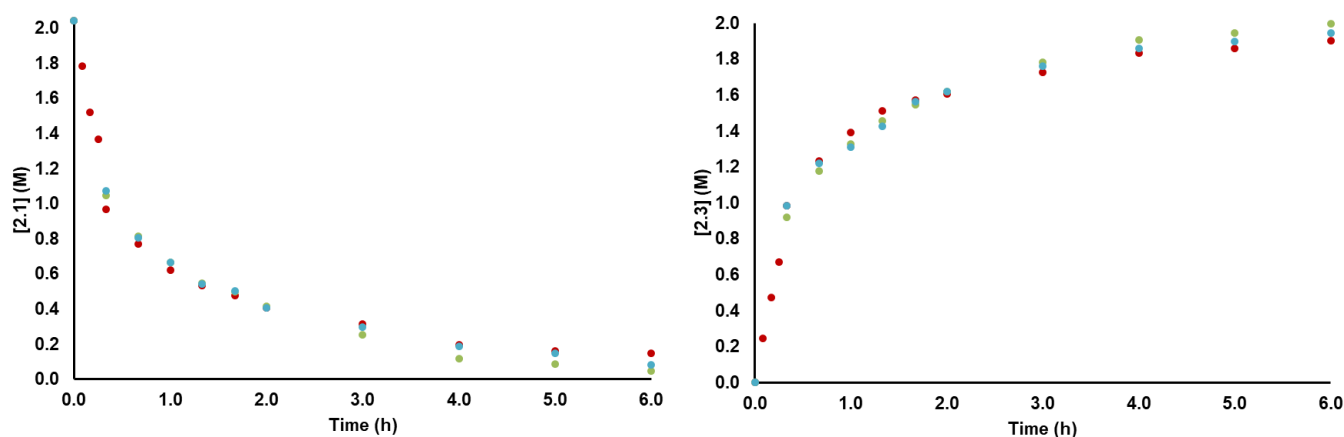
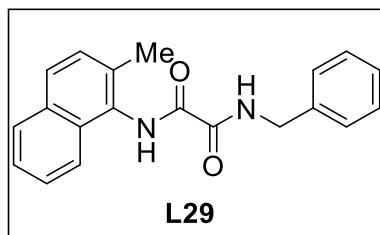
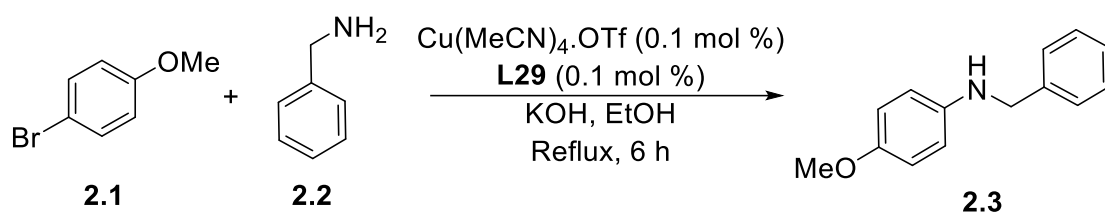


Figure 2.6 Concentration profile for reactions with $\text{Cu}(\text{MeCN})_4\cdot\text{OTf}$ as copper source.

2.2.3 Obtaining a Constant Temperature Profile

The concentration profiles reported thus far have been obtained from reactions which were performed at reflux in EtOH. Given that the reaction mixture is concentrated, and starting materials **2.1** and **2.2** have much higher boiling points than EtOH (**2.1** = 223 °C, **2.2** = 185 °C), the reflux temperature of the reaction mixture (measured to be 112 °C) was higher than the boiling point of EtOH (78 °C). The reaction proceeded too slowly to be monitored manually at the literature reported temperature of 80 °C. Under standard reaction conditions, as the reaction progressed and the starting materials were consumed, the reflux temperature of the reaction mixture decreased by 22 °C over 2 hours, stabilising at 90 °C when over 70 % of **2.1** had been consumed (**Figure 2.7**, red). Under same excess conditions (which will be introduced in section **2.2.4**), since the initial concentration of **2.1** and **2.2** is decreased by half, the starting temperature is 88 °C and the temperature difference is not as pronounced, with a change of 5 °C during the reaction to stabilise at 83 °C (**Figure 2.7**, green). All temperatures were recorded with a mercury thermometer placed inside the reaction mixture.



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[$\text{Cu}(\text{MeCN})_4\cdot\text{OTf}$] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)
●	2.0	3.0	0.002	0.002	2.7
●	0.8	1.8	0.002	0.002	1.5

Time (h)	Temperature (°C)	Temperature (°C)
	●	●
0	112.0	112.0
0.5	98.5	98.5
1	94.5	94.5
1.5	91.0	91.0
2	90.0	90.0
2.5	90.0	90.0
3	90.0	90.0
4	90.0	90.0
5	90.0	90.0
6	90.0	90.0

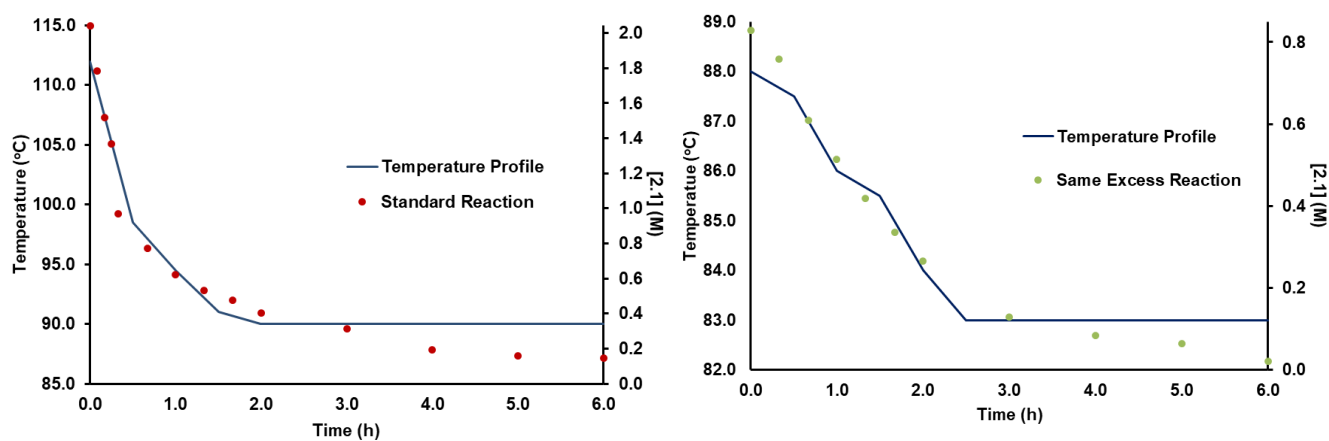
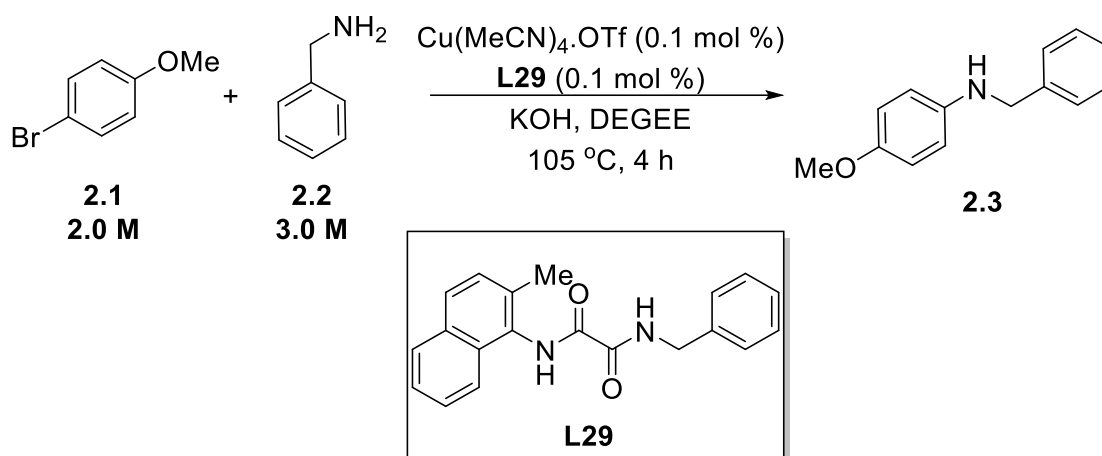


Figure 2.7 Temperature profiles for reactions run at reflux in EtOH.

With a changing temperature profile, reliable rate information cannot be obtained from reactions performed under these conditions.¹⁴ Unfortunately, this was only noticed later in the project and thus the work could not be repeated in a higher boiling point solvent to obtain a constant temperature profile due to time constraints. In this instance, same excess experiments were run under reflux conditions and have been reported in this chapter due to the fact that deactivation behaviours can still be observed under these conditions. In the case of different excess reactions, it is imperative to have a constant reaction temperature so these reactions were performed in a higher boiling point solvent, diethylene glycol monoethyl ether (DEGEE), which showed similar reactivity to EtOH (**Figure 2.8**). A stable reaction temperature at 105 °C allowed the reaction to complete after 4 hours with yields of 96 % **2.3**, 2 % **2.1** and 2 % **2.4** (as determined by ¹H NMR, **Figure 2.9**).



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[$\text{Cu}(\text{MeCN})_4\cdot\text{OTf}$] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)
● ● ●	2.0	3.0	0.002	0.002	2.7

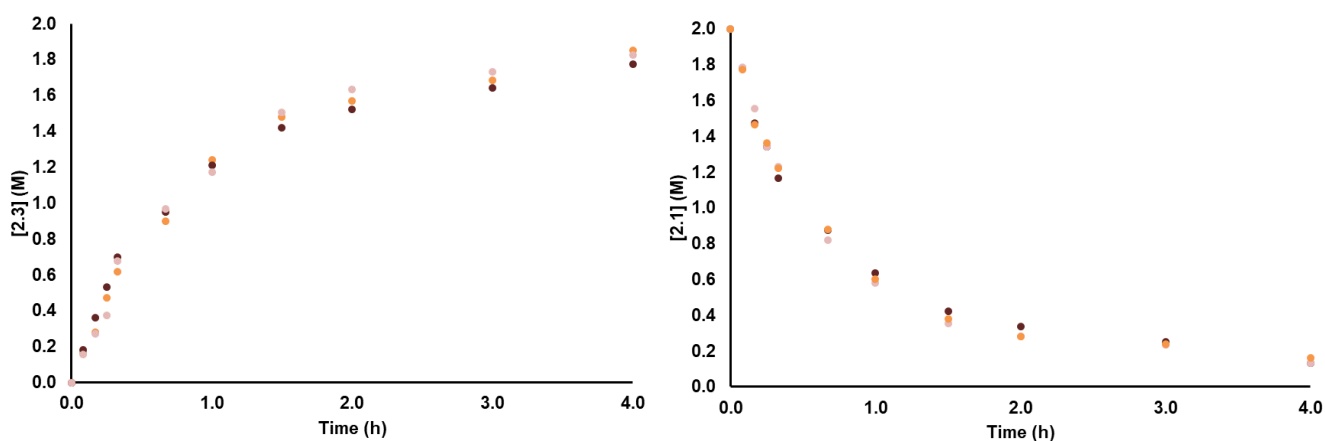


Figure 2.8 Reproducibility with DEGEE as a solvent.

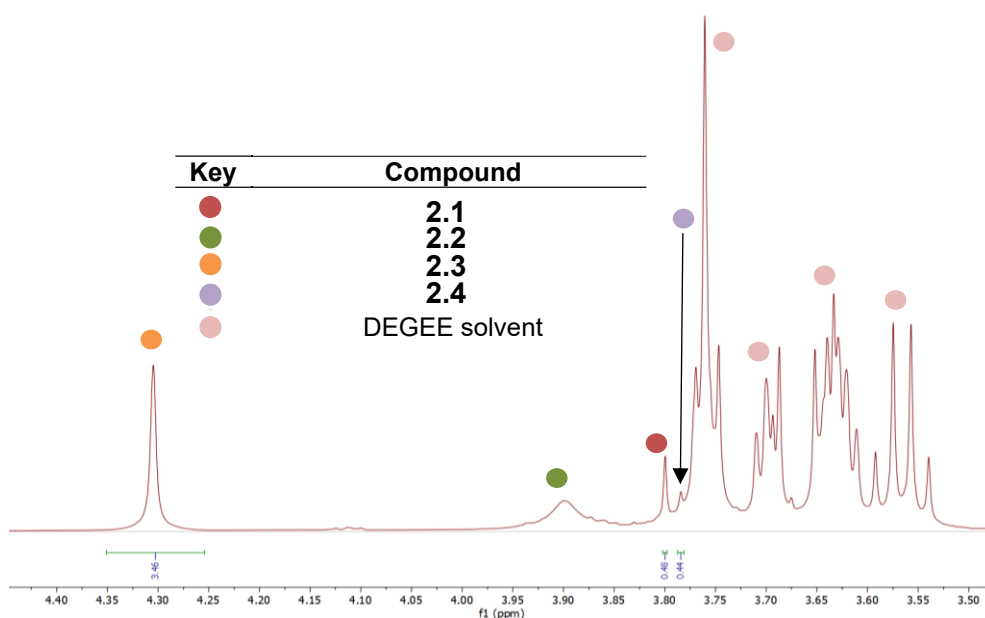
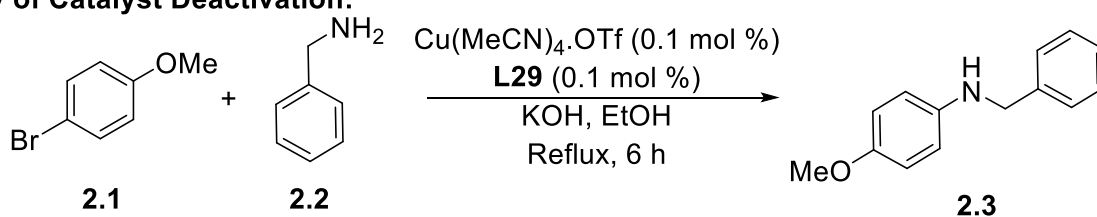


Figure 2.9 ^1H NMR in CDCl_3 of crude reaction mixture from reaction in DEGEE.

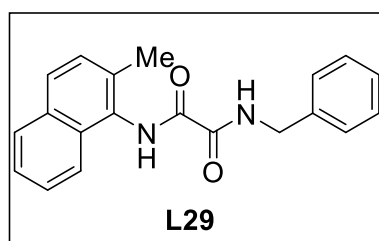
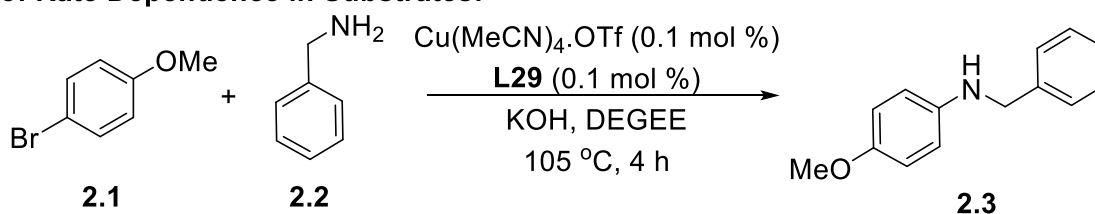
2.2.4 Kinetic Studies

With the optimised conditions above, the reactions in **Scheme 2.3** were employed for kinetic studies.

Study of Catalyst Deactivation:



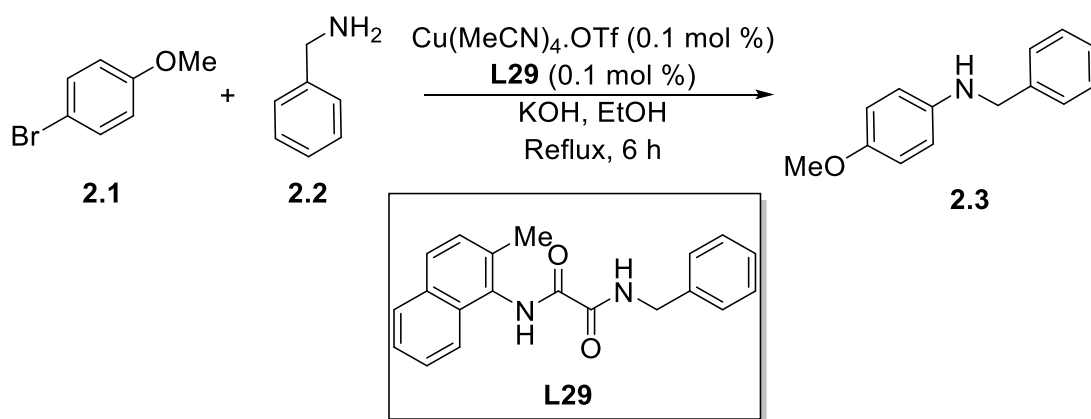
Study of Rate Dependence in Substrates:



Scheme 2.3 Optimised conditions for kinetic studies.

2.2.4.1 Catalyst Deactivation

Same excess experiments were conducted to investigate whether there were any catalyst deactivation processes occurring in the reaction. Experiments were conducted following the 'same excess' protocol reported by Blackmond and highlighted in section 1.4.4.1.¹⁵ A reaction was performed under standard concentrations (3 replicates), then a second reaction was performed whereby the difference in concentration of **2.1**, **2.2** and KOH was kept the same ($[e] = 1 \text{ M}$) but their initial concentration was decreased by 1.2 M (2 replicates). The same excess experiment was shifted on the x-axis until the first point overlays with the standard reaction (0.6 h). The curves continue to overlay after the first point, but towards the end the same excess experiment (green curve) seems to deviate slightly from the original experiment. It can be concluded that there is no significant catalyst deactivation or product inhibition occurring in this reaction. (**Figure 2.10**).



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[Cu(MeCN) ₄ .OTf] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)
●	2.0	3.0	0.002	0.002	2.7
●	0.8	1.8	0.002	0.002	1.5

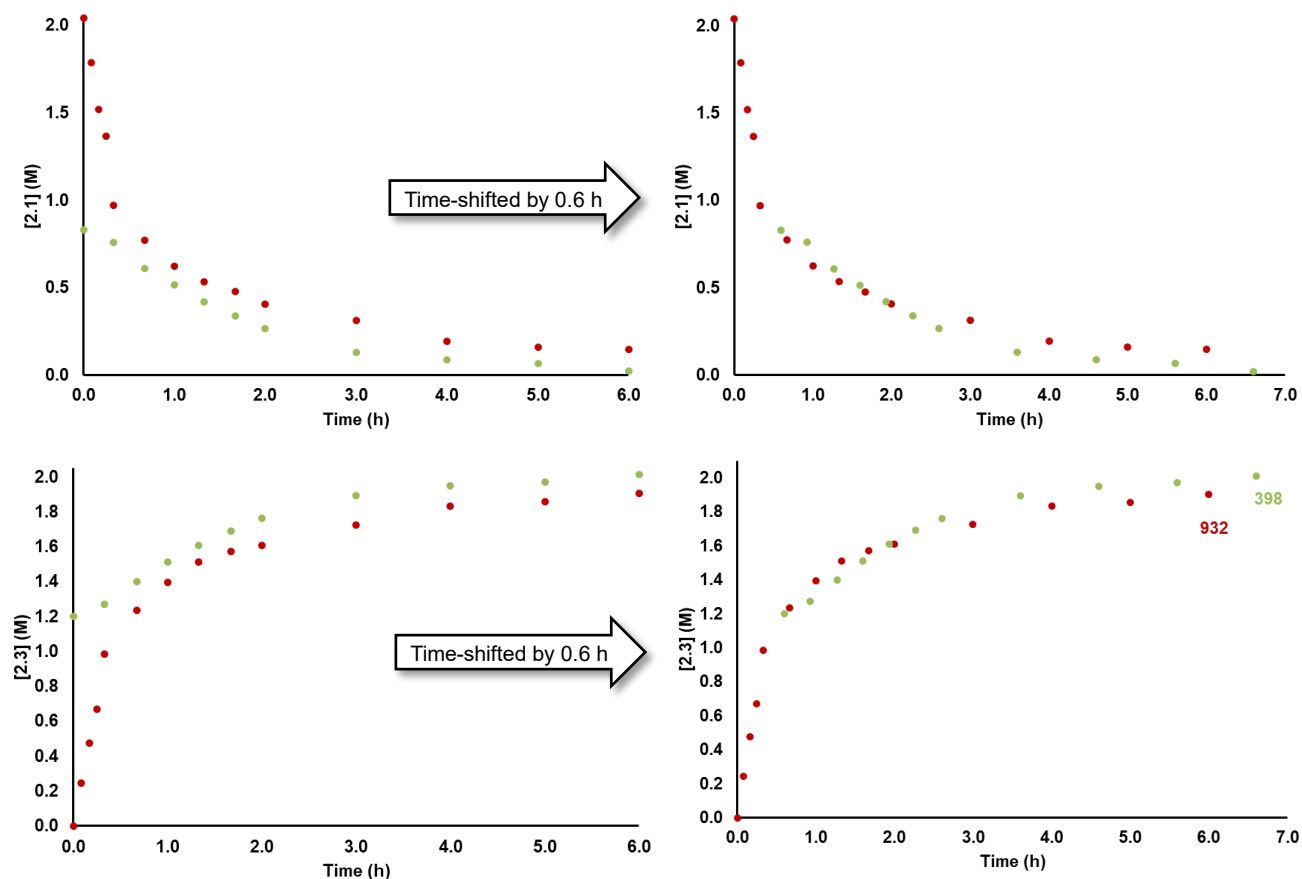


Figure 2.10 Time-adjusted analysis of standard and same excess experiments. Left: before time-shift. Right: after time-shift of 0.6 h. TONs are reported in the bottom right graph.

The effects of lowering the concentration of copper and ligand were then investigated. When the catalyst loading was decreased to 0.005 M, the reaction began to stall after 2 hours. This was investigated by performing a same excess reaction ($[e] = 1 \text{ M}$), which showed that there was significant catalyst deactivation or product inhibition at this lower catalyst loading, since the same excess experiment does not overlay with the standard experiment after a time-shift of 0.7 h (**Figure 2.11**, pink curve). To rule out product inhibition, a third same excess experiment (**Figure 2.11**, green curve), was performed with the addition of the major products of the reaction (**2.3**, KBr and H_2O). Since this experiment overlays with the first same excess experiment, it is concluded that product inhibition does not occur in this reaction, and catalyst deactivation is occurring.

To investigate whether **L29** could play a key role in preventing deactivation of the catalyst, a third set of experiments were performed with an increased concentration of **L29**. With the concentration of copper and **L29** in a ratio of 1:2, a same excess experiment was performed ($[e] = 1 \text{ M}$), and in this case the curves exhibit a greater overlay after a time-shift of 1.2 h (**Figure 2.12**) compared to that seen in the graphs in **Figure 2.11**. This indicates that with a higher loading of **L29**, catalyst deactivation does not occur at such a great extent, which may suggest that the ligand is able to prevent catalyst deactivation, or it is being depleted during the reaction and a larger reservoir of ligand is required to keep the catalytic cycle active.

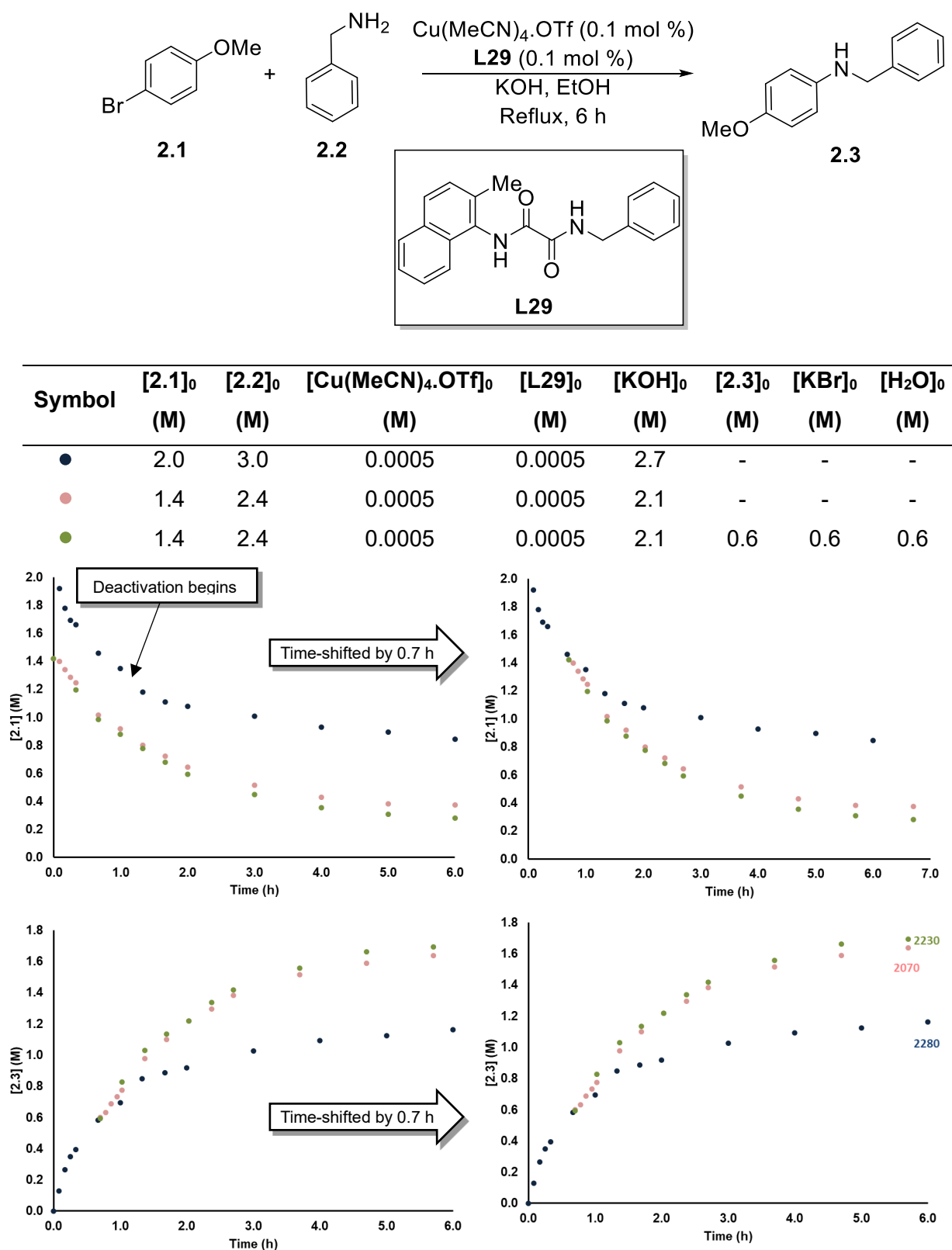
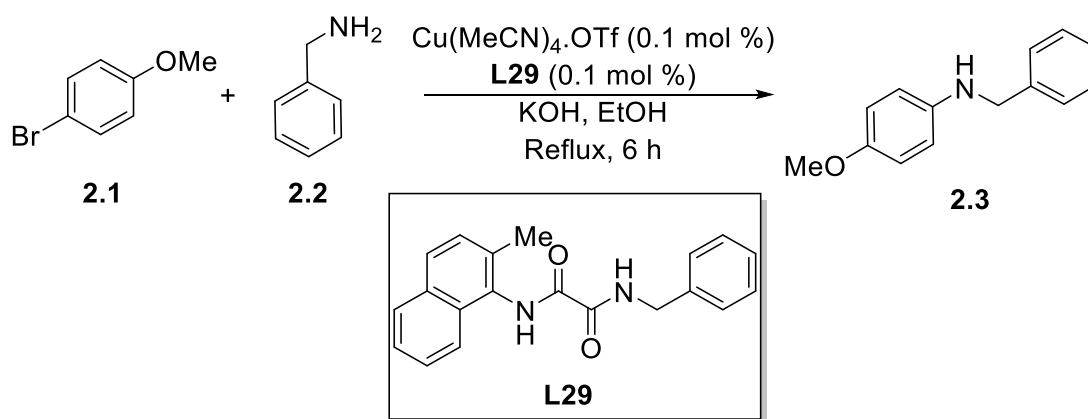


Figure 2.11 Concentration profiles of same excess experiments with 0.005 M Cu and **L29**. Left: before time-shift. Right: after time-shift of 0.7 h. TONs are reported in the bottom right graph.



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[Cu(MeCN) ₄ .OTf] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)
●	2.0	3.0	0.0005	0.001	2.7
●	0.8	1.8	0.0005	0.001	1.5

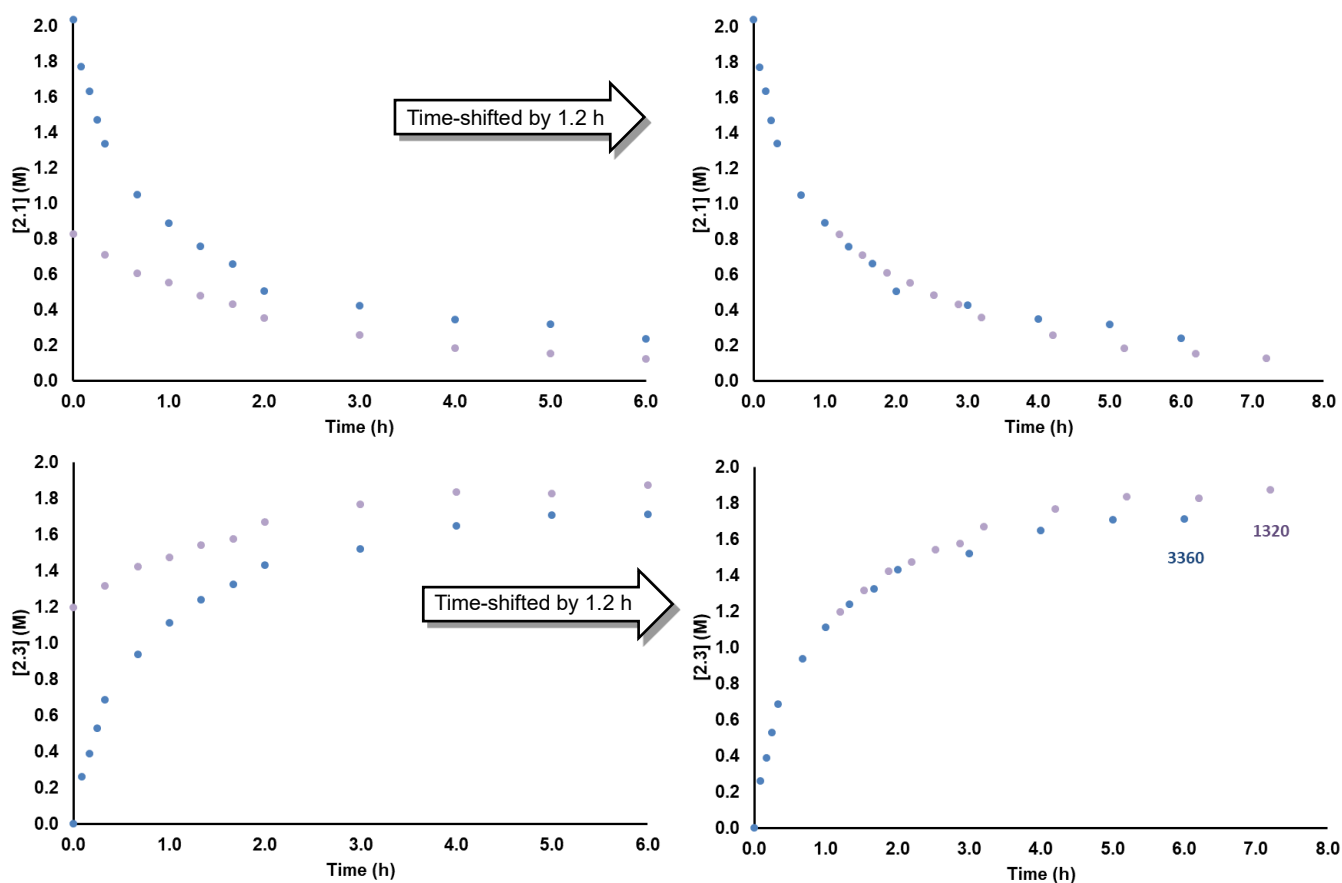
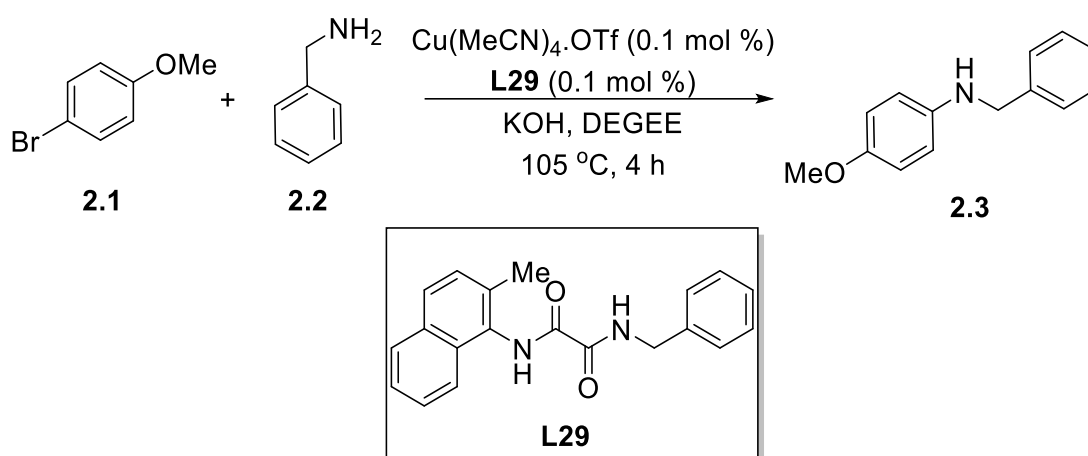


Figure 2.12 Concentration profiles of same excess experiments with higher loading of **L29**. Left: before time-shift. Right: after time-shift of 1.2 h. TONs are reported in the bottom right graph.

2.2.4.2 Rate Dependence In Substrates

The 'different excess' protocol was employed to determine the rate dependence in substrates **2.1**, **2.2** and KOH. As outlined in section 1.4.4.1, this involves changing the concentration of the substrate of interest while keeping all other concentrations the same. The orders in substrates can be determined whilst keeping the reaction under synthetically relevant conditions. The conditions in **Scheme 2.4** and VTNA were utilised to obtain the rate dependence in substrates. When changing the concentration of **2.1**, the reaction was confirmed to be first order in [**2.1**] since the curves overlayed when the power was raised to one (**Figure 2.13**). This is comparable to previous studies of the Ullmann C-N cross-coupling reaction and indicates that the aryl halide activation step is rate-determining.^{1-3,16} In changing the concentration of **2.2** and KOH individually, both concentration profiles overlay with the standard reaction which indicates that the reaction is zero order in [**2.2**] and [KOH] and they do not affect the rate (**Figure 2.14** and **Figure 2.15**). This is consistent with previous research from Davies *et al.* when NaOH was used as a base, whereby they claim that the deprotonated amine is present in the kinetically meaningful steps of the reaction.³ Contrastingly, recent reports from Blackmond *et al.* suggest that zero-order rate dependence of [amine] indicates that addition of the nucleophile to the copper centre occurs after the aryl halide activation step.¹⁶ The latter is more likely to occur since the amine would not be deprotonated under the conditions with KOH as a base.



Scheme 2.4 Conditions employed for different excess experiments.

Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[Cu(MeCN) ₄ .OTf] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)
●	2.0	3.0	0.002	0.002	2.7
●	1.6	3.0	0.002	0.002	2.7
●	2.3	3.0	0.002	0.002	2.7

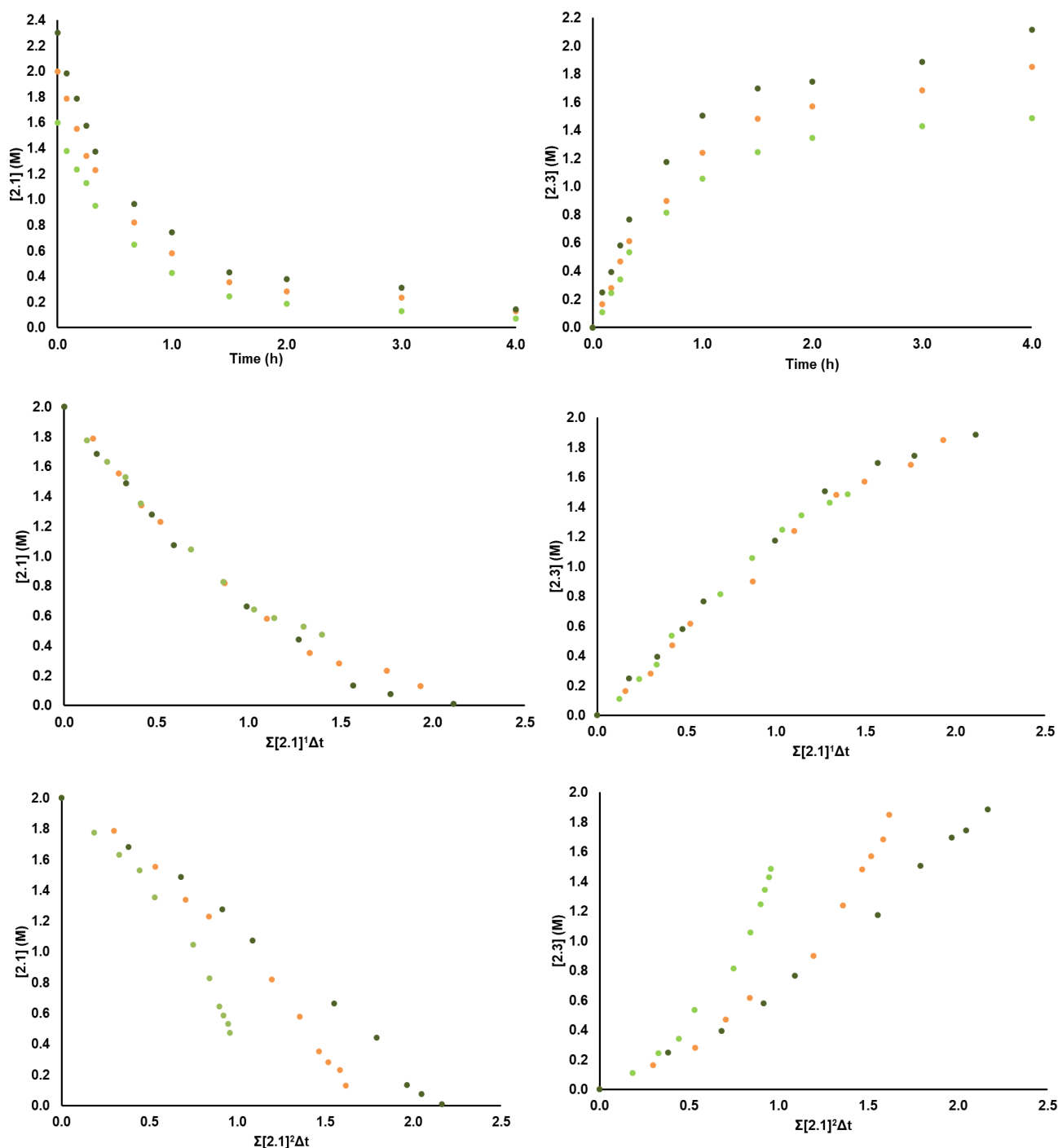


Figure 2.13 VTNA analysis to confirm order in [2.1]. Top: concentration profiles before VTNA. Middle: concentration profiles with data normalised to the power of 1. Bottom: Concentration profiles with data normalised to the power of 2.

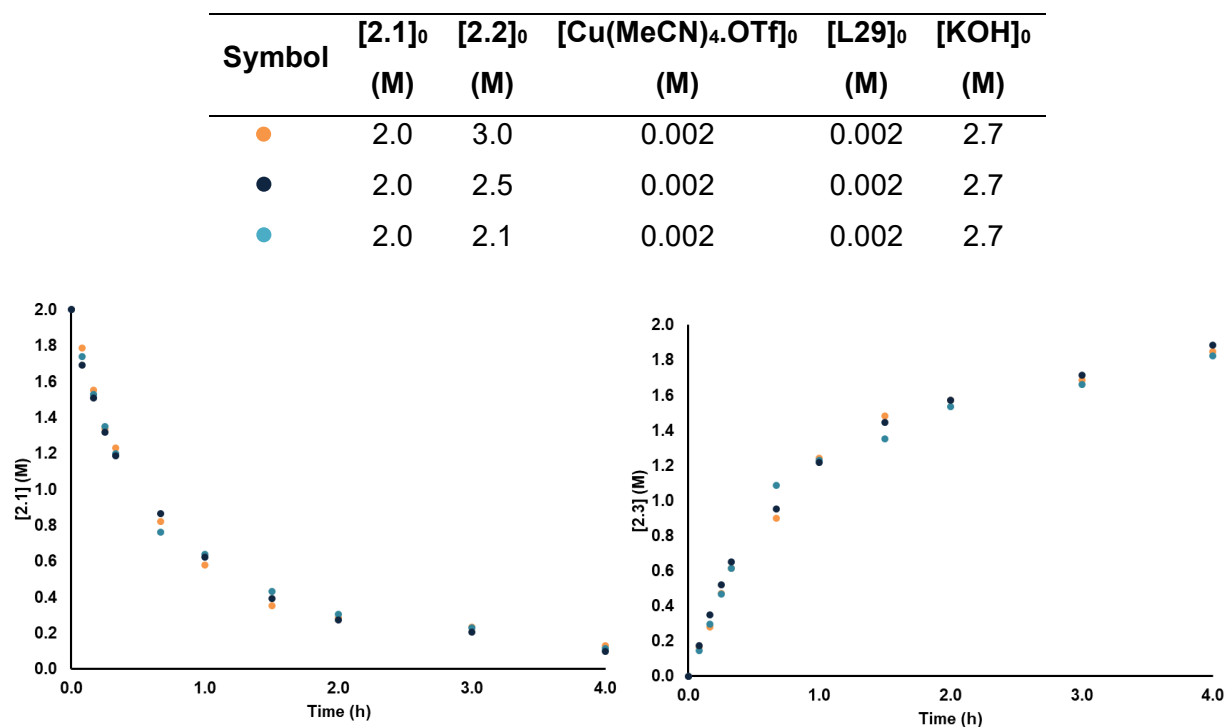


Figure 2.14 Concentration profiles of reactions with different [2.2]₀.

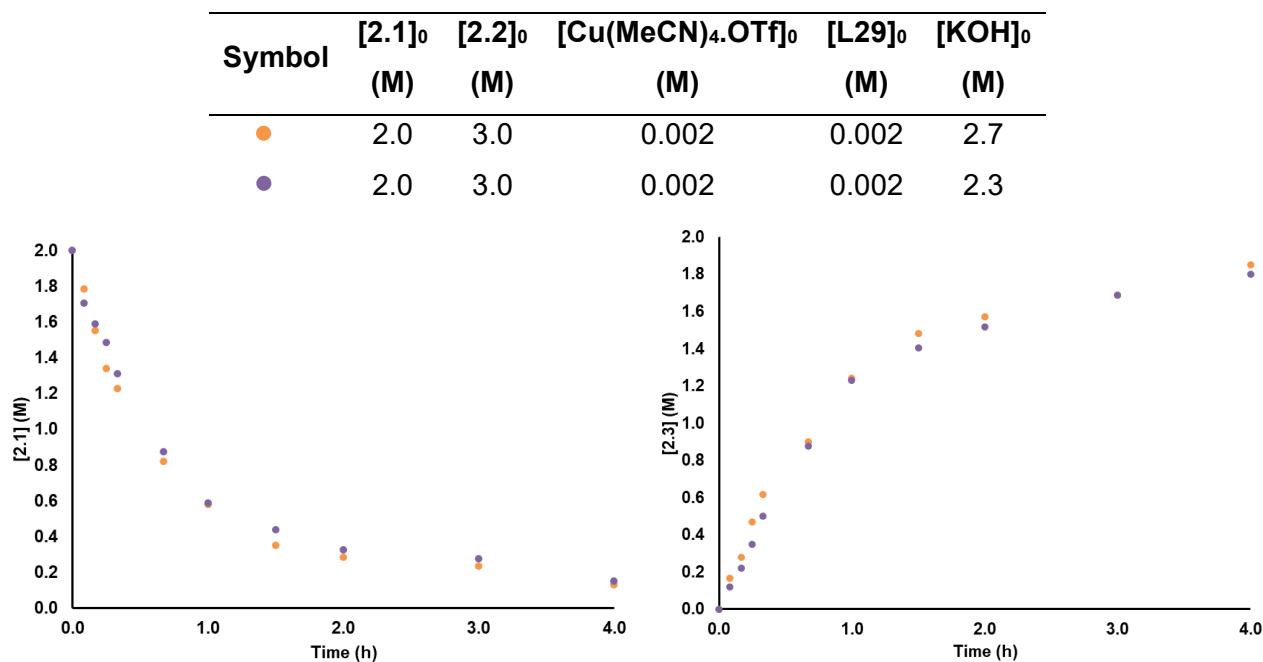
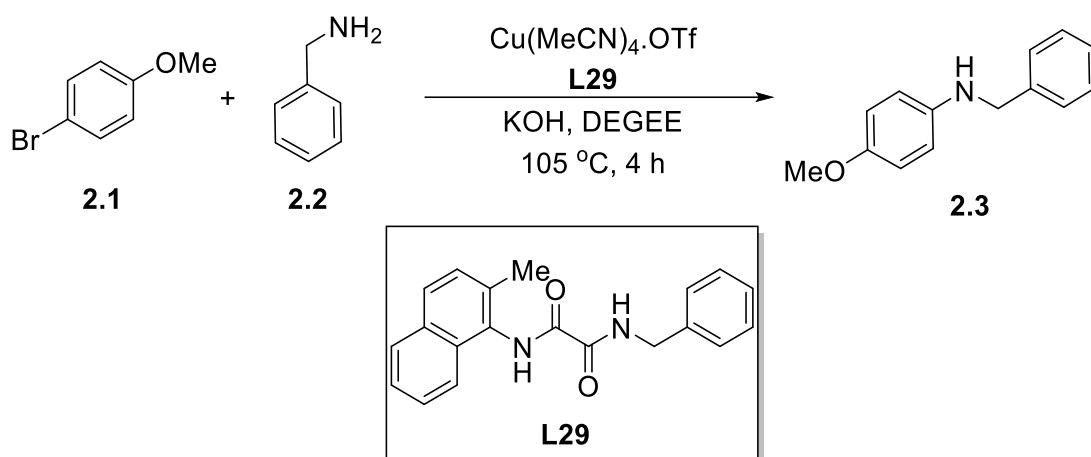


Figure 2.15 Concentration profiles of reactions with different [KOH]₀.

The elucidation of reaction order in [copper] and [L29] has been attempted (**Figure 2.16**). It is assumed that one molecule of **L29** binds to the copper centre during the reaction, but the order in the active catalytic species cannot be accurately determined since its exact nature is unknown. The concentration of **L29** may not be constant during

the reaction (e.g. if it reacts with other species) so it may not be possible to elucidate the order in **L29**.

Nonetheless, assuming that the ratio of Cu:**L29** in the catalytic species is 1:1, addition of different concentrations of copper and **L29** led to a rate dependence of 1, with the first portion of the curves overlaying when the power is raised to 1. Later in the reaction, the curves deviate and no longer overlay, which may be due to the deactivation of the catalyst or the depletion of **L29**.



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[Cu(MeCN) ₄ .OTf] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)
●	2.0	3.0	0.002	0.002	2.7
●	2.0	3.0	0.001	0.001	2.7
●	2.0	3.0	0.0005	0.0005	2.7

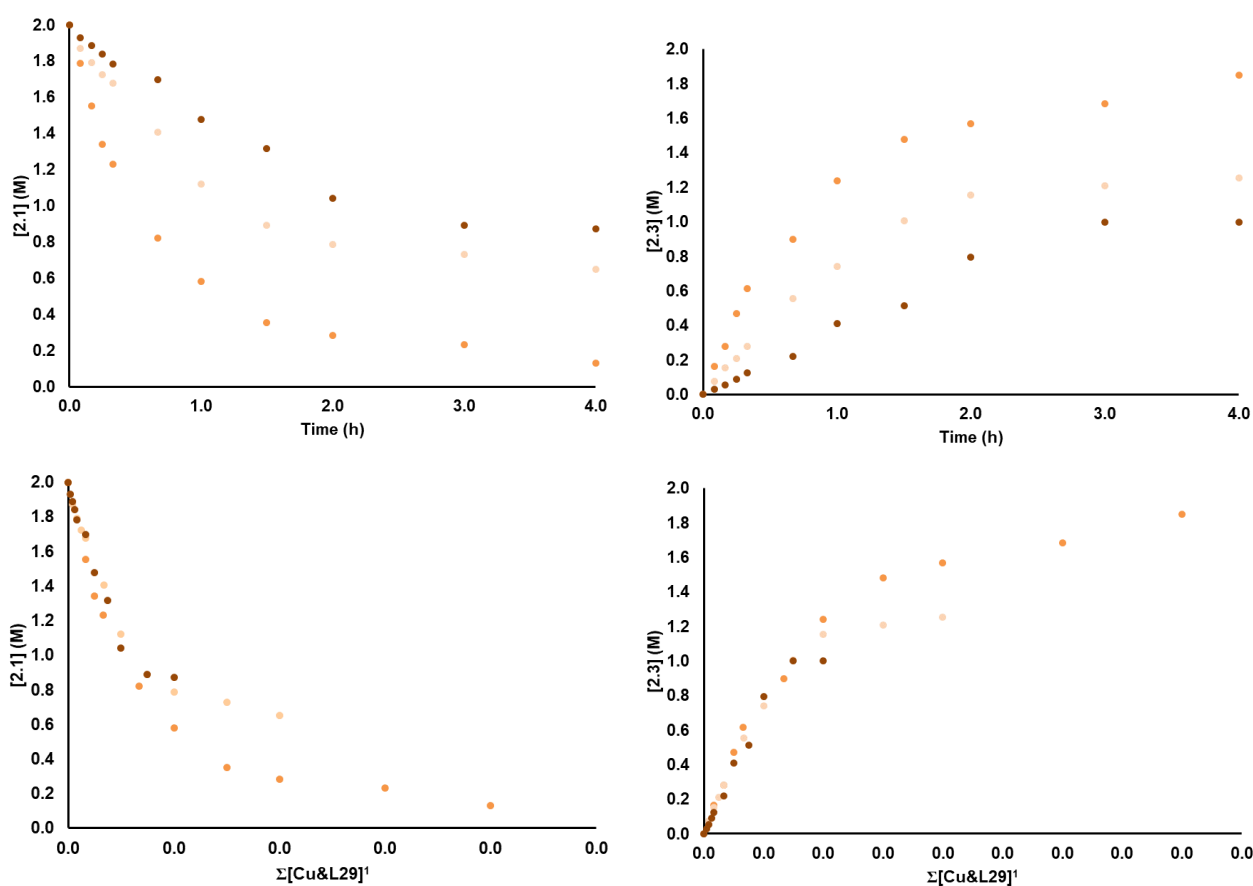
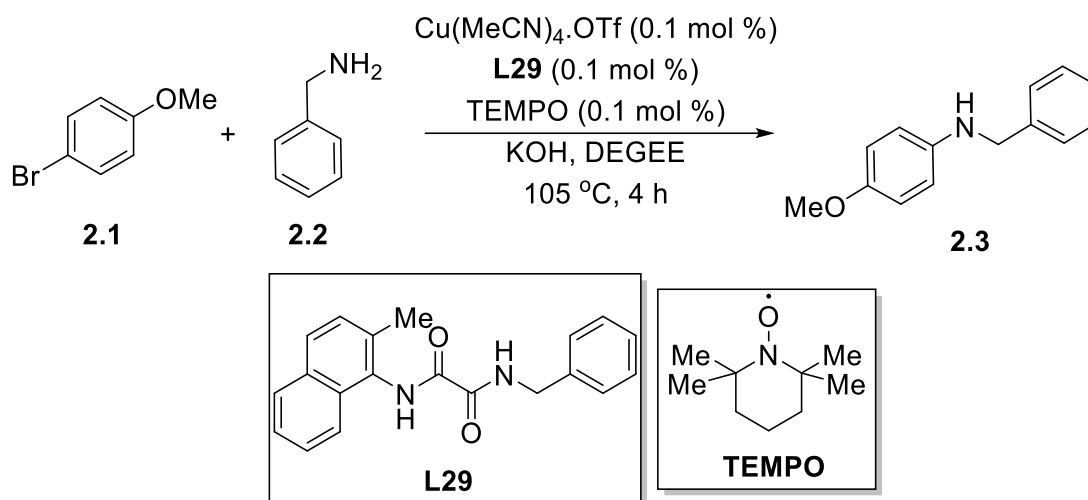


Figure 2.16 VTNA analysis to determine order in $[\text{Cu}]_{\text{tot}}$ and $[\text{L29}]_0$. Top: concentration profiles before VTNA. Bottom: Concentration profiles with data normalised to the power of 1.

2.2.4.3 Aryl Bromide Activation

In order to determine if the aryl bromide activation step occurs via a radical-based mechanism, TEMPO was added as a radical scavenger. If the reaction followed a radical-based pathway, TEMPO would be expected to react with any radicals formed during the reaction and prevent them from forming the desired product, thus the reaction would not proceed in its presence. As can be seen in **Figure 2.17**, while catalytic amounts of TEMPO did not affect the formation of product, addition of a stoichiometric amount of TEMPO prevented the formation of the expected cross-coupled product. This indicates that a radical-based pathway may be followed in this reaction. This technique has been utilised by previous researchers to determine if radical-based pathways have been followed, and similar results were obtained by Antenucci *et al.*¹⁷ Further experiments such as a radical clock reaction could validate these results, since radical-based Ullmann reactions have rarely been proven experimentally. In particular, it would clarify whether the radicals are formed from the aryl bromide substrate, or if there are other radicals present, such as from the ligand.



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[$\text{Cu}(\text{MeCN})_4\cdot\text{OTf}$] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)	[TEMPO] (M)
●	2.0	3.0	0.002	0.002	2.7	0
●	2.0	3.0	0.002	0.002	2.7	0.002
●	2.0	3.0	0.002	0.002	2.2	2.0

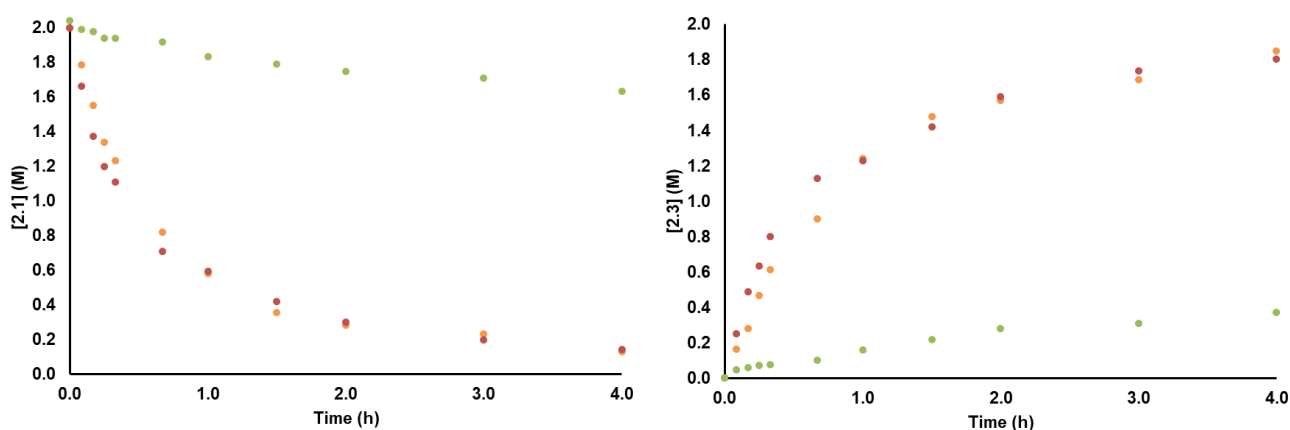


Figure 2.17 Concentration profiles of reactions with and without TEMPO.

2.2.4.4 Hammett Study

Hammett studies can provide insights into the effects of electron density on the rate-determining step of the reaction. The theory of this method is summarised in **Chapter 1**, section 1.4.3.3. By employing different substituents on the aryl bromide substrate, the resonance or inductive effects will either stabilise or destabilise the copper intermediate involved in the rate-determining step of the reaction.¹⁸ A range of aryl bromide substrates with different substituents in the para-position were employed and the initial reaction rate was obtained. This was used to calculate the $\log\left(\frac{k_H}{k_X}\right)$

values and led to the plot in **Figure 2.18**. The graph exhibits a ρ value of -0.7702. It demonstrates that the more electron donating the substituent, the faster the initial reaction rate, and it suggests a build up of positive charge in the transition state of the reaction. This result does not agree with previous literature whereby a positive correlation is observed which indicates that oxidative addition of the aryl halide is the rate determining step of the reaction.¹⁹⁻²¹ It also does not agree with the literature of radical-based reactions, whereby the substituents are not expected to greatly influence the reaction rate and a smaller ρ value would be expected.²² However, the results may align with the work recently reported by Hartwig *et al.* which suggests that oxalamide ligands may be able to exhibit radical character and aid in the oxidative addition of the copper species in the reaction cycle (**Figure 2.19**). If development of radical cation character on the oxalamide ligand occurs, electron withdrawing substituents on the aryl bromide would decrease the ability of the ligand to promote oxidative addition of the aryl bromide to the copper centre.⁷ In addition, a low R^2 value of 0.5569 may indicate that there is not a strong correlation between the substituent effects and the rate of the reaction, which may elude to radical-based processes.

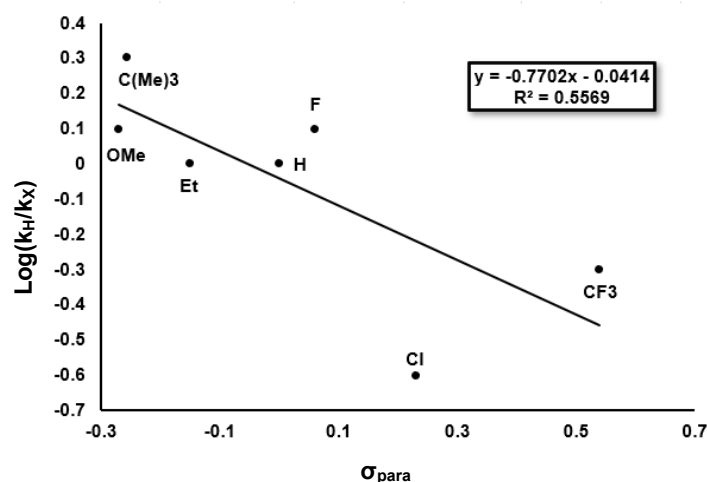
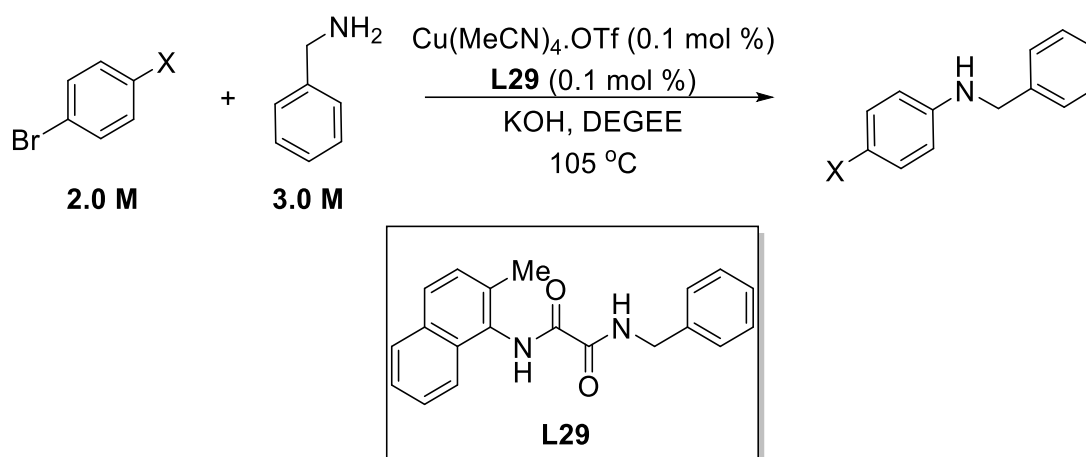


Figure 2.18 Hammett study with different aryl bromide substrates.

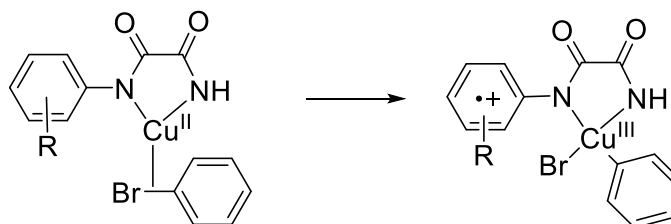


Figure 2.19 Work by Hartwig *et al.* which suggests that oxidative addition of aryl halide is induced by radical character on oxalamide ligands.⁷

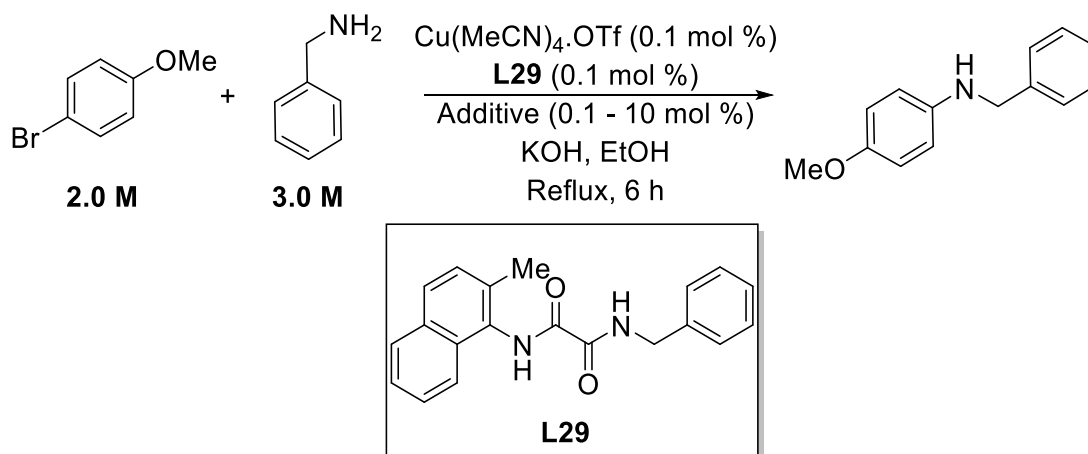
2.2.4.5 Addition of Oxidants and Reductants

As discussed in section 1.4.1, the active catalytic species of the Ullmann C-N cross-coupling reaction is commonly agreed to be a Cu^I complex which is bound to a ligand and nucleophile. If the reaction follows an oxidative addition/reductive elimination pathway, the oxidation state of copper is expected to change from Cu^I to Cu^{III} throughout the reaction. The addition of an oxidant may aid in the formation of higher oxidation state Cu complexes (i.e. Cu^{III}) since they can accept the electrons that would be transferred from the Cu centre. Given that the formation of the Cu^{III} species

may be involved in the rate-determining step of the reaction, an oxidant may be able to facilitate this step and lower the activation barrier for the oxidative addition step.^{23,24} Conversely, a reductant may help to reduce any higher oxidation state complexes to the Cu^I oxidation state. In this instance, reductants could be employed to help prevent catalyst deactivation, for example by reducing Cu^{II} to Cu^I. Disproportionation of Cu^I to Cu^{II} and Cu⁰ is cited as a common cause for catalyst deactivation in the Ullmann reaction.^{1,25} Reductants may also help to increase the rate of reaction by aiding in the reduction of Cu^{III} to Cu^I in the catalytic cycle.^{26–28}

The reductants and oxidants chosen have been previously used successfully in cross-coupling reactions.^{27,29} In particular, the reductant Hantzsch ester was utilised in a Cu-catalysed C-N cross-coupling reaction with sterically hindered nucleophiles.²⁵ However, recent mechanistic insights into the reaction from Blackmond *et al.* determined the reductant was not necessary for a successful reaction.¹⁶

The effect of adding oxidants/reductants can be seen in **Figure 2.20**. Generally, they did not positively improve the reaction yield. Addition of 0.17 M hydroquinone (yellow curve) slightly improved the rate of reaction, but not to a significant extent. Interestingly, addition of Hantzsch ester led to a less successful reaction (purple curve). The reason for this is unclear and it has not been investigated in this work due to time constraints. These results may indicate that an external agent is not required to recycle the copper into more active species.



Symbol	[2.1] ₀ (M)	[2.2] ₀ (M)	[Cu(MeCN) ₄ . OTf] ₀ (M)	[L29] ₀ (M)	[KOH] ₀ (M)	Additive	[Additive] ₀ (M)
●	2.0	3.0	0.002	0.002	2.7	-	-
●	2.0	3.0	0.002	0.002	2.7	PhI(OAc) ₂	0.002
●	2.0	3.0	0.002	0.002	2.7	PhI(OAc) ₂	0.2
●	2.0	3.0	0.002	0.002	2.7	Ascorbic Acid	0.002
●	2.0	3.0	0.002	0.002	2.7	Hydroquinone	0.2
●	2.0	3.0	0.002	0.002	2.7	Hantzsch Ester	0.1

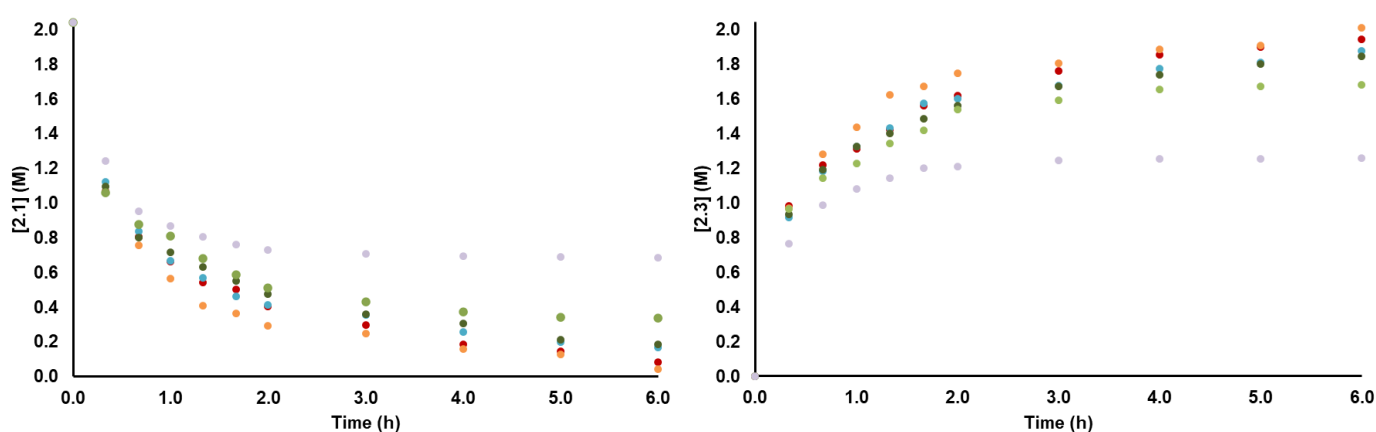
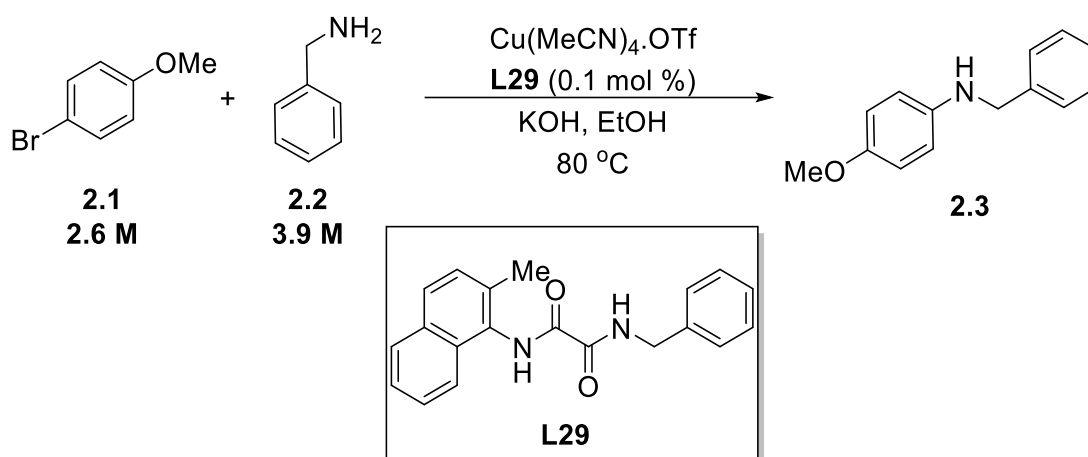


Figure 2.20 The effect of adding oxidants/reductants to the reaction.

2.2.5 Reaction Optimisation

Given that the same excess experiments indicated that a higher loading of **L29** led to a decrease in the extent of catalyst deactivation, it was thought that the copper loading could be decreased if **L29** was kept in excess. For this study, the original conditions reported by Ma *et al.* were used (**Figure 2.21**).⁵ The loading of **L29** was kept constant at 1000 ppm (0.1 mol %), whilst the loading of Cu(MeCN)₄.OTf was decreased. It was observed that the reaction was successful even at copper loadings of 50 ppm, but the yield started decreasing at this loading, reaching a yield of 83 % (entry 5) and a TOF of 1383 h⁻¹. The decreasing yield is likely due to a decrease in reaction rate due to lower copper concentration. To confirm this, the reaction was conducted for 48 hours, after which a yield of 99 % was obtained, confirming that the reaction had not deactivated (entry 9). This led to a high TON of 1.99×10^4 , however a lower TOF of 415 h⁻¹ was obtained, confirming that despite the higher yield and higher catalyst stability, the activity of the catalyst is lower. Decreasing the loading of copper to 25 ppm led to a decreased yield of 53 % which may be due to the rate of reaction decreasing further (entry 11). This was validated by increasing the reaction time to 144

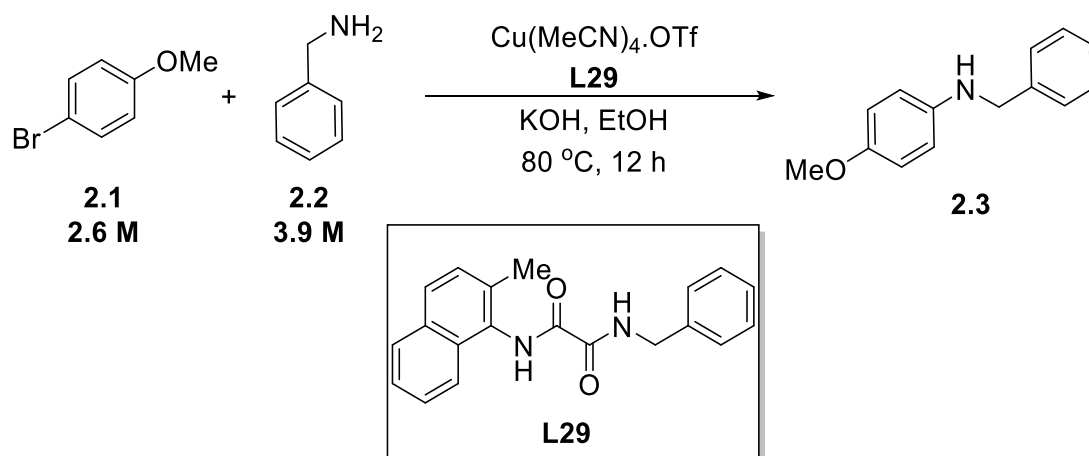
hours which led to a high yield of 92 %. At 5 ppm loading of copper, only 7 % yield of **2.3** formed (entry 13); however, the yield could be improved to 33 % with a large excess of **L29** ($2 \times 10^4 \times \text{Cu}$) which led to a TON of 6.6×10^4 (entry 14), further confirming the high stability of the catalyst. With a TOF of 1375 h^{-1} , this catalyst loading proves to be both highly stable and active in this reaction. Additional attempts to increase the yield by increasing reaction time and **L29** loading was not successful (entries 15 and 16). With the reaction able to proceed at copper loadings of 5 ppm, this may open new pathways for the synthesis of compounds in industry. Typically, the loading of metal catalyst impurities must be between 10 – 20 ppm to be deemed safe for consumption.³⁰ Thus, with loadings of 5 ppm, additional catalyst removal steps can potentially be avoided.



Entry	Time (h)	Cu(MeCN) ₄ .OTf (ppm)	NMR Yield of 2.3 (%)	TON	TOF (h ⁻¹)
1	12	1000	93	923	77
2	12	250	99	3970	331
3	12	100	95	9475	790
4	12	75	85	11300	942
5	12	50	83	16600	1383
6	24	75	95	12600	525
7	48	75	99	13267	276
8	24	50	89	17750	740
9	48	50	99	19900	415
10 ^a	48	50	78	15500	323
11	48	25	52	20600	429
12	144	25	92	36600	254
13	48	5	7	13250	276
14 ^b	48	5	33	66000	1375
15 ^b	144	5	32	64800	450
16 ^b	288	5	34	68800	239

Figure 2.21 1000 ppm = 0.1 mol %. Reactions were performed at a 10 mmol scale based on **2.1** for copper loadings of 1000 – 50 ppm, and a 20 mmol scale for 5 ppm copper. ^aDEGEE used as solvent. ^b**L29** loading increased to 10000 ppm (1 mol %).

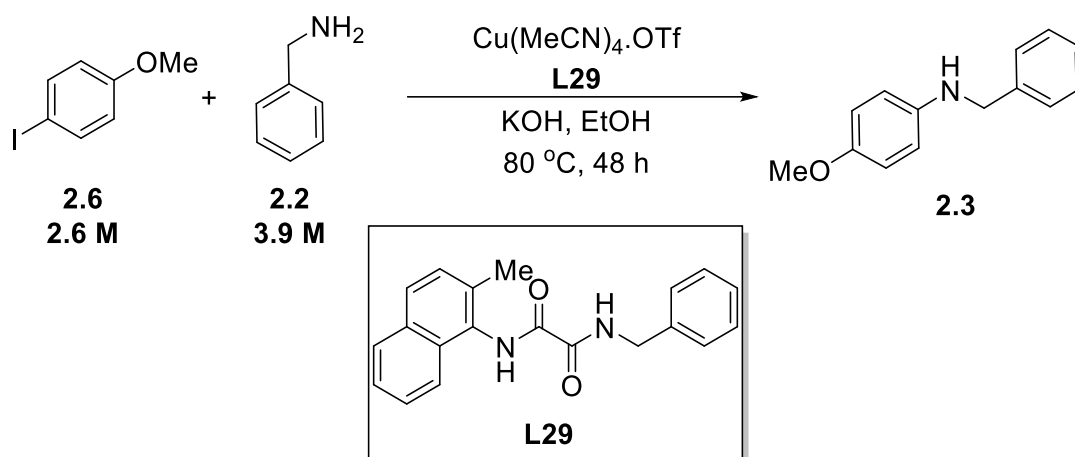
The loading of **L29** was also decreased to determine the effect on reaction yield, but the reactions were not successful and high TONs comparable to those in **Figure 2.21** were not achieved below 750 ppm (**Figure 2.22**). These results may further validate that an excess of **L29** is imperative to a high reaction yield, and this may be due to its role in preventing catalyst deactivation.



Entry	Cu(MeCN) ₄ .OTf (ppm)	L29 (ppm)	NMR Yield of 2.3 (%)	TON	TOF (h ⁻¹)
1	150	750	93	6183	515
2	150	500	89	5933	494
3	50	750	73	14650	1221
4	50	500	9	1750	146
5	50	250	4	800	67

Figure 2.22 Yields obtained from lowering the loading of **L29**. The reactions were performed on a 10 mmol scale based on **2.1**.

The protocol of using a large excess of **L29** was also applied to aryl iodide substrate **2.6**. This was successful as the copper loading could be decreased to as little as 5 ppm, which led to a very high TON of 1.9×10^5 and TOF of 3958 h⁻¹, confirming high catalyst activity under these reaction conditions (**Figure 2.23**).



Entry	Cu(MeCN) ₄ .OTf (ppm)	L29 (ppm)	NMR Yield of 2.3 (%)	TON	TOF (h ⁻¹)
1	5	100	55	109250	2276
2	5	1000	95	190000	3958

Figure 2.23 High TON achieved with 4-iodoanisole (20 mmol scale).

2.2.6 Substrate Scope

The scope of using a large excess of **L29** in the cross-coupling of aryl bromides and amines has been explored. In this case, the conditions reported in **Figure 2.21**, entry 9, have been utilised since they offer the highest yield of **2.3** at the lowest loading of copper (50 ppm) at a reasonable reaction time. A wide range of aryl bromides and primary amines have been explored and the results are presented in **Figure 2.24**.

Various aryl bromide substrates containing both electron-rich and electron-poor substrates in the para- and meta-position reacted successfully with yields over 70 % (**2.3**, **2.7 – 2.10**, **2.22**). It is interesting that employing a CF₃ group in the meta position of the aryl bromide (**2.10**) led to high yields, since in the Hammett analysis, CF₃ had a slow initial reaction rate when employed in the para position. With a lower pK_a when in the meta-position, it may be acting as a better electrophile in the reaction, or a different mechanism could be followed, but more in-depth kinetic studies would be required to understand this. Employing an aryl bromide substrate with an ortho-substituent was not successful, even with increased loading of **L29** and a longer reaction time, likely due to steric hindrance (**2.11**). Coupling with furfurylamine as the amine substrate was less successful than benzylamine (**2.12 – 2.15**, **2.20**), but the yields could be improved by increasing the loading of **L29**. Lower nucleophilicity of furfurylamine could be due to the presence of the electron-withdrawing oxygen atom on the aromatic ring. Additionally, the opposite trend in aryl bromide substrates can be seen, whereby the presence of an electron withdrawing phenyl group greatly enhanced the reaction viability (**2.14**), while electron donating OMe and Me groups led to lower product yields (**2.12**, **2.13**). Various functionalised benzylamine substrates were tested; those with electron withdrawing groups led to high yields (**2.17**, **2.18**), but **2.19**, which contained an electron donating -OMe group, was formed in lower yields. This could suggest the electronic effects of the amine has an important effect on the reaction. Performing Hammett analysis with benzylamine derivatives would help to determine this. Coupling with 5- and 6-membered secondary (hetero)cyclic amines was less successful (**2.16**, **2.21**), which is surprising due to their higher nucleophilicity than benzylamine, as were less nucleophilic amines such as *p*-phenylenediamine (**2.23**). Aliphatic hexylamine reacted well with both para and meta substituted aryl bromides (**2.24**, **2.25**).

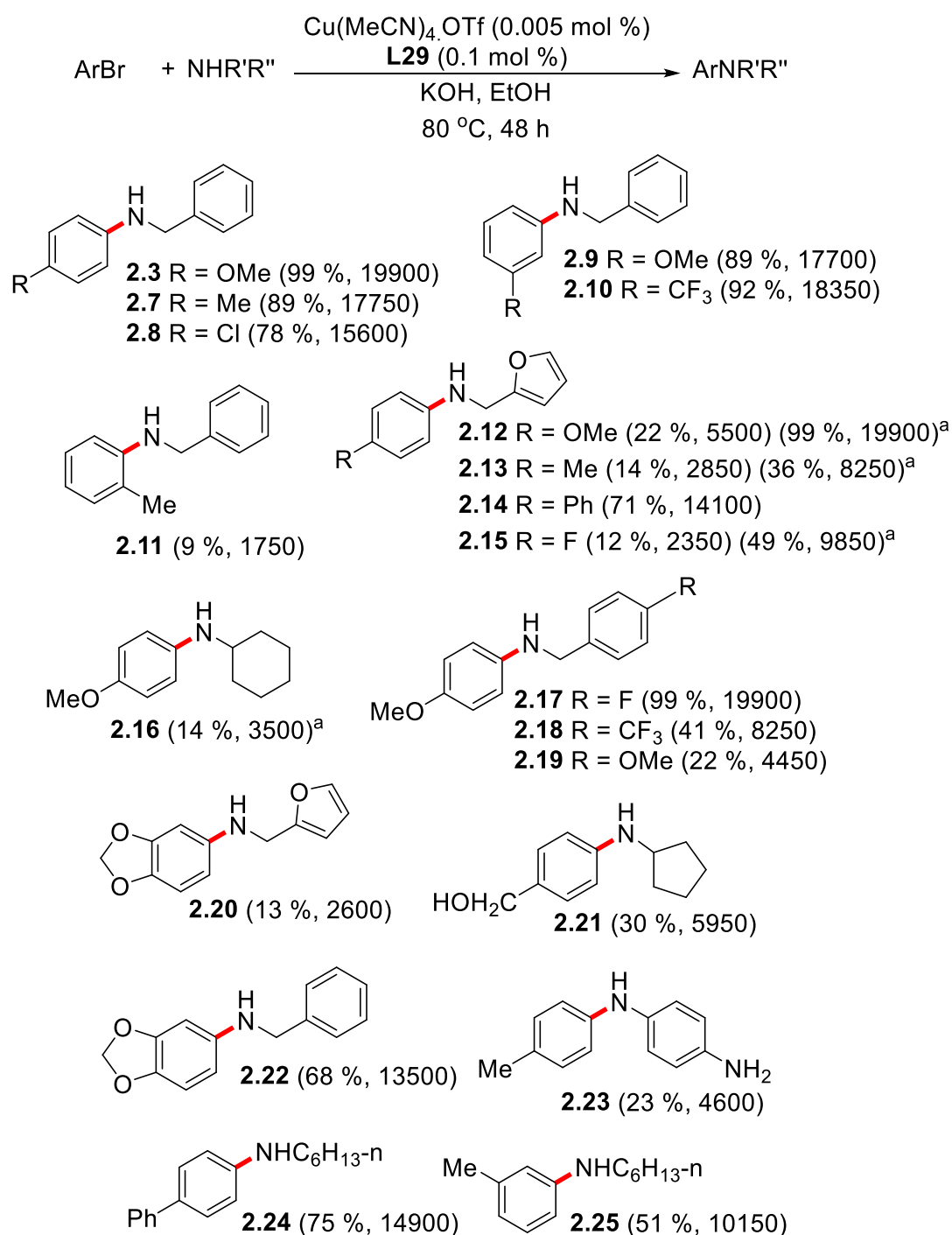


Figure 2.24 Substrate scope for Ullmann C-N coupling with 0.005 mol % (50 ppm) Cu. Yields are reported as NMR yields using naphthalene as an internal standard. Reactions performed at a scale of 5 mmol based on aryl bromide substrate. ^a**L29** loading was increased to 1 mol %.

2.3 Conclusions and Future Work

To conclude, a Cu(MeCN)₄.OTf/**L29** catalysed cross-coupling reaction between 4-bromoanisole and benzylamine has been extensively studied to gain insights into the

reaction mechanism. The reaction employed KOH and EtOH as the base and solvent which allowed for homogeneous reaction conditions, thus mitigating any mass-transfer effects which would invalidate the kinetic data. Additionally, low loadings of copper and ligand could be investigated (0.1 mol %), which has not been widely explored in current literature. Concentration profiles of 4-bromoanisole and the product were produced by ^1H NMR, and visual analyses were applied to derive kinetic information.

Kinetic studies revealed that catalyst deactivation occurred in the reaction at lower loadings of ligand. With increased ligand present, the extent of deactivation was decreased. This led to the conclusion that the ligand may be able to prevent catalyst deactivation at higher loadings, or it is being consumed or transformed during the reaction.

With the knowledge that a higher loading of ligand led to less deactivation occurring, the loading of copper was decreased to as low as 5 ppm to achieve product **2.3** in 34 % yield. This led to a high TON of 6.88×10^4 . While this reaction required 144 hours to reach this yield, the reaction with more reactive 4-iodoanisole gave the desired product in 48 hours at a yield of 95 % and TON of 1.9×10^5 , leading to a high TOF of 3958 h^{-1} . Currently the highest reported TONs for the aryl amination reaction with aryl bromides is 980, which was reported by Ma *et al.* in the original reaction that this work is based on.⁵ For reactions with aryl iodides, Ma *et al.* reported a TON of 9500 and a TOF of 396 h^{-1} in the same work, while Norrby *et al.* previously reported a TON of 8.6×10^4 and TOF of 3583 h^{-1} .^{4,5} Thus, the TONs and TOFs reported in this work exceed those previously reported, and highlight the importance of employing mechanistic insights in the reaction optimisation process.

A reaction scope with loadings of 50 ppm copper and 1000 ppm ligand was explored, and led to high yields in 16 examples. The reaction conditions employed utilise a cheap and readily available base and solvent system, with economical quantities of copper, thus making it desirable for industrial applications.

The reaction was first order in [4-bromoanisole] and zero order in [benzylamine] and [KOH]. This confirmed that the aryl bromide is present in a kinetically meaningful step in the reaction and the benzylamine may not be present in the transition state for the rate determining step. The reaction was found to be first order in copper and ligand prior to catalyst deactivation occurring. Addition of radical scavenger TEMPO inhibited the reaction which may indicate the presence of a radical based pathway. A Hammett study indicated that electron donating substituents on the aryl halide increase the reaction

rate, but the correlation between substituents and reaction rate is weak, which may elude to radical-based processes occurring.

The information derived from kinetic studies has aided in the improvement of the reaction by allowing higher TONs to be achieved with extremely low loadings of copper. However, certain aspects of the mechanism remain unclear. The influence of [Cu] and [L29] on the reaction rate is unclear, particularly individual effects, so further experiments with different [Cu] and [L29] may give more insights into ligand effects and catalyst deactivation. Investigations into the initial reaction rates of reactions with oxidants and reductants may give an insight into catalyst activation processes. A radical clock experiment confirm if an aryl radical forms during the reaction, or if radical character is present on the oxalamide ligand. Hammett analysis with amine **2.2** and various substituents would help to determine if the amine is present in the rate determining step of the reaction.

Additionally, the exact role of oxalamide ligand **L29** is still unclear. **Chapter 3** endeavours to explore the nature of **L29** throughout the reaction and in particular its role when using low 5 ppm loadings of copper.

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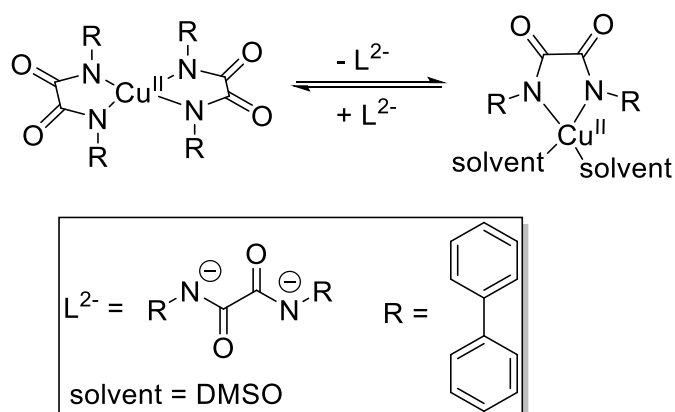
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3 Exploring the Role of Oxalamide Ligands in the Ullmann C-N Cross-Coupling Reaction

3.1 Introduction

While mechanistic insights into the Ullmann reaction can aid in the improvement of reaction conditions by allowing for optimisation of substrate/catalyst concentrations and prevention of catalyst deactivation, kinetic studies provide limited details about the role of the ligand in the reaction mechanism. To delve deeper, spectroscopic studies are required to better monitor changes occurring during the reaction. On rare occasions, it has been possible to isolate complexes of copper and ligand bound together, and for these complexes to be studied in cross-coupling reactions to determine how the reaction proceeds¹⁻³. While studies of Cu-oxalamide complexes are rare, a recent report by Hartwig *et al.* has shown the successful isolation and characterisation of copper-oxalamide complexes with ligand bis-(2-phenylphenyl)oxalamide (BPPO, **Scheme 3.1**).⁴ The isolation of these compounds allowed for insights into its interactions between aryl halide and phenoxide substrates, and indicates which species are likely present in the catalytic cycle. It was also possible to characterise the oxidation state of copper in the active catalytic species which led to the determination that the active species was in fact a Cu^{II} species rather than the commonly thought Cu^I species.



Scheme 3.1 Cu-oxalamide structures isolated by Hartwig *et al.*⁴

Previously researchers have attempted to gain insights into the role of ligands through kinetic and spectroscopic studies. As highlighted in section 1.4.2, Buchwald *et al.* suggested that the ligand plays a key role in preventing multiple ligation of the amine (**Chapter 1**, section 1.4.2, **Scheme 1.36**).⁵ Reports from Taillefer *et al.* and Hartwig *et al.* support the finding that the ligand is able to increase electron density on the copper centre and thus increase the oxidation potential, which in turn promotes and facilitates

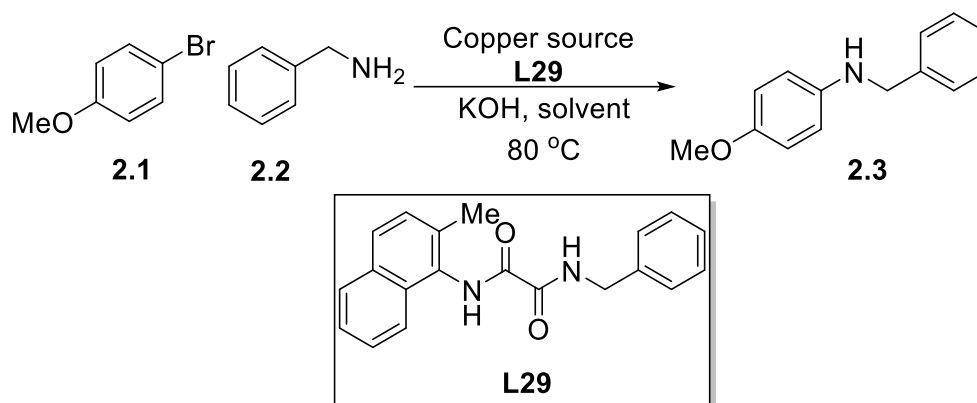
the oxidative addition of the aryl halide, which is generally agreed to be the rate-determining step (**Chapter 1**, section **1.4.1**, **Scheme 1.26**).^{2,6} In the study by Hartwig *et al.*, ligands which were more electron donating provided faster reaction rates.² In more recent work, Hartwig *et al.* highlighted that certain ligands can enhance the reaction rate in C-O cross-couplings; however, they did not correlate these findings with the structure of the ligands and they did not provide in-depth studies around this.⁷ Additional works by Buchwald and Blackmond highlight the impact more electron donating ligands can have on the reaction rate.^{3,8}

Work by Davies *et al.* in 2018 and 2022 investigated the effects of different ligands by comparing reaction rates.^{9,10} There is little discussion correlating the structure of the ligand and its reaction performance; however, it was identified that certain ligands may be able to prevent catalyst deactivation. In similar work, Hartwig *et al.* has highlighted that some ligands may have a detrimental effect on the reaction.² In the case of Hartwig's work, the concentration of a Cu^{II} complex (which is thought to form due to catalyst deactivation) at the end of reactions with different ligands was compared. As certain ligands led to a greater concentration of the Cu^{II} complex, it was thought that these ligands may not be able to prevent deactivation of the catalyst as effectively as other ligands.

In addition to the work presented here, there has been very little reported of the structure-activity relationship with oxalamide ligands, and in particular, insights into their enhanced reaction rate compared to other ligands. It was suggested by Morarji *et al.* that oxalamide ligands bind via the two oxygen atoms in the oxalamide backbone, while later, Roy *et al.* suggested they bind via the two nitrogen atoms.^{11,12} These are discussed further in **Chapter 1**, **Figure 1.11**, and **Scheme 1.53**. Neither study provide sound experimental evidence for these suggestions however, and they do not investigate the success of the ligands compared to other ligands. Recent work by Hartwig *et al.* proposed that oxalamide ligands with a phenyl moiety can exhibit radical character and promote the oxidative addition of Cu^I to Cu^{III}.¹³

These works highlight the necessity for further insights into the role of the ligand through a range of techniques. It is possible that ligands are able to exhibit a range of roles during the reaction; 1) they may increase electron density on the copper centre which in turn would help to facilitate the oxidative addition step of the reaction, 2) they may aid in the stability of Cu^I/Cu^{III} intermediates which may help to form the active catalytic species and may prevent catalyst deactivation by pathways such as disproportionation.

As seen in **Chapter 2**, kinetic studies suggest that ligand **L29** may be able to prevent deactivation, or it may be degraded during the reaction shown in **Scheme 3.2**. This chapter seeks to gain information on the role of **L29** in the reaction through EPR, CV, NMR and kinetic studies.



Scheme 3.2 The reaction with **L29** which was investigated in this work.

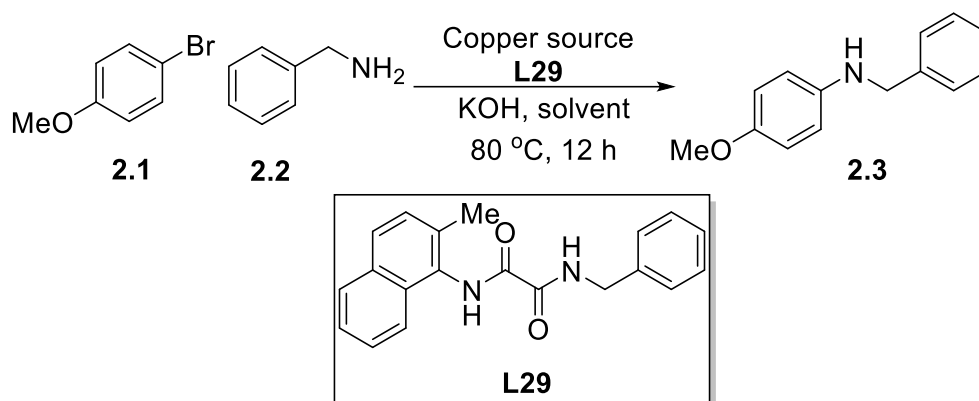
3.2 Results and Discussion

3.2.1 Electron Paramagnetic Resonance Spectroscopy

Electron Paramagnetic Resonance (EPR) Spectroscopy is a useful technique to observe oxidation states of transition metal catalysts during a reaction. It allows for the detection of compounds with unpaired electrons by detecting the interaction of magnetic dipoles with an applied magnetic field and microwave radiation.¹⁴ Cu^{II} species have a d^9 configuration, resulting in an unpaired electron, and thus can be detected by EPR. The interaction between oxalamide ligands and copper species can be investigated by EPR to determine if the ligand plays a key role in the formation or recycling of the active catalytic species, which is widely accepted to be a Cu^{I} complex which would have a d^{10} configuration, and hence would not be observed by EPR.

It was vital that the EPR measurements were taken under reaction conditions, since interactions between the ligand and copper species could be greatly affected by temperature and solubility. In order to perform the experiment safely at $80\text{ }^{\circ}\text{C}$, EtOH could not be used. Instead, 1-propanol was chosen as a suitable solvent – it showed similar reactivity in the cross-coupling reaction examined in **Chapter 2**. CuBr_2 was chosen as the copper source, since it has high solubility in 1-propanol and showed good reactivity with **L29** in the reaction in **Figure 3.1** (entries 4 and 5). Mixtures of CuBr_2 , **L29** and various reaction components were analysed by EPR. The sensitivity of the measurements are compromised due to a high measurement temperature of $80\text{ }^{\circ}\text{C}$, which leads to a decreased rate of spin-lattice relaxation times. Spin-lattice

relaxation results from the interaction of Cu^{II} species with the thermal vibrations of the lattice. As thermal energy increases, the rate of relaxation decreases, resulting in broader EPR signals with a lower signal-to-noise ratio.¹⁵ The Cu^{II} species present in the samples can be identified by a peak at 314.5 mT.



Entry	Copper Source	Solvent	NMR Yield (%)
1	Cu(MeCN) ₄ .OTf	EtOH	93
2	Cu(MeCN) ₄ .OTf	1-propanol	92
3	Cu(MeCN) ₄ .OTf	^t BuOH	81
4	CuBr ₂	EtOH	88
5	CuBr ₂	1-propanol	88

Figure 3.1 Yields obtained with different copper sources and solvents.

First, the detection limit of CuBr₂ in 1-propanol was established (**Figure 3.2**). Cu^{II} species could be detected from 3 mM, which is higher than the amount used in the standard conditions reported by Ma *et al.*¹⁶ and those optimised in **Chapter 2**. A concentration of 10 mM Cu was chosen so that any decreases in Cu^{II} concentration could be detected. The other reaction components were also added at a concentration of 10 mM. While this concentration of copper is not representative of the reaction conditions in **Chapter 2**, it will highlight the stoichiometric interactions between Cu and oxalamide ligand **L29** which would occur during the catalytic cycle.

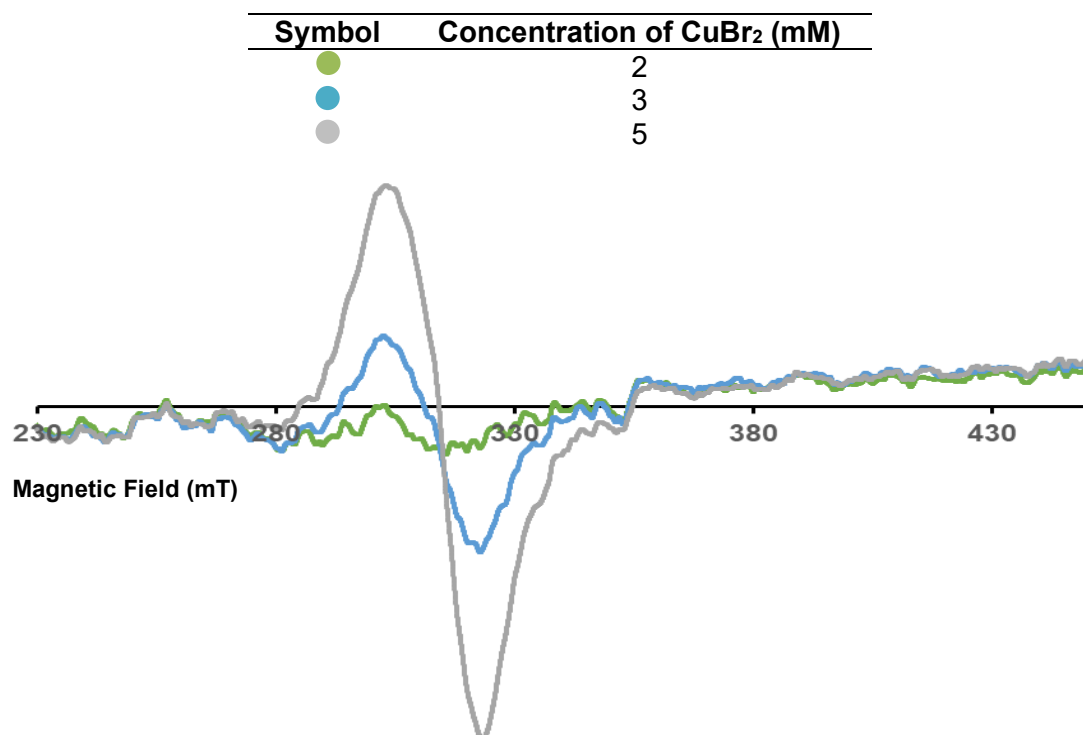


Figure 3.2 Detection limit of CuBr₂ in EPR.

EPR spectra were then obtained of various mixtures of reaction components. Comparing the spectrum obtained for a solution of CuBr₂ with that of CuBr₂ and **L29**, it can be seen that addition of **L29** to CuBr₂ did not lead to any change in the EPR spectrum (**Figure 3.3**, red curve). This indicates that the ligand does not aid in the reduction of Cu^{II} to Cu^I on its own. It could be that **L29** needs to be deprotonated before it can bind to the copper centre, and upon addition of KOH, there is a decrease in the Cu^{II} peak, which suggests that deprotonated **L29** may aid in the formation of the active species, and that the deprotonated ligand can bind to the Cu centre (**Figure 3.3**, green curve). However, this finding is dispelled by the results obtained with the mixture of CuBr₂ and KOH on their own, which led to complete disappearance of the Cu^{II} peak (**Figure 3.3**, orange curve). This indicates that the base is capable of reducing Cu^{II} species, even in the absence of ligand, to a Cu^I species. If the active catalytic species is a Cu^I species (as suggested by previous literature), the base may be responsible for the recycling of the active catalyst during the reaction cycle.

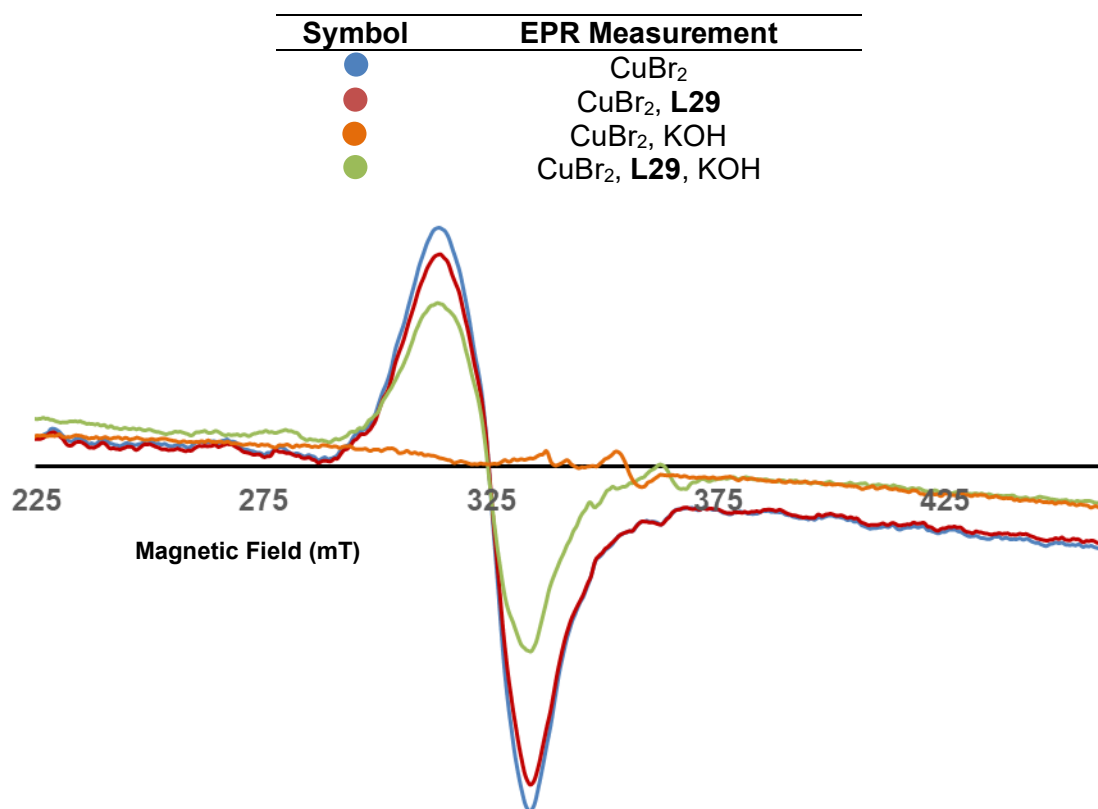


Figure 3.3 EPR spectra obtained for various reaction mixtures with 1-propanol as a solvent.

To validate these findings, EPR measurements were also performed in EtOH and ^tBuOH solvents (at 70 °C due to equipment constraints). EtOH is the reaction solvent, and may interact differently with KOH and **L29** compared to 1-propanol. However, as seen in **Figure 3.4**, KOH is able to reduce the Cu^{II} species without the presence of **L29** (orange curve), and **L29** is unable to reduce Cu^{II} alone (red curve).

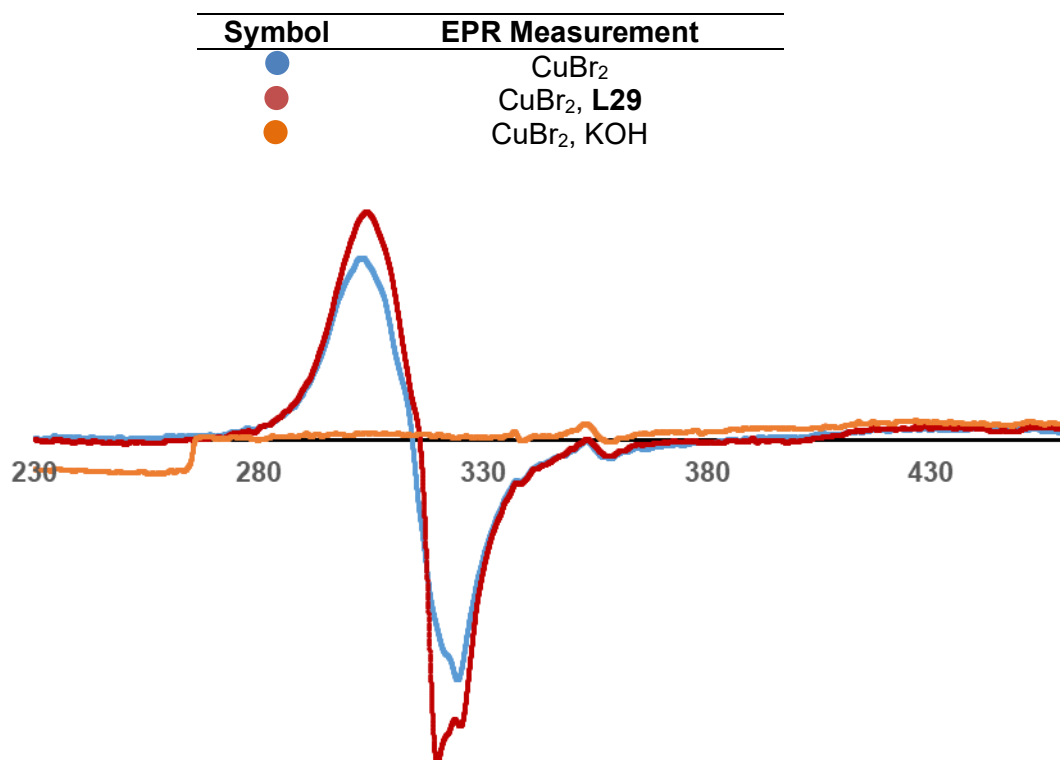


Figure 3.4 EPR spectra obtained for samples with EtOH as a solvent.

Both 1-propanol and EtOH may be susceptible to β -hydride elimination in the presence of a strong base such as KOH. Therefore, ^tBuOH was employed which would not be able to undergo β -hydride elimination (**Figure 3.5**). Significant line broadening was observed which may be due to the lower polarity of ^tBuOH.¹⁷ Despite this, it is clear that KOH is still able to reduce Cu^{II} (orange curve) which confirms the base is able to aid in the formation and/or recycling of the active catalytic species. KOH has been previously used as a reducing agent in the formation of Cu^I nanoparticles from a Cu^{II} precursor which demonstrates its potential to aid in the formation of the active Cu^I catalytic species.¹⁸ Further work should focus on investigating the original reaction conditions which utilise Cu(MeCN)₄OTf as the copper source, to determine if indeed Cu^{II} species form and if the base is responsible for their re-entry into the catalytic cycle. Additionally, addition of reagents after formation of Cu^I species would confirm if the species being formed after addition of KOH is the active catalytic species.

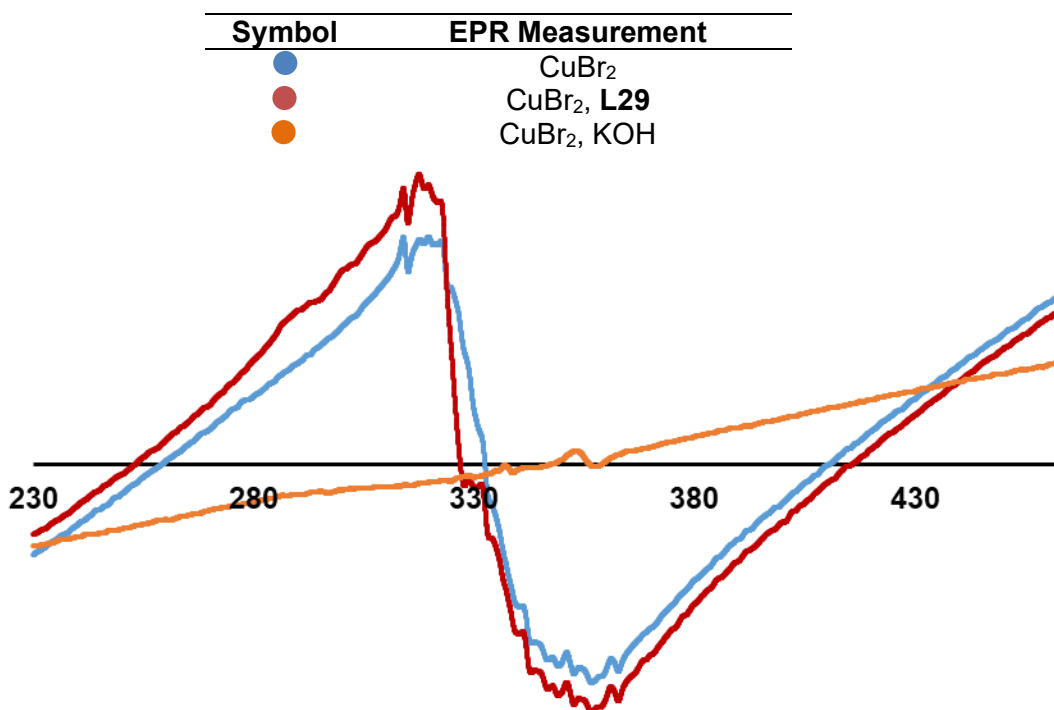


Figure 3.5 EPR spectra obtained for samples with ^tBuOH as solvent.

3.2.2 Cyclic Voltammetry

Cyclic voltammetry (CV) can be utilised to determine changes in the oxidation and reduction potential of metal complexes in catalytic reactions.¹⁹ By addition of the reaction components to the copper species Cu(MeCN)₄OTf, any changes in redox potential can be identified. CV measurements were taken under reaction conditions at 75 °C to avoid any differences in temperature and solubility, with EtOH as the solvent (the temperature was kept below boiling to prevent noise in the measurements). KOH was used as the supporting electrolyte due to limited solubility of other commonly used salts. The measurements were taken under an N₂ atmosphere to remove any interference from oxygen. The copper species was added at a concentration of 5 mM due to no detection at lower concentrations, substrates **2.1** and **2.2** were added at a concentration of 1.0 M and KOH was added at a concentration of 1.5 M (**Figure 3.6**).

The results are highlighted in **Figure 3.7**. The redox process is quasi-reversible since there are peaks during the positive and negative sweeps of potential, but with a large ΔE_p (~200 mV) (**Figure 3.7**, a). The peak at -0.24 V corresponds to the oxidation of Cu⁺ to Cu²⁺, while the peak at -0.58 V corresponds to the reduction of Cu²⁺ to Cu⁺.²⁰ There is a smaller second peak at +0.16 V which has not been identified, but it may correspond to a second copper species in equilibrium. With addition of **L29**, there is no significant shift in oxidation or reduction potentials of the copper species (**Figure**

3.7, b), however, the impurity at +0.16 V is not present in this spectrum. This may indicate that **L29** is able to stabilise the Cu^I species in solution. Upon addition of 4-bromoanisole, an increase in ΔE_p is observed, which suggests coordination of aryl bromide to copper may have occurred (**Figure 3.7**, c). On addition of benzylamine, a second peak at +0.20 V is observed, which indicates another Cu species in equilibrium has formed, perhaps due to displacement of the ligand and binding of the amine (**Figure 3.7**, d).

A CV measurement of **L29** without the presence of Cu(MeCN)₄.OTf was also taken to determine if the ligand itself was redox active. As seen in **Figure 3.7** e, no peaks were observed, thus it is concluded that the ligand is not redox active.

Together these results suggest that the ligand plays a key role in stabilising the Cu^I complex, however further investigations are required to understand how the ligand interacts with copper species during the entire catalytic cycle, and in any off-cycle species.

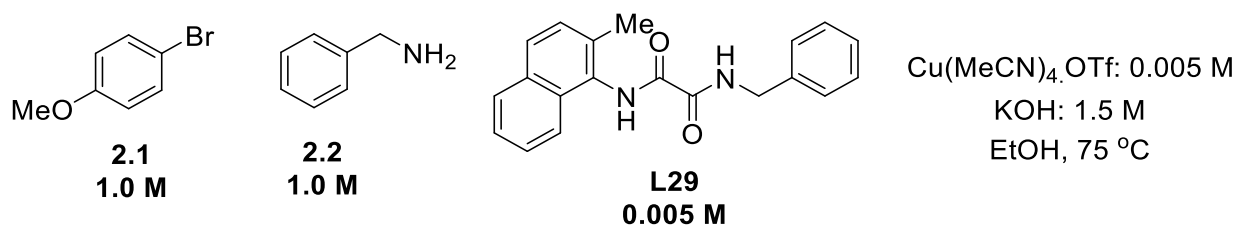


Figure 3.6 The conditions employed for CV measurements.

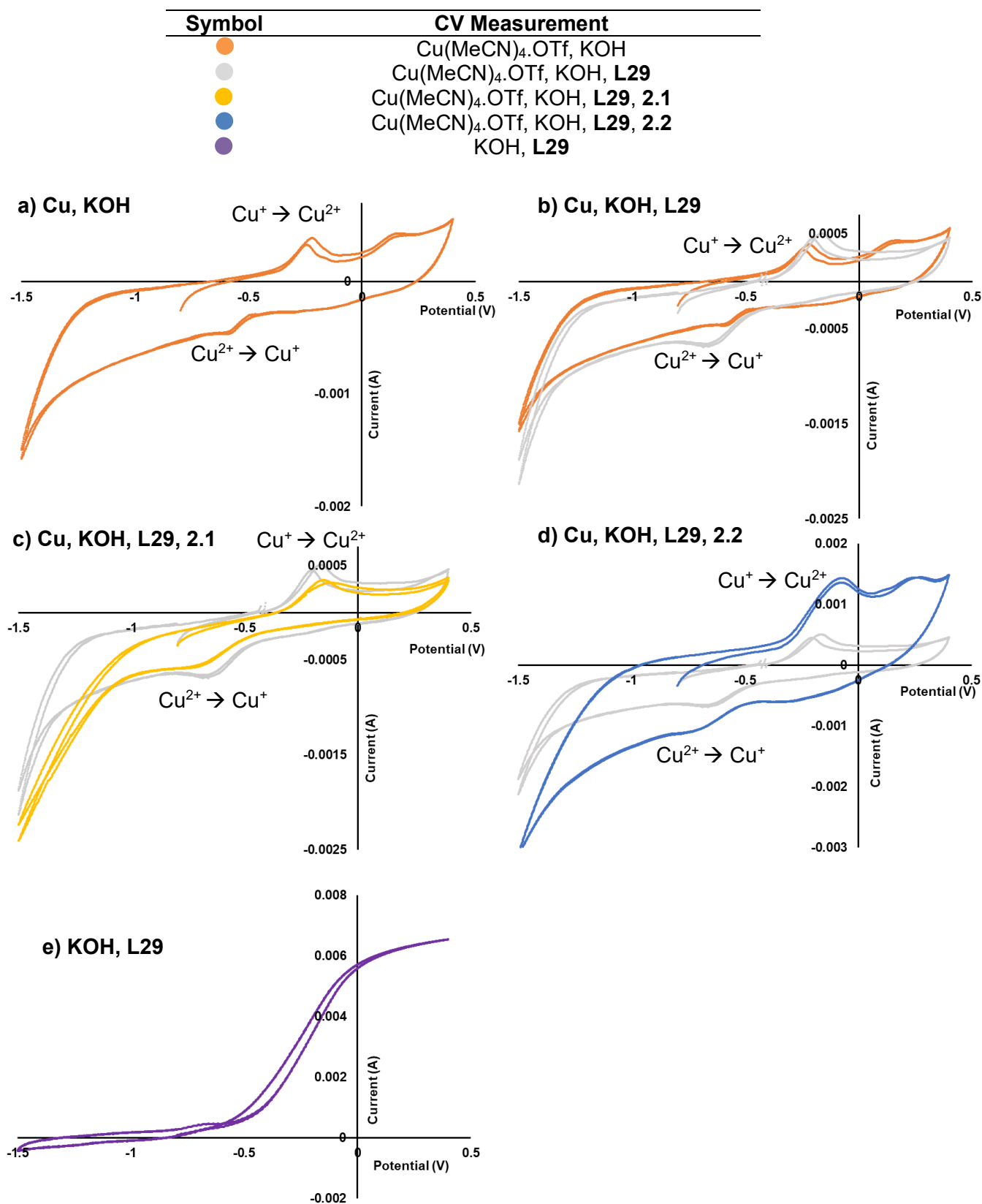
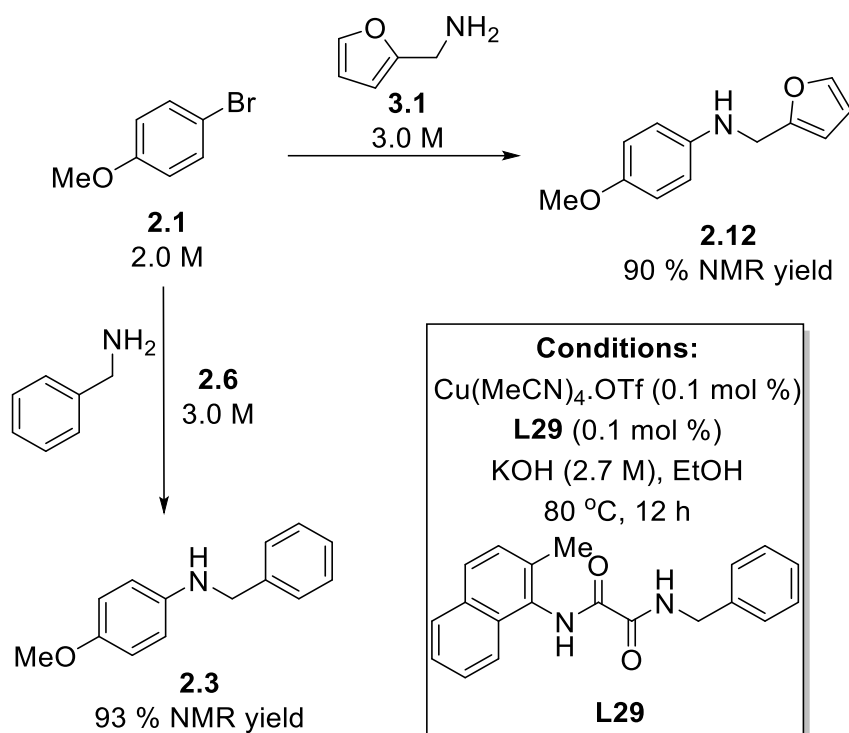


Figure 3.7 Cyclic voltammograms obtained for the copper-catalysed C-N cross-coupling reaction. A scan rate of 0.1 Vs⁻¹ was applied with a potential range from -1.5 to +0.5 V. A silver wire quasi-reference electrode was used.

3.2.3 Mass Spectrometry

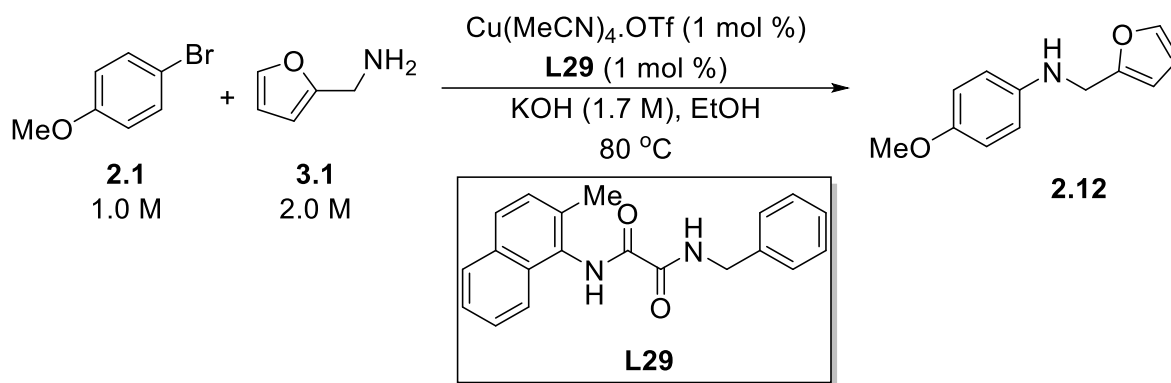
Mass spectrometry is a useful technique to identify complexes which are present in the reaction mixture. It can also help to identify unknown intermediates of a reaction. A set-up was employed in this work whereby aliquots of a reaction mixture were injected into a mass spectrometer via direct infusion. Both negative and positive ion modes were employed to detect the various species which may be present.

To avoid overlapping signals of the benzylamine nucleophile and the benzyl-moiety present in **L29**, furfurylamine was chosen as the amine, since it showed similar reactivity to benzylamine (**Scheme 3.3**).



Scheme 3.3 Furfurylamine exhibited similar reactivity to benzylamine under standard reaction conditions.

Lower concentrations of substrates **2.1**, **3.1** and KOH were employed to ensure solubility of KOH at room temperature, which would prevent solid formation in the transfer tubes. Higher loadings of copper and **L29** were employed to improve chances of their detection. Thus, the reaction in **Scheme 3.4** was employed.



Scheme 3.4 The reaction with **L29** analysed by mass spectrometry.

The deaminated portion of **3.1**, copper source $\text{Cu}(\text{MeCN})_4\cdot\text{OTf}$ and the triflate fragment, and major product **2.12** could be observed in the spectra obtained (**Figure 3.8**). However, no assignments to copper or ligand species could be made.

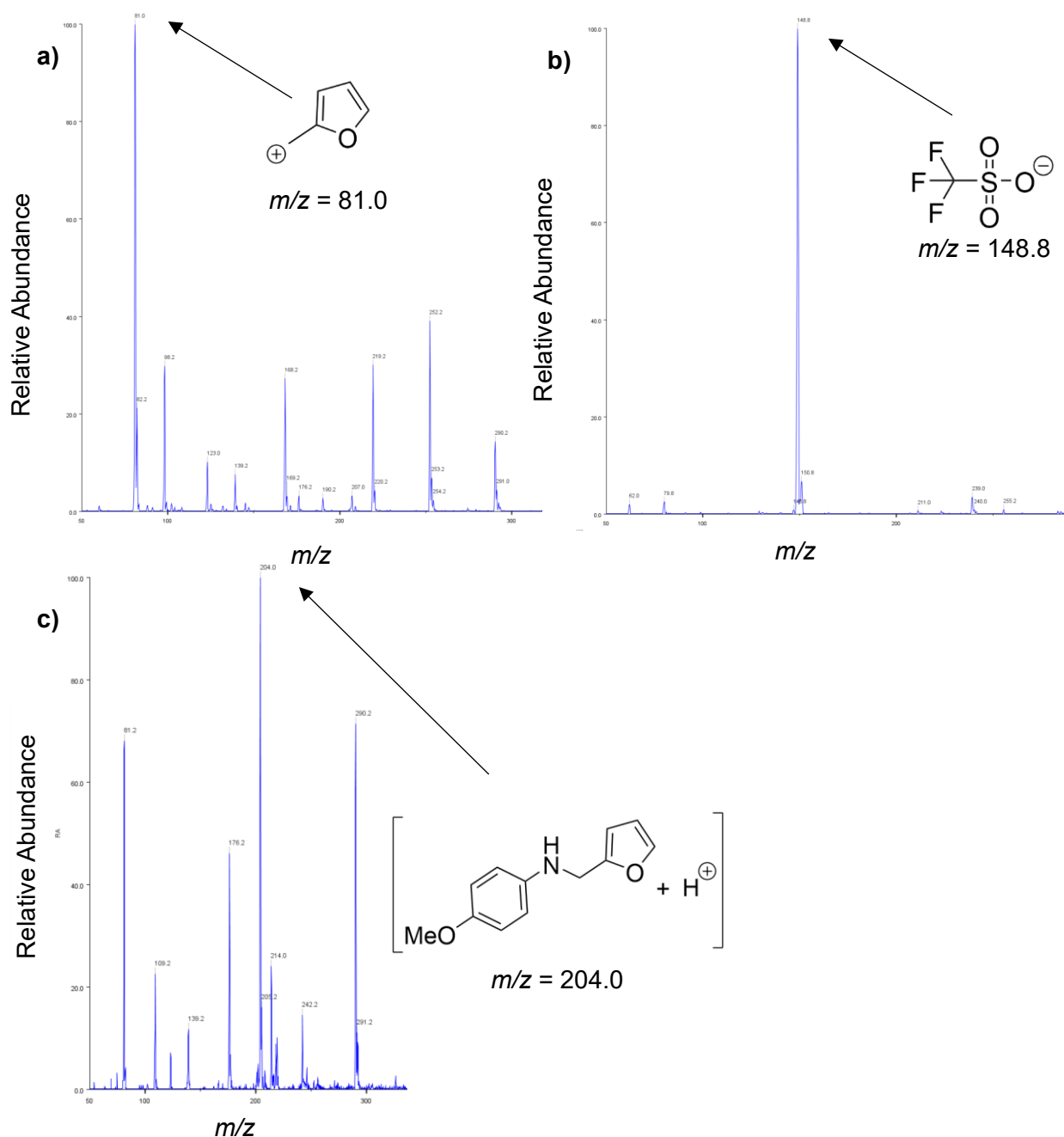
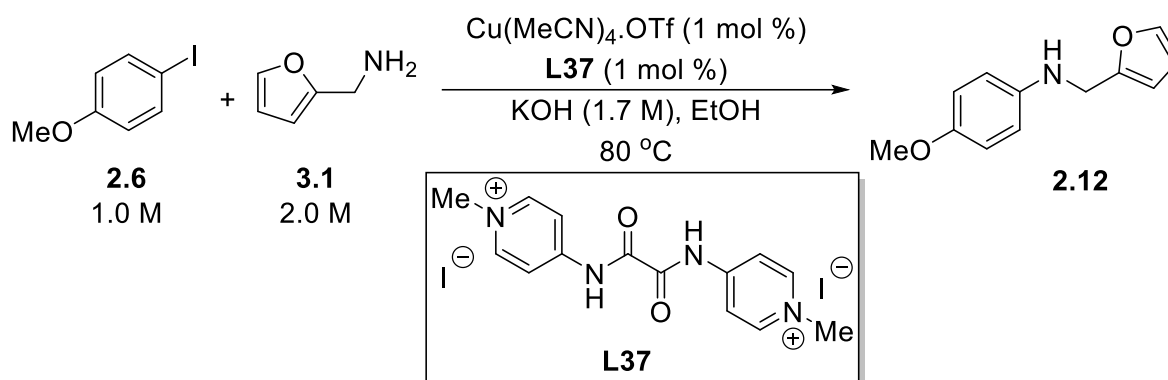


Figure 3.8 Mass spectra obtained with samples containing **L29**. a) Sample was diluted in MeCN and measurement taken in positive ion mode. b) Sample was diluted in MeCN and measured in negative ion mode. c) Sample was measured in positive ion mode.

Due to the neutrality of **L29**, it can be difficult to detect in mass spectrometry. Charged ligand **L37** was applied successfully to the original reaction with benzylamine (this will be discussed further in **Chapter 3**) and due to its charged nature, it was thought to be more visible in mass spectrometry analysis. Thus, the reaction in **Scheme 3.5** was also explored with direct infusion mass spectrometry. In positive ion mode, there was

evidence of a **L37**-Cu complex, without the presence of the I⁻ ions. The *m/z* value of 167.0 suggests to the coordination of Cu with **L37** (**Figure 3.9**). The peak exhibits the expected isotopic pattern for Cu species, with two peaks with relative abundance of 25 and 8. The exact mode of binding cannot be exclusively determined by mass spectrometry, so further work would be required to investigate whether the ligand binds via O,O, N,N or N,O atoms.²¹



Scheme 3.5 The reaction with **L37** analysed by mass spectrometry.

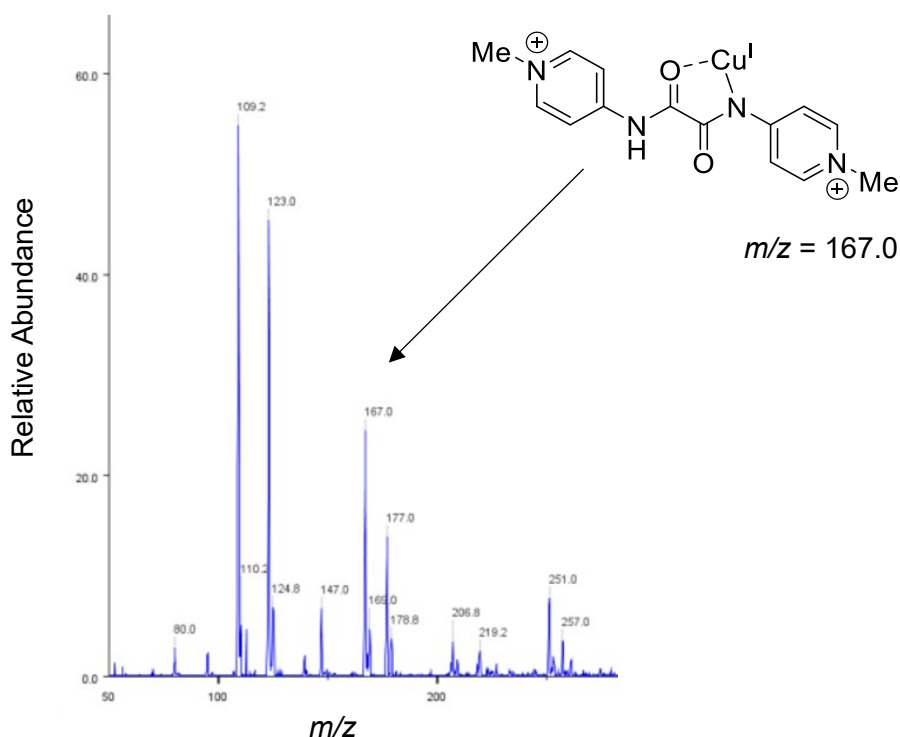


Figure 3.9 Mass spectrum of sample containing **L37** measured in positive ion mode.

In situ mass spectrometry has been reported in literature previously, in particular works by Shyu *et al.* were discussed in **Chapter 1** sections **1.4.1** and **1.4.3.2**. Their spectra showed peaks with *m/z* values corresponding to complexes such as a L-Cu-L complex

and a copper complex containing a ligand, aryl halide and deprotonated amine. Bisamido-Cu complexes were also observed in negative ion mode. Attempts to assign peaks based on these possible structures were made, as well as complexes bound by common ions such as Na⁺ and K⁺, but no corresponding *m/z* values were found.

3.2.4 The Effect of Substituents on Oxalamide Ligands

It has been suggested by previous studies that substituents on ligands can have a significant influence on the success of the reaction. As discussed in **Chapter 1**, section **1.4.2**, Hartwig *et al.* found that electron donating substituents enhanced the efficiency of the ligands employed.² In order to probe whether the electronic effects of oxalamide ligands can influence the reaction, a range of oxalamide ligands based on **L29** with different substituents on the benzyl-ring were synthesised and employed in the C-N cross-coupling reaction. Since electronic effects of ligands can be subtle, higher density data points were required to determine any changes to the reaction. Therefore, these reactions were monitored by in situ calorimetry alongside NMR sampling. Due to the nature of the equipment, the reactions were performed in sealed vials, so 1-propanol was chosen as a solvent to ensure the reaction could run safely at 80 °C. 4-iodoanisole was chosen as the aryl halide substrate to ensure reactions were complete in the monitored time period. With **L29**, the reaction was complete in 4 hours with 4-methoxyphenol and 1-methoxy-4-propoxybenzene by-products formed in 3 % and 2 % yield respectively. The raw data obtained from the calorimeter has been tau-corrected to account for the time between when the heat is released from the reaction and the signal is detected by the calorimeter. A correction for the heat of mixing was not required since addition of the copper/ligand stock solution did not change the heat output of the solution.

Repeat reactions with **L29** consistently produced ΔH_{rxn} (reaction enthalpy) within a 5 % error margin ($\Delta H_{rxn} = 198 \pm 9.9 \text{ kJ mol}^{-1}$), which suggests the heat flow from the side reactions forming the side-products is negligible compared to the reaction forming the major product, **2.3**. The heat flow from these reactions also correlated to the calculated conversion from offline ¹H NMR sampling, which validates calorimetry as an in situ monitoring technique (**Figure 3.10**).

The ligands shown in **Figure 3.10** were synthesised and applied to the C-N cross-coupling reaction, and compared to **L29**. Ligands **L38** to **L41** have not been previously reported or synthesised. As seen in the table in **Figure 3.11**, the difference in fractional conversion of **2.6** is not significant. However, looking at the graphical rate equations produced based on the calorimetric data, there is a clear difference in the rate of the

reactions. In particular, reactions with ligands **L39** and **L40** have a slower rate than those with **L29**, **L38** and **L41**. This indicates that ligands with electron withdrawing substituent groups on the benzyl-ring have a decelerating effect on the reaction. This is confirmed by a Hammett analysis which employed the rates of the reactions at 15 minutes to determine if there was a correlation between the substituents and the reaction rate (**Figure 3.12**). There is a weak negative correlation which confirms electron withdrawing substituents decrease the reaction rate, but the electronic effects of the substituents are likely not potent due to their distance from the oxalamide backbone, where any electronic effects on the copper centre will be greater. Alternatively, the weak correlation may indicate that radical character is present in the ligand, as suggested by Hartwig. Nevertheless, these findings are consistent with the work produced by Hartwig *et al.*² It may indicate that the ligand plays a key role in increasing the electron density on the copper centre, which would allow for more facile oxidative addition to take place.

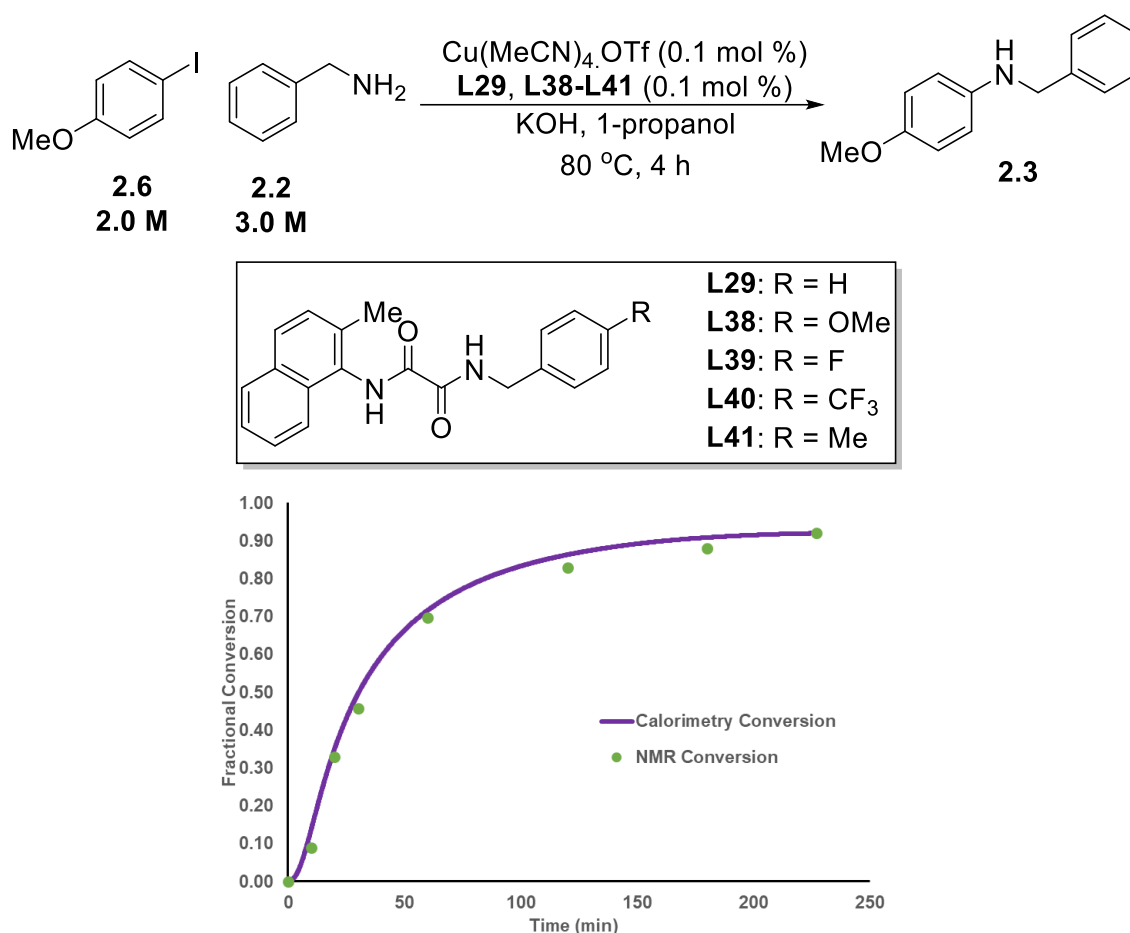


Figure 3.10 Reaction heat-flow and offline sampling were in agreement.

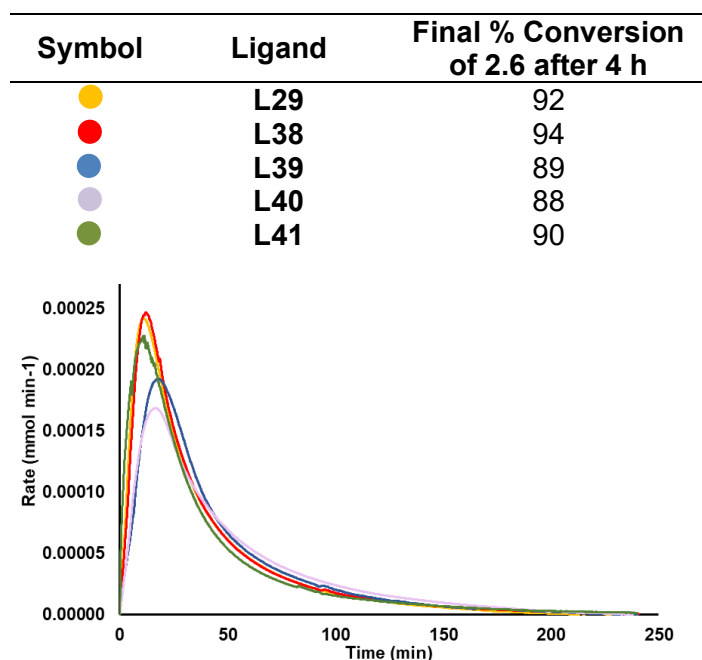


Figure 3.11 The graphical rate equations when different oxalamide ligands were employed.

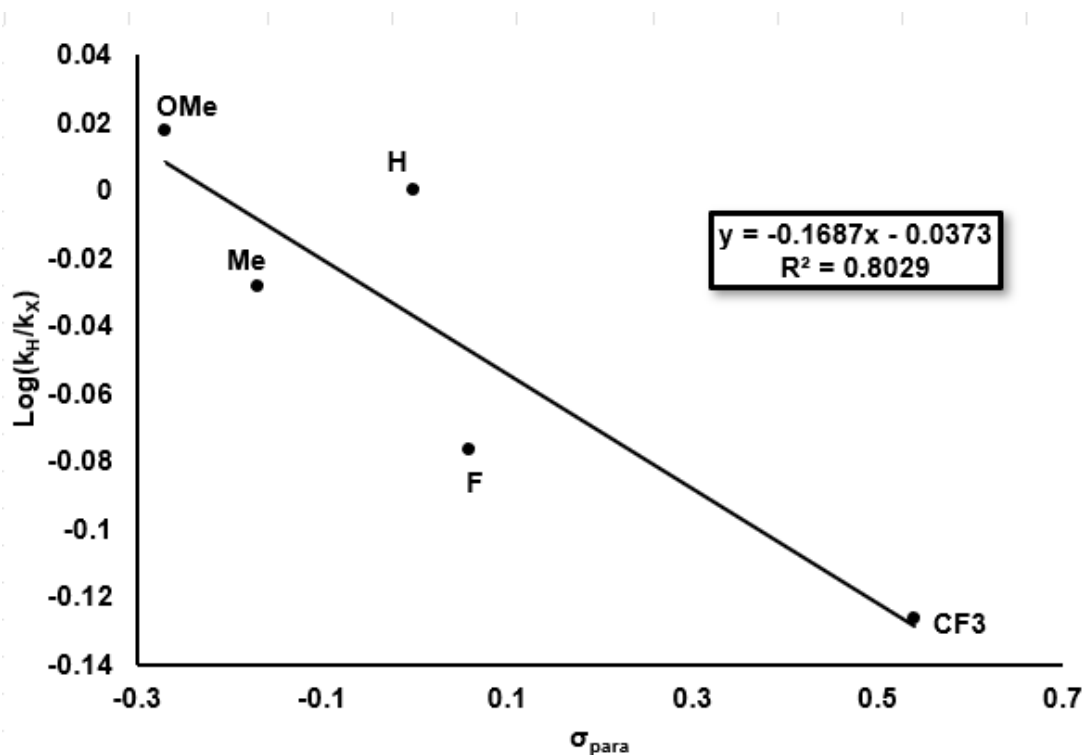
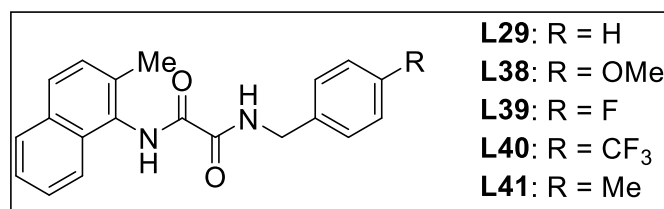
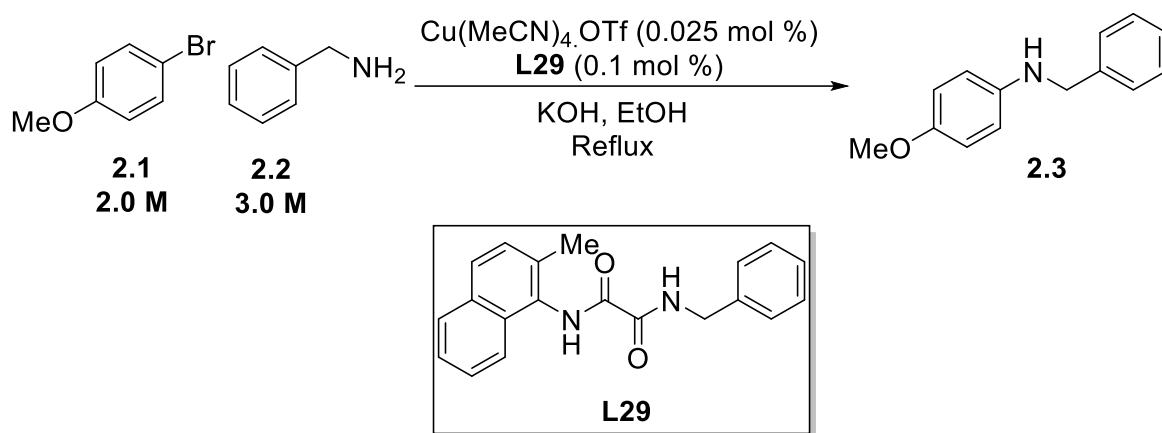


Figure 3.12 Hammett plot with oxalamide ligands with different substituents on the benzyl ring.

3.2.5 Multiple Addition of Ligand

With the same excess experiments outlined in **Chapter 2**, it was noted that **L29** may be a key component in the deactivation of the reaction at lower concentrations of copper and ligand. It was highlighted that **L29** could be consumed or converted during the reaction, and thus at lower concentrations its supply would deplete quicker, leading to more deactivation. Alternatively, the ligand could be aiding in the prevention of catalyst deactivation, and at higher concentrations this effect could be more prevalent. To probe this, an experiment was performed under the deactivation conditions (0.0005 M Cu(MeCN)₄OTf and **L29**) whereby a second portion of ligand was added after deactivation started occurring in the reaction. As seen in **Figure 3.13**, the reaction was able to restart after a second addition of **L29**, since the rate of reaction increases upon addition of **L29** at 2.5 hours and the concentration of product formed increases. This indicates that the ligand may be being consumed or transformed into an inactive form, or it is able to recycle the catalyst after deactivation to a more active form. From the data presented in the sections above, in particular the data from EPR measurements and calorimetry, it appears that while the ligand affects the electron density of the copper centre, it may not be responsible for the formation of the active catalytic species in this reaction. Thus, it is likely that the ligand is being consumed and its efficacy is compromised during the reaction.



Symbol	$[\text{Cu}(\text{MeCN})_4\text{OTf}]_0$ (M)	$[\text{L29}]_0$ added at $t = 0$ h (M)	$[\text{L29}]_0$ added at $t = 2.5$ h (M)
●	0.0005	0.0005	-
●	0.0005	0.0005	0.0005

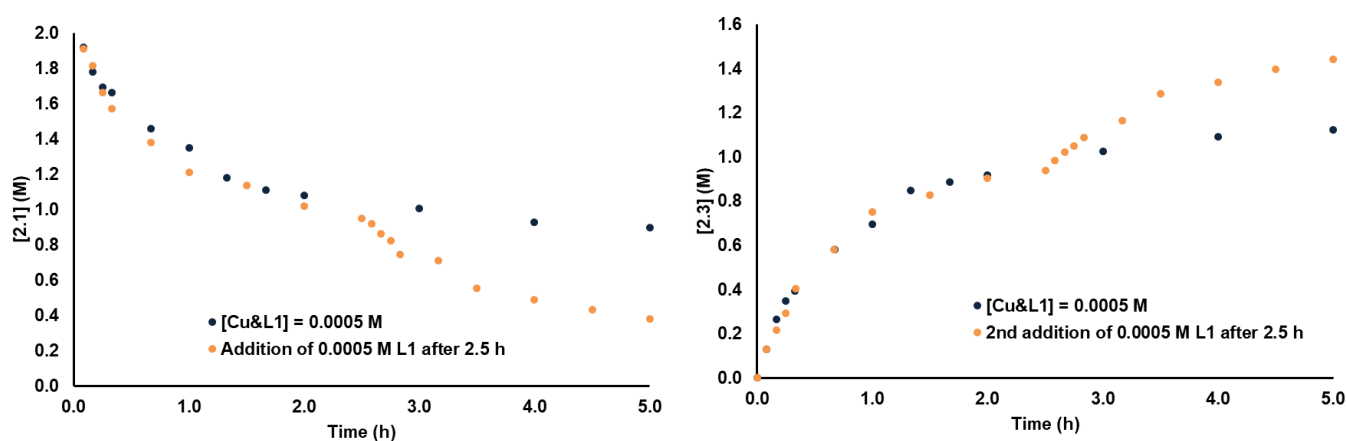


Figure 3.13 Multiple addition of **L29**.

3.2.6 NMR Studies with Fluorine-Tagged Ligand

Previously unreported ligand **L39** (Figure 3.14) has been employed to probe the interaction between the oxalamide ligand and the various reaction components. ^{19}F NMR can be utilised since it is a sensitive technique which can allow for the monitoring of minor changes to compound structures. In addition, due to only one fluorine environment being present in **L39**, any changes will be simplified in the ^{19}F NMR spectrum compared to the ^1H or ^{13}C NMR spectra and thus can be easily spotted. **L39** was stirred overnight in CDCl_3 , with the addition of various reaction components as outlined in Figure 3.14. A ^{19}F resonance peak corresponding to **L39** is seen between -114.0 and -114.5 ppm. It is evident that both 4-bromoanisole and H_2O did not react

with **L39**, since there is no shift in the resonance peak compared to the spectrum for **L39**, and no additional peaks. There was a slight shift with both solvents DEGEE and EtOH, but with a difference of 0.5 ppm this is not thought to be significant. The addition of both KOH and benzylamine led to the observation of additional peaks. For addition of KOH, an additional peak at -116.4 ppm is seen, while with addition of benzylamine, peaks at -115.1 and -116.3 ppm are observed. The peaks at -116.4 and -116.3 ppm likely correspond to 4-fluorobenzylamine (its ^{19}F spectrum exhibits a peak with the same splitting pattern at -116.4 ppm, **Figure 3.15**) which may form in small amounts via hydrolysis in the presence of KOH, and by exchange with benzylamine to form **L29** in the presence of benzylamine.²²

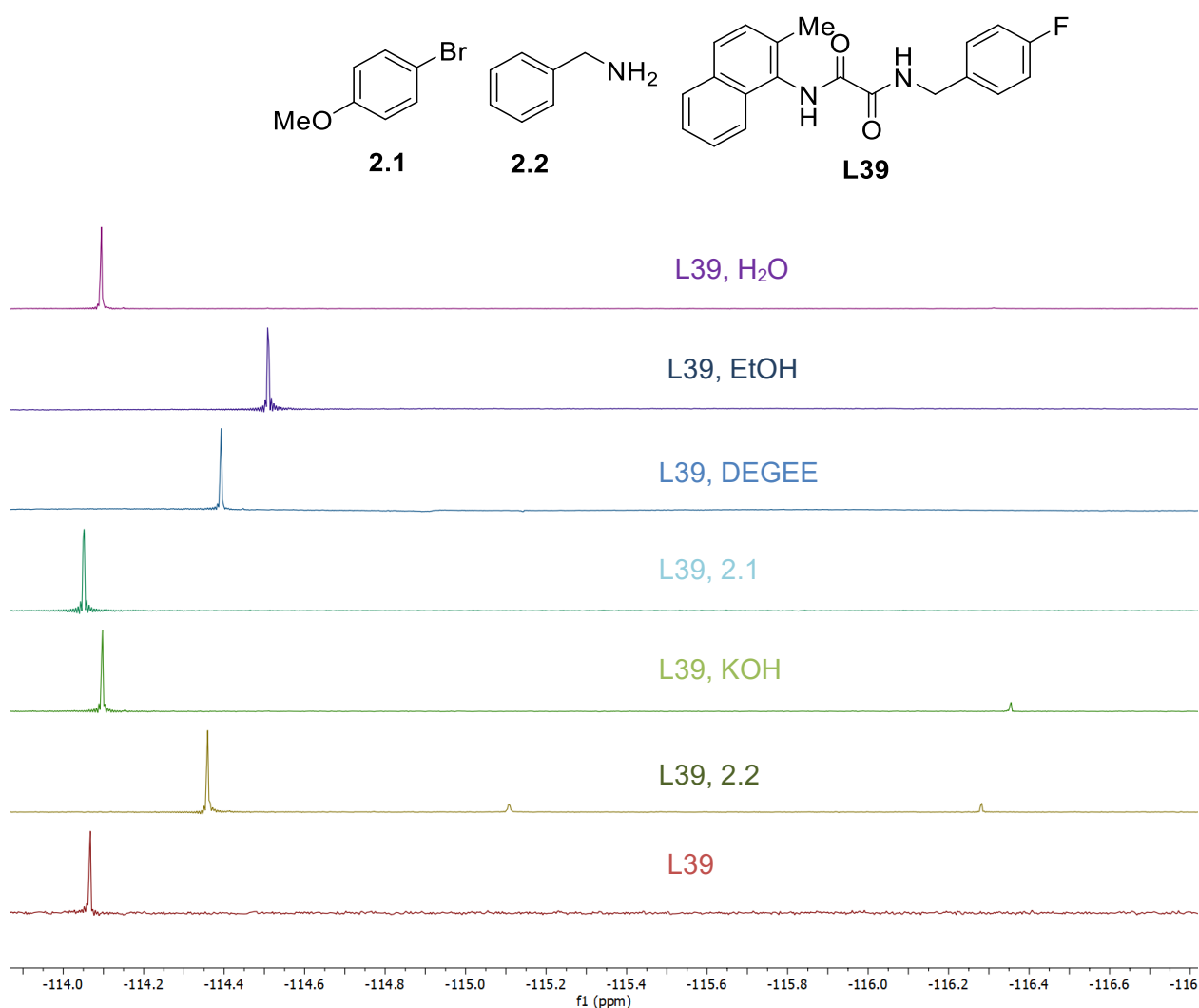


Figure 3.14 ^{19}F NMR spectrum of various mixtures with **L39** in CDCl_3 .

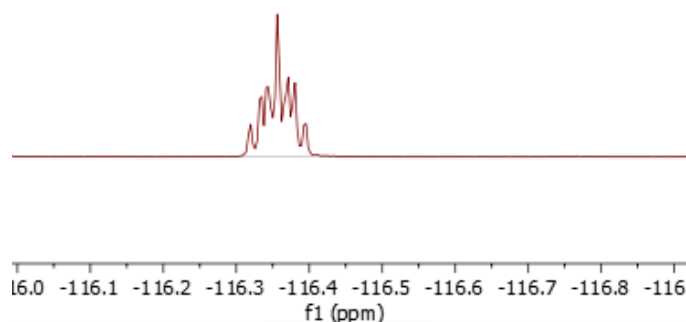


Figure 3.15 ^{19}F NMR spectrum of 4-fluorobenzylamine in CDCl_3 .

The mixture of **L39** with benzylamine was heated to 50 °C and stirred overnight again to induce further formation of degradation product. The nature of the additional peaks were then investigated by ^1H NMR. There were additional peaks at 8.41 and 4.87 ppm which correspond to *N*-benzylidenebenzylamine, a degradation product of benzylamine, but there was no evidence of ligand decomposition products and the peak in the ^{19}F NMR spectrum at -115.11 ppm could not be characterised. Further work should focus on quantifying the amount of **L39** remaining after the reaction, e.g. by addition of an internal standard.

3.2.7 NMR Studies with **L29**

Inspired by the possibility that benzylamine leads to the consumption of oxalamide ligands, further investigations were employed with **L29**. **L29** was stirred in EtOH and an excess of benzylamine at reflux for one week. Upon cooling, a solid precipitate formed which was collected and characterised by ^1H NMR and GC-MS. Evidence of a second species in addition to **L29** was observed due to the presence of a second doublet at 4.52 ppm (**Figure 3.16**) next to the doublet at 4.63 ppm which corresponds to the CH_2 of the benzyl moiety in **L29**. ^1H , ^{13}C , DOSY, COSY and TOCSY NMR and GC-MS suggest that structure **3.2** forms by reaction of ethanol with **L29** in the presence of a base. The filtrate was also characterised by ^1H NMR, but there was no evidence of degradation species.

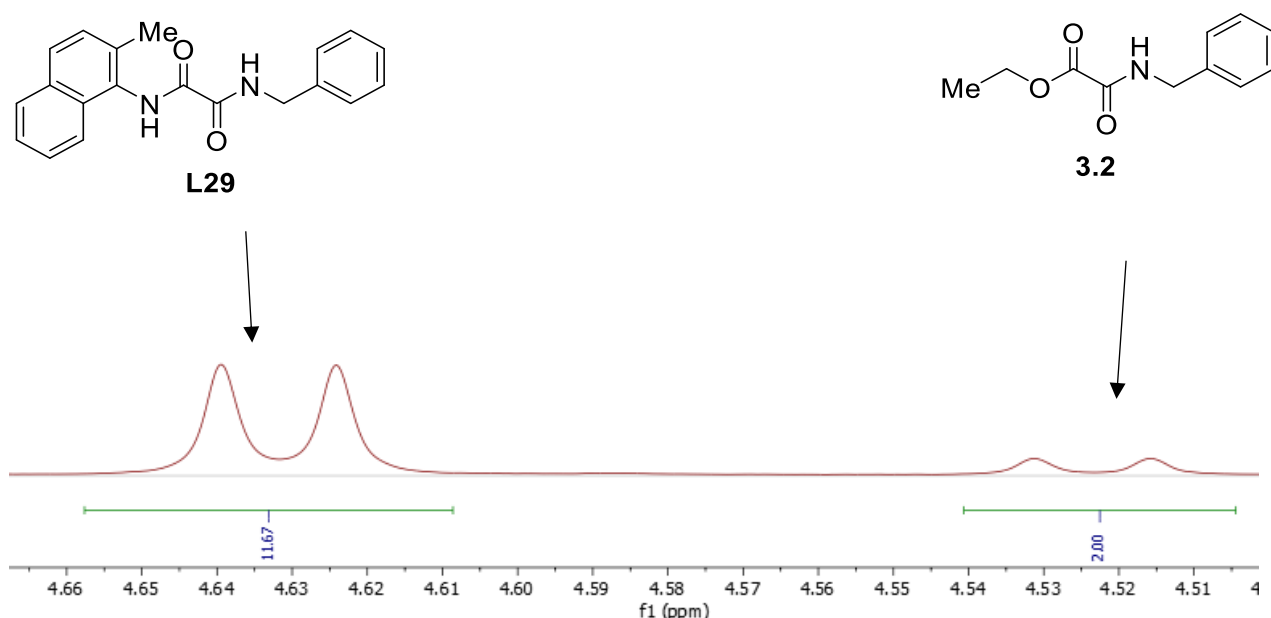


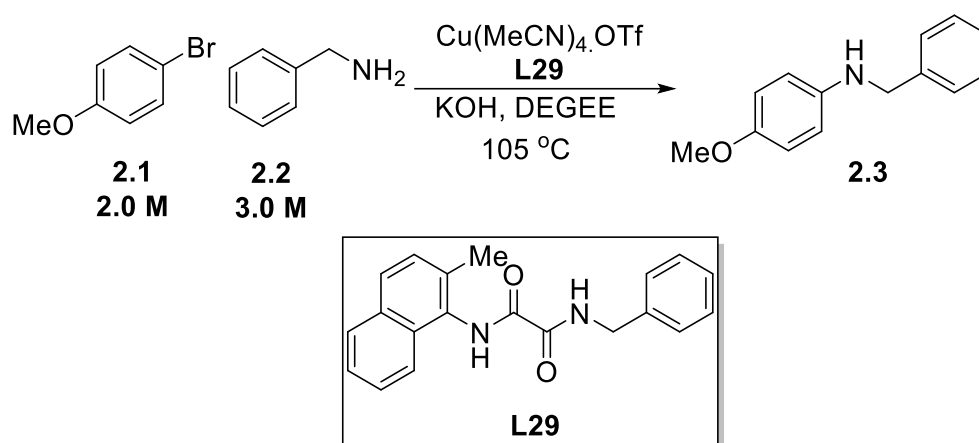
Figure 3.16 ^1H NMR spectrum of precipitate in CDCl_3 showing two doublets corresponding to the CH_2 group in **L29** and **3.2**.

Since **3.2** seemed to form in small quantities, even with a reaction time of one week, it was thought that a stronger base such as KOH which is used in the cross-coupling reaction could enhance the formation of **3.2** in a shorter time frame. Thus, **L29** was stirred in EtOH with excess KOH and benzylamine for 6 hours. After washing with acid, the precipitate was collected, dried and characterised by ^1H NMR. Resonances within the spectrum corresponded only to pure **L29** and did not correspond to any decomposition products. The filtrate was also collected, the organic phase dried and solvent removed. NMR analysis did not show evidence of any degradation products in the filtrate.

These findings suggest that **L29** is not being consumed within the reaction time frame in the presence of excess base and benzylamine. Further experiments are required to probe the degradation nature of **L29**. For example, the addition of Cu to the mixture of EtOH, KOH, benzylamine and **L29** would determine whether Cu catalyses the formation of **3.2**. In addition, stoichiometric reactions with benzylamine, KOH and EtOH may demonstrate interactions that occur within the catalytic cycle; however, low solubility of **L29** in EtOH can prevent this.

3.2.8 Initial Rate Investigation

The influence of the concentration of **L29** on the initial reaction rate with low copper loadings of 50 ppm (0.005 mol %) was investigated according to the conditions in **Figure 3.17**, whereby the initial reaction rate, k_{obs} , corresponds to the gradient of the graph. The conditions of 0.005 mol % $\text{Cu}(\text{MeCN})_4\text{OTf}$ and 0.1 mol % **L29** (orange graph) are representative of the optimised conditions highlighted in **Chapter 2** section **2.2.5** and an initial rate of 0.1539 Ms^{-1} is observed. With 0.005 mol % copper loading and 0.75 mol % ligand loading, an increase in the initial reaction rate is observed, with a k_{obs} of 0.4065 Ms^{-1} (pink graph). Increasing the concentration of **L29** 10-fold to 7.5 mol % did not show a large increase in the initial reaction rate (green graph), leading to a k_{obs} of 0.5139 Ms^{-1} . This may indicate that the reaction is saturated in the ligand at these concentrations. The rate of reactions with 0.005 mol % copper are much slower than that with 0.1 mol % copper (1.8564 Ms^{-1}) which indicates the concentration of copper may have a large influence on the reaction rate.



Symbol	$\text{Cu}(\text{MeCN})_4\text{OTf}$ (mol %)	L29 (mol %)
●	0.1	0.1
●	0.005	0.1
●	0.005	0.75
●	0.005	7.5

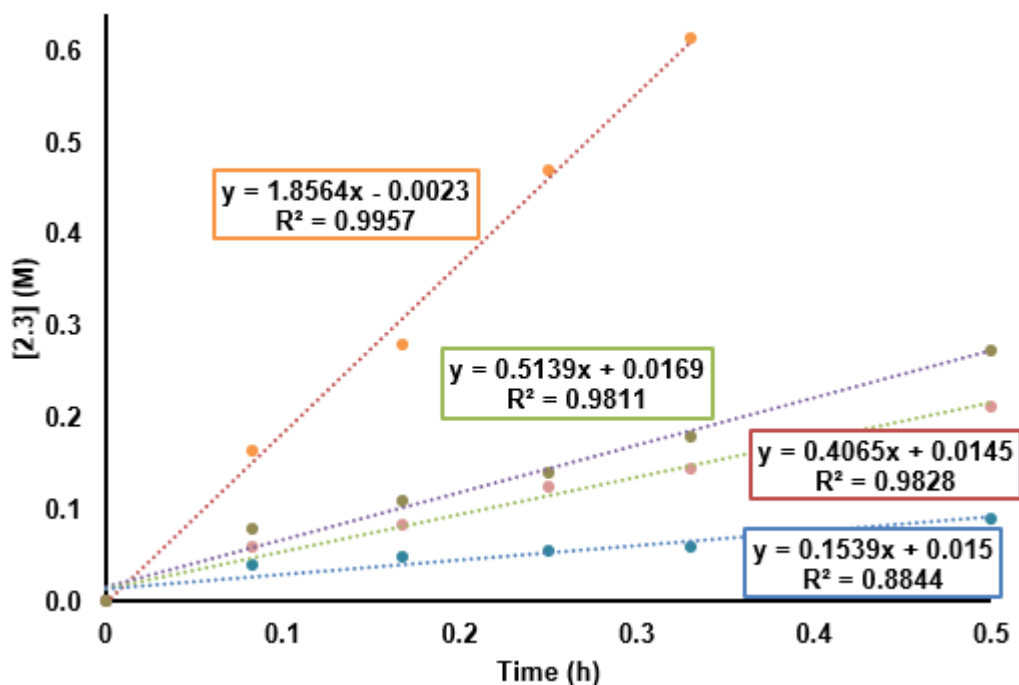


Figure 3.17 The affect on initial reaction rate with different concentrations of **L29**.

3.3 Conclusions and Future Work

Oxalamide ligands are some of the most active ligands to have been reported in the Ullmann C-N cross-coupling reaction, but the reason for their reactivity has not been widely explored. In this chapter, various techniques have been employed to try to determine the key role of oxalamide ligands in Ullmann cross-coupling reactions.

EPR measurements determined that the ligand is not capable of reducing Cu^{II} species into Cu^{I} species alone, the latter of which is widely accepted to be the active catalytic species. It also indicated that the base, KOH, may aid in the reformation of the active catalytic species as it is able to reduce Cu^{II} species which may form during the reaction. Alternatively, these results may agree with the work presented by Hartwig *et al.* which suggests that a Cu^{II} species is formed upon binding of the oxalamide ligand, rather than a Cu^{I} complex.²³ To further this work, in situ EPR measurements in reactions with a Cu^{I} species would be greatly beneficial in determining whether any Cu^{II} species form during the course of the reaction, and to confirm if they are reduced and recycled by the base or other reaction components. In addition, changing the base to other commonly used bases such as K_3PO_4 may determine whether KOH is responsible for forming the active species, since if the reaction proceeds without the presence of KOH then there is likely another component in the reaction that is responsible for reaction success. However, limited solubility of common inorganic bases may hinder these reactions.

CV measurements suggested that **L29** could stabilise the equilibrium between copper species, while addition of amine lead to further formation of copper species in equilibrium. As with EPR, observing changes over the course of the reaction may be useful in determining how the components interact with the copper centre during the whole catalytic cycle. In addition, comparison with other more well-known ligands such as 1,10-phenanthroline may help to provide a benchmark comparison to the data.

Prior to direct infusion, on-line mass spectrometry was attempted on the systems outlined in section 3.2.3, but there were limitations to the data acquisition. For example, when EtOH was used for the make-up flow, ion clusters formed in both negative and positive mode which hindered data analysis. When acetonitrile was used instead, poor detection of ions occurred. Addition of water to the make-up flow was more successful; however, only the amine and ligand species could be detected and there was no evidence of copper species. With more time, more methods and make-up solutions could be investigated to aid in the improvement of ion detection in these reactions. Direct infusion allowed for the detection of fragments corresponding to the amine, product and copper source, but no evidence of oxalamide ligand **L29** could be found. Employing charged ligand **L37** was more successful, with evidence of a copper-ligated complex forming. Evidence of copper species containing additional substrates or product was not found. Further work could employ IR to investigate the binding mode of the ligand to the copper centre, e.g. through monitoring any changes in the C=O or N-H bonds of the ligand.

Calorimetry experiments aided in the determination that derivatives of oxalamide ligand **L29** which were more electron withdrawing gave a slower reaction rate than those with more electron donating substituents. This may indicate that a key role of **L29** in the reaction is to stabilise the copper complexes which form throughout the cycle, and to increase electron density on the copper centre which would allow for more facile oxidative addition to occur.

A multiple addition experiment with **L29** alluded to the fact that the ligand is degrading during the reaction. NMR studies showed that ethanol reacts with **L29** in the presence of the base to form structure **3.2** in small quantities, but this is unlikely to happen within the timeframe of the reaction and may not have significant effects on the efficacy of **L29**. Further work could focus on investigating the ligand interactions with d-EtOH, however low solubility of the ligand means it is difficult to detect degradation processes at low concentrations.

Investigating the initial rate of the reaction with various loadings of **L29**, ranging from 0.1 to 7.5 mol %, it was observed that the rate did not increase proportional to the increase in ligand loading. This may suggest the reaction was saturated in the ligand at higher concentrations, but also indicates that the ligand may not have a direct influence on the rate of the reaction. A greater difference in rate was observed when copper loading was increased from 0.005 to 0.1 mol %, which may indicate the reaction rate is more dependent on the copper species than **L29**.

Overall, these investigations have indicated that **L29** may have a strong stabilising effect on the copper centre, but it is not directly responsible for the formation of the active catalytic species, nor for increasing the rate of the reaction.

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4 Application of Alternative Ligands in the C-N Cross-Coupling Reaction

4.1 Introduction

The reaction explored in **Chapter 2** and **3** is a highly economical system, due to the simple and readily available base and solvent employed (KOH and EtOH). However, the asymmetric oxalamide **L29** has a fairly intensive synthesis procedure, with the requirement of purification by column chromatography and a multi-step synthesis.¹ This reduces the economic viability for the reaction to be employed in industrial applications. In this chapter, the scope of the reaction has been expanded to determine if simpler or symmetrical ligands can exhibit a similar reactivity to that of **L29**. The ligands shown in **Figure 4.1** have been tested in the reaction in **Scheme 4.1**. The ligands tested in this chapter have been compared to the reaction with **L29** and aryl halide **2.1** (**Table 4.1**).

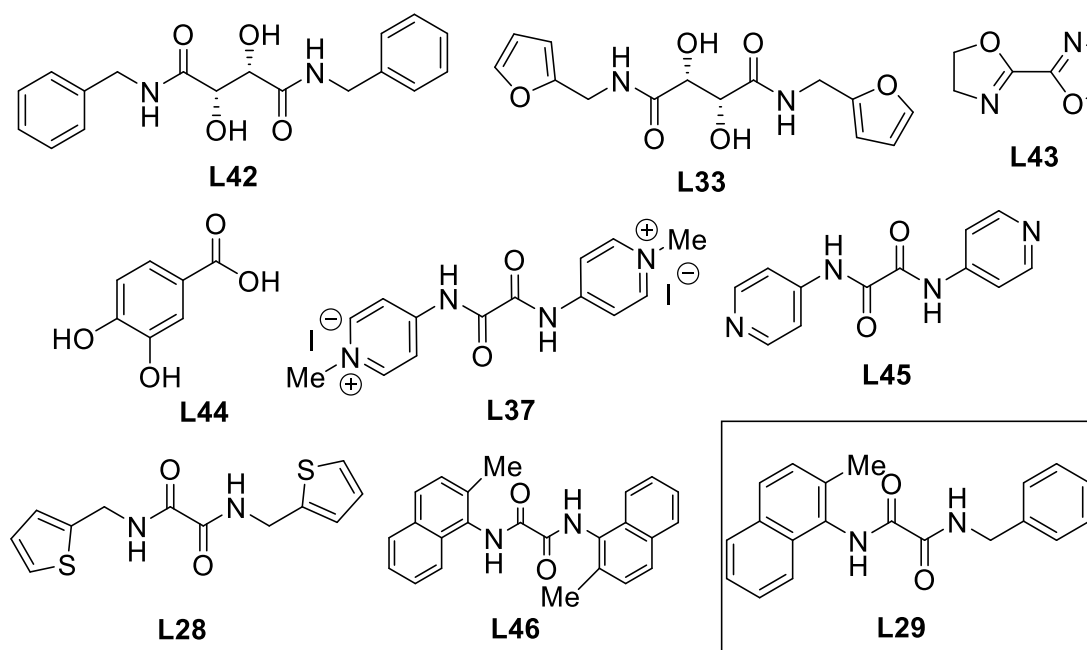
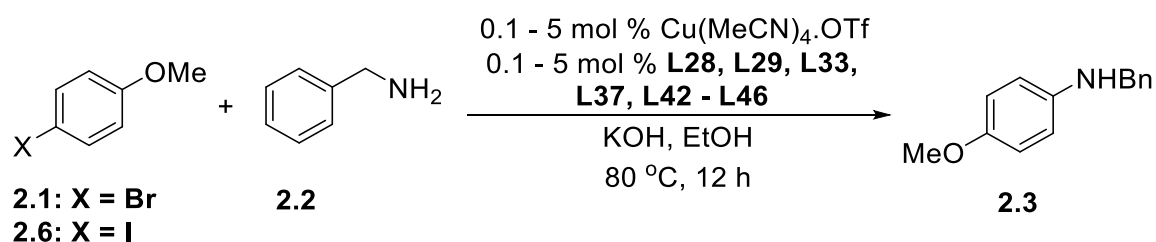


Figure 4.1 Simple and symmetrical ligands employed in the C-N cross-coupling reaction.



Scheme 4.1 General scheme for reactions with **L29** and alternative ligands.

Entry	Ligand and Copper Loading (mol %)	NMR Yield (%)
1	0.1	93
2	1	93

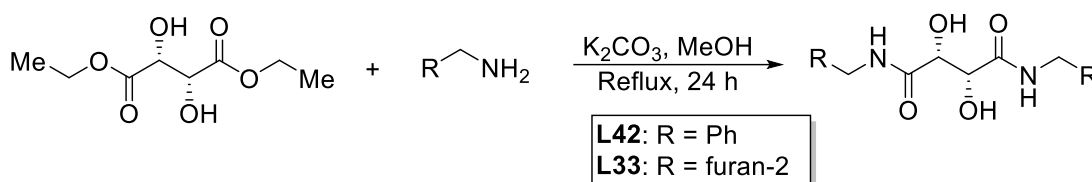
Table 4.1 Reaction with aryl halide **2.1** and oxalamide ligand **L29**.

4.2 Results and Discussion

4.2.1 Tartaric Diamide Ligands

Tartaric diamide ligands were recently reported by Davies *et al.*, and they are structurally very similar to oxalic diamides.² The added hydroxy-groups on the backbone of the ligand can aid in providing additional binding sites and can also add flexibility to the structure. The synthesis of tartaric diamides utilises cheap and commercially available diethyl-D-tartrate, and high activity has been shown with tartaric diamides involving simple amines. Additionally, the synthesis is performed in one step, with no purification or energy intensive procedures necessary.

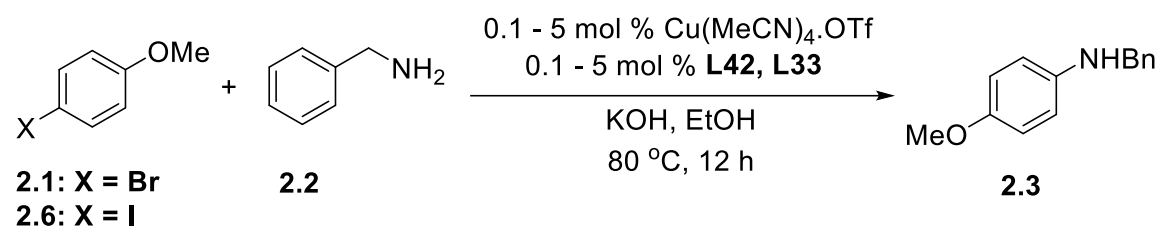
The synthetic procedure reported by Davies *et al.* was followed and is outlined in **Scheme 4.2**. **L42** and **L33** were synthesised in 68 and 72 % yield respectively at high purity.



Scheme 4.2 Synthesis of **L42** and **L33**.²

L42 and **L33** were reported by Davies *et al.* to work successfully in the cross-coupling of 4-iodoanisole (**2.6**) and benzylamine (**2.2**) under mild, room temperature conditions, with NaOH and DEG as the base and solvent system. In this work using EtOH and KOH and a temperature of 80 °C, the reaction was less successful. At a loading of 1 mol % copper and ligand, reactions with aryl bromide **2.1** gave low yields with both **L42** and **L33** (**Figure 4.2**, entries 2 and 5). However, with aryl iodide **2.6**, the yields improved to 53 % (entries 3 and 6). Increasing the copper and **L42** loading to 5 mol % improved the yield of **2.3** to 85 % (entry 5). Compared to the previous protocol from Davies *et al.*, the tartaric diamide ligands did not work as effectively at improving the reaction, since even with elevated temperatures the activation of the aryl bromide substrate was not successful, and higher loadings of copper and ligand were required to achieve comparable yields with the aryl iodide substrate. Davies *et al.* suggested that the deactivation of catalyst could be due to an inhibition effect from water formed

in situ from NaOH, or from disproportionation of the copper.² The former could be likely in this system whereby both water and EtOH may react with the ligand and inhibit its activity. It may be that tartaric diamides are more susceptible to this degradation process than oxalic diamide ligands. Additionally, tartaric diamide ligands may be more likely to bind to copper via at least one of the two -OH groups rather than -NH, which may have a different stabilising effect on the copper centre compared to oxalic diamide ligands.



Entry	Ligand	Aryl Halide Substrate	Ligand and Copper Loading (mol %)	NMR Yield (%)
1	L42	2.1	0.1	0
2	L42	2.1	1	6
3	L42	2.6	1	53
4	L42	2.6	5	85
5	L33	2.1	1	3
6	L33	2.6	1	53

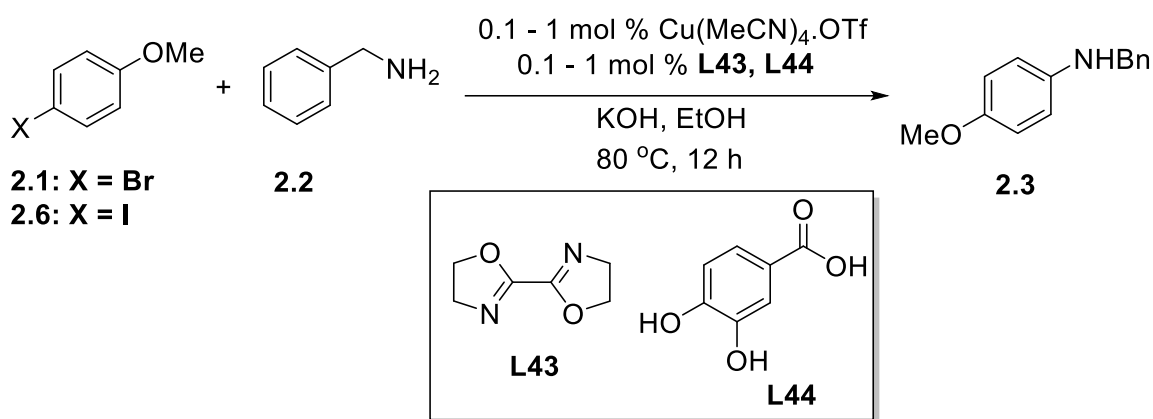
Figure 4.2 Yields obtained with **L42** and **L33**.

4.2.2 O,O-Bidentate Ligands

Ligands containing dative nitrogen and/or oxygen groups have been employed in the Ullmann reaction. Some ligands such as ethylene glycol (**L21**) and *rac*-BINOL (**L24**, section 1.3) were used successfully and acted as O,O-bidentate ligands. Bioxazole (**L43**) was recently reported by Stahl *et al.* as a successful ligand in the copper-catalysed benzylic C-H cross-coupling with methanol.³ In addition to a reductant which aided in the formation of radical intermediates from Cu^{II} species, bioxazole proved to be a successful ligand and may have aided in the stabilisation of the copper species, although the role of bioxazole was not discussed in the work. 3,4-Dihydroxybenzoic acid (**L44**) has not been used previously in copper-catalysed cross-coupling reactions, but it has multiple binding sites which could aid in the stability of copper, and it has similar features to other acidic ligands such as *N*-methylglycine (**L18**, section 1.3.1)

and oxalic diamide **L30** (section 1.3.2). Both **L43** and **L44** are commercially available compounds.

As seen in **Figure 4.3**, the reactions with **L43** and **L44** did not lead to the formation of product **2.3** at all with aryl bromide **2.1** (entries 1, 2, 4, 5). With aryl iodide **2.6**, the yield was slightly improved to 22-27 % (entries 3 and 6). These results may indicate that *O,O*-bidentate ligands are not as successful as *N,O*- or *N,N*-bidentate ligands in this reaction system. Since nitrogen atoms are more electron donating than oxygen atoms, they are likely to provide more donicity to the copper centre and aid in its reactivity.



Entry	Ligand	Aryl Halide Substrate	Ligand and Copper Loading (mol %)	NMR Yield (%)
1	L43	2.1	0.1	0
2	L43	2.1	1	0
3	L43	2.6	1	27
4	L43	2.1	0.1	0
5	L44	2.1	1	0
6	L44	2.6	1	22

Figure 4.3 Yields obtained with **L43** and **L44**.

4.2.3 Pyridylidene Amide (PYA) Ligands

Structure **L37** is classed as a pyridylidene amide (PYA) ligand. This class of ligand was introduced by Albrecht *et al.* in a ruthenium-catalysed olefin oxidation process.⁴ The ligand aided in the formation of a highly efficient catalyst and it can be synthesised from cheap and readily available 4-aminopyridine with a simple and atom economical process. It displays structural similarity with oxalic diamide ligands since it contains the same backbone. However, a key difference is the presence of the pyridylidene amide structure. These structures are able to form two limiting resonance structures: a

zwitterionic structure containing a π -basic *N*-donor site (**Figure 4.4, 4.1a**) or a neutral structure with a π -acidic *N*-donor site (**4.1b**). The dominant structure in a reaction can vary depending on many factors such as the polarity of the solvent and the oxidation state of the metal centre, but PYA ligands have shown potential in the promotion of both reductive elimination and oxidative addition of metal centres.

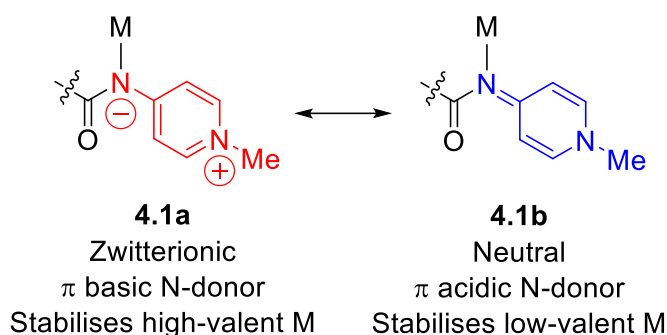
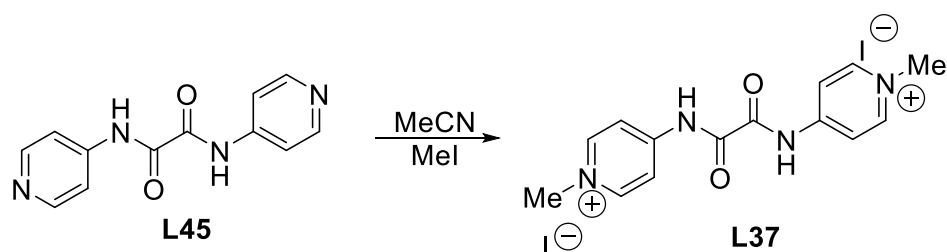


Figure 4.4 Limiting resonance structures formed from pyridylidene amide ligands.⁴

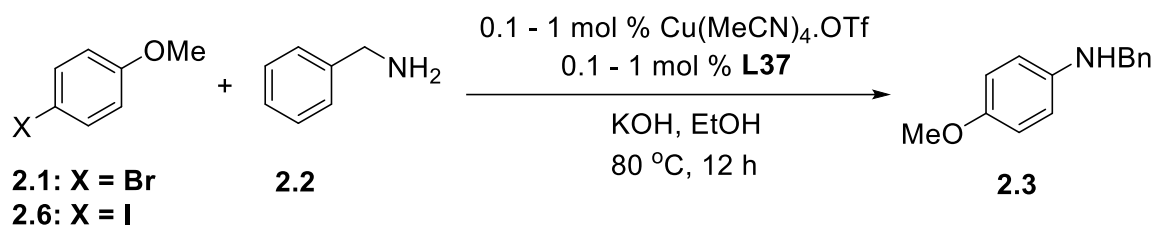
L37 was synthesised in 90 % yield by reaction of **L45** with methyl iodide, as shown in **Scheme 4.3**. The synthesis is advantageous as it is highly atom economical, simple and cheap.



Scheme 4.3 Synthesis of **L37**.⁴

Figure 4.5 highlights the yields obtained with **L37**. Reactivity was low with aryl bromide substrate **2.1** (entries 1 and 2), but the product yield was greatly improved when aryl iodide substrate **2.6** was employed. At a loading of 1 mol % and temperature of 80 °C, the yield of **2.3** was 96 % (entry 3). Dropping the temperature down to 50 °C was possible without decreasing the product formation. However, further lowering the temperature inhibited the reaction. In general, PYA ligand **L37** leads to lower yields than previously used oxalic diamide ligands, particularly due to its decreased ability to activate aryl bromides. However, it shows promising reactivity with aryl iodide substrates, given that high yields could be obtained with a relatively mild temperature of 50 °C. It may have improved stability to deactivation processes due to the flexible binding mode of the ligand, which may aid in the catalyst stability and in the oxidation

or reduction of inactive copper species which may form during the reaction. Albrecht *et al.* observed the ability of PYA ligands to stabilise different oxidation states of metal centres to facilitate olefin oxidation and water oxidation reactions.^{5,6}



Entry	Aryl halide Substrate	Temperature (°C)	Ligand and Copper Loading (mol %)	NMR Yield (%)
1	2.1	80	0.1	0
2	2.1	80	1	38
3	2.6	80	1	96
4	2.6	50	1	98
5	2.6	23 (r.t.)	1	0

Figure 4.5 Yields obtained with **L37** as the ligand.

4.2.4 Oxalic Diamide Ligands

While **L29** performs exceptionally well in the C-N cross-coupling reaction, and can be used at low loadings of 0.1 mol %, its synthesis is an energy intensive, multi-step process due to the asymmetrical nature of the structure. The employment of symmetrical oxalic diamides have been successful in a range of cross-coupling reactions developed by Ma *et al.* (see **Chapter 1**, section **1.3.2** for examples).⁷⁻¹⁰ These ligands can be synthesised from a simple reaction between the relevant amine and oxalic acid, then purified by recrystallisation if necessary. Three symmetrical oxalic diamides have been tested in the reaction in **Scheme 4.1** to determine if they are equally or more reactive than **L29**.

L45 contains additional nitrogen atoms on the aromatic portion of the ligand. Recently, a class of oxalamide ligands containing this pyridine moiety were reported by Ma *et al.* to be successful in the formation of C-C bonds (**Figure 4.6**).¹¹ They suggested that the additional nitrogen atom could provide another binding site for the copper, but this was not explored experimentally. Simple and easily prepared oxalamide ligand **L45** has not been tested in Ullmann coupling previously.

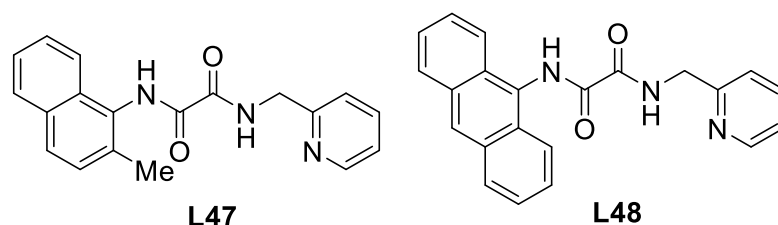
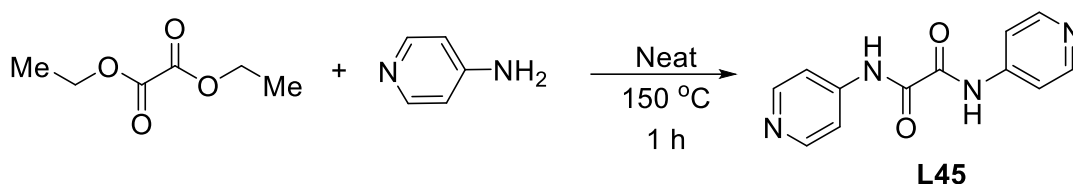


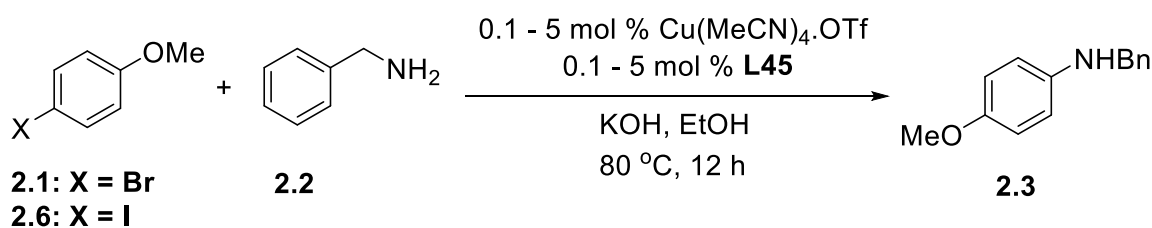
Figure 4.6 Examples of ligands employed by Ma *et al.* in C-C cross-coupling reactions.¹¹

L45 was synthesised from the procedure reported by Albrecht *et al.* in 81 % yield (**Scheme 4.4**).⁴



Scheme 4.4 The synthesis of **L45**.⁴

Figure 4.7 reveals that **L45** has limited reactivity in C-N cross-coupling reactions under the conditions employed. No activity was seen with aryl bromide substrate **2.1**, even with increased ligand loading of 5 mol % (entries 1 – 3). Some reactivity occurred with aryl iodide substrate **2.6**, but with high copper and ligand loading of 5 mol %, the yield of **2.3** did not reach above 40 % (entries 4 – 6). Thus, **L45** proved to have much lower reactivity than **L29**, and the ligands employed by Ma *et al.* in C-C reactions such as **L47** and **L48**.¹¹ Given the asymmetrical nature of **L47** and **L48**, and the presence of a bulky naphthalenyl-methyl group on one side, the added steric bulk may aid in the rigidity and stability of binding to copper, which may enhance its role as a catalyst and also make it less susceptible to catalyst deactivation.

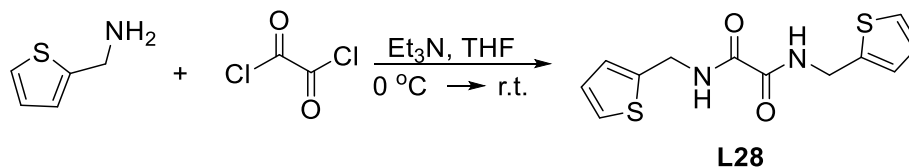


Entry	Aryl Halide Substrate	Ligand and Copper Loading (mol %)	NMR Yield (%)
1	2.1	0.1	0
2	2.1	1	0
3	2.1	5	0
4	2.6	0.1	21
5	2.6	1	23
6	2.6	5	40

Figure 4.7 Yields obtained with **L45**.

L28 was suggested by Nett *et al.* to be successful in copper-catalysed C-O coupling.¹² Through DFT studies and crystal structure analysis, they determined that **L28** binds to the Cu^I centre as an amidate ligand, with monodentate binding of the nitrogen atom and weak interaction of the carbonyl oxygen with the copper centre. With a Cu^{III} centre, the ligand is bidentate and forms a Cu-N and Cu-O bond. Based on these findings, they suggest that the ligand is able to adopt different modes of coordination depending on the oxidation state of the copper centre. They also confirm from their calculations that the sulphur atom does not participate in binding with the Cu centre.

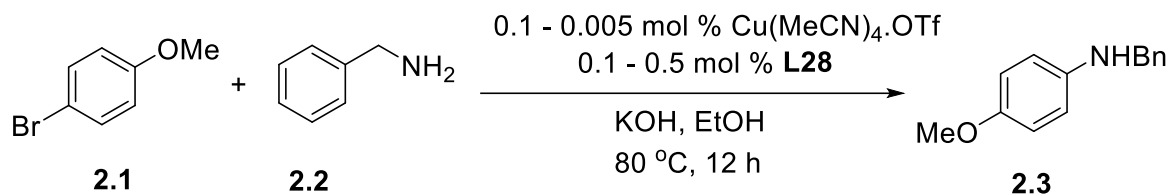
L28 was synthesised according to the procedure from Ma *et al.* in 72 % yield (**Scheme 4.5**).¹³



Scheme 4.5 Synthesis of **L28**.¹³

L28 showed less reactivity in the reaction medium than **L29**. A yield of only 40 % (**Figure 4.8**, entry 1) was obtained compared to 93 % for **L29**. Increasing the ligand loading helped to increase the final yield slightly to 64 % (entry 3). Attempting to apply

the optimised conditions from **Chapter 2** of copper loading of 50 ppm copper led to a yield of only 3 % **2.3** (entry 4) which indicates **L28** is not as active a ligand as **L29**.

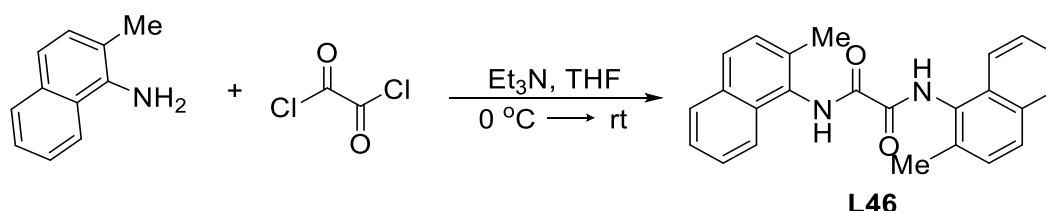


Entry	Copper Loading (ppm)	Ligand Loading (mol %)	NMR Yield (%)	TON	TOF (h ⁻¹)
1	1000	0.1	40	400	33
2	1000	0.2	37	370	31
3	1000	0.5	64	640	53
4	50	0.1	3	550	46

Figure 4.8 Yields obtained with **L28**.

L46 was reported by Ma *et al.* in the same publication as **L29** so has already been reported.¹ With copper and **L46** loadings of 0.1 mol % and the conditions outlined in **Table 4.1**, they reported a yield of 60 %, which is lower than the 93 % obtained with **L29**. However, it was not reported with loadings of copper lower than 0.1 mol % with aryl bromide substrates, so **L46** was tested with the optimised conditions reported in **Chapter 2**.

L46 was synthesised according to the procedure outlined by Ma *et al.* in 72 % yield (**Scheme 4.6**).¹



Scheme 4.6 Synthesis of **L46**.¹

L46 showed similar reactivity to **L28**, although the yields obtained with **L46** are slightly higher, ranging from 55 – 88 % (**Figure 4.9**^{Error! Reference source not found.}). Employing a copper loading of 50 ppm Cu was more successful with **L46** than with **L28**, achieving a yield of 53 % and a high TON of 10550 after 12 hours (entry 4). This may be a promising alternative to using **L29**, since **L46** has a less energy intensive

synthesis. As shown in **Chapter 2**, reactions with low loadings of copper were able to reach high yields after increasing the concentration of **L29**. This protocol was tested with **L46** by increasing the ligand loading to 1 mol % in the reaction with 50 ppm copper (entry 5). A high yield of 88 % could be achieved, which may indicate a higher concentration allows for greater stability of the catalyst. Decreasing the copper loading to 5 ppm led to a less successful reaction, with a yield of 29 % achieved (entry 6).

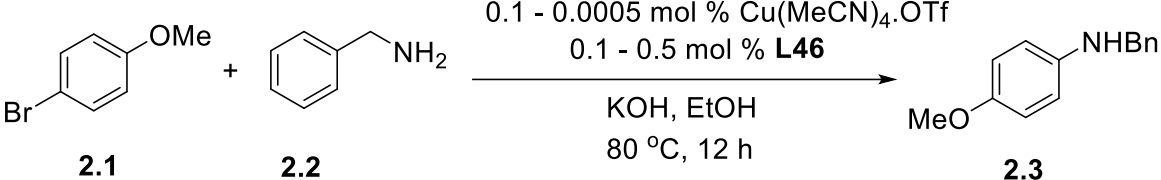
					
Entry	Copper Loading (ppm)	Ligand Loading (mol %)	NMR Yield (%)	TON	TOF (h ⁻¹)
1 ^a	1000	0.1	60	600	50
2	1000	0.2	55	550	46
3	1000	0.5	71	710	59
4	50	0.1	53	10550	879
5 ^b	50	1	88	88250	613
6 ^{b,c}	5	0.1	29	57250	398

Figure 4.9 Yields obtained with **L46**. ^aYield reported by Ma *et al.* and repeated to check for reproducibility.¹ ^bReaction time of 144 h. ^c20 mmol scale.

4.3 Conclusions and Future Work

A range of ligands with alternative structures to **L29** were tested in the reaction medium with EtOH and KOH as the solvent and base system. None of the ligands tested had a similar reactivity to that of **L29** and they were not as active in the chosen reaction. The highest yields obtained with each ligand are summarised in FIG X.

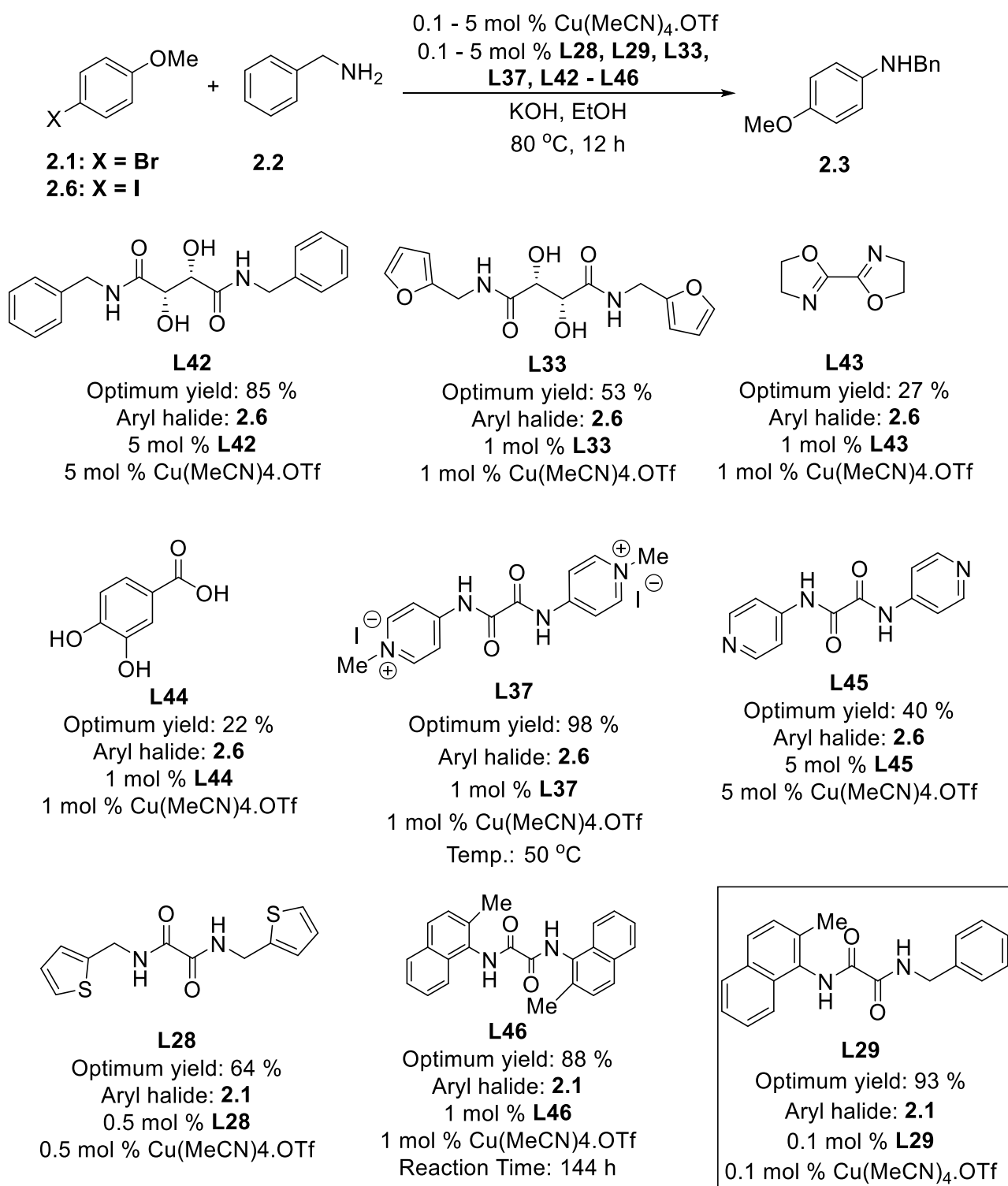


Figure 4.10 Summary of the optimum yields obtained with the various ligands tested in this chapter.

Tartaric diamides **L42** and **L33**, which were reported previously as a successful ligand in a similar system by Davies *et al.*, were less active than **L29** but showed promise with slightly higher loadings of copper and ligand of 5 mol % and an aryl iodide substrate.²

Ligands **L43** and **L44** exhibited the possibility to act as O,O-bidentate ligands, but their reactivity was low in the employed reaction system, which may indicate that ligands containing nitrogen atoms are required to aid in the stabilisation of copper species.

Pyridylidene amide (PYA) ligand **L37** showed success with aryl iodide substrate **2.6**. The reaction could be performed at mild conditions of 1 mol % copper and ligand, and 50 °C.

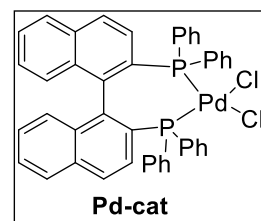
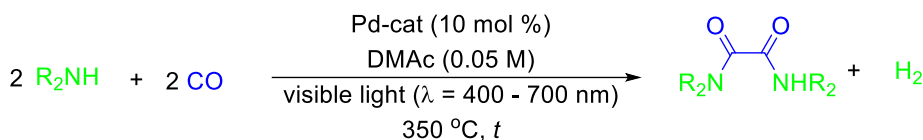
Symmetrical oxalic diamide ligands **L45**, **L28** and **L46** showed lower reactivity than **L29**, but **L46** showed some promise since it was able to achieve 53 % yield of **2.3** with 50 ppm copper, leading to high TONs. Increasing the loading of **L46** led to high yields of 88 % and a high TON of 8.8250×10^5 which is similar to that achieved with **L29**. However, **L29** proves to be a more active catalyst since a TOF of 1383 was achieved, while **L46** only reached a TOF of 879.

These ligands provide an advantage over **L29** given that their synthesis is simpler and in some cases cheaper. Tartaric diamides **L42** and **L33** and PYA ligand **L37** are cheaper to produce due to their cheap and readily available starting materials. **L29** requires the use of 2-methylnaphthalenylamine which is expensive. In the interest of enhancing the economic viability of the reaction, it may be more advantageous to use a less active but more accessible alternative such as **L46** instead of **L29**.

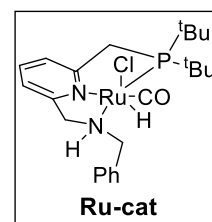
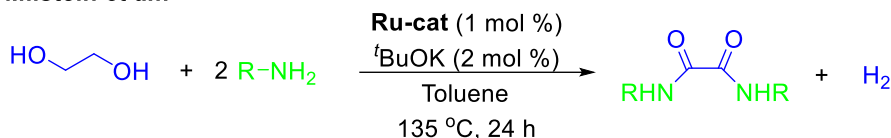
Further studies could be conducted to develop reaction profiles with **L42**, **L33**, **L37** and **L46** to understand their influence and continue increasing their efficacy in the reaction. For example, exploring a wider range of copper and ligand loadings, solvents, bases and copper sources. In particular, an alternative solvent may be required with **L35** since it is highly polar.

Since the main consideration of this chapter was to find alternatives to **L29** due to its multi-step synthesis, different synthesis routes to **L29** could also be investigated. Some reports have been released which address this. For example, work from Wu *et al.* employed a visible light-induced palladium catalyst for a mild, green synthesis route¹⁴, Milstein *et al.* found ruthenium could catalyse the coupling of ethylene glycol and amines¹⁵, Volkova *et al.* employed sulphur for a one-pot synthesis method¹⁶, and Wang *et al.* employed bromodifluoroacetamide as a reactant to form asymmetric oxalamides¹⁷ (**Figure 4.11**). The scope of these works are still limited, but with further optimisation they could be employed as alternative synthesis methods for oxalamide ligands.

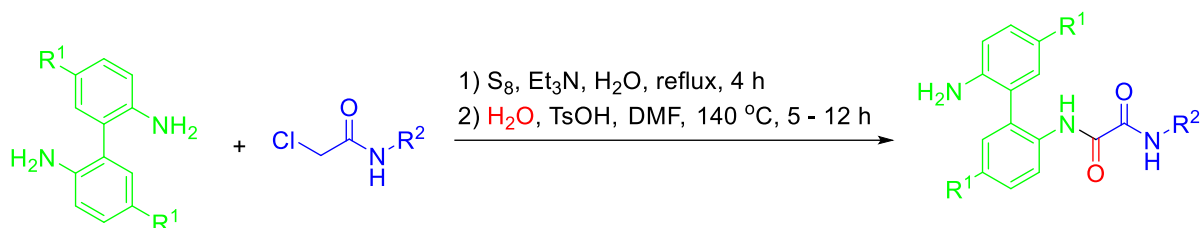
Wu et al.:



Milstein et al.:



Volkova et al.:



$\text{R}^1 = \text{H, Me, Br}$

Wang et al.:

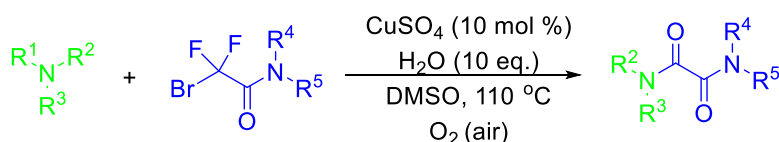


Figure 4.11 Alternative routes to oxalamide ligands.^{14,15,16,17}

4.4 References

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5 Conclusion

5.1 Conclusions and Future Work

The aim of the work in this thesis was to gain insights into the mechanism of the Cu/oxalamide catalysed C-N cross-coupling reaction. In **Chapter 2**, a model reaction involving 4-bromoanisole (**2.1**), benzylamine (**2.2**) and a soluble base/solvent system of KOH and EtOH allowed for the acquisition of kinetic data through monitoring the concentration of product formed and 4-bromoanisole consumed. Through same excess experiments, catalyst deactivation was seen to occur at lower concentrations of copper and oxalamide ligand **L29**. At higher loadings of **L29**, the deactivation process could be prevented. These findings led to improved reaction conditions whereby the loading of copper could be decreased to as low as 5 ppm, while the ligand loading was kept in high excess (1000 – 10,000 ppm). High TONs were achieved, up to 6.6×10^4 for aryl bromide substrate **2.1** and 1.9×10^5 for aryl iodide substrate **2.6**. These are higher than the highest TONs currently reported in literature for Cu-catalysed C-N cross-coupling reactions (8.6×10^4 for aryl iodides and 8000 for aryl bromides).^{1,2} A variety of substrates reacted successfully in the improved reaction, with yields ranging from 9 – 99 % and TONs ranging from 1750 – 1.99×10^4 .

Different excess experiments led to the conclusion that aryl bromide substrate **2.1** is present in a kinetically meaningful step of the reaction, but no rate dependence was seen with KOH and amine substrate **2.2** which suggests they are not present in the rate-determining step of the reaction. The reaction was first order in $[\text{Cu}]_{\text{total}}$ and oxalamide ligand [**L29**] although this deviated as the reaction progressed, which may be due to catalyst deactivation or the degradation of **L29**.

The reaction was inhibited upon addition of TEMPO which indicates that radical species are present in the reaction. A Hammett analysis with different aryl bromides highlights that more electron donating substituents on the aryl halide enhance the reaction rate, but may elude to radical-based processes in the rate-determining step due to low correlation between reaction rate and substituents.³

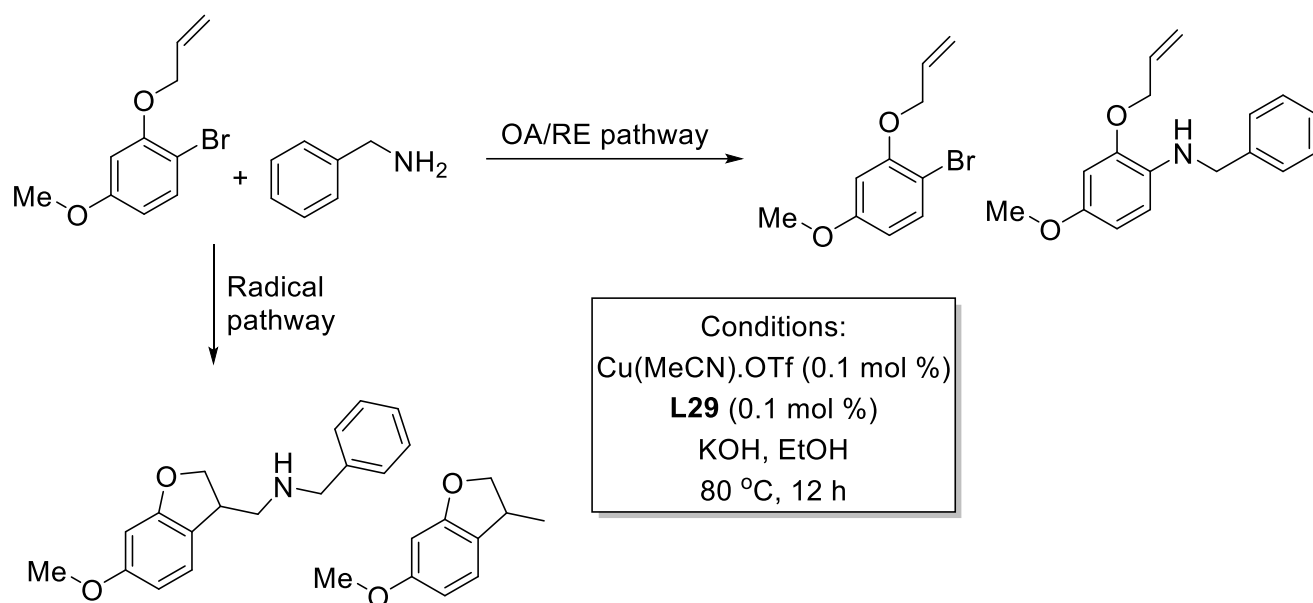
Chapter 3 focussed on using a range of characterisation techniques to probe the copper and oxalamide ligand species in the reaction. EPR measurements with a Cu^{II} source suggest that the oxalamide ligand is not responsible for formation of a Cu^{I} species. Unexpectedly, the base, KOH, is able to transform the Cu^{II} species without the presence of **L29**. Calorimetry measurements were employed to determine the electronic effects of oxalamide ligands. It was found that ligands with electron withdrawing groups

decreased the reaction rate, which may indicate a key role of the ligand is to donate electron density to the copper centre and stabilise the complexes which form during the cycle. A Cu/oxalamide complex was detected in mass spectrometry which indicates the ligand binds to the copper centre, but the exact binding mode could not be confirmed.

Multiple addition of the ligand indicates that the ligand is being consumed during the reaction, since deactivation processes can be prevented with further addition of **L29**. Attempts to determine the decomposition process of **L29** under the reaction conditions were unsuccessful, due to limited solubility of **L29** which prevented the monitoring of stoichiometric interactions.

Combining the kinetic studies from **Chapter 2** and the characterisation data from **Chapter 3**, the precise role of oxalamide ligand **L29** in the model reaction is still unclear. The kinetic data obtained agrees with recent literature which suggests that the aryl halide is present in the rate-determining step and coordination of the amine occurs later.^{4,5} Previous work from Davies *et al.* suggests that zero order rate dependence in [amine] indicates that the amine is present in its deprotonated form in the rate-determining step, however KOH is unlikely to deprotonate benzylamine in the reaction medium.⁶ The kinetic data should be validated against a kinetic model – the experimental data can be compared with models of various mechanistic scenarios, to find the model which best fits the experimental data and thus the mechanism which is likely to be followed. A Hammett analysis would decipher whether the amine exhibits electronic influences on the transition state of the rate-determining step – no correlation would indicate that it has no influence and is not present in the rate-determining step.

Recent work by Hartwig *et al.* highlights that oxalamide ligands may exhibit radical character which would aid in the formation of Cu^{III} species through oxidative addition. The addition of TEMPO inhibited the reaction which suggests that radical species may be present in the reaction, but a radical-clock experiment would determine whether a radical is formed from the aryl bromide species (**Scheme 5.7**). If the cross-coupled product forms rather than the cyclised product, this would suggest the radical species is generated by the oxalamide ligand.



Scheme 5.7 Radical clock experiment with 2-(allyloxy)bromobenzene.

Further efforts could also be extended to the EPR and CV measurements. For EPR, in situ reaction monitoring would be beneficial to decipher the changes in copper species upon addition of the various reaction components. Similarly, while independent samples suggest the various reaction components interact with the copper species, monitoring the reaction by CV may give further insights into the redox changes with respect to the copper species in the reaction cycle. Further research should also focus on the isolation of Cu/oxalamide species which can be characterised by single crystal XRD. The limited solubility of **L29** may hinder this, so other oxalamide ligands could be explored. This would provide insights into how the ligand binds to the copper centre, and may indicate what the catalyst resting state is. These insights combined should help to build a bigger picture of the role of oxalamide ligands. Ultimately, these insights should be applied to aid in the activation of aryl chloride substrates, which are preferable in industrial applications due to their low cost. This hurdle prevents the Ullmann reaction from gaining popularity over the Pd-catalysed Buchwald-Hartwig amination, which can activate aryl chlorides with very low loadings of Pd. With continued research and understanding, the Ullmann reaction could become the more viable reaction.

Chapter 4 explored the use of alternative ligands to **L29** within the model reaction conditions. While none of the ligands tested improved the reaction, they were simpler and cheaper to synthesise (or they were commercially available). In future, the structure of the ligand employed should be informed based on the mechanistic insights obtained from kinetic and spectroscopic data. To expand this work, alternative synthesis routes

could be explored for **L29**, for example through one-pot synthesis methods or more mild conditions induced by microwaves or visible light.^{7,8}

5.2 References

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6 Experimental

6.1 General Information

All optimisation and scope reactions were prepared and carried out in air. Kinetic reactions were carried out in a nitrogen atmosphere unless otherwise specified. All glassware was dried overnight in a 120 °C oven before use. All reagents were purchased commercially and were used as received. KOH ($\geq 85\%$ purity) and absolute EtOH were used in catalytic reactions. Stock solutions of $\text{Cu}(\text{MeCN})_4\text{OTf}$ and **L29** were prepared in glass vials with septum lids and heated to 75 °C prior to addition.

All yields reported (aside from those of synthesised ligands) were determined by quantitative ^1H NMR, where naphthalene was used as an internal standard. Naphthalene was added as a solid along with reagents at the beginning of the reaction. The multiplet signal at 7.83 – 7.91 ppm was used to quantify the concentration of starting material and product. ^1H , ^{13}C and ^{19}F NMR spectroscopy data were obtained at room temperature using Bruker AV-400 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) and are referenced to the residual ^1H and ^{13}C signal of deuterated solvents. Coupling constants (J) are given in Hz units. All spectra were analysed using MESTRELAB MestReNova software.

Melting points were recorded using a Stuart SMP11 Melting Point machine and a mercury thermometer.

GC-MS and EI-MS analyses were carried out on a Micromass Autospec Premier Spectrometer. For GC-MS the following conditions were employed: 50 °C held for 5 mins, then 10 °C/min to 290 °C, flow rate of 1 mL/min He, DB5 column with dimensions 30 m x 2.5 mm x 0.25 μm , EtOAc solvent. ESI-MS analysis was carried out on a Waters LCT Premier Spectrometer.

PXRD analysis was carried out on a Bruker 2D Phaser machine with Cu-K α radiation (1.51184 Å) between 5 ° and 50 ° (2 θ).

EPR measurements were taken on a Magnettech ESR5000 spectrometer at 80 °C in X-band with 10 mW microwave power, a modulation frequency of 100 kHz and a modulation amplitude of 0.2 mT.

CV measurements were conducted at 75 °C using a Metrohm Autolab PGStat30 Potentiostat Galvanostat connected to a three-electrode cell equipped with a graphite working electrode, silver wire quasi-reference electrode and gold wire counter electrode. Electrodes were rinsed in EtOH and polished before each measurement. KOH (1.5 M)

was used as a supporting electrolyte. A scan rate of 0.1 Vs⁻¹ and a step potential of 2 mV were employed. A potential range of -1.5 to +0.5 V was applied twice per sample. Data processing was performed with NOVA 2.1.6 software.

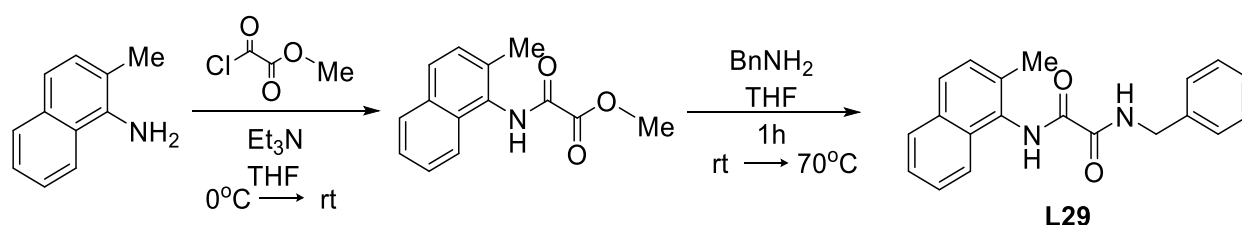
Calorimetry measurements were taken on an Omnical 8 well calorimeter and the results were analysed with Winsight software, in which the data was tau-corrected. The temperature was maintained using a silicone oil circulator. The heat flow from the reaction vials were measured every 3 seconds.

Mass spectrometry analysis by direct infusion was carried out using a Microsaic 4500 MiD spectrometer and data was analysed by Masscape software.

6.2 Experimental Details for Chapter 2

6.2.1 Synthesis of L29

L29 was synthesised according to the procedure reported by Ma *et al* (**Scheme 6.1**).¹



Scheme 6.1 Synthesis route of **L29**.

To a 250 mL round bottom flask under nitrogen, mono-methyloxalyl chloride (3.0 mL, 33 mmol, 1.1 eq.) was added dropwise to a mixture of 2-methylnaphthalenylamine (2.8 mL, 30 mmol, 1.0 eq.), Et₃N (5.0 mL, 36 mmol, 1.2 eq.) and THF (60 mL) at 0 °C. The mixture was stirred at room temperature for 2 hours. Water (30 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organics were dried over MgSO₄. The solvent was removed via rotary evaporation to yield an orange viscous oil. The crude product was purified with silica gel chromatography using n-hexane:EtOAc (10:0 → 8:2) to afford a pale yellow viscous oil (4.3 g, 18 mmol, 59 %). The product was dissolved in THF (20 mL), and BnNH₂ (2.3 mL, 21 mmol, 1.2 eq.) was added at room temperature. The mixture was then heated to 70 °C and stirred for 1 hour. The mixture was cooled to room temperature, then to 0 °C. n-Hexane (~5 mL) was added to induce precipitation. The solid product was obtained via suction filtration and washed with cold diethyl ether (15 mL) to afford **L29** as a white powder (4.2 g, 13 mmol, 40 %). Mp.: 190 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.27 (s, 1H, NH), 7.95 (s, 1H, NH), 7.90 – 7.83 (m, 2H, Ar), 7.80 (d, 1H, *J* = 8.4 Hz, Ar), 7.60 – 7.46 (m, 2H, Ar), 7.44 – 7.35 (m, 5H, Ar), 4.62 (d, 2H, *J* = 6.3 Hz, CH₂), 2.44 (s, 3H, CH₃). ¹³C NMR (100 MHz,

CDCl₃) δ 159.7 (C=O), 158.5 (C=O), 136.6 (Ar), 133.0 (Ar), 132.7 (Ar), 129.9 (Ar), 128.9 (Ar), 128.8 (Ar), 128.3 (Ar), 128.2 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 126.9 (Ar), 125.6 (Ar), 122.0 (Ar), 44.1 (CH₂), 18.8 (CH₃). HRMS (ES⁺, TOF): m/z 319.1447 [M+H]⁺, calculated for [C₂₀H₁₉N₂O₂]⁺: 319.1447.

6.2.2 General Procedure for Initial Suitability Check and Optimisation for Kinetic Studies

4-bromoanisole (1.25 mL, 10.0 mmol, 1 eq.), benzylamine (1.64 mL, 15.0 mmol, 1.5 eq.), copper source (Cu₂O: 1.4 mg, Cu(MeCN)₄.OTf: 3.8 mg, 0.010 mmol, 0.001 eq.), **L29** (3.2 mg, 0.010 mmol, 0.001 eq.), KOH (0.729 g, 13.0 mmol, 1.3 eq.), EtOH (1 or 2 mL) and naphthalene (0.641 g, 5.00 mmol) were placed in a 14 mL glass vial. The mixture was stirred and heated at 80 °C for 12 hours, then cooled to room temperature and diluted with ethyl acetate (7 mL). The mixture was washed with brine (2 x 7 mL) and the organic phase was dried over MgSO₄. The solvent was removed by rotary evaporation to yield an orange oil. For NMR yields: an NMR was taken of the crude product in CDCl₃, and the yield calculated by quantitative NMR with naphthalene as the internal standard. For isolated yield: the crude product was purified with silica gel chromatography using n-hexane:EtOAc (19:1 → 9:1) to afford a pale yellow solid (1.855 g, 8.71 mmol, 87 %).

6.2.3 General Procedure for Optimisation of Reaction for Kinetic Studies at Increased Scale

To a 3-neck 100 mL round bottom flask (either open to air or under N₂) naphthalene (3.203 g, 25.0 mmol), KOH (3.647 g, 65.00 mmol), EtOH (9 mL if Cu/ligand stock solution used, 10 mL if not), benzylamine (8.19 mL, 75.0 mmol), 4-bromoanisole (6.28 mL, 50.0 mmol), and **L29** if added as solid (0.016 g, 0.050 mmol) were added and heated to reflux (112 °C). The mixture was stirred for 20 minutes until the solids were dissolved. The copper source was then added, either as a solid (Cu₂O: 0.007 g, 0.05 mmol, CuI: 0.01 g, 0.05 mmol) or via stock solution with **L29** (Cu₂O, CuI or Cu(MeCN)₄.OTf: 0.05 M, 1 mL) to initiate the reaction. ~0.1 mL aliquots were collected over the course of the reaction (6 h) and were placed in a screw-cap vial with brine (0.6 mL) and CDCl₃ (0.6 mL). The aqueous layer was washed with further CDCl₃ (0.6 mL). The combined organic layers were dried over MgSO₄ and filtered into an NMR tube.

6.2.4 General Procedure for Kinetic Studies

For all kinetic reactions, the total volume was kept at 24.5 mL by adjusting the volume of solvent used.

6.2.4.1 General Procedure for Reactions in EtOH

The reactions performed in EtOH at 50 mmol scale followed the procedure outlined in section 6.2.3, whereby Cu(MeCN)₄.OTf was used as a copper source, and the reaction was initiated with a copper and **L29** stock solution. The concentrations used for the same excess experiments are outlined in Table 6.1.

Reactions	Substrate	Quantity Added		
		M	Mmol	mL or g
Same excess, [e] = 1 M	2.1	0.8	20	2.55 mL
	2.2	1.8	46	5.07 mL
Same excess, higher [L29], [e] = 1 M	KOH	1.5	35	1.953 g
	2.1	1.4	35	4.37 mL
Same excess, lower [Cu], [e] = 1 M	2.2	2.4	61	6.65 mL
	KOH	2.1	49	2.766 g
	2.3	0.6	15	3.092 g
	KBr	0.6	15	1.726 g
	H ₂ O	0.6	15	0.261 mL

Table 6.1 The concentrations of substrates used in kinetic reactions with EtOH.

6.2.4.2 General Procedure for Reactions in DEGEE

The reactions performed in DEGEE at 50 mmol scale followed the procedure outlined in section 6.2.3, using 9 mL of DEGEE instead of EtOH. Cu(MeCN)₄.OTf was used as a copper source, and the reaction was initiated with a copper and **L29** stock solution. The reactions were run for 4 hours. The concentrations used for the different excess experiments are outlined in Table 6.2.

Reactions	Substrate	Quantity Added		
		M	mmol	mL or g
Different [2.1] ₀ , [e] = 1.4 M	2.1	1.6	40	4.98 mL
Different [2.1] ₀ , [e] = 0.7 M	2.1	2.3	58	7.28 mL
Different [2.2] ₀ , [e] = 0.5 M	2.2	2.5	61	6.65 mL
Different [2.2] ₀ , [e] = 0.1 M	2.2	2.1	52	5.7 mL
Different [KOH] ₀ , [e] = 1 M	KOH	2.3	53	2.929 g
Different [Cu&L29] ₀ , [e] = 1 M	Cu and L29	0.001	0.029	1 mL of 0.05 M stock solution
		0.0005	0.015	0.5 mL of 0.05 M stock solution

Table 6.2 The concentrations of substrates used in kinetic reactions with DEGEE.

6.2.4.3 Procedure for Reaction with TEMPO

The reaction with addition of TEMPO was performed following the procedure outlined in section 6.2.4.2, but with the addition of TEMPO (0.002 M: 0.008 g, 0.05 mmol, 2.0 M: 7.813 g, 50.0 mmol) prior to heating the reaction mixture.

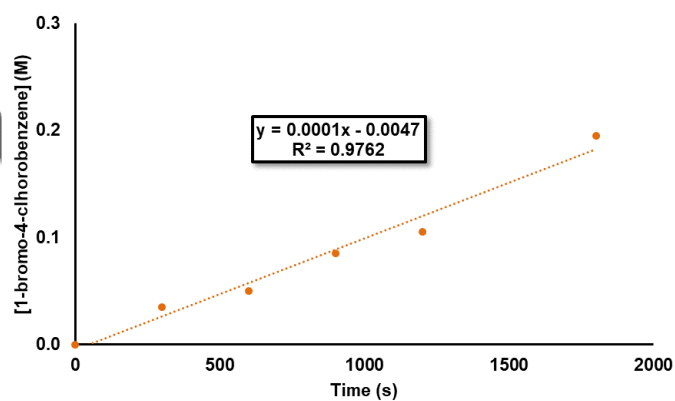
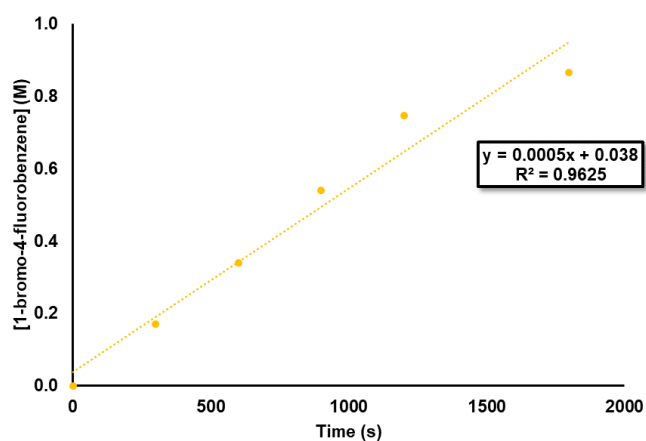
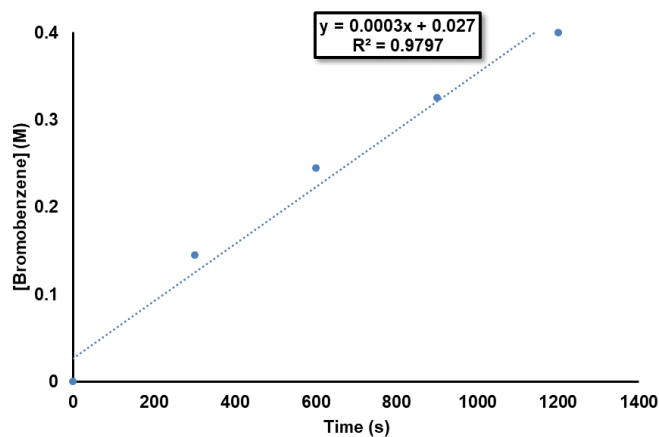
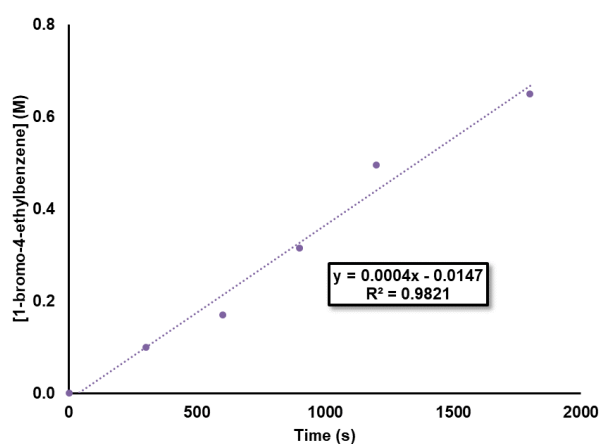
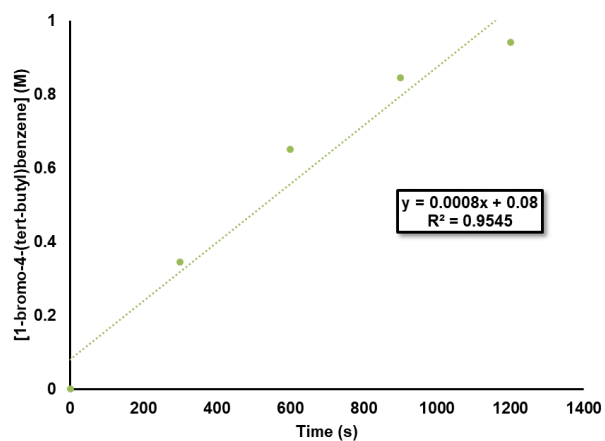
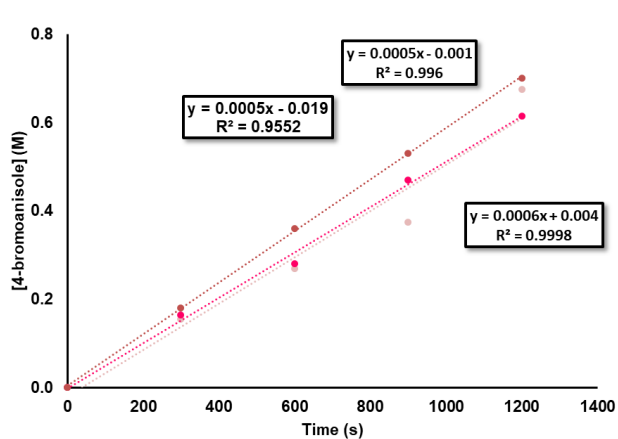
6.2.5 General Procedure for Hammett Study

To a 3-neck 100 mL round bottom naphthalene (3.203 g, 25.0 mmol), KOH (3.647 g, 65.00 mmol), DEGEE (amount to make total mixture 24.5 mL), benzylamine (8.19 mL, 75.0 mmol) and aryl bromide (50.0 mmol, see **Table 6.3**) were added and heated to 105 °C. The mixture was stirred for 20 minutes until the solids were dissolved. Cu(MeCN)₄.OTf and L29 were added via stock solution (0.05 M, 1 mL) to initiate the reaction. ~0.1 mL aliquots were collected over the course of the reaction (0.5 h) and were placed in a screw-cap vial with brine (0.6 mL) and CDCl₃ (0.6 mL). The aqueous layer was washed with further CDCl₃ (0.6 mL). The combined organic layers were dried over MgSO₄ and filtered into an NMR tube.

Aryl Bromide Substrate	Quantity Added
4-bromoanisole	6.28 mL
1-bromo-4-(tert-butyl)benzene	8.67 mL
1-bromo-4-ethylbenzene	6.89 mL
Bromobenzene	5.27 mL
1-bromo-4-fluorobenzene	5.49 mL
1-bromo-4-chlorobenzene	9.573 g
4-bromobenzotrifluoride	7.11 mL

Table 6.3 Aryl bromides used in Hammett study.

6.2.5.1 Calculating k_{obs}



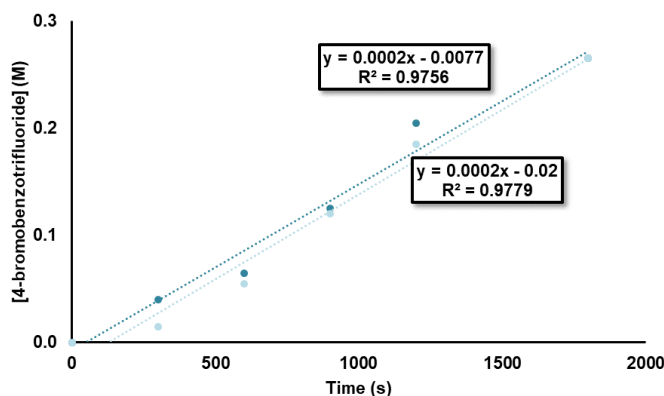


Figure 6.1 Initial rate calculations for use in Hammett study.

	OMe	C(Me) ₃	Et	H	F	Cl	CF ₃
k_{obs} (Ms⁻¹)	0.0005	0.0008	0.0004	0.0004	0.0005	0.0001	0.0002
σ_{para}	-0.27	-0.256	-0.15	0	0.06	0.23	0.54
k_x/k_H	1.25	2	1	1	1.25	0.25	0.5
log(k_x/k_H)	0.09691	0.30103	0	0	0.09691	-0.60206	-0.30103

Table 6.4 Calculation of log (k_x/k_H).

6.2.6 General Procedure for Reactions with Oxidants/Reductants

The reactions with addition of oxidants/reductants were performed following the procedure outlined in section 6.2.4.2, but with the addition of an oxidant or reductant according to **Table 6.5**.

Oxidant/Reductant	Quantity Added	
	mmol	g
Diacetoxiodobenzene	0.05	0.016
	5	1.611
Ascorbic Acid	0.05	0.009
Hydroquinone	5	0.551
Hantzsch Ester	2.5	0.633

Table 6.5 Oxidants and reductants used and the quantities added.

6.2.7 General Procedure for Reaction Optimisation

For copper loadings of 1000 – 25 ppm:

4-Bromoanisole (1.25 mL, 10.0 mmol, 1 eq.), benzylamine (1.64 mL, 15.0 mmol, 1.5 eq.), Cu(MeCN)₄.OTf (3.8 – 0.1 mg, 0.01 mmol – 0.00025 mmol), **L29** (3.2 – 0.8 mg, 0.01 – 0.0025 mmol), KOH (0.729 g, 13.0 mmol, 1.3 eq.), EtOH (1 mL) and

naphthalene (0.641 g, 5.00 mmol) were placed in a 14 mL glass vial. The mixture was stirred and heated at 80 °C for 12-48 hours. The mixture was cooled to room temperature and diluted with ethyl acetate (7 mL). The mixture was washed with brine (3 x 7 mL) and the organic phase was dried over MgSO₄. The solvent was removed by rotary evaporation. An NMR was taken of the crude product, and the yield calculated by quantitative NMR with naphthalene as the internal standard.

For copper loadings of 5 ppm:

4-Bromoanisole (2.50 mL, 20.0 mmol, 1 eq.), benzylamine (3.28 mL, 30.0 mmol, 1.5 eq.), Cu(MeCN)₄.OTf (1 × 10⁻⁵ mmol added via stock solution in EtOH - 1 × 10⁻⁶ M, 2 mL), **L29** (6.4 g, 0.010 mmol, 0.001 eq.), KOH (1.459 g, 26.00 mmol, 1.3 eq.) and naphthalene (0.641 g, 5.00 mmol) were placed in a 14 mL glass vial. The mixture was stirred and heated at 80 °C for 48 hours. The mixture was cooled to room temperature and diluted with ethyl acetate (7 mL). The mixture was washed with brine (3 x 7 mL) and the organic phase was dried over MgSO₄. The solvent was removed by rotary evaporation. An NMR was taken of the crude product, and the yield calculated by quantitative NMR with naphthalene as the internal standard.

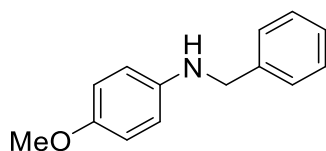
6.2.8 General Procedure for Substrate Scope

Aryl bromide (5.0 mmol, 1 eq.), amine (7.5 mmol, 1.5 eq.), KOH (0.365 g, 6.50 mmol, 1.3 eq.), **L29** (1.6 mg, 0.0050 mmol, 0.001 eq.), Cu(MeCN)₄.OTf (2.5 x 10⁻⁴ mmol, 1 x 10⁻⁵ eq., added via stock solution in EtOH – 0.0005 M, 0.5 mL) and naphthalene (0.320 g, 2.50 mmol, 0.5 eq.) were added to a 7 mL screw-neck vial. The mixture was heated to 80 °C and stirred for 48 hours. Once cooled to room temperature, the reaction was quenched with EtOAc (3 mL) and washed with brine (3 x 3 mL). The organic phase was dried over MgSO₄ and the solvent removed on a rotary evaporator. An NMR was taken of the resulting crude product, and the yield calculated by quantitative NMR using naphthalene as the internal standard.

6.2.9 ¹H and ¹³C NMR of C-N Cross-Coupling Products

The products reported in this section were synthesised according to the procedure in section 6.2.8. All yields were calculated using quantitative NMR, with naphthalene as the internal standard.

2.3 - *N*-Benzyl-4-methoxyaniline

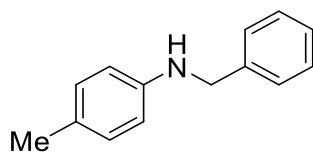


N-Benzyl-4-methoxyaniline (**2.3**) was formed from 4-bromoanisole (0.63 mL, 5.0 mmol, 1 eq.) and benzylamine (0.82 mL, 7.5 mmol, 1.5 eq.) in 99 % yield.

^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.45 (m, 5H, Ar), 6.93 (dt, 2H, $J = 8$ Hz, $J = 3.6$ Hz, Ar) 6.70 (dt, 2H, $J = 8$ Hz, $J = 3.6$ Hz, Ar), 4.36 (s, 2H, CH_2), 3.93 (s, 1H, NH), 3.83 (s, 3H, CH_3).

This compound has been previously reported.¹

2.7 - *N*-Benzyl-4-methylaniline

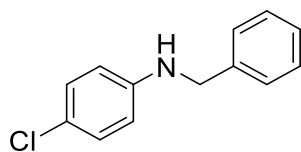


N-Benzyl-4-methylaniline (**2.7**) was formed from 1-bromo-4-methylbenzene (0.855 g, 5.00 mmol, 1 eq.) and benzylamine (0.82 mL, 7.5 mmol, 1.5 eq.) in 89 % yield.

^1H NMR (400 MHz, CDCl_3) δ 7.48 – 7.37 (m, 5H, Ar), 7.16 - 7.11 (m, 2H, Ar), 6.69 (dt, 2H, $J = 8$ Hz, $J = 2.8$ Hz, Ar), 4.41 (s, 2H, CH_2), 3.97 (s, 1H, NH), 2.40 (s, 3H, CH_3).

This compound has been previously reported.²

2.8 - *N*-Benzyl-4-chloroaniline

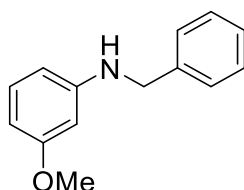


N-Benzyl-4-chloroaniline (**2.8**) was formed from 1-bromo-4-chlorobenzene (0.957 g, 5.00 mmol, 1 eq.) and benzylamine (0.82 mL, 7.5 mmol, 1.5 eq.) in 78 % yield.

^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.33 (m, 5H, Ar), 7.21 (dt, $J = 8.8$ Hz, $J = 3.4$ Hz, 2H, Ar), 6.60 (dt, $J = 8.8$ Hz, $J = 3.4$ Hz, 2H, Ar), 4.34 (s, 2H, CH_2), 3.93 (s, 1H, NH).

This compound has been previously reported.²

2.9 - *N*-Benzyl-3-methoxyaniline

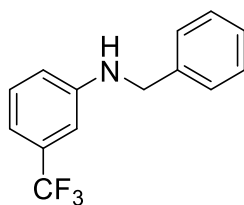


N-Benzyl-3-methoxyaniline (**2.9**) was formed from 1-bromo-3-methoxybenzene (0.63 mL, 5.0 mmol, 1 eq.) and benzylamine (0.82 mL, 7.5 mmol, 1.5 eq.) in 89 % yield.

¹H NMR (400 MHz, CDCl₃) δ 7.46 – 7.35 (m, 5H, Ar), 7.21 - 7.16 (m, 1H, Ar), 6.40 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H, Ar), 6.35 (dd, *J* = 8 Hz, *J* = 2 Hz, 1H, Ar), 6.29 (t, 1H, *J* = 2 Hz, Ar), 4.38 (s, 2H, CH₂), 3.94 (s, 1H, NH), 3.83 (s, 3H, CH₃).

This compound has been previously reported.²

2.10 - *N*-benzyl-3-(trifluoromethyl)aniline

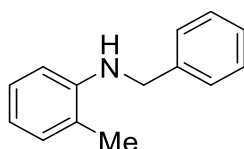


N-Benzyl-3-(trifluoromethyl)aniline (**2.10**) was formed from 3-bromobenzotrifluoride (0.79 mL, 5.0 mmol, 1 eq.) and benzylamine (0.82 mL, 7.5 mmol, 1.5 eq.) in 92 % yield.

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.31 (m, 5H, Ar), 7.31 – 7.27 (m, 1H, Ar), 7.05 - 7.02 (d, 1H, *J* = 8 Hz, Ar), 6.93 – 6.89 (m, 1H, Ar), 6.81 – 6.75 (m, 1H, Ar), 4.37 (s, 2H, CH₂), 3.92 (s, 1H, NH).

This compound has been previously reported.²

2.11 - *N*-Benzyl-2-methylaniline

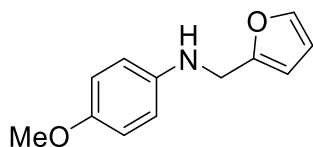


N-Benzyl-2-methylaniline (**2.11**) was formed from 2-bromotoluene (0.604 mL, 5.00 mmol, 1 eq.) and benzylamine (0.82 mL, 7.5 mmol, 1.5 eq.) in 9 % yield. Since a low yield was obtained, there is overlay with starting material peaks in the crude material, so only isolated peaks with no overlay have been reported.

^1H NMR (400 MHz, CDCl_3) δ 6.90 – 6.86 (m, 1H, Ar), 6.81 – 6.76 (m, 2H, Ar), 6.71 – 6.68 (d, 1H, J = 8 Hz, Ar), 4.43 (s, 2H, CH_2), 2.24 (s, 3H, CH_3).

This compound has been previously reported.²

2.12 - *N*-(Furan-2-ylmethyl)-4-methoxyaniline

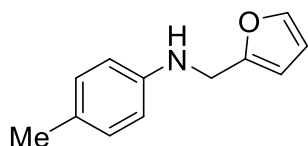


N-(Furan-2-ylmethyl)-4-methoxyaniline (**2.12**) was formed from 4-bromoanisole (0.63 mL, 5.0 mmol, 1 eq.) and furfurylamine (0.66 mL, 7.5 mmol, 1.5 eq.) in 99 % yield.

^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.40 (m, 1H, Ar), 6.86 (dt, 2H, J = 8 Hz, J = 3.5 Hz, Ar), 6.70 (dt, 2H, J = 8 Hz, J = 3.5 Hz, Ar), 6.40 – 6.36 (m, 1H, Ar), 6.30 – 6.25 (m, 1H, Ar), 4.32 (s, 2H, CH_2), 3.87 (s, 1H, NH), 3.80 (s, 3H, CH_3).

This compound has been previously reported.³

2.13 - *N*-(Furan-2-ylmethyl)-4-methylaniline

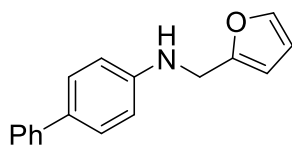


N-(Furan-2-ylmethyl)-4-methylaniline (**2.13**) was formed from 4-bromotoluene (0.855 g, 5.00 mmol, 1 eq.) and furfurylamine (0.66 mL, 7.5 mmol, 1.5 eq.) in 36 % yield. Since a low yield was obtained, there is overlay with starting material peaks in the crude material, so only isolated peaks with no overlay have been reported.

^1H NMR (400 MHz, CDCl_3) δ 6.65 – 6.61 (m, 2H, Ar), 6.25 (m, 1H, Ar), 4.31 (s, 2H, CH_2), 2.28 (s, 3H, CH_3).

This compound has been previously reported.¹

2.14 - *N*-(Furan-2-ylmethyl)-[1,1'-biphenyl]-4-amine



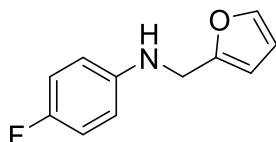
N-(Furan-2-ylmethyl)-[1,1'-biphenyl]-4-amine (**2.14**) was formed from 4-bromobiphenyl (1.166 g, 5.000 mmol, 1 eq.) and furfurylamine (0.66 mL, 7.5 mmol, 1.5 eq.) in 71 %

yield. Since the NMR was taken from the crude mixture, only isolated peaks with no significant overlay from starting materials have been reported.

^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.29 (m, 1H, Ar), 6.82 – 6.76 (dt, 2H, $J = 8$ Hz, $J = 2.8$ Hz, Ar), 6.40 – 6.37 (m, 1H, Ar), 6.33 – 6.29 (m, 1H, Ar), 4.40 (s, 2H, CH_2).

This compound has been previously reported.¹

2.15 - 4-Fluoro-*N*-(furan-2-ylmethyl)aniline

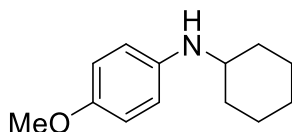


4-Fluoro-*N*-(furan-2-ylmethyl)aniline (**2.15**) was formed from 1-bromo-4-fluorobenzene (0.55 mL, 5.0 mmol, 1 eq.) and furfurylamine (0.66 mL, 7.5 mmol, 1.5 eq.) in 49 % yield. Since the NMR was taken from the crude mixture, only isolated peaks with no significant overlay from starting materials have been reported.

^1H NMR (400 MHz, CDCl_3) δ 7.00 – 6.87 (m, 4H, Ar), 6.66 – 6.58 (m, 2H, Ar), 6.28 – 6.22 (m, 2H, Ar), 4.27 (s, 2H, CH_2).

This compound has been previously reported.¹

2.16 - *N*-Cyclohexyl-4-methoxyaniline

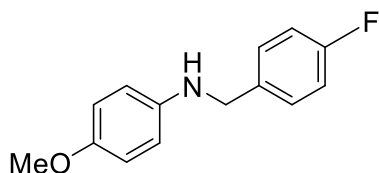


N-Cyclohexyl-4-methoxyaniline (**2.16**) was formed from 4-bromoanisole (0.63 mL, 5.0 mmol, 1 eq.) and cyclohexylamine (0.86 mL, 7.5 mmol, 1.5 eq.) in 14 % yield. Since a low yield was obtained, there is overlay with starting material peaks in the crude material, so only isolated peaks with no overlay have been reported.

^1H NMR (400 MHz, CDCl_3) δ 6.58 (dt, 2H, $J = 8$ Hz, $J = 3.4$ Hz, Ar), 3.74 (s, 3H, CH_3), 3.18 (m, 1H, CH).

This compound has been previously reported.¹

2.17 - *N*-(4-Fluorobenzyl)-4-methoxyaniline

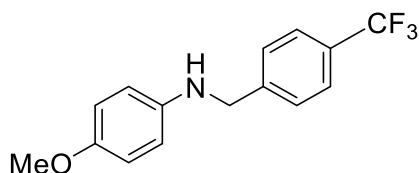


N-(4-Fluorobenzyl)-4-methoxyaniline (**2.17**) was formed from 4-bromoanisole (0.63 mL, 5.0 mmol, 1 eq.) and 4-fluorobenzylamine (0.86 mL, 7.5 mmol, 1.5 eq.) in 99 % yield.

^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.35 (m, 2H, Ar), 7.08 (tt, 3H, $J = 8$ Hz, $J = 3.2$ Hz, Ar), 6.85 (dt, 2H, $J = 8$ Hz, $J = 3.6$ Hz, Ar), 6.64 (dt, 2H, $J = 8$ Hz, $J = 3.6$ Hz, Ar), 4.28 (s, 2H, CH_2), 3.88 (s, 1H, NH), 3.80 (s, 3H, CH_3).

This compound has been previously reported.¹

2.18 - 4-Methoxy-*N*-(4-(trifluoromethyl)benzyl)aniline

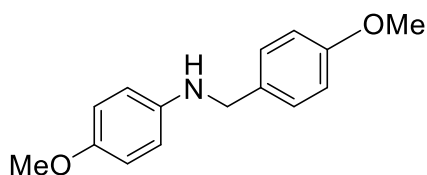


4-Methoxy-*N*-(4-(trifluoromethyl)benzyl)aniline (**2.18**) was formed from 4-bromoanisole (0.63 mL, 5.0 mmol, 1 eq.) and 4-trifluorobenzylamine (1.07 mL, 7.50 mmol, 1.5 eq.) in 41 % yield.

^1H NMR (400 MHz, CDCl_3) δ 7.32 (d, 2H, $J = 8$ Hz, Ar), 7.27 (dt, 2H, $J = 9$ Hz, $J = 3.3$ Hz, Ar), 6.70 – 6.65 (m, 2H, Ar), 6.46 (dt, 2H, $J = 9$ Hz, $J = 3.6$ Hz, Ar), 4.25 (s, 2H, CH_2), 3.63 (s, 3H, CH_3).

This compound has been previously reported.⁴

2.19 - 4-Methoxy-*N*-(4-methoxybenzyl)aniline



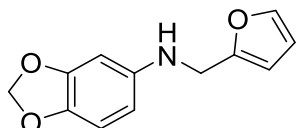
4-Methoxy-*N*-(4-methoxybenzyl)aniline (**2.19**) was formed from 4-bromoanisole (0.63 mL, 5.0 mmol, 1 eq.) and 4-methoxybenzylamine (0.98 mL, 7.5 mmol, 1.5 eq.) in 22 %

yield. Since a low yield was obtained, there is overlay with starting material peaks in the crude material, so only isolated peaks with no overlay have been reported.

^1H NMR (400 MHz, CDCl_3) δ 8.18 (s, 1H, NH), 7.61 (dt, 2H, $J = 8$ Hz, $J = 2.7$ Hz, Ar), 6.82 (dt, 2H, $J = 8$ Hz, $J = 2.8$ Hz, Ar), 4.62 (s, 2H, CH_2), 3.71 (s, 6H, CH_3).

This compound has been previously reported.⁵

2.20 - *N*-(Furan-2-ylmethyl)-4-methylaniline

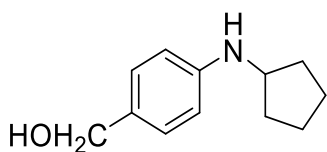


N-(Furan-2-ylmethyl)-4-methylaniline (**2.20**) was formed from 1-bromo-3,4-(methylenedioxy)benzene (0.60 mL, 5.0 mmol, 1 eq.) and furfurylamine (0.66 mL, 7.5 mmol, 1.5 eq.) in 13 % yield. Since a low yield was obtained, there is overlay with starting material peaks in the crude material, so only isolated peaks with no overlay have been reported.

^1H NMR (400 MHz, CDCl_3) δ 6.54 (s, 1H, Ar), 6.12 – 6.10 (m, 1H, Ar), 6.02 – 5.98 (m, 2H, Ar), 5.74 (s, 2H, CH_2), 4.13 (s, 2H, CH_2).

This compound has been previously reported.¹

2.21 - (4-(Cyclopentylamino)phenyl)methanol

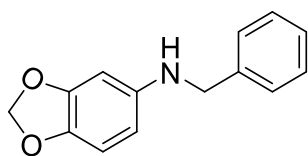


(4-(Cyclopentylamino)phenyl)methanol (**2.21**) was formed from 4-bromobenzylalcohol (0.935 g, 5.00 mmol, 1 eq.) and cyclopentylamine (0.74 mL, 7.5 mmol, 1.5 eq.) in 30 % yield. Since a low yield was obtained, there is overlay with starting material peaks in the crude material, so only isolated peaks with no overlay have been reported.

^1H NMR (400 MHz, CDCl_3) δ 7.07 (d, 2H, $J = 8$ Hz, Ar), 6.49 (d, 2H, $J = 8$ Hz, Ar), 4.44 (s, 2H, CH_2), 3.74 – 3.65 (m, 1H, CH), 1.99 – 1.86 (m, 2H, CH_2), 1.41 – 1.29 (m, 2H, CH_2).

This compound has been previously reported.¹

2.22 - *N*-Benzylbenzo[d][1,3]dioxol-5-amine

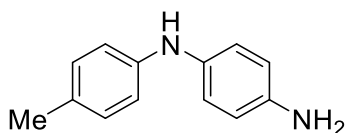


N-Benzylbenzo[d][1,3]dioxol-5-amine (**2.22**) was formed from 1-bromo-3,4-(methylenedioxy)benzene (0.60 mL, 5.0 mmol, 1 eq.) and benzylamine (0.82 mL, 7.5 mmol, 1.5 eq.) in 68 % yield. Since the NMR was taken from the crude mixture, only isolated peaks with no significant overlay from starting materials have been reported.

^1H NMR (400 MHz, CDCl_3) δ 6.12 (d, 1H, J = 4 Hz, Ar), 5.95 – 5.89 (dd, 1H, J = 8 Hz, J = 2 Hz, Ar), 5.78 (s, 1H, Ar), 5.68 (s, 2H, CH_2), 4.10 (s, 2H, CH_2).

This compound has been previously reported.⁶

2.23 - *N*'-(*p*-Tolyl)-benzene-1,4-diamine

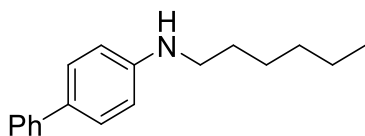


N'-(*p*-Tolyl)-benzene-1,4-diamine (**2.23**) was formed from 1-bromo-4-methylbenzene (0.855 mL, 5.00 mmol, 1 eq.) and *p*-phenylenediamine (0.811 g, 7.50 mmol, 1.5 eq.) in 23 % yield.

^1H NMR (400 MHz, CDCl_3) δ 7.06 – 7.01 (m, 2H, Ar), 6.96 (dt, 2H, J = 8 Hz, J = 3.2 Hz, Ar), 6.82 (dt, 2H, J = 8 Hz, J = 3.2 Hz, Ar), 6.68 (dt, 2H, J = 8 Hz, J = 3.2 Hz, Ar), 5.34 (s, 1H, NH), 2.33 (s, 3H, CH_3).

This compound has been previously reported.¹

2.24 - *N*-Hexyl-[1,1'-biphenyl]-4-amine

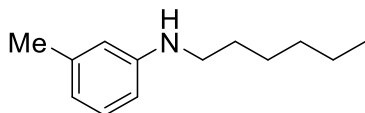


N-Hexyl-[1,1'-biphenyl]-4-amine (**2.24**) was formed from 4-bromobiphenyl (1.166 g, 5.000 mmol, 1 eq.) and hexylamine (0.99 mL, 7.5 mmol, 1.5 eq.) in 75 % yield. Since the NMR was taken from the crude mixture, only isolated peaks with no significant overlay from starting materials have been reported.

^1H NMR (400 MHz, CDCl_3) δ 7.36 – 7.26 (m, 1H, Ar), 6.72 (dt, 2H, $J = 12$ Hz, $J = 2.9$ Hz, Ar), 3.19 (t, 2H, $J = 7$ Hz, CH_2), 2.73 (t, 2H, $J = 8$ Hz, CH_2), 1.73 – 1.64 (m, 2H, CH_2), 1.54 – 1.45 (m, 4H, CH_2).

This compound has been previously reported.¹

2.25 - *N*-Hexyl-3-methylaniline



N-Hexyl-3-methylaniline (**2.25**) was formed from 3-bromotoluene (0.61 mL, 5.0 mmol, 1 eq.) and hexylamine (0.99 mL, 7.5 mmol, 1.5 eq.) in 51 % yield. Since the NMR was taken from the crude mixture, only isolated peaks with no significant overlay from starting materials have been reported.

^1H NMR (400 MHz, CDCl_3) δ 7.31 (s, 1H, NH), 6.55 (d, 1H, $J = 8$ Hz, Ar), 6.47 – 6.42 (m, 2H, Ar), 3.11 (t, 2H, $J = 4$ Hz, CH_2), 2.31 (s, 3H, CH_3), 1.67 – 1.57 (m, 2H, CH_2), 1.50 – 1.39 (m, 6H, CH_2).

This compound has been previously reported.¹

6.3 Experimental Details for Chapter 3

6.3.1 Procedure for Small Scale Reactions with Different Cu Sources and Solvents

The procedure outlined in section **6.2.2** was followed, with substitutions for CuBr_2 (2.2 mg, 0.010 mmol, 0.001 eq.), 1-propanol (1 mL) or $t\text{BuOH}$ (1 mL).

6.3.2 Procedure for EPR Measurements

In 3.5 mL screw-cap glass vials, reaction components in **Table 6.6** were added in various combinations (0.01 mmol), along with 1-propanol, $t\text{BuOH}$ or EtOH (1 mL). The mixtures were sonicated, then stirred at 70 °C until dissolved. The mixtures were transferred to borosilicate capillary tubes (diameter 1.55 mm) and transferred to the EPR spectrometer pre-heated to 80 °C. The samples were allowed to reach thermal equilibrium for 10 minutes before the measurement was taken.

Compound	Quantity Added
CuBr ₂	0.002 g (added via stock solution, 0.02 M)
L29	0.0032 g
KOH	0.0006 g (added via stock solution, 4×10^{-5} mM)
Benzylamine	1 μ L
4-bromoanisole	2 μ L

Table 6.6 Quantities of reaction components used in EPR measurements.

6.3.3 Procedure for CV Measurements

All liquids were degassed prior to each measurement. To a 25 mL 3-neck round bottom flask EtOH (4.9 mL), KOH (0.391 g, 7.00 mmol, 1.5 M), Cu(MeCN)₄OTf (0.011 g, 0.029 mmol, 0.005 M) and **L29** if using (0.009 g, 0.029 mmol, 0.005 M) were added. In one neck of the flask, the silver reference electrode and gold counter electrode were placed in the mixture through a Suba seal. The graphite electrode was attached to an insulated wire pierced through a Suba seal and added through the second neck. If required, benzylamine (0.55 mL, 5.0 mmol, 1.0 M) or 4-bromoanisole (0.63 mL, 5.0 mmol, 1.0 M) were added (with a decreased quantity of EtOH to keep the total volume at 4.9 mL). The mixture was stirred under N₂ for 10 minutes, then heated to 75 °C, at which point the measurements were taken.

6.3.4 Procedure for Direct Infusion Mass Spectrometry Experiments

In a 3-neck round bottom flask 4-bromoanisole (3.15 mL, 25.0 mmol, 1.0 M), furfurylamine (5.46 mL, 50.0 mmol, 2.0 M), KOH (1.953 g, 35.0 mmol), EtOH (9 mL if stock solution used, 10 mL if not) and **L37** if using (0.263g, 0.5 mmol) were added. In one neck a mercury thermometer was placed, and in another a Suba seal. Tubing was inserted into the reaction mixture via the Suba seal and was connected to a HPLC pump which allowed for aliquots to be taken during the reaction and transported to a dilution unit and then the mass spectrometer. The mixture was heated to reflux and initiated with a copper and **L29** (if using) stock solution (0.063 M, 1 mL). Aliquots were taken during the course of the reaction for analysis. Acetonitrile was used as the diluent and measurements were taken in both positive and negative ion mode.

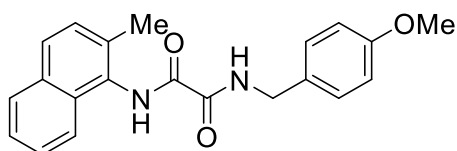
6.3.5 Synthesis of L38 – L41

The synthesis of **L38 – L41** followed the same procedure as that outlined in section 6.2.1, but the substituted benzylamines outlined in **Table 6.7** were used instead of benzylamine.

Compound	Quantity Added	
	Mmol	mL
4-methoxybenzylamine (L38)	3.8	0.50
4-fluorobenzylamine (L39)	3.8	0.44
4-trifluoromethylbenzylamine (L40)	3.8	0.55
4-methylbenzylamine (L41)	3.8	0.49

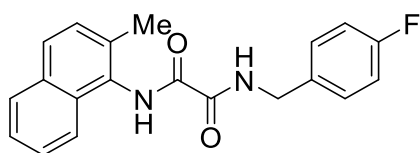
Table 6.7 Compounds used in synthesis of **L38** – **L41**.

L38



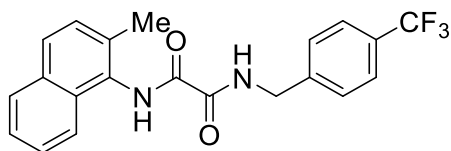
L38 was synthesised as a white powder (1.028 g, 2.95 mmol, 34 %). Mp.: 188 – 190 °C. ^1H NMR (400 MHz, CDCl_3) δ 9.24 (s, 1H, NH), 7.89 - 7.82 (m, 3H, Ar, NH), 7.80 (d, 1H, J = 8 Hz, Ar), 7.57 – 7.45 (m, 2H, Ar), 7.42 (d, 1H, J = 8 Hz, Ar), 7.32 (d, 2H, J = 8 Hz, Ar), 6.93 (dt, 2H, J = 8 Hz, J = 3 Hz, Ar), 4.56 (d, 2H, J = 8 Hz, CH_2), 3.84 (s, 3H, OMe), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 159.6 (C=O), 159.4 (C=O), 158.6 (Ar), 133.0 (Ar), 132.7 (Ar), 129.9 (Ar), 129.5 (Ar), 128.8 (Ar), 128.3 (Ar), 128.2 (Ar), 126.9 (Ar), 125.6 (Ar), 122.0 (Ar), 114.3 (Ar), 114.0 (Ar), 55.4 (OMe), 43.6 (CH_2), 18.8 (CH_3). HRMS (ES $^+$, TOF): m/z 349.1561 [$\text{M}+\text{H}$] $^+$, calculated for [$\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_3$] $^+$: 349.1552.

L39



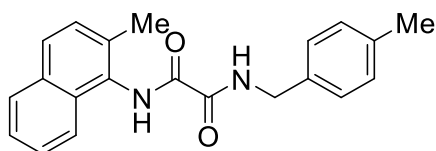
L39 was synthesised as a white powder (0.999 g, 2.97 mmol, 36 %). Mp.: 175 – 176 °C. ^1H NMR (400 MHz, CDCl_3) δ 9.22 (s, 1H, NH), 7.96 – 7.89 (m, 1H, NH), 7.89 - 7.79 (m, 3H, Ar), 7.57 – 7.45 (m, 2H, Ar), 7.42 (d, 1H, J = 8 Hz, Ar), 7.39 – 7.32 (m, 2H, Ar), 7.13 - 7.05 (m, 2H, Ar), 4.58 (d, 2H, J = 4 Hz, CH_2), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 159.7 (C=O), 158.5 (C=O), 133.0 (Ar), 132.7 (Ar), 132.5 (Ar), 129.9 (Ar), 129.8 (Ar), 128.8 (Ar), 128.3 (Ar), 128.2 (Ar), 126.9 (Ar), 125.6 (Ar), 122.0 (Ar), 115.9 (Ar), 115.7 (Ar), 43.3 (CH_2), 18.8 (CH_3). $^{19}\text{F}\{^1\text{H}\}$ NMR (400 MHz, CDCl_3) δ 114.07 (s, 1F, Ar). HRMS (ESI $^-$, FT): m/z 335.1201 [$\text{M}-\text{H}$] $^-$, calculated for [$\text{C}_{20}\text{H}_{16}\text{FN}_2\text{O}_2$] $^-$: 335.1201.

L40



L40 was synthesised as a white powder (0.877 g, 2.27 mmol, 28 %). Mp.: 225 – 226 °C. ^1H NMR (400 MHz, CDCl_3) δ 9.22 (s, 1H, NH), 8.10 – 8.00 (m, 1H, NH), 7.90 – 7.78 (m, 3H, Ar), 7.65 (d, 2H, J = 12 Hz, Ar), 7.58 – 7.45 (m, 3H, Ar), 7.42 (d, 1H, J = 8 Hz, Ar), 4.67 (d, 2H, J = 8 Hz, CH_2), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 160.0 (C=O), 158.3 (C=O), 140.8 (CF_3), 133.5, (Ar), 133.0 (Ar), 132.7 (Ar), 129.8 (Ar), 128.8 (Ar), 128.3 (Ar), 128.2 (Ar), 127.0 (Ar), 125.7 (Ar), 121.9 (Ar), 43.5 (CH_2), 18.8 (CH_3). HRMS (ESI-, FT): m/z 385.1172 $[\text{M}-\text{H}]^-$, calculated for $[\text{C}_{21}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_2]^-$: 385.1169.

L41



L41 was synthesised as a white powder (0.646 g, 1.95 mmol, 24 %). Mp.: 188 – 189 °C. ^1H NMR (400 MHz, CDCl_3) δ 9.23 (s, 1H, NH), 7.90 – 7.82 (m, 3H, Ar, NH), 7.80 (d, 1H, J = 8 Hz, Ar), 7.57 – 7.45 (m, 2H, Ar), 7.42 (d, 1H, J = 8 Hz, Ar), 7.25 – 7.19 (m, 2H, Ar), 7.16 (s, 1H, Ar), 4.59 (d, 2H, J = 4 Hz, CH_2), 2.44 (s, 3H, CH_3), 2.39 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 159.7 (C=O), 158.6 (C=O), 137.8 (Ar), 133.6 (Ar), 133.0 (Ar), 132.7 (Ar), 129.9 (Ar), 129.6 (Ar), 128.8 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 126.9 (Ar), 125.6 (Ar), 122.0 (Ar), 43.9 (CH_2), 21.2 (CH_3), 18.8 (CH_3). HRMS (ES+, TOF): m/z 333.1605 $[\text{M}+\text{H}]^+$, calculated for $[\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_2]^+$: 333.1603.

6.3.6 Procedure for In Situ Calorimetry Measurements

4-iodoanisole (2.340 g, 10.0 mmol, 1 eq.), KOH (0.729 g, 13.0 mmol, 1.3 eq.), and naphthalene (0.641 g, 5.00 mmol, 0.5 eq.) were placed in a 14 mL glass vial with a stirrer bar. The vial was loosely capped and transferred to a nitrogen-filled glovebox. Once inside, the vial was sealed with septum lids. The vial was taken out of the glovebox and benzylamine (1.64 mL, 15.0 mmol, 1.5 eq.) and 1-propanol (3.06 mL) were added (both liquids were degassed prior to use). The vial was placed in the calorimeter pre-heated to 90 °C and left for 40 minutes to equilibrate. The reaction was initiated with a stock solution of $\text{Cu}(\text{MeCN})_4\text{OTf}$ and ligands **L29**, **L38** – **L41** (0.20 mL,

0.1 M) and left to react for 4 hours until the heat output flattened. A Tau-correction was applied to the data before processing. A final yield was obtained by sampling ~ 0.2 mL reaction solution and adding to a vial containing 0.6 mL CDCl₃ and 0.6 mL brine. The mixture was separated and a second portion of CDCl₃ was added to the brine layer. The combined organic layers were dried over MgSO₄ and filtered into an NMR tube.

6.3.7 Procedure for NMR studies with Fluorine-Tagged Ligands.

To 6 glass vials, **L39** was added (0.003 g, 0.01 mmol). The components outlined in **Table 6.8** were added individually to the vials, along with CDCl₃ (1 mL). The mixtures were stirred at room temperature for 24 hours, then ¹⁹F NMR analyses was performed. After this, the mixtures containing benzylamine and KOH were stirred at 50 °C for a further 24 hours, then ¹H NMR analysis was performed.

Compound	Quantity Added
KOH	0.0006 g
Benzylamine	1 µL
4-bromoanisole	2 µL
DEGEE	1 µL
EtOH	1 µL
H ₂ O	1 µL

Table 6.8 Quantities added in NMR study.

6.3.8 Procedure for Multiple Addition of L29

To a 3-neck 100 mL round bottom flask naphthalene (3.203 g, 25.00 mmol), KOH (3.647 g, 65.00 mmol), EtOH (9.4 mL), benzylamine (8.19 mL, 75.0 mmol) and 4-bromoanisole (6.28 mL, 50.0 mmol) were added and heated to reflux (112 °C). The mixture was stirred for 20 minutes until the solids were dissolved. Cu(MeCN)₄.OTf and **L29** were added via stock solution (0.02 M, 0.6 mL) to initiate the reaction. ~0.1 mL aliquots were collected over the course of the reaction (2.5 h) and were placed in a screw-cap vial with brine (0.6 mL) and CDCl₃ (0.6 mL). The aqueous layer was washed with further CDCl₃ (0.6 mL). The combined organic layers were dried over MgSO₄ and filtered into an NMR tube. At 2.5 h, a second addition of a stock solution of **L29** (0.02 M, 0.6 mL) was added to the mixture. Aliquots were taken for a further 2.5 h as described above.

6.3.9 Procedure for NMR studies with L29.

To a round bottom flask, **L29** (0.159 g, 0.500 mmol), benzylamine (1.07 mL, 1.00 mmol), EtOH (10 mL) and/or KOH (0.561 g, 1.00 mmol), was added. The mixture was

stirred at reflux for 6 hours or 1 week. Upon cooling a white precipitate formed. The precipitate was filtered and washed with HCl (10 mL, 0.1 M) and hexane (10 mL), then dried overnight and characterised by ^1H NMR in both DMSO- d_6 and CDCl_3 . The organic phase of the filtrate was collected and dried over MgSO_4 , then the solvents were removed under vacuum to form a brown liquid, which was then characterised by ^1H NMR.

6.3.10 Procedure for Initial Rate Investigation

0.005 mol % $\text{Cu}(\text{MeCN})_4\text{OTf}$, 0.1 mol % **L29**:

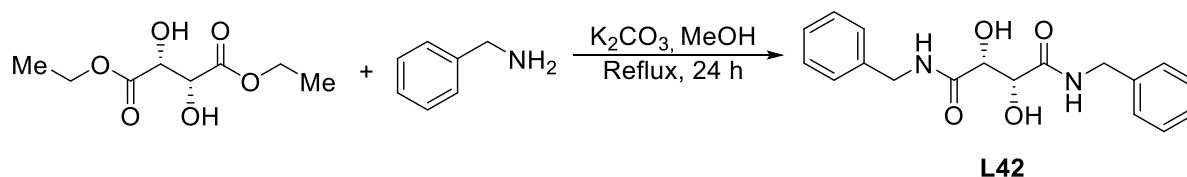
To a 3-neck 100 mL round bottom flask naphthalene (3.203 g, 25.00 mmol), KOH (3.647 g, 65.00 mmol), DEGEE (9.6 mL), benzylamine (8.19 mL, 75.0 mmol) and 4-bromoanisole (6.28 mL, 50.0 mmol) were added and heated to 105 °C. The mixture was stirred for 20 minutes until the solids were dissolved. $\text{Cu}(\text{MeCN})_4\text{OTf}$ and **L29** were added via stock solution (0.04 M **L29**, 0.0062 M $\text{Cu}(\text{MeCN})_4\text{OTf}$, 0.4 mL) to initiate the reaction. ~0.1 mL aliquots were collected over the course of the reaction (0.5 h) and were placed in a screw-cap vial with brine (0.6 mL) and CDCl_3 (0.6 mL). The aqueous layer was washed with further CDCl_3 (0.6 mL). The combined organic layers were dried over MgSO_4 and filtered into an NMR tube.

0.005 mol % $\text{Cu}(\text{MeCN})_4\text{OTf}$, 0.75 – 7.5 mol % **L29**:

To a 3-neck 100 mL round bottom flask naphthalene (3.203 g, 25.00 mmol), KOH (3.647 g, 65.00 mmol), **L29** (0.75 mol %: 0.119 g, 7.5 mol %: 1.194 g), DEGEE (9.6 mL), benzylamine (8.19 mL, 75.0 mmol) and 4-bromoanisole (6.28 mL, 50.0 mmol) were added and heated to 105 °C. The mixture was stirred for 20 minutes until the solids were dissolved. $\text{Cu}(\text{MeCN})_4\text{OTf}$ was added via stock solution (0.0062 M, 0.4 mL) to initiate the reaction. ~0.1 mL aliquots were collected over the course of the reaction (0.5 h) and were placed in a screw-cap vial with brine (0.6 mL) and CDCl_3 (0.6 mL). The aqueous layer was washed with further CDCl_3 (0.6 mL). The combined organic layers were dried over MgSO_4 and filtered into an NMR tube.

6.4 Experimental Details for Chapter 4

6.4.1 Synthesis of L42

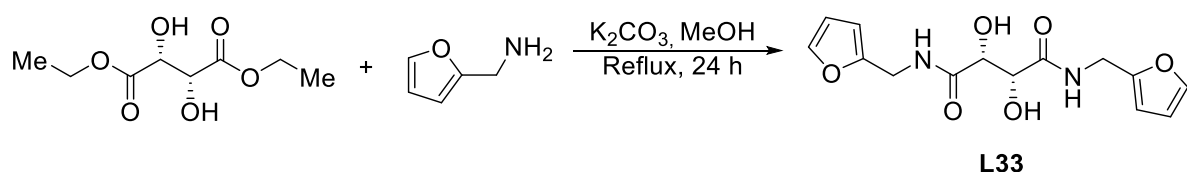


Scheme 6.2 Synthesis route of **L42**.

L42 was synthesised according to the procedure outlined by Davies *et al.*²

(+)-Diethyl-L-tartrate (1.72 mL, 10.0 mmol, 1 eq.), benzylamine (2.79 mL, 26.0 mmol, 2.6 eq.), K₂CO₃ (49.8 mg, 0.360 mmol, 0.036 eq.) and MeOH (25 mL) were stirred at reflux for 24 hours. A suspension of crystals in MeOH formed. Once cooled to room temperature, water (25 mL) was added to induce further precipitation. The mixture was filtered under suction and washed with water to obtain colourless crystals (2.233 g, 6.80 mmol, 68 %). M.p.: 200 – 202 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.26 (t, *J* = 8 Hz, 2H, NH), 7.33 – 7.28 (m, 8H, Ar), 7.26 – 7.18 (m, 2H, Ar), 5.75 (d, *J* = 8 Hz, 2H, CH), 4.43 – 4.34 (m, 4H, CH₂), 4.34 – 4.27 (m, 2H, OH). ¹³C NMR (100 MHz, DMSO-d₆) δ 172.7 (C=O), 139.9 (Ar), 128.6 (Ar), 127.6 (Ar), 127.1 (Ar), 73.2 (OH), 42.3 (CH₂). HRMS (ES⁺, TOF): *m/z* 329.1506 [M+H]⁺, calculated for [C₁₈H₂₁N₂O₄]⁺: 329.1501.

6.4.2 Synthesis of L33



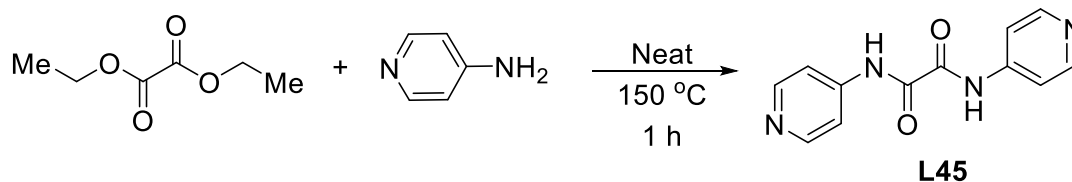
Scheme 6.3 Synthesis route of **L33**.

L33 was synthesised according to the procedure outlined by Davies *et al.*²

(+)-Diethyl-L-tartrate (1.72 mL, 10.0 mmol, 1 eq.), furfurylamine (2.30 mL, 26.0 mmol, 2.6 eq.), K₂CO₃ (49.8 mg, 0.360 mmol, 0.036 eq.) and MeOH (25 mL) were stirred at reflux for 24 hours. A suspension of crystals in MeOH formed. Once cooled to room temperature, water (25 mL) was added to induce further precipitation. The mixture was filtered under suction and washed with water to obtain colourless crystals (2.220 g, 7.20 mmol, 72 %). M.p.: 180 – 181 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.10 (t, *J* = 8 Hz, 2H, NH), 7.56 (s, 2H, Ar), 6.40 – 6.36 (m, 2H, Ar), 6.25 – 6.23 (m, 2H, Ar), 5.69 (d, *J* = 4 Hz, 2H, CH), 4.39 – 4.31 (m, 2H, OH), 4.30 – 4.38 (m, 4H, CH₂). ¹³C NMR (100

MHz, DMSO- d_6) δ 172.5 (C=O), 152.8 (Ar), 142.4 (Ar-O), 110.9 (Ar), 107.1 (Ar), 73.1 (CH), 36.0 (CH₂). HRMS (ES⁺, TOF): m/z 309.1086 [M+H]⁺, calculated for [C₁₄H₁₇N₂O₆]⁺: 309.1087.

6.4.3 Synthesis of L45

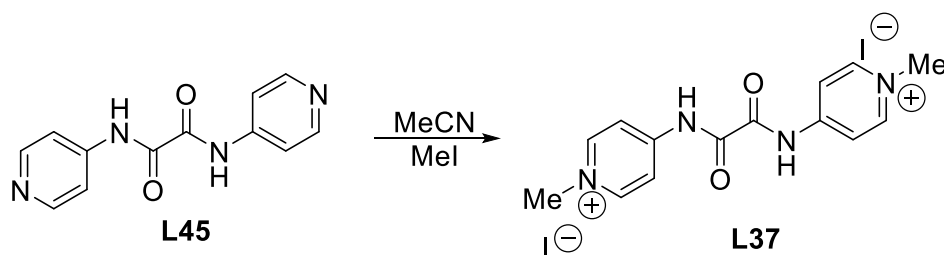


Scheme 6.4 Synthesis route of **L45**.

L45 was synthesised according to the procedure outlined by Tzeng *et al.*⁷

4-Aminopyridine (1.884 g, 20.00 mmol, 2 eq.) and diethyl oxalate (1.4 mL, 10 mmol, 1 eq.) were stirred at 150 °C for 1 hour. The resulting solid was washed with acetone, filtered by suction filtration and dried to yield a white powder (1.962 g, 8.10 mmol, 81 %). ¹H NMR (400 MHz, DMSO- D_6) δ 11.29 (s, 2H, NH), 8.58 – 8.51 (m, 4H, Ar (N-CH)), 7.92 – 7.84 (m, 4H, Ar (C-CH)). ¹³C NMR (100 MHz, DMSO- D_6) δ 159.4 (C=O), 151.0 (Ar (N-CH)), 144.9 (Ar), 114.8 (Ar (C-CH)). HRMS (ES⁺, TOF): m/z 243.0874 [M+H]⁺, calculated for [C₁₂H₁₁N₄O₂]⁺: 243.0804.

6.4.4 Synthesis of L37



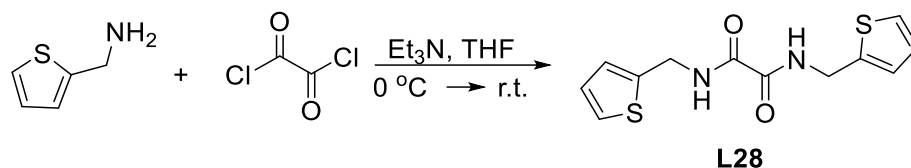
Scheme 6.5 Synthesis route of **L37**.

L37 was synthesised according to the procedure outlined by Salzmann *et al.*⁸

Methyl iodide (0.90 mL, 15 mmol, 2.9 eq.) was added to a solution of **L45** (1.211 g, 5.000 mmol, 1 eq.) and MeCN (150 mL). The mixture was heated to 80 °C for 18 hours. A cloudy yellow solution formed. After cooling to room temperature, the resulting solid was filtered by suction filtration and washed with MeCN (5 mL). The solid was dried overnight to yield a bright yellow powder (2.368 g, 0.45 mmol, 90 %). ¹H NMR (400 MHz, DMSO- D_6) δ 12.20 (s, 2H, NH), 8.87 – 8.82 (m, 4H, Ar (N-CH)), 8.41 – 8.37 (m,

4H, Ar (C-CH)), 4.24 (s, 6H, CH₃). ¹³C NMR (100 MHz, DMSO-D₆) δ 159.5 (C=O), 151.1 (Ar), 146.9 (Ar (N-CH)), 116.6 (Ar (C-CH)), 47.3 (CH₃). HRMS (ES⁺, TOF): *m/z* 524.9289 [M-H]⁻, calculated for C₁₄H₁₆I₂N₄O₂: 524.9290.

6.4.5 Synthesis of L28

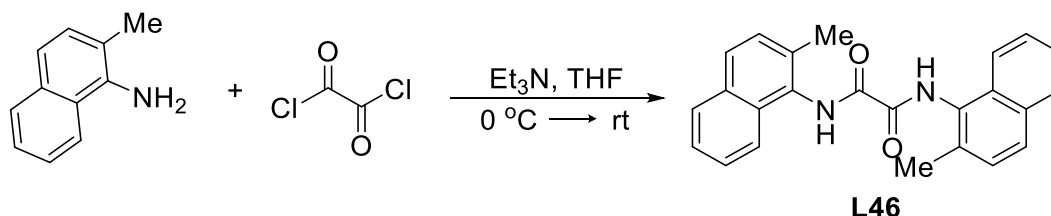


Scheme 6.6 Synthesis route of **L28**.

L28 was synthesised according to the procedure outlined by Ma *et al.*⁹

Oxalyl chloride (0.86 mL, 10 mmol, 1 eq.) was added drop-wise to a solution of 2-thiophenylmethanamine (2.05 mL, 20.0 mmol, 2 eq.), Et₃N (3.49 mL, 25.0 mmol, 2.5 eq.) and THF (30 mL) at 0 °C. The mixture was stirred at room temperature for 2 hours. The solvent was removed via rotary evaporation to give a yellow solid. Water (30 mL) was added to the resulting solid to dissolve Et₃N.HCl. The solid product was removed via suction filtration and washed with water (3 mL) and cold diethyl ether (3 mL). The solid was dried overnight in a vacuum oven at 40 °C. The pure product was obtained by recrystallisation in EtOAc. **L28** was formed as a white solid (2.015 g, 7.20 mmol, 72 %). M.p.: 190 – 191 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.43 (t, *J* = 8 Hz, 2H, NH), 7.39 (d, *J* = 8 Hz, 2H, Ar), 7.09 – 6.85 (m, 4H, Ar), 4.48 (d, *J* = 8 Hz, 4H, CH₂). ¹³C NMR (100 MHz, DMSO-*d*₆) δ 160.2 (C=O), 141.7 (Ar-S), 127.1 (Ar), 126.4 (Ar), 125.7 (Ar), 37.8 (CH₂). HRMS (ES⁺, TOF): *m/z* 281.0419 [M+H]⁺, calculated for [C₁₂H₁₃N₂O₂S₂]⁺: 281.0418.

6.4.6 Synthesis of L46



Scheme 6.7 Synthesis route of **L46**.

L46 was synthesised according to the procedure outlined by Ma *et al.*¹

Oxalyl chloride (0.4 mL, 5 mmol, 1 eq.) was added drop-wise to a solution of 2-methylnaphthalenylamine (0.9 mL, 10 mmol, 2 eq.), Et₃N (1.4 mL, 11 mmol, 2.1 eq.) and THF (20 mL) while the reaction vessel was in ice. The mixture was stirred at room temperature for 2 hours. The solvent was removed via rotary evaporation to give a yellow solid. Water (5 mL) was added to the resulting solid to dissolve Et₃N.HCl. The solid product was removed via suction filtration and washed with water (3 mL) and cold diethyl ether (3 mL). The solid was dried overnight in a vacuum oven at 40 °C. The pure product was obtained by recrystallisation with EtOAc. **L46** was formed as a pale yellow solid (1.333 g, 3.62 mmol, 72 %). ¹H NMR (400 MHz, CDCl₃) δ 9.35 (s, 2H, NH), 7.96 (d, 2H, *J* = 8 Hz, Ar), 7.91 (d, 2H, *J* = 8 Hz, Ar), 7.85 (d, 2H, *J* = 8 Hz, Ar), 7.62 (t, 2H, *J* = 4 Hz, Ar), 7.53 (t, 2H, *J* = 4 Hz, Ar), 7.48 (d, 2H, *J* = 8 Hz, Ar), 2.56 (s, 6H, Me). ¹³C NMR (100 MHz, CDCl₃) δ 158.6 (C=O), 133.0 (Ar), 132.8 (Ar), 130.0 (Ar), 128.8 (Ar), 128.3 (Ar), 128.3 (Ar), 128.2 (Ar), 127.1 (Ar), 125.7 (Ar), 122.0 (Ar), 18.9 (Me). HRMS (ES+, TOF): *m/z* 367.1452 [M+H]⁺, calculated for [C₂₄H₂₁N₂O₂]⁺: 367.1525.

6.4.7 General Procedure for Cross-Coupling Reactions with Alternative

Ligands

4-Bromoanisole (1.25 mL, 10.0 mmol, 1 eq.) or 4-iodoanisole (2.340 g, 10.00 mmol, 1 eq.), benzylamine (1.64 mL, 15.0 mmol, 1.5 eq.), Cu(MeCN)₄.OTf (0.1 mol %: 3.8 mg, 0.010 mmol, 0.001 eq., 1 mol %: 0.0376 g, 0.10 mmol, 0.01 eq., 5 mol %: 0.1884 g, 0.5 mmol, 0.05 eq.), ligand (0.1, 1 or 5 mol %, 0.01, 0.1 or 0.5 mmol), KOH (0.729 g, 13.0 mmol, 1.3 eq.), EtOH (2 mL) and naphthalene (0.641 g, 5.00 mmol) were placed in a 14 mL glass vial. The mixture was stirred and heated at 80 °C for 12 hours, then cooled to room temperature and diluted with ethyl acetate (7 mL). The mixture was washed with brine (2 x 7 mL) and the organic phase was dried over MgSO₄. The solvent was removed by rotary evaporation. An NMR was taken of the crude product, and the yield calculated by quantitative NMR with naphthalene as the internal standard.

6.5 References

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Supporting Information

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Figure S1. ¹H NMR of L29.

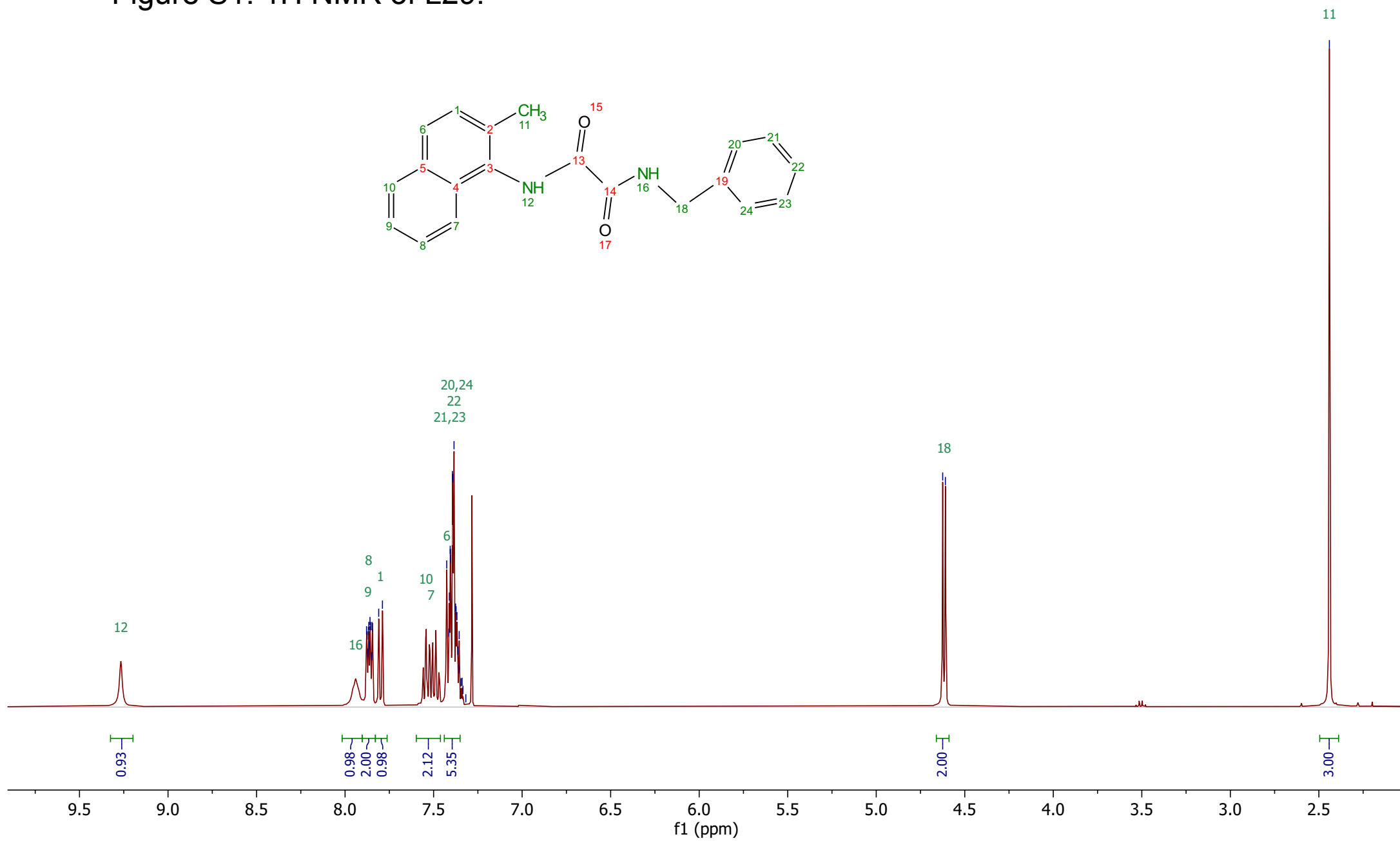


Figure S2. ¹³C NMR of L29.

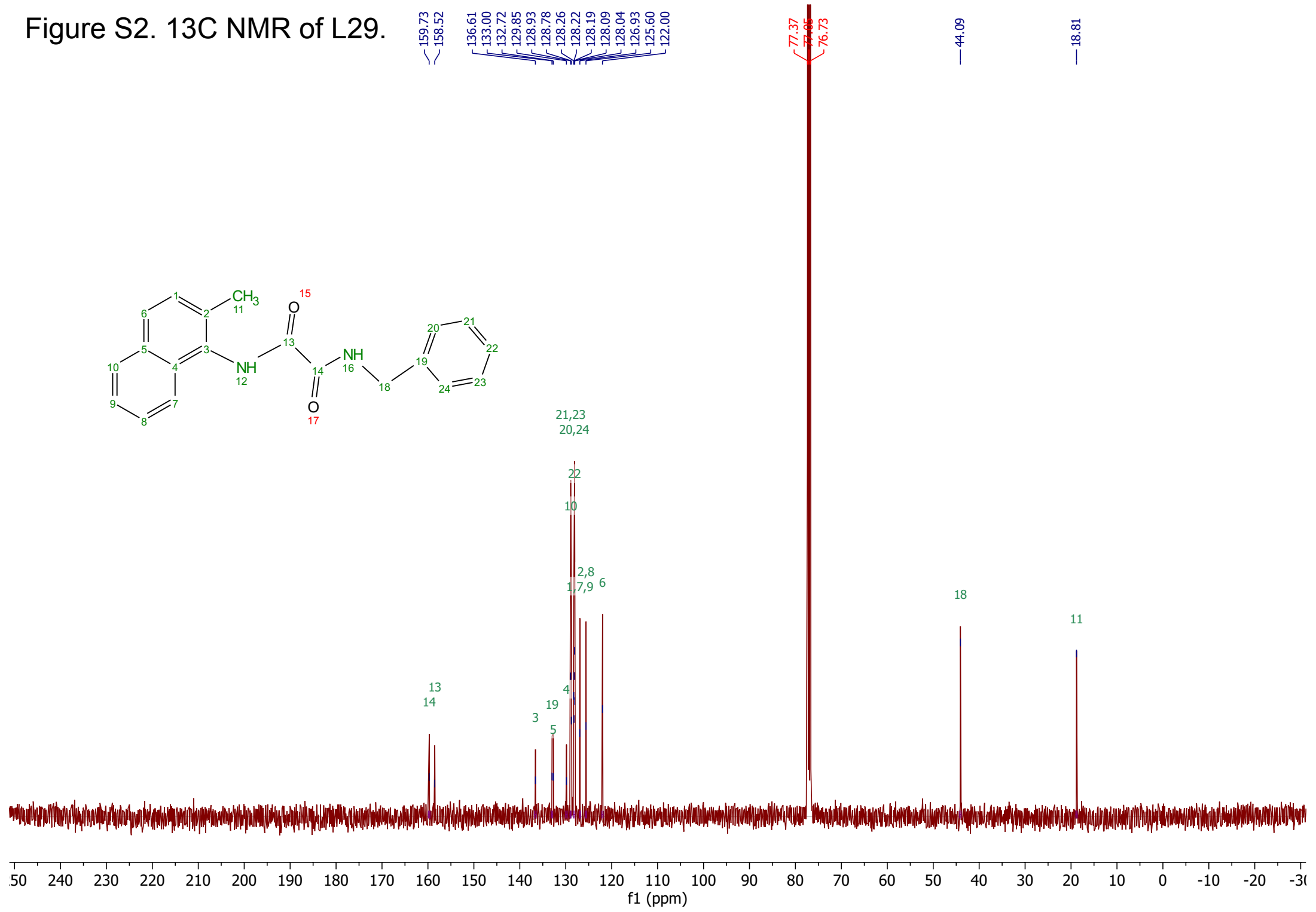


Figure S3. ^1H NMR of 2.3.

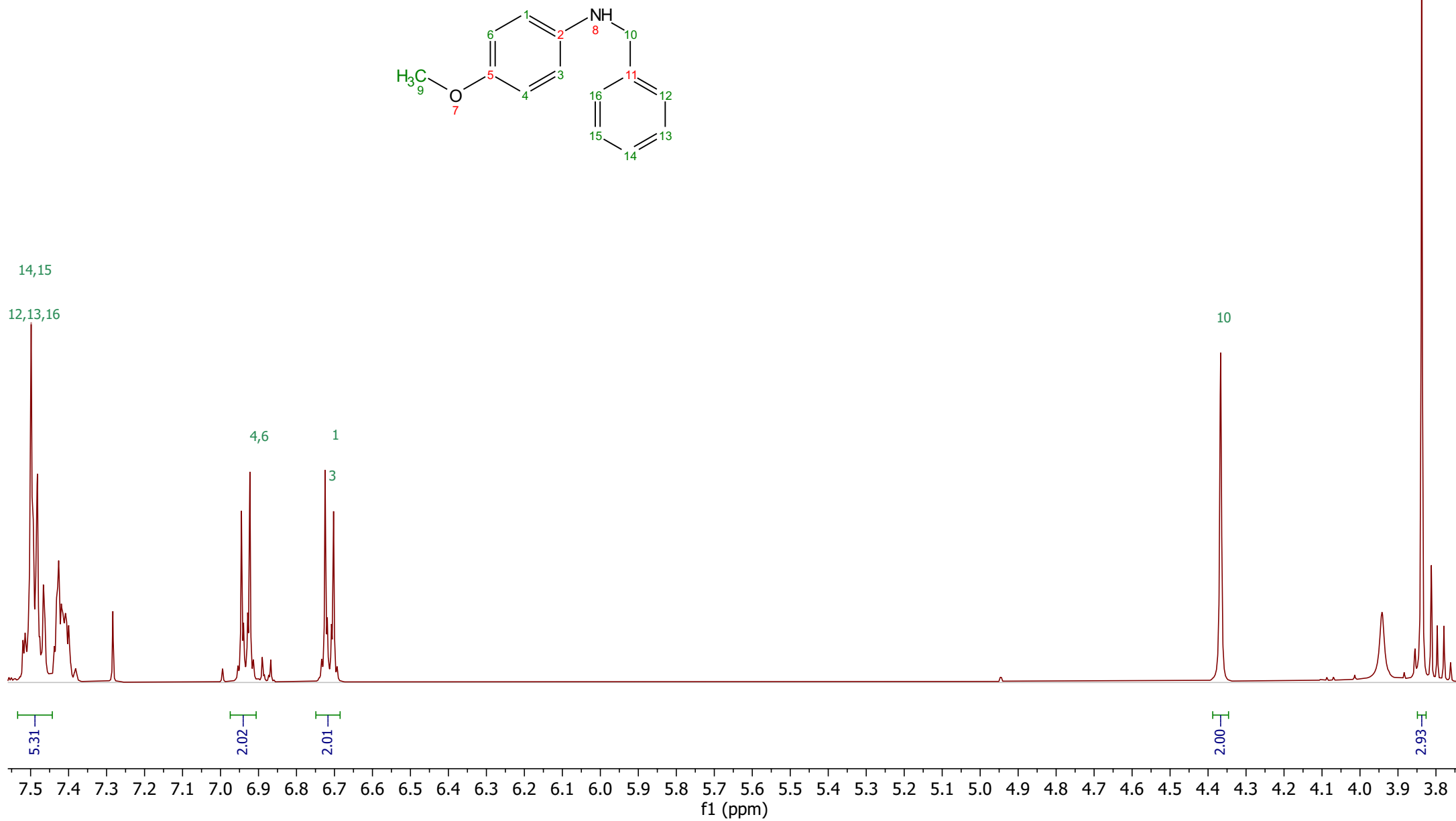


Figure S4. ^1H NMR of isolated 2.3.

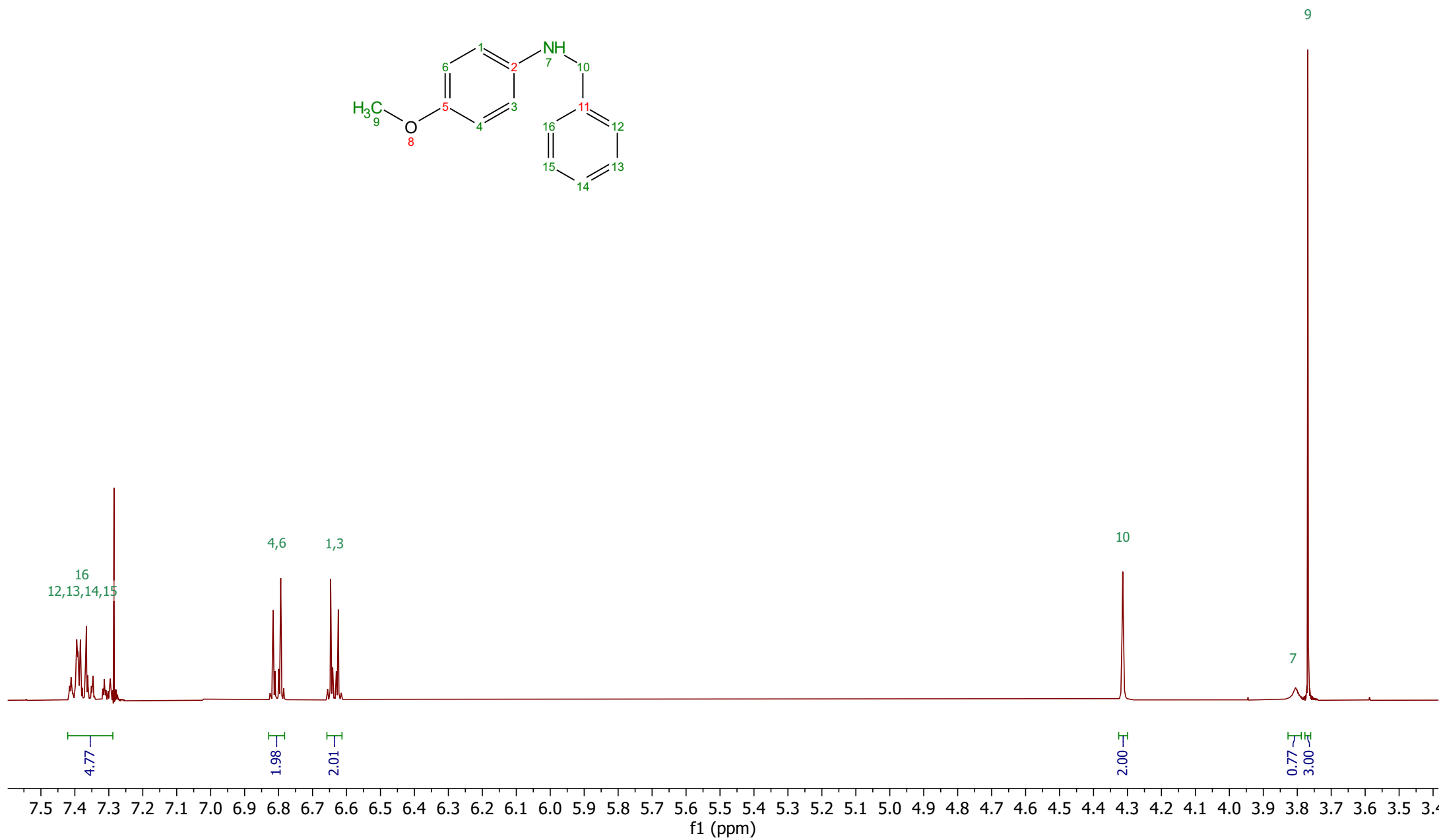


Figure S5. ¹H NMR of 2.7.

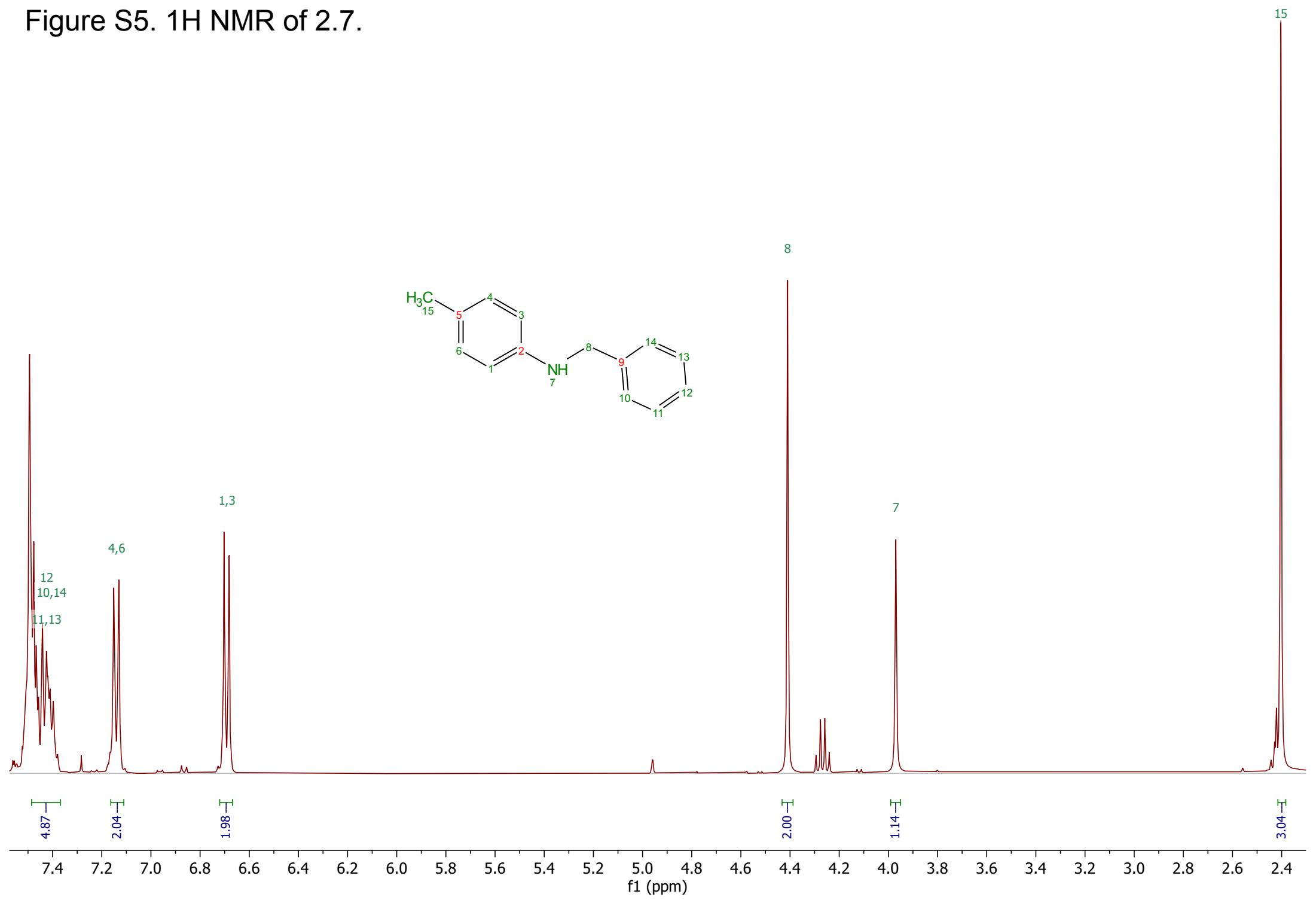


Figure S6. ^1H NMR of 2.8.

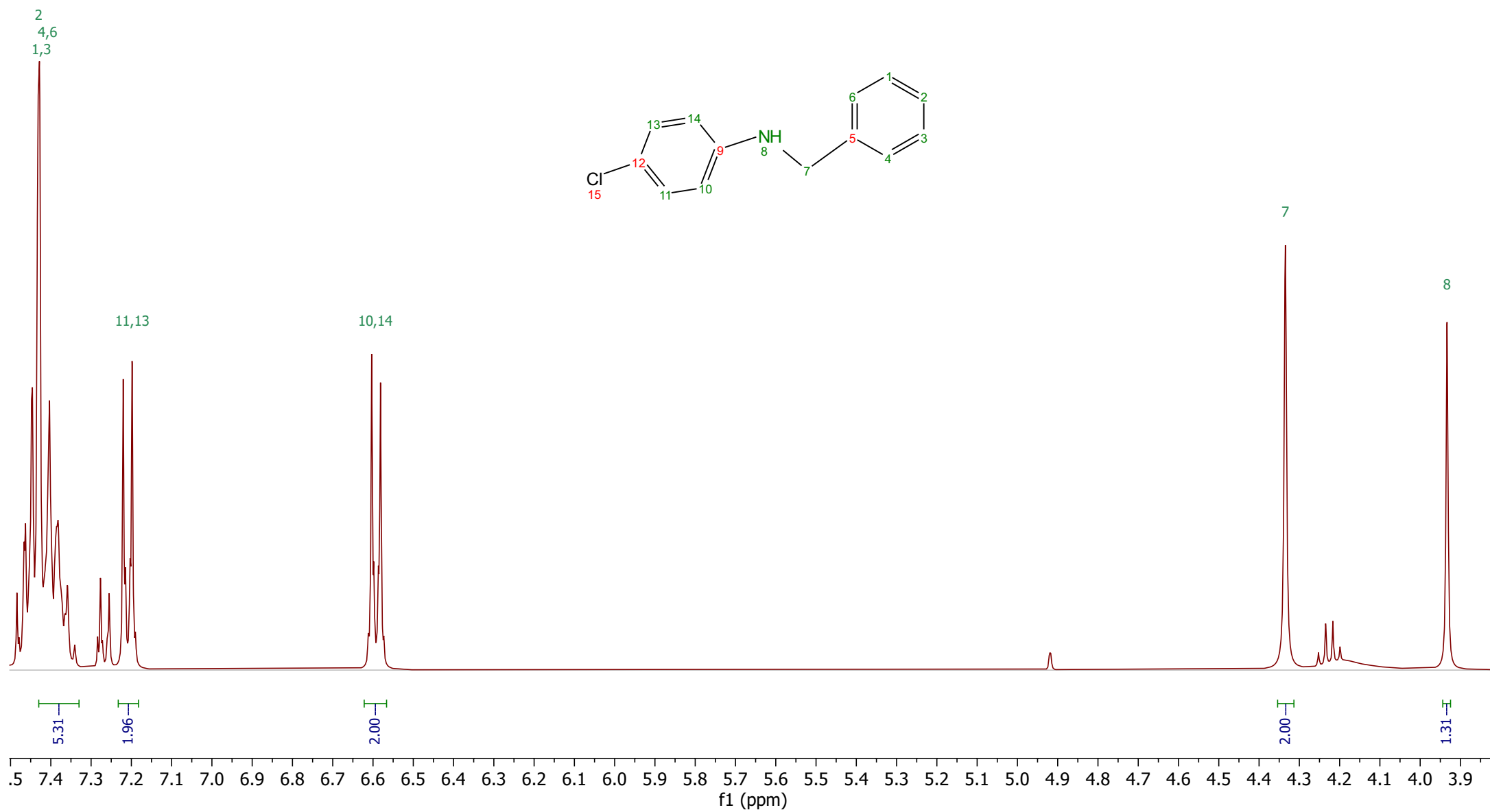


Figure S7. ¹H NMR of 2.9.

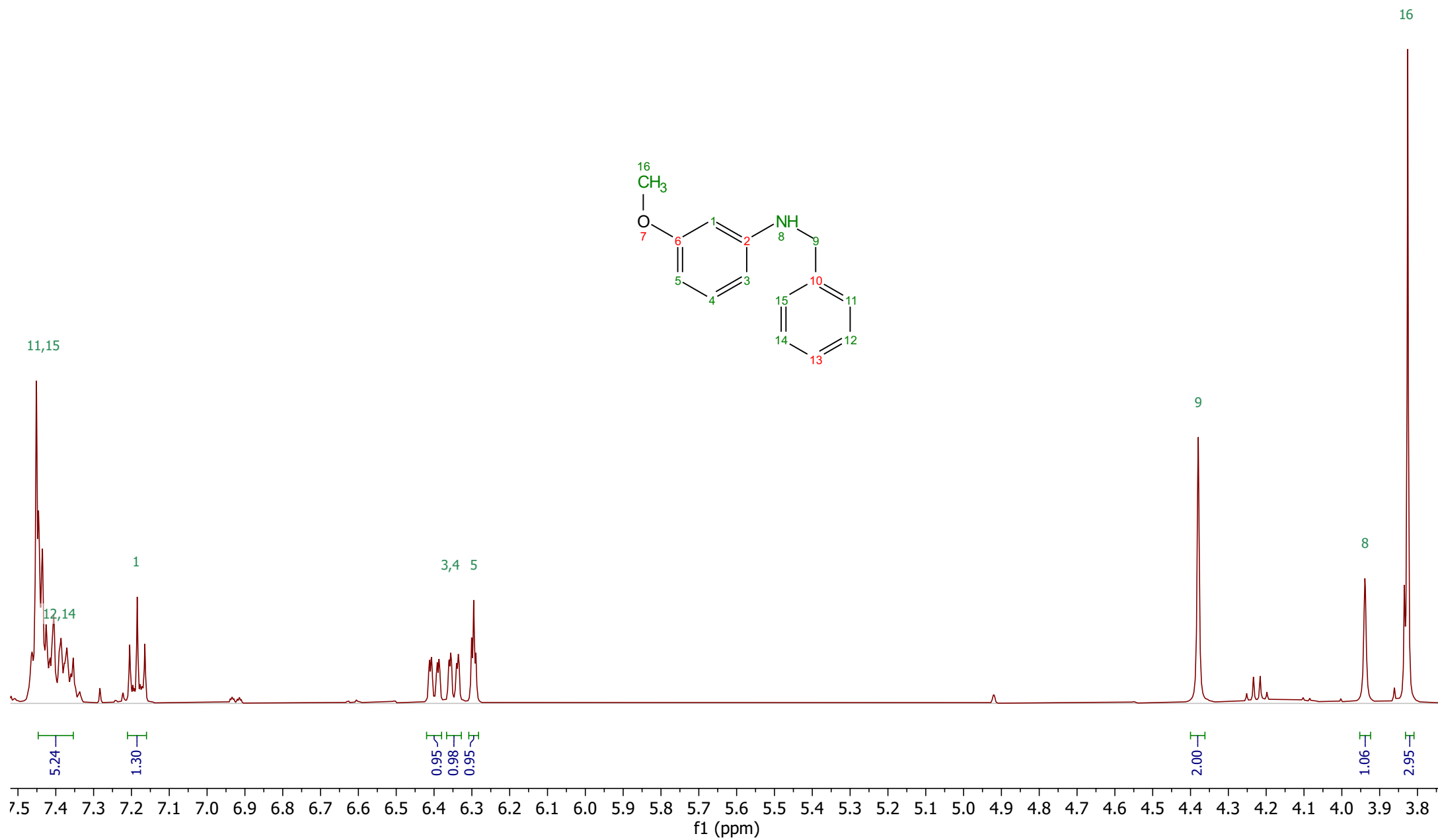


Figure S8. ¹H NMR of 2.10.

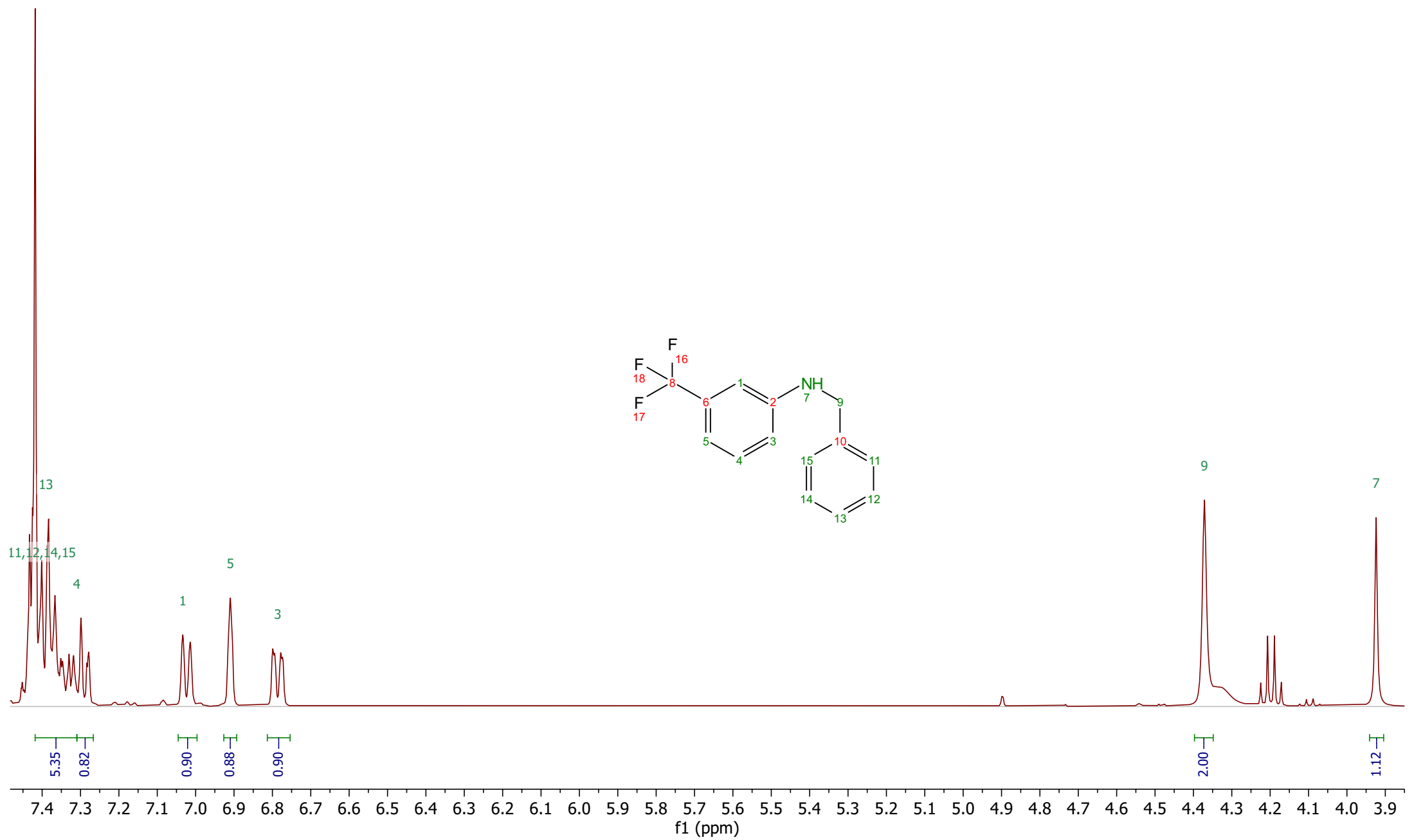


Figure S9. ^1H NMR of 2.11.

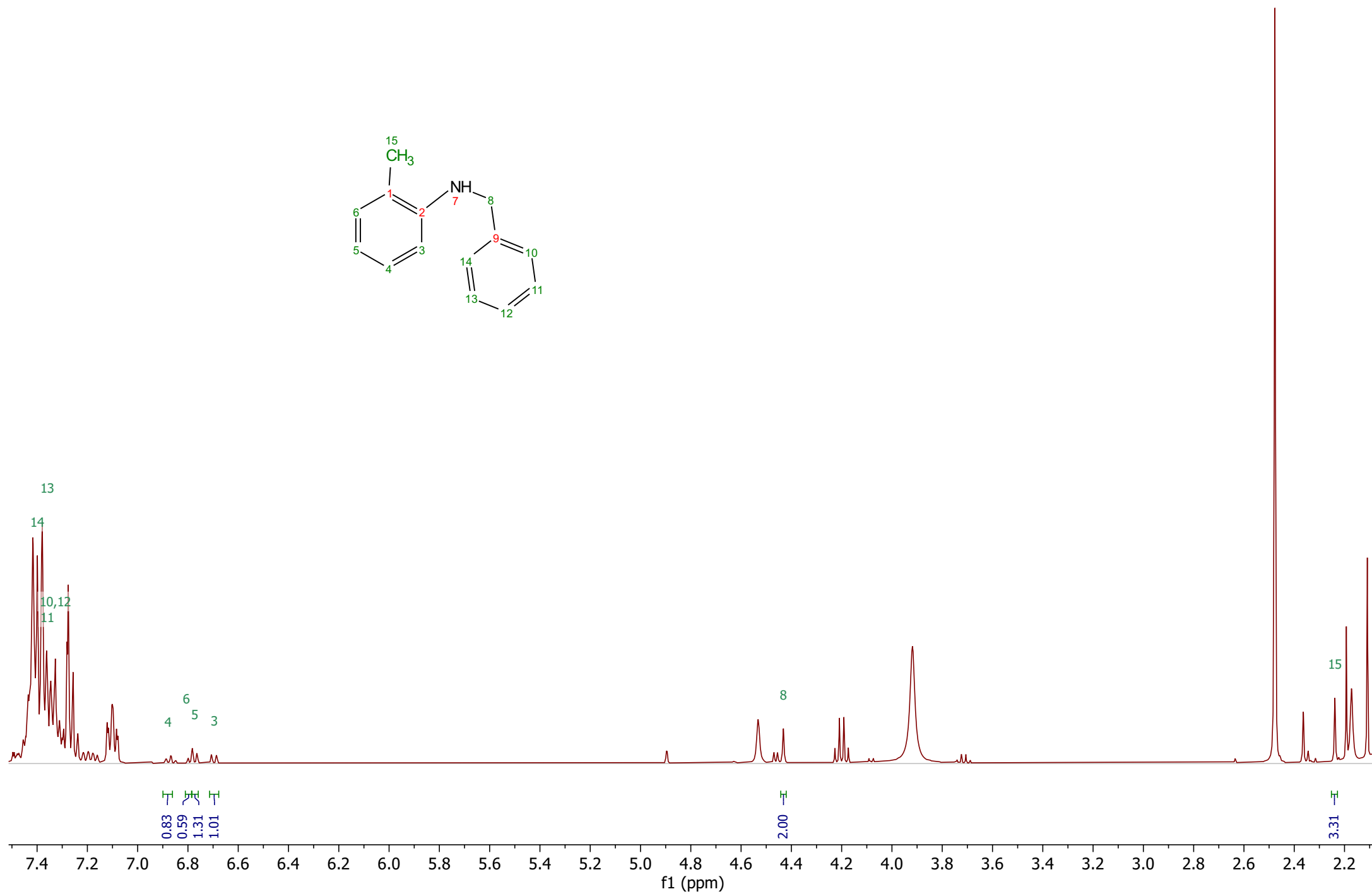


Figure S10. ¹H NMR of 2.12.

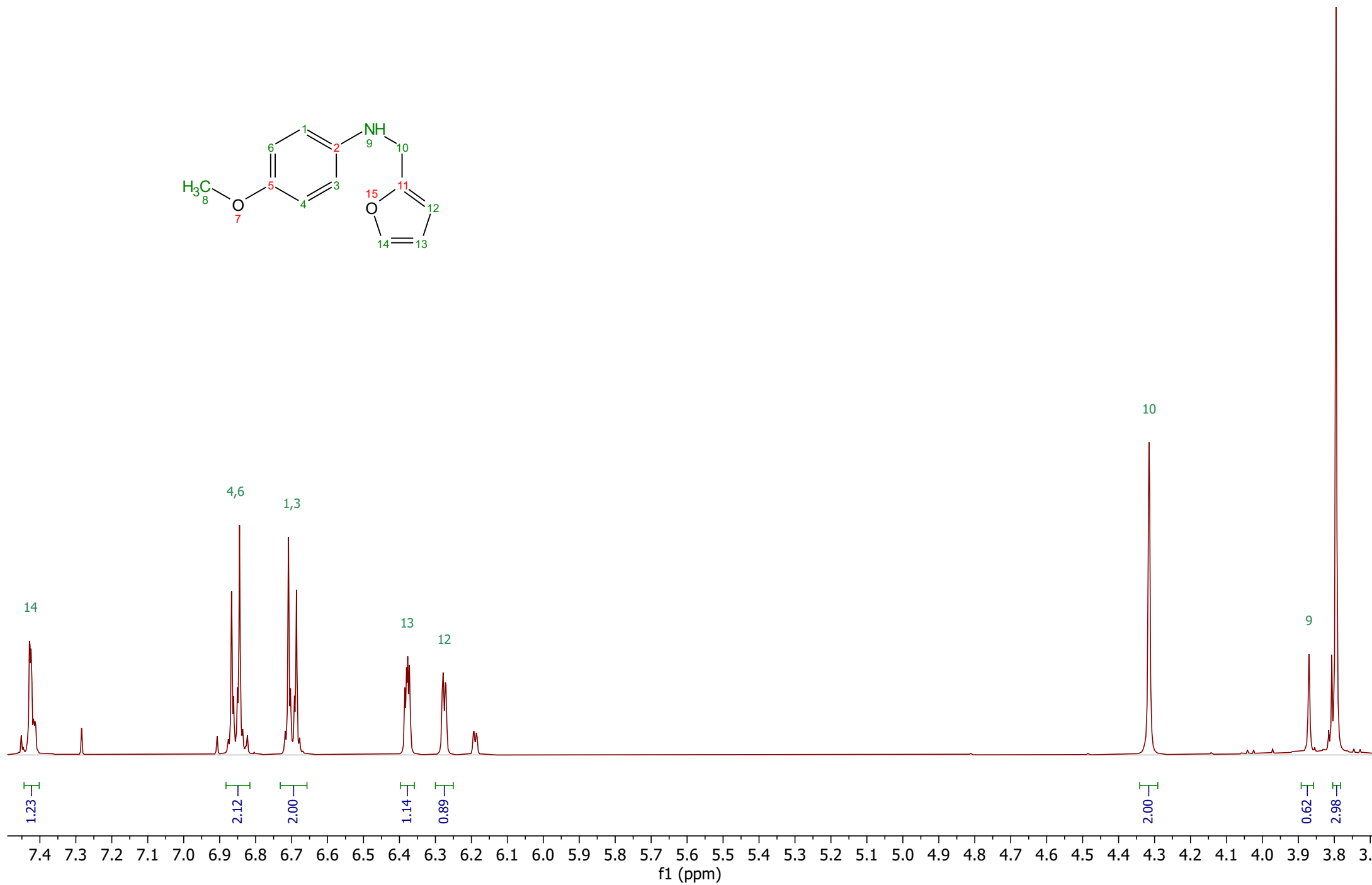
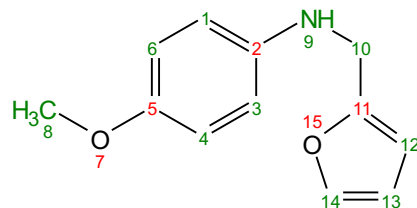


Figure S11. ^1H NMR of 2.13.

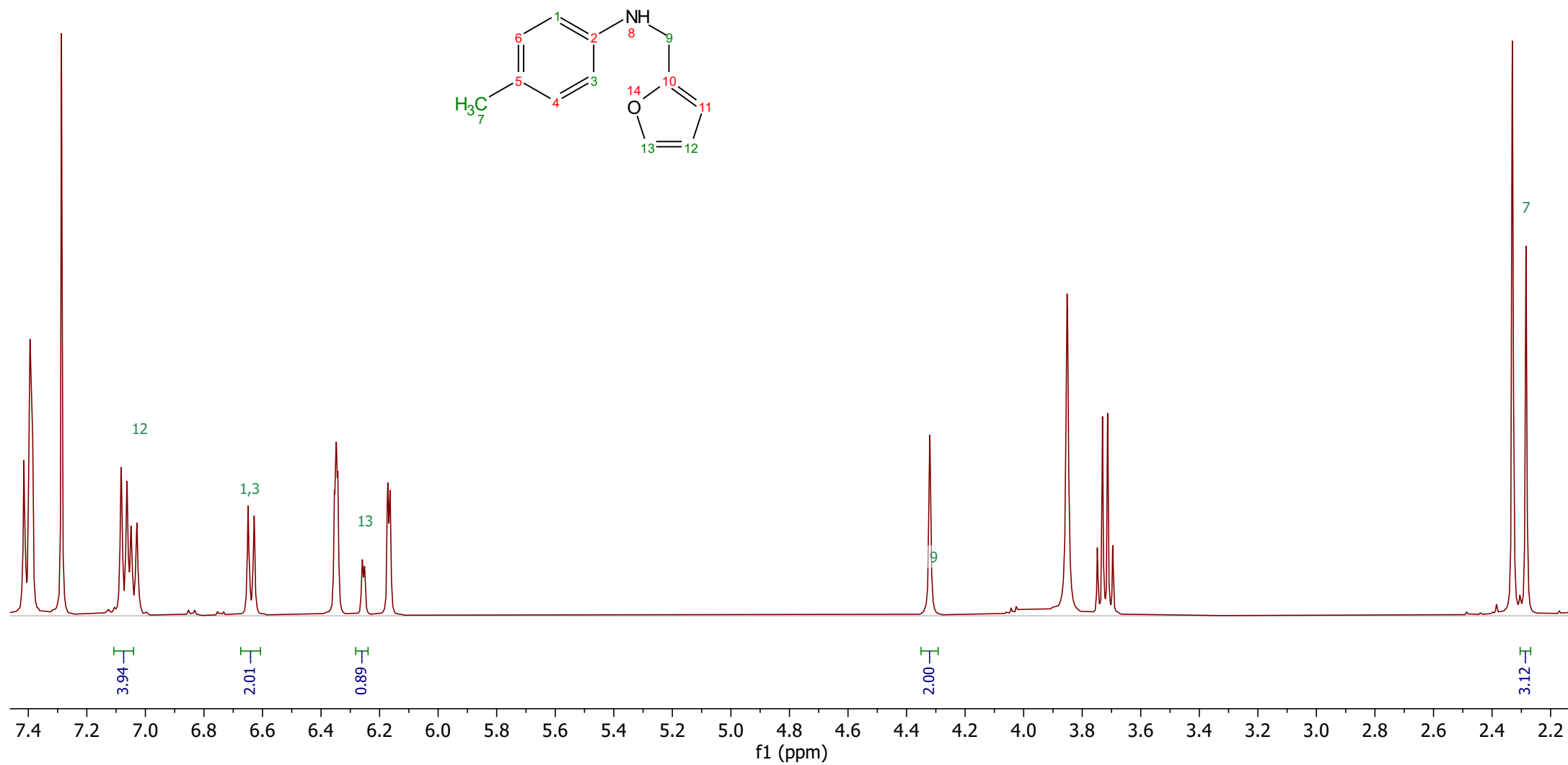


Figure S12. ^1H NMR of 2.14.

8,9,10,11,12

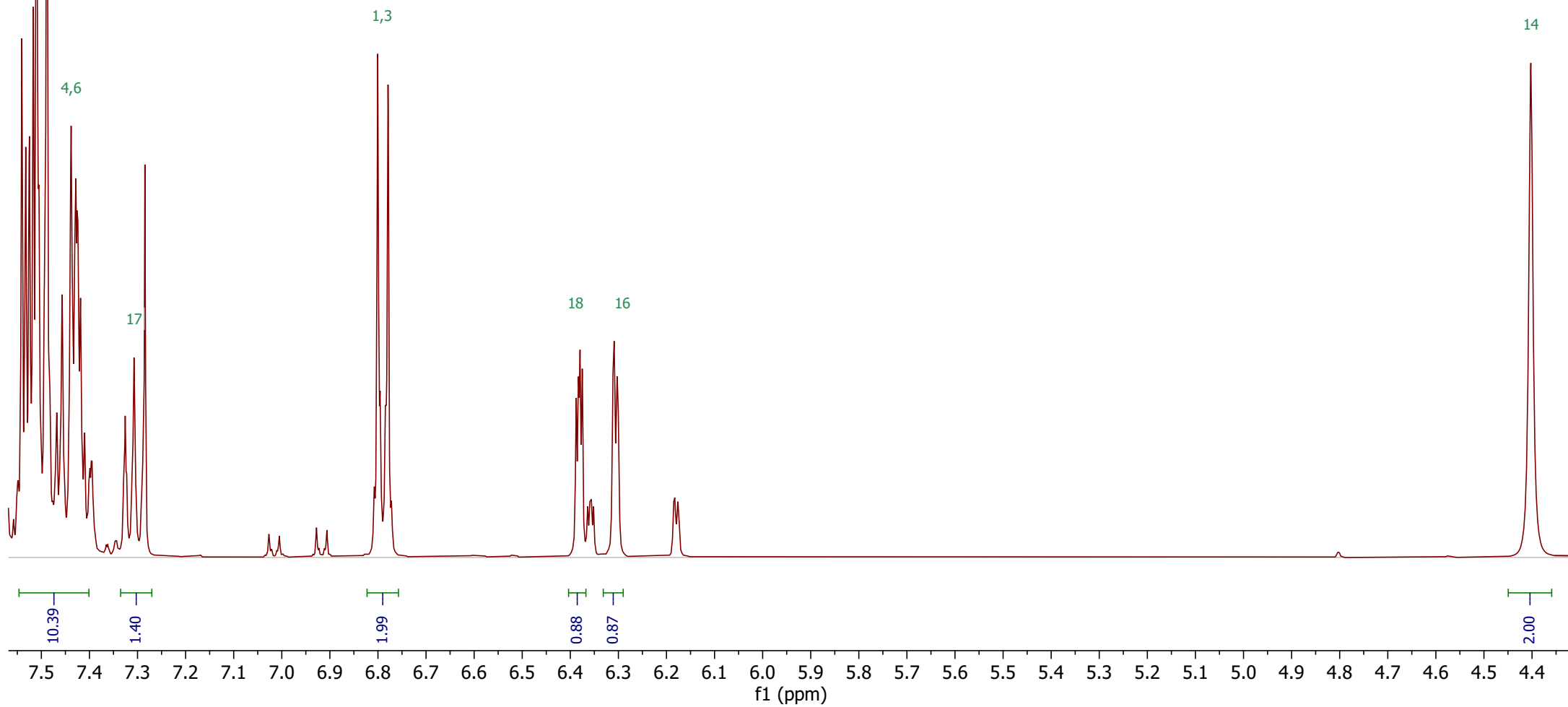
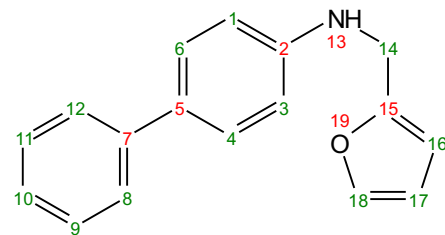


Figure S13. ^1H NMR of 2.15.

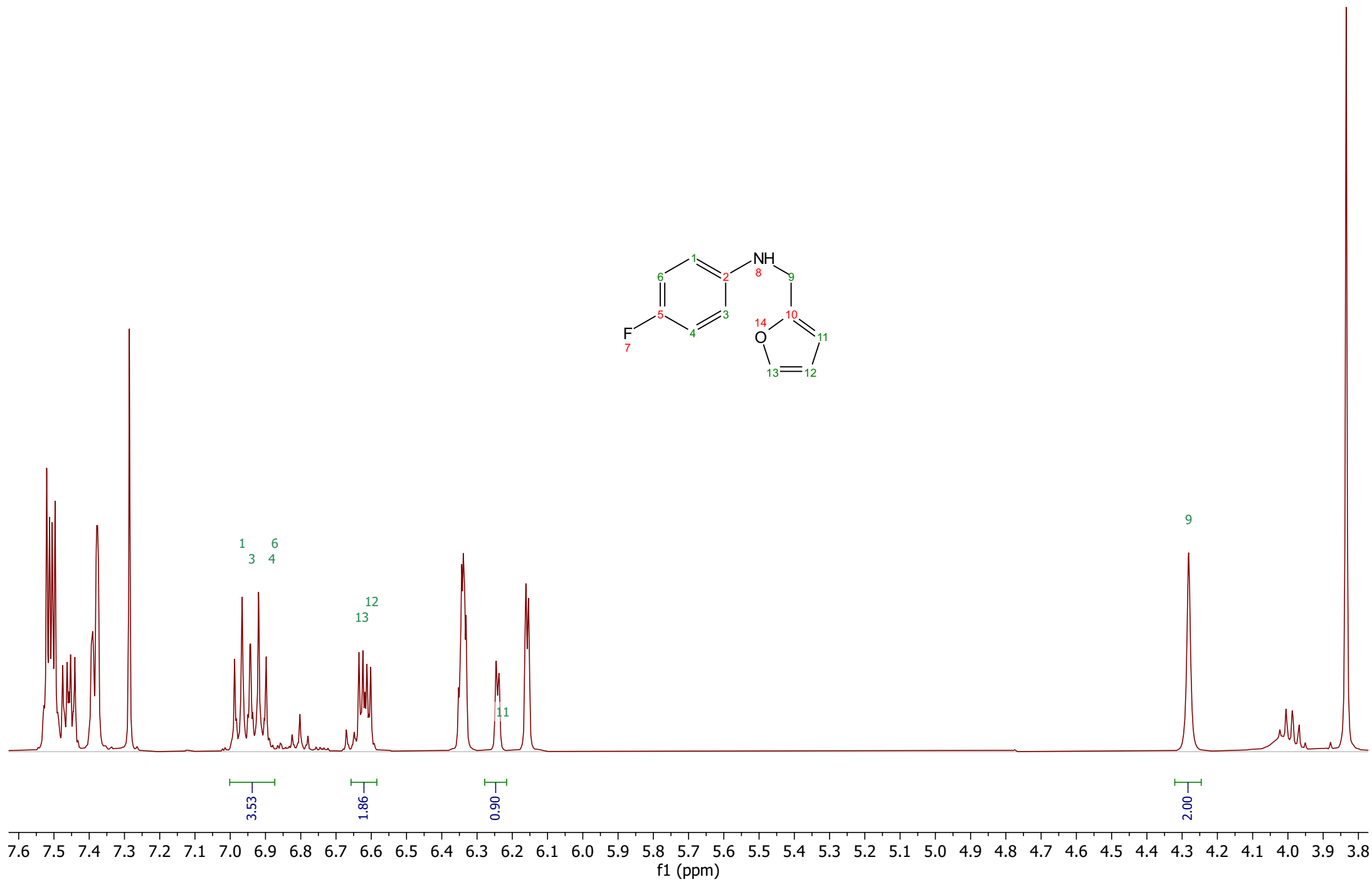


Figure S14. ^1H NMR of 2.16.

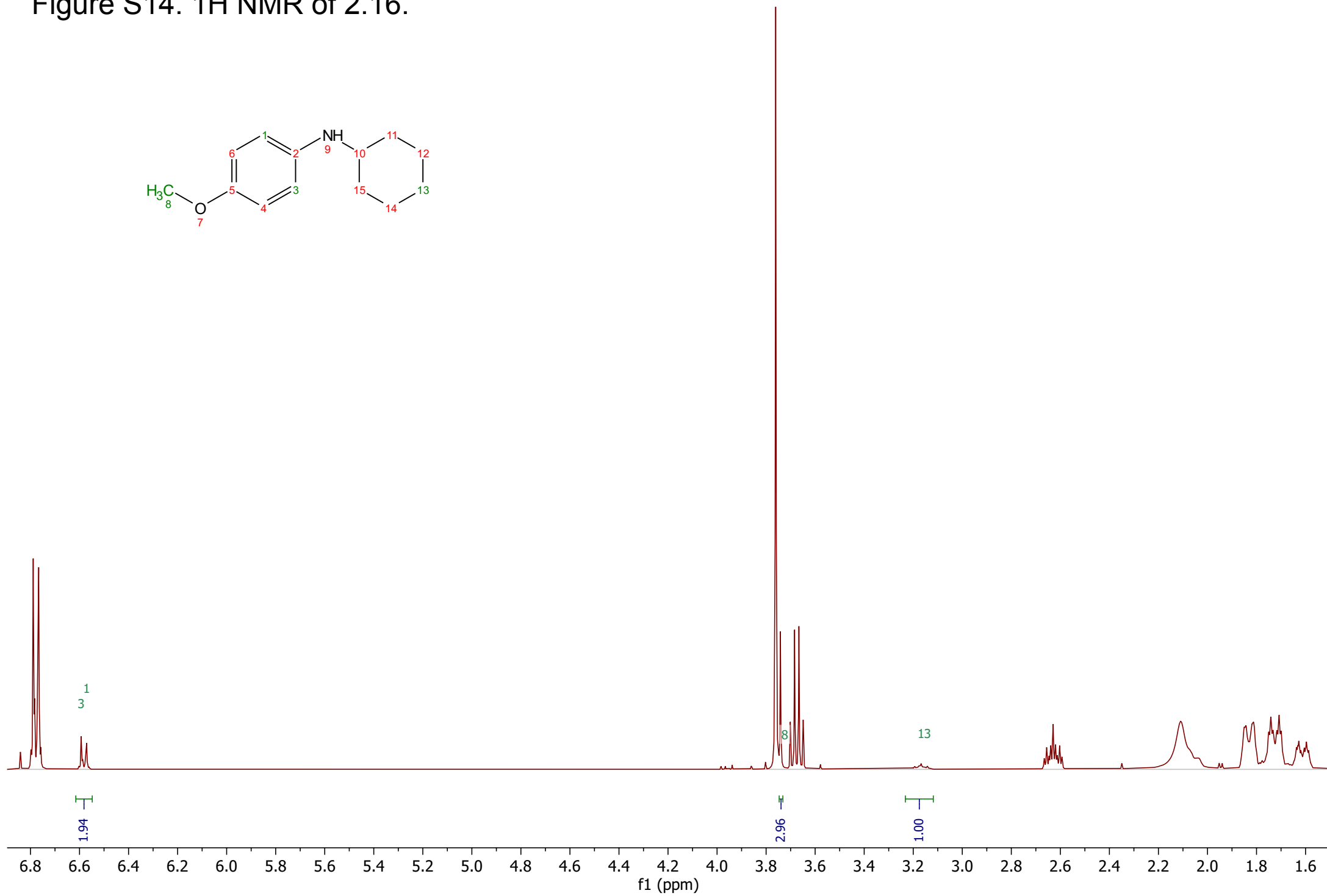
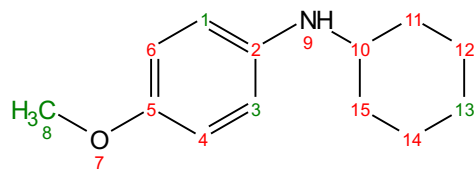


Figure S15. ^1H NMR of 2.17.

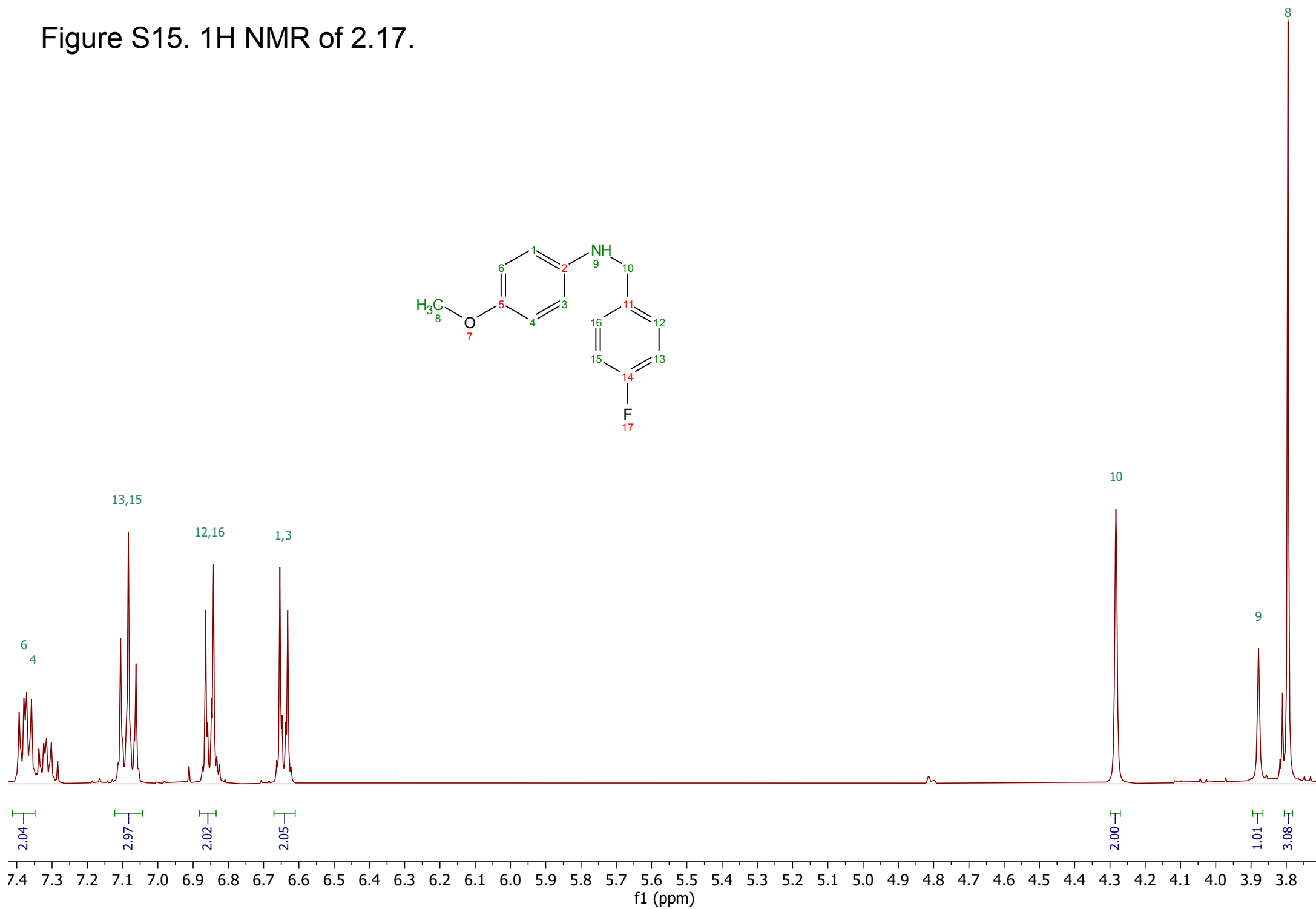


Figure S16. ^1H NMR of 2.18.

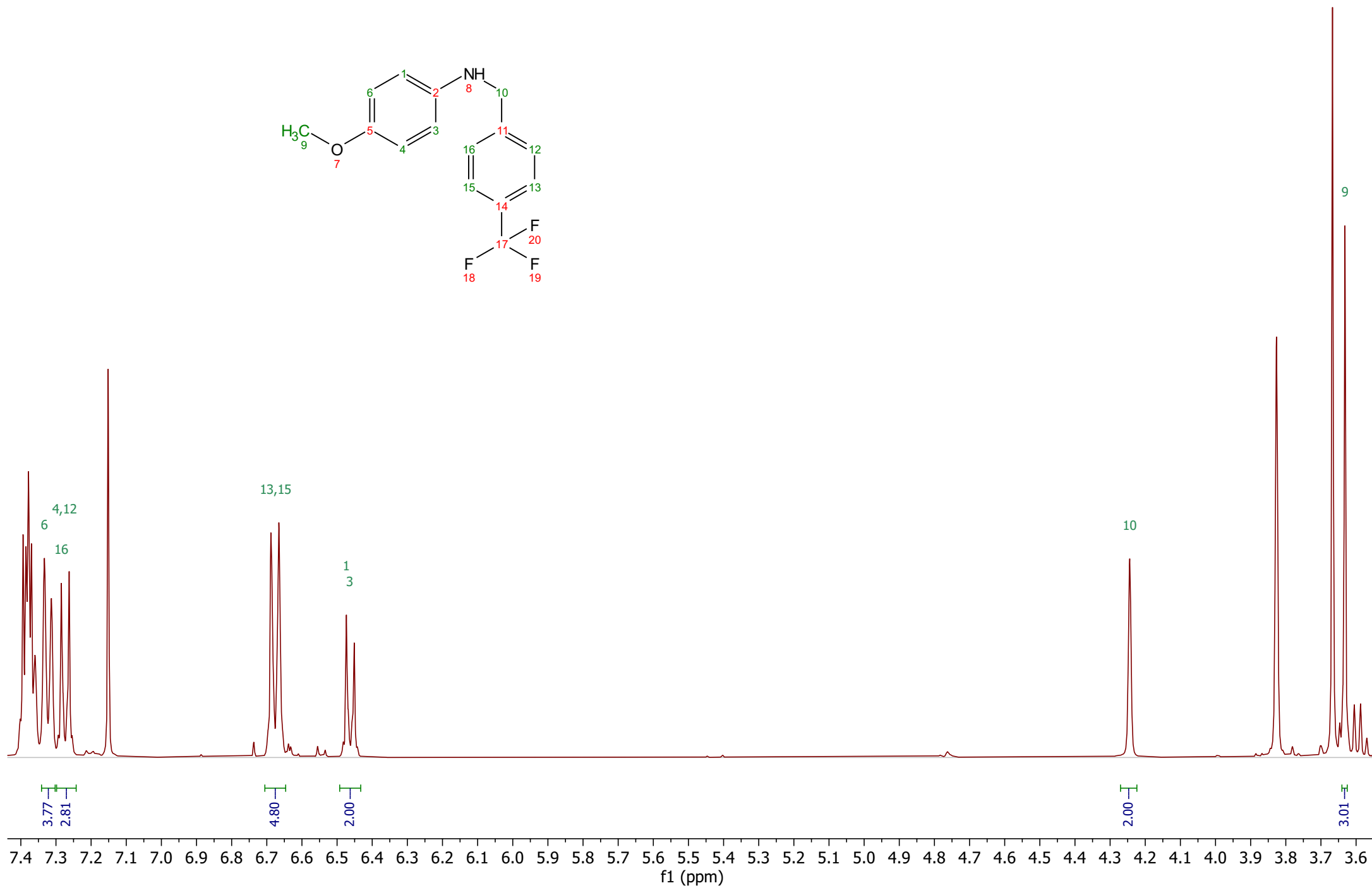


Figure S17. ^1H NMR of 2.19.

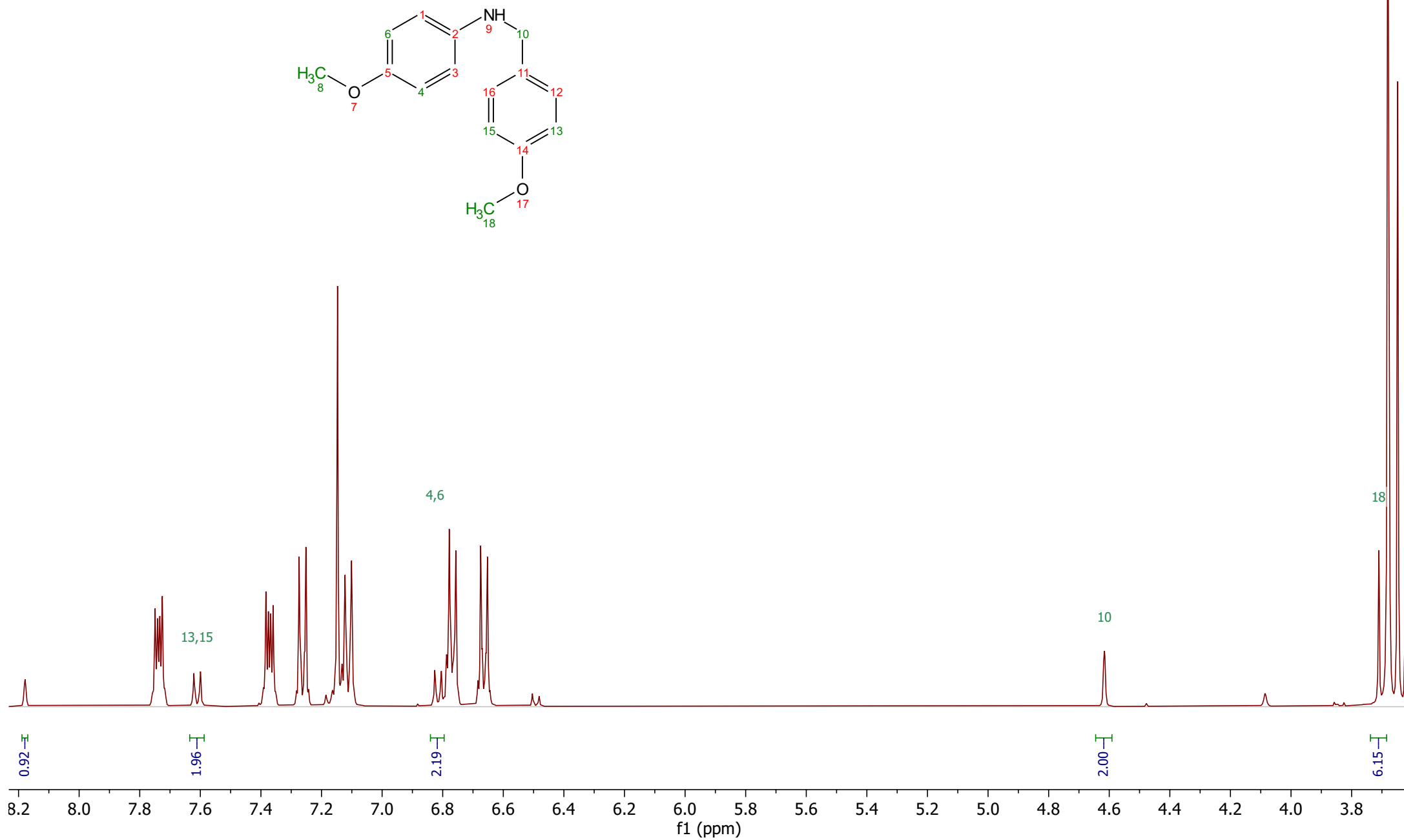


Figure S18. ¹H NMR of 2.20.

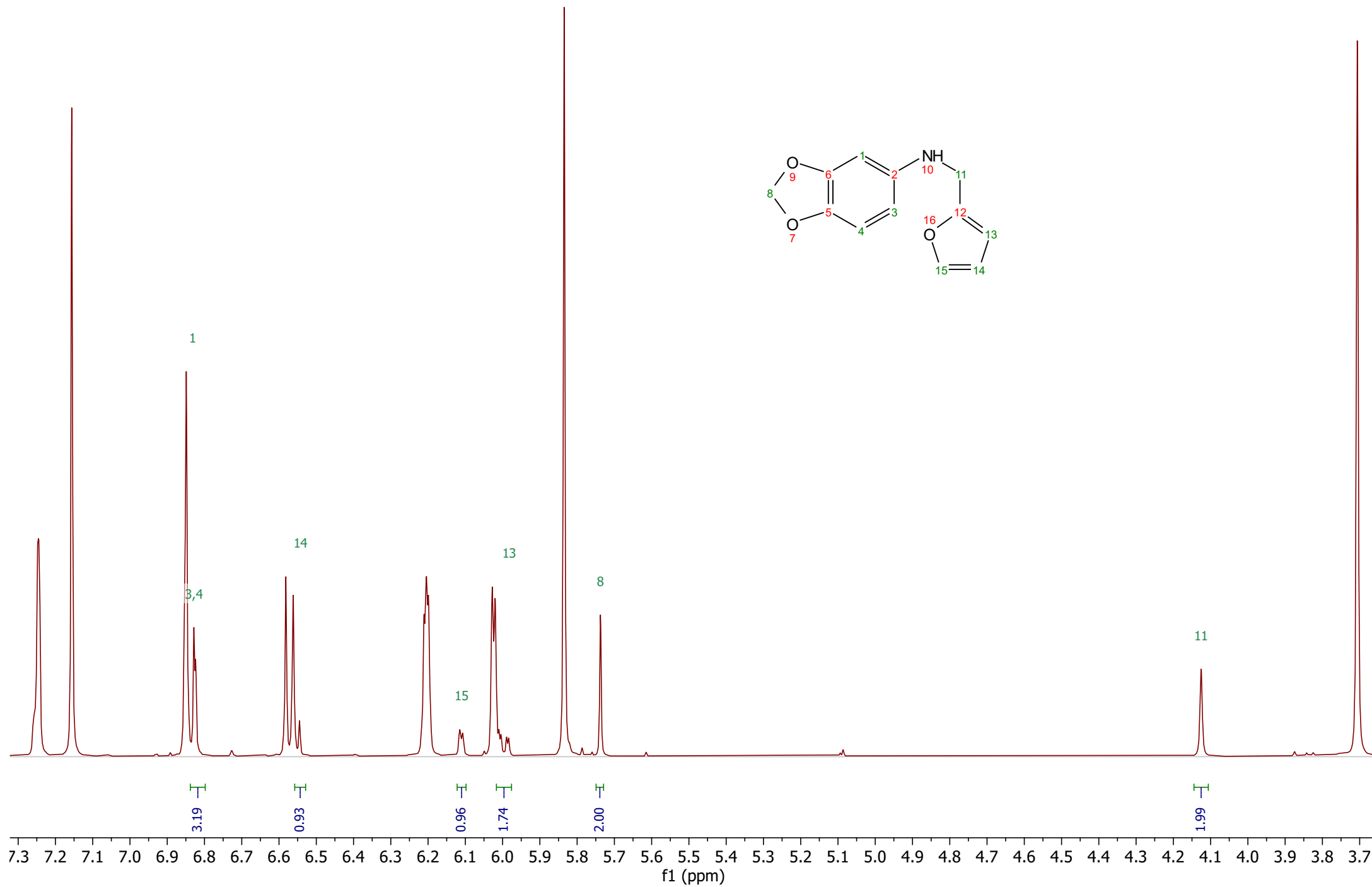


Figure S19. ^1H NMR of 2.21.

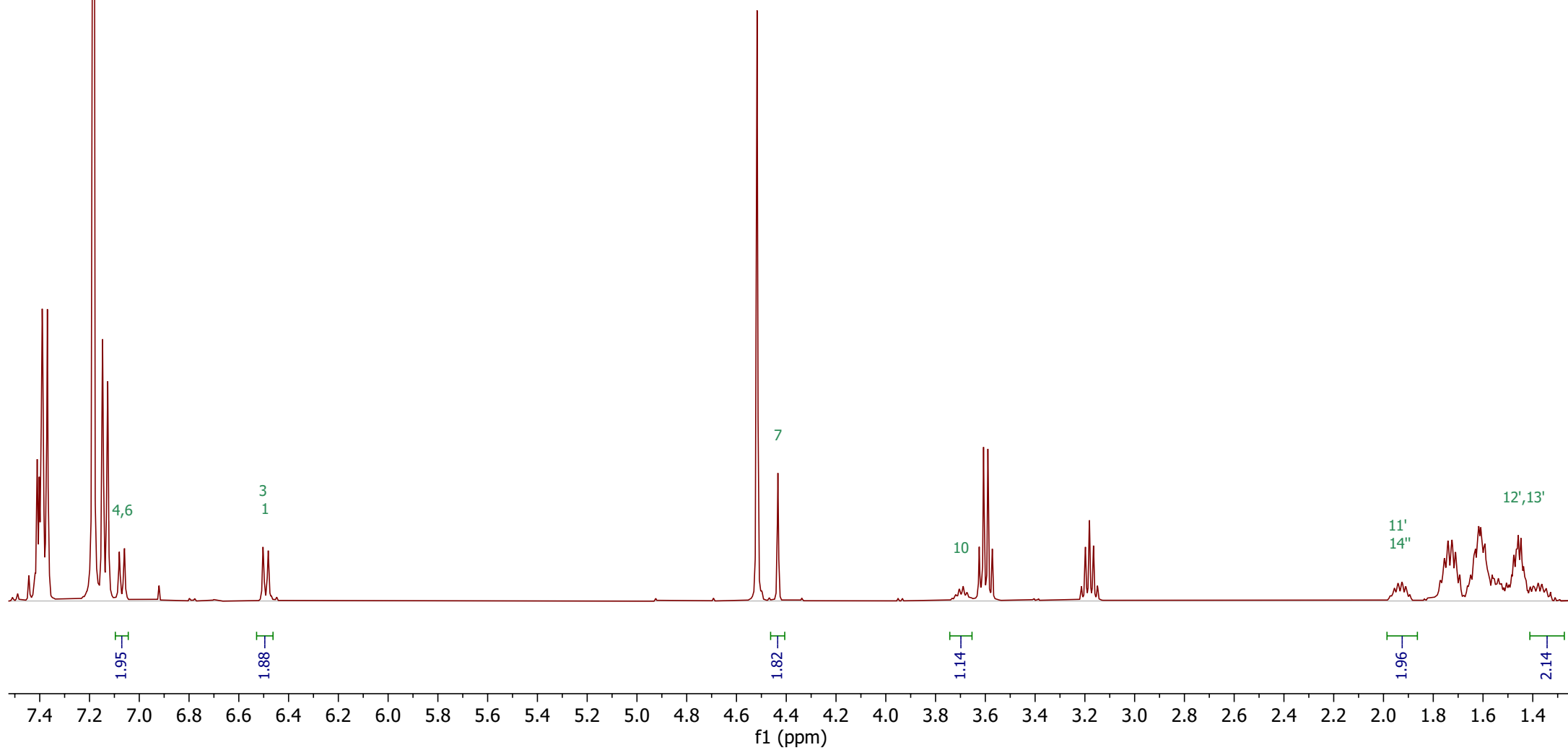
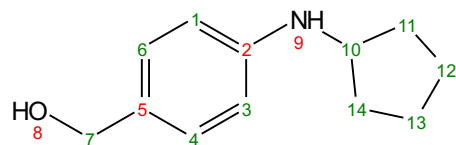


Figure S20. ^1H NMR of 2.22.

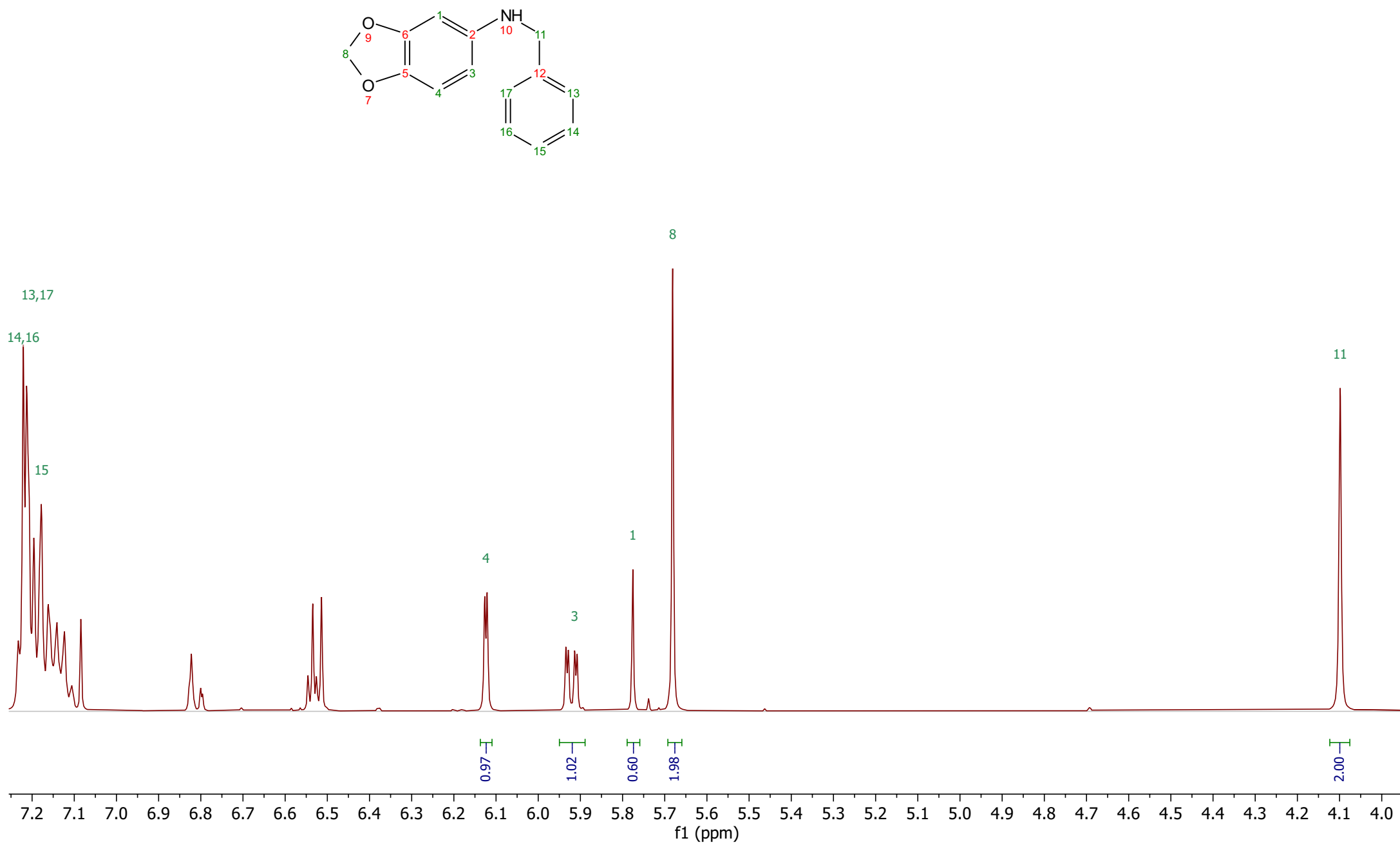


Figure S21. ¹H NMR of 2.23.

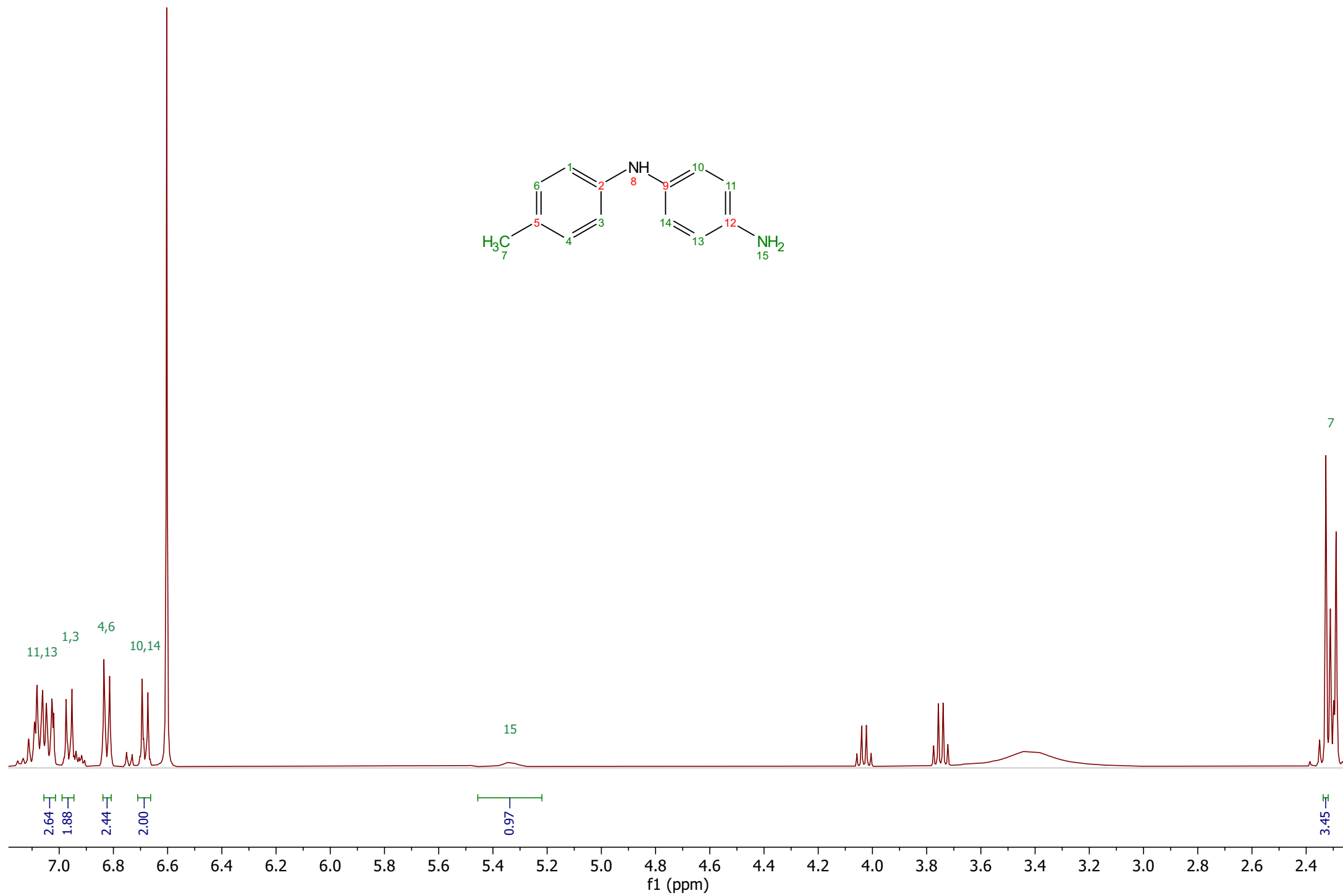


Figure S22. ^1H NMR of 2.24.

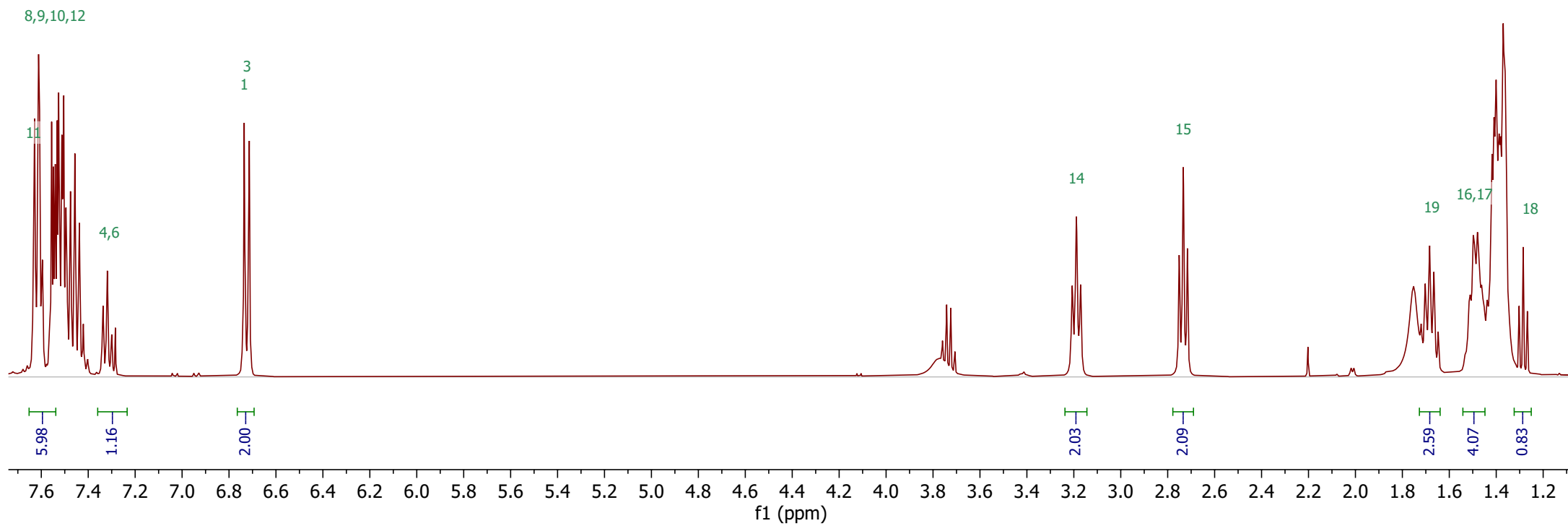
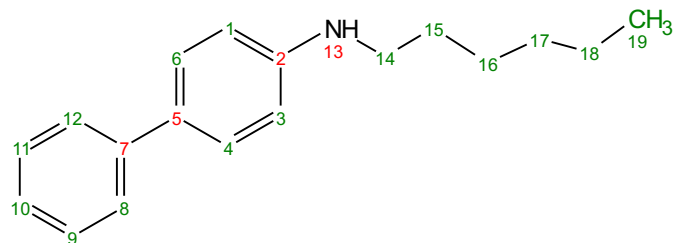


Figure S23. ^1H NMR of 2.25.

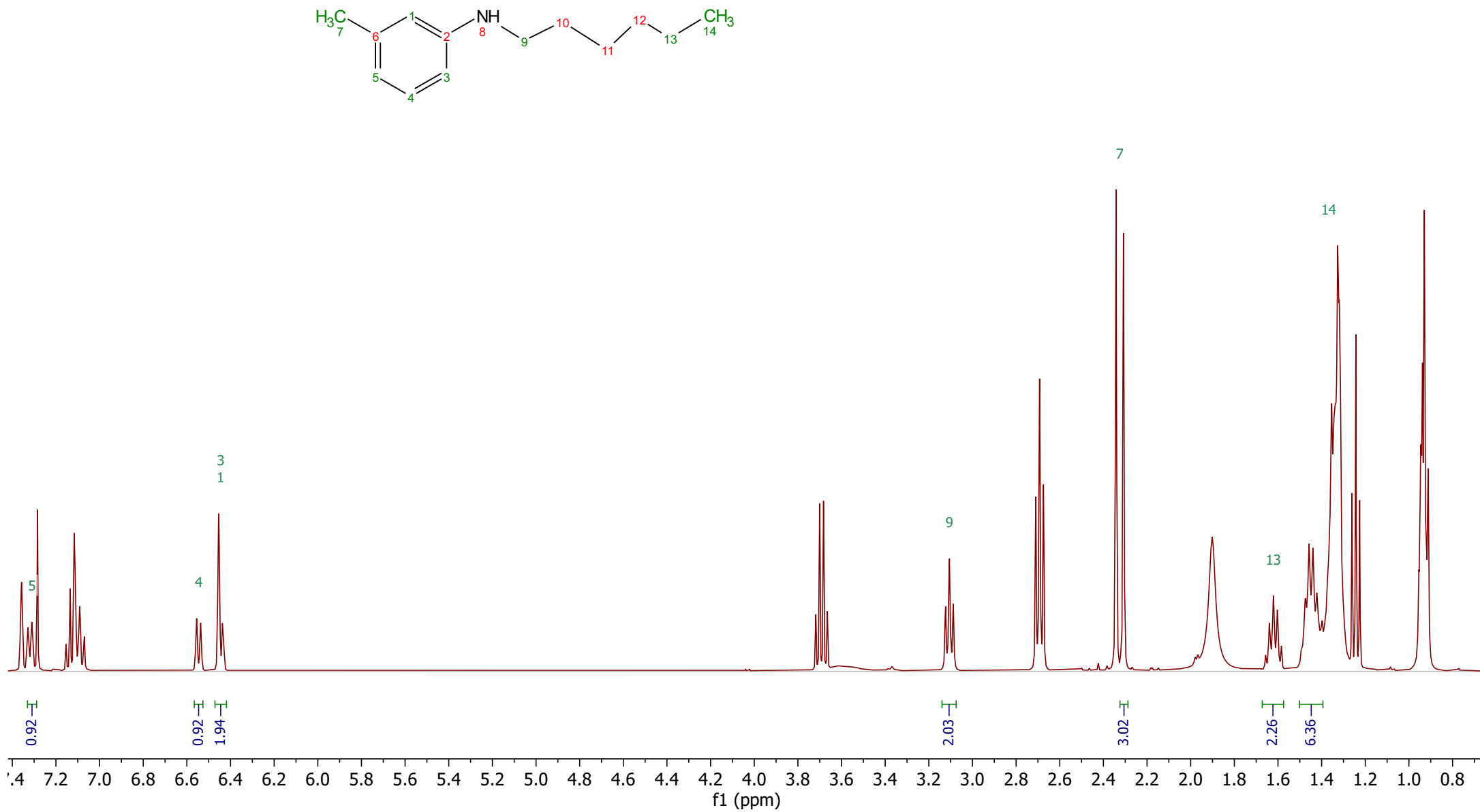


Figure S24. ¹H NMR of L38.

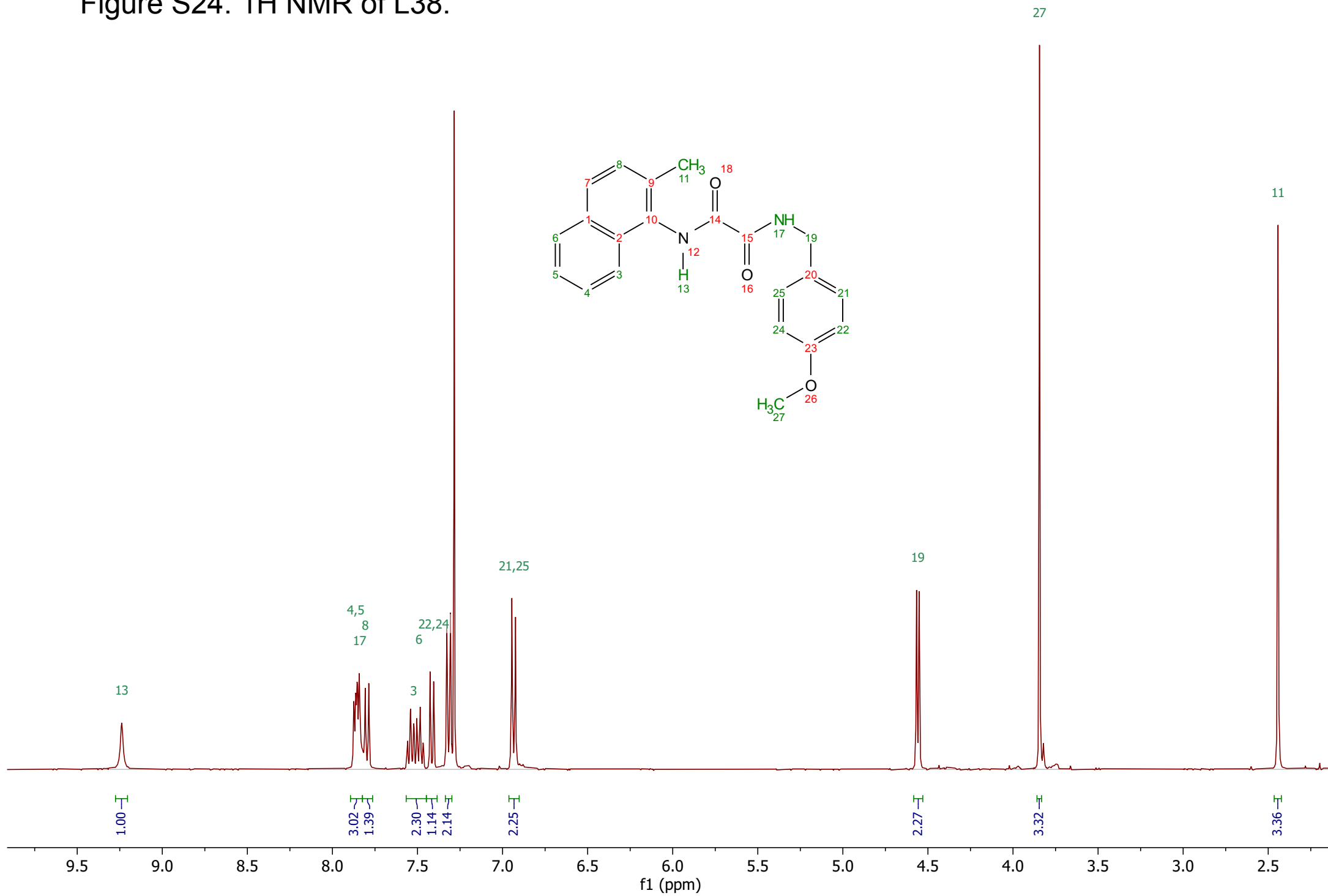


Figure S25. ^{13}C NMR of L38.

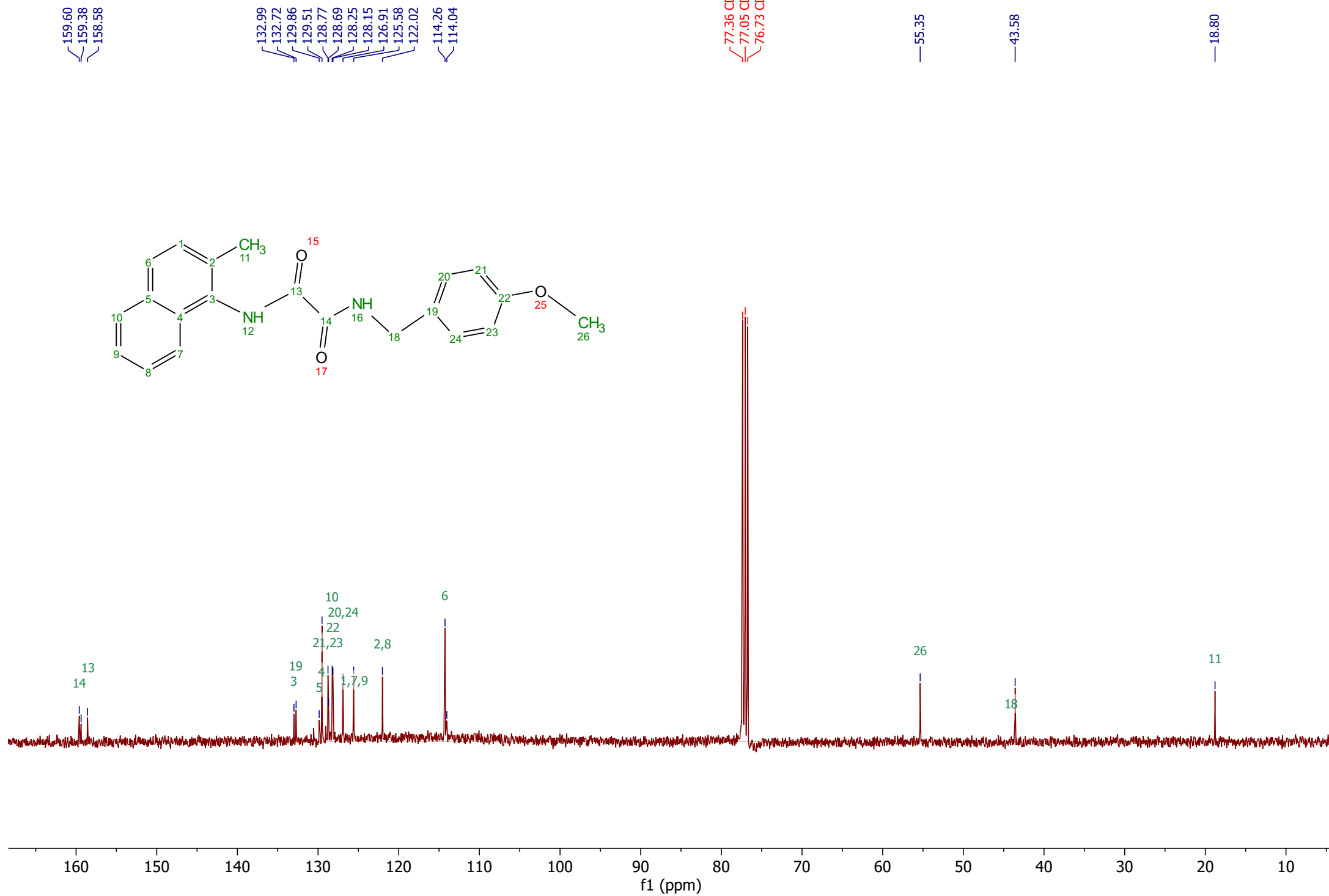


Figure S26. ^1H NMR of L39.

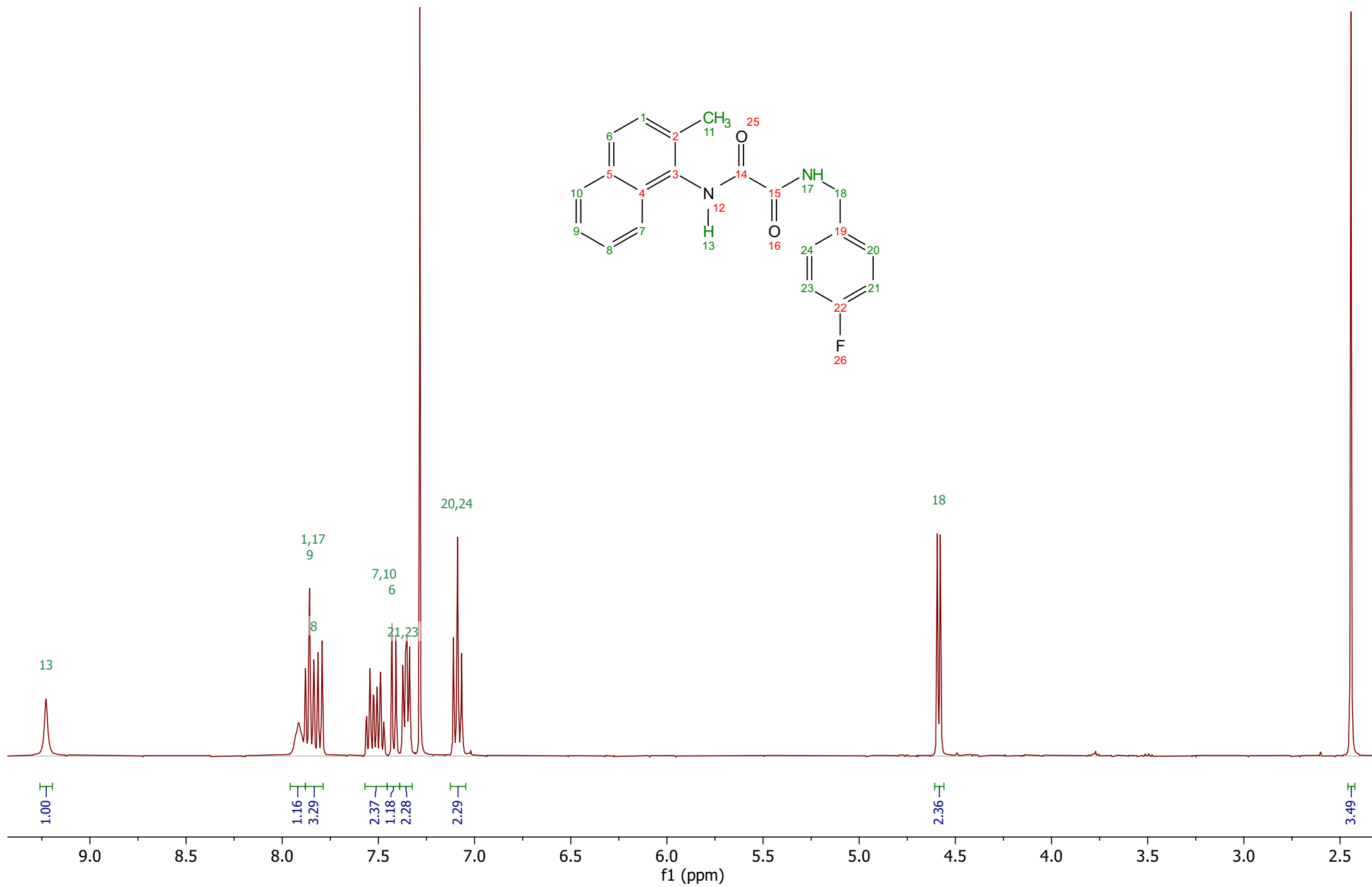


Figure S27. ^{13}C NMR of L39.

159.74
158.48

132.98
132.72
132.46
129.89
129.81
128.76
128.28
128.22
126.94
125.62
121.96
115.90
115.68

77.36 CDCl₃
77.01 CDCl₃
76.72 CDCl₃

43.34

18.79

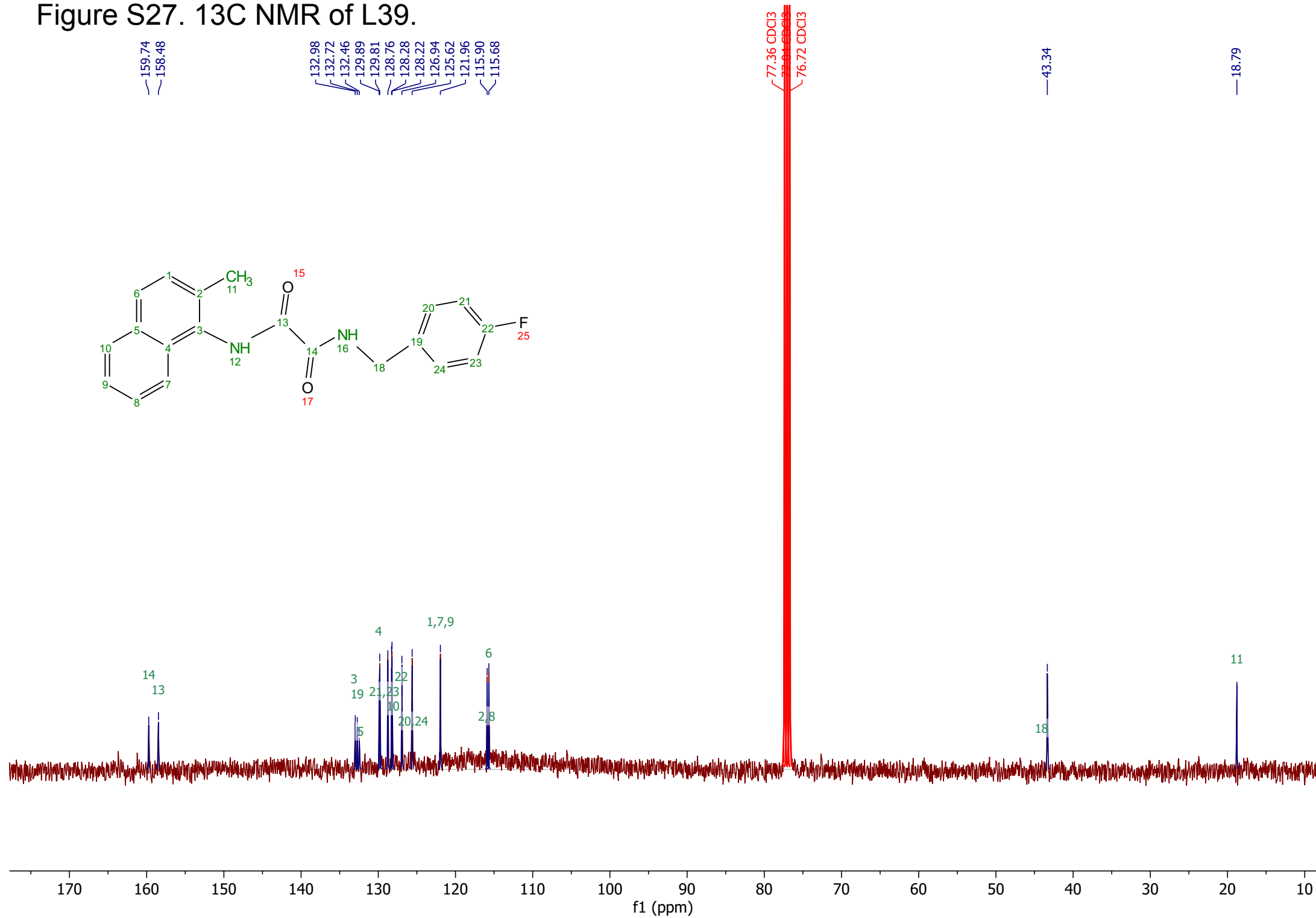
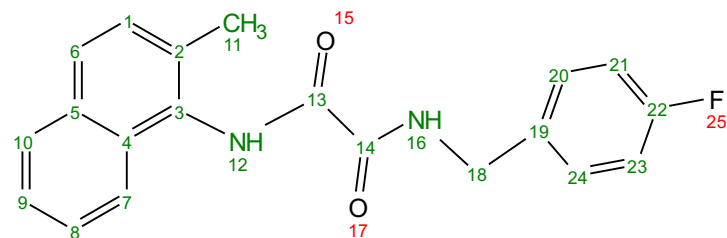


Figure S28. ^{19}F NMR of L39.

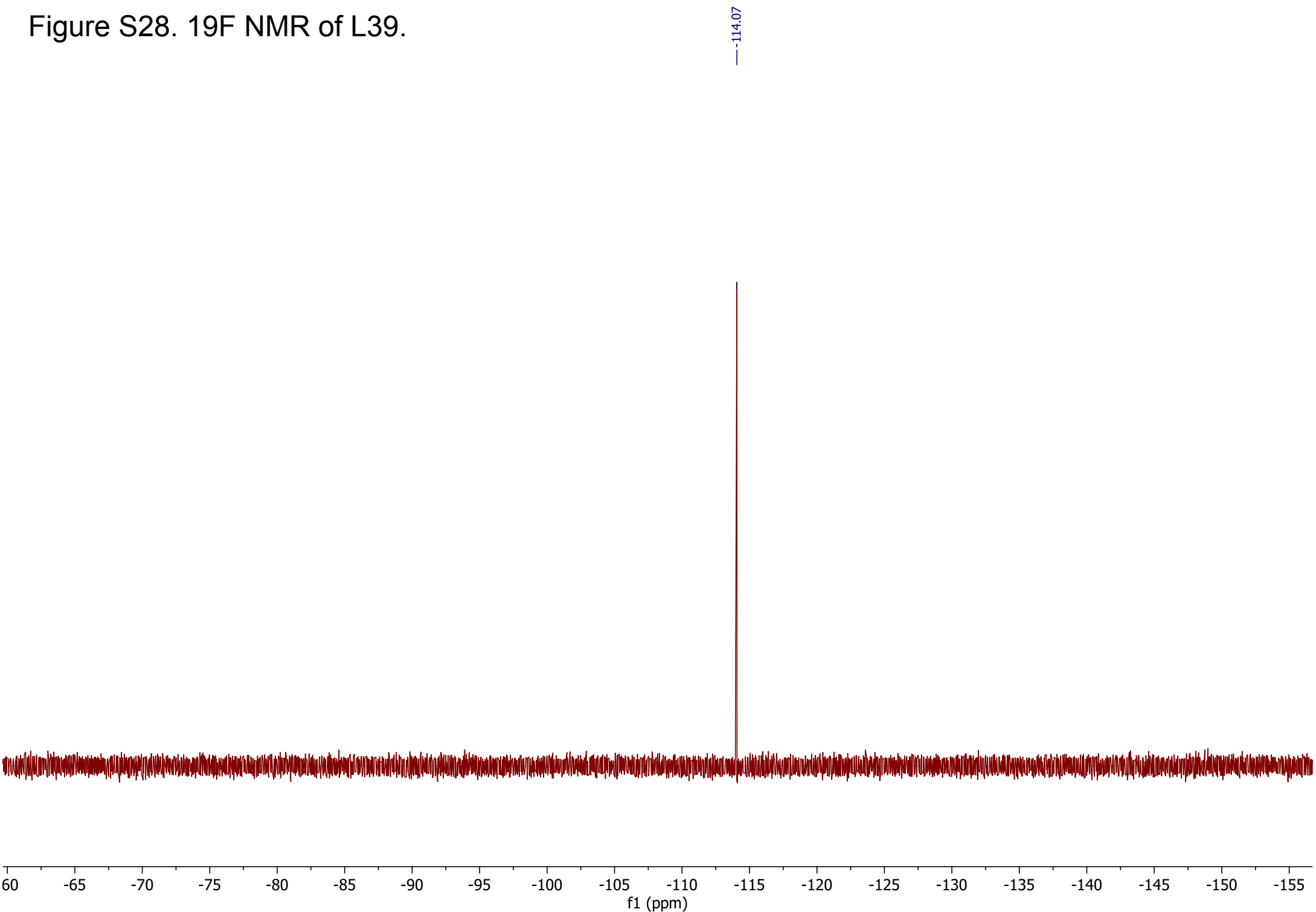


Figure S29. ¹H NMR of L40.

11

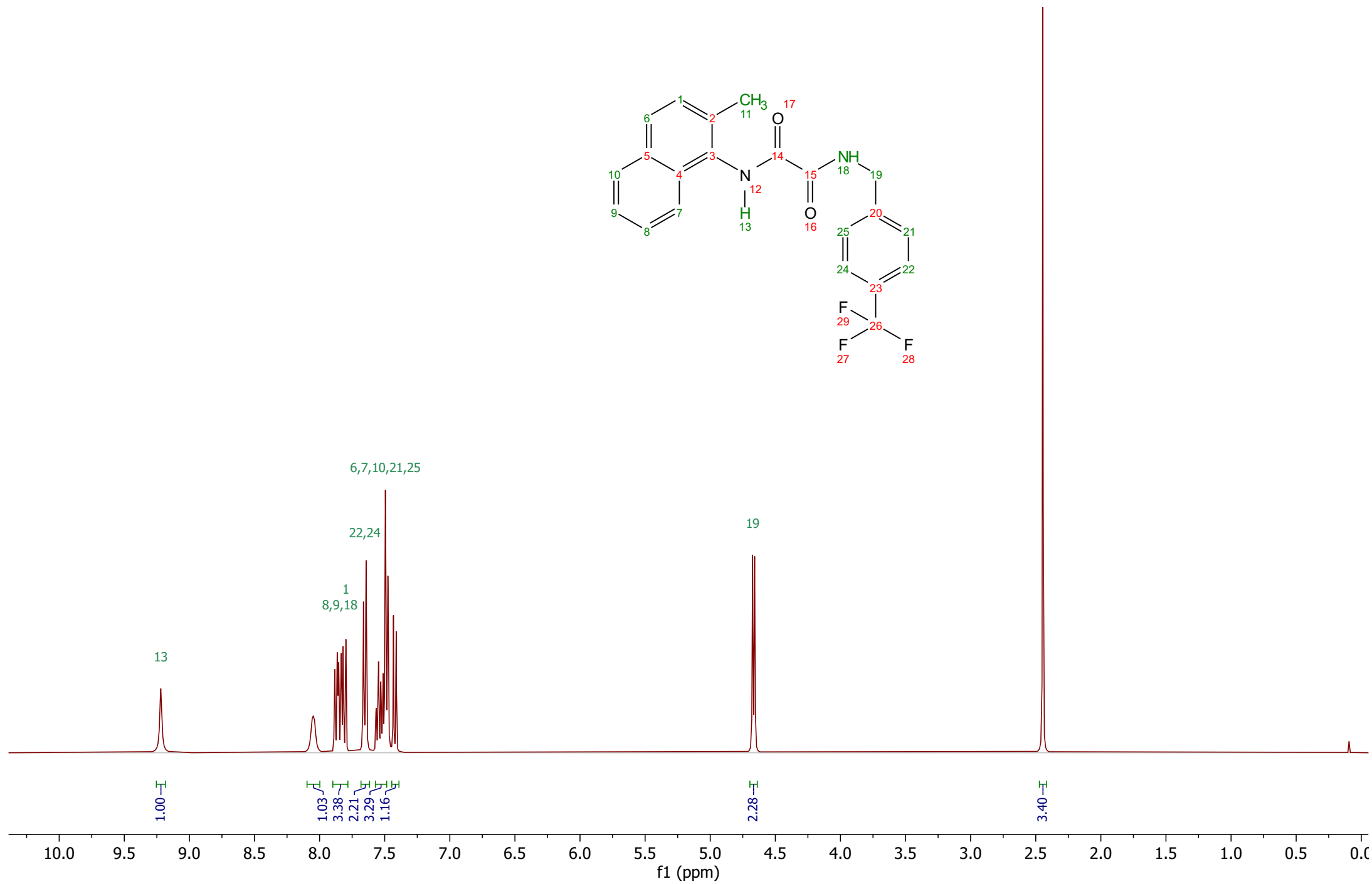


Figure S30. ¹³C NMR of L40.

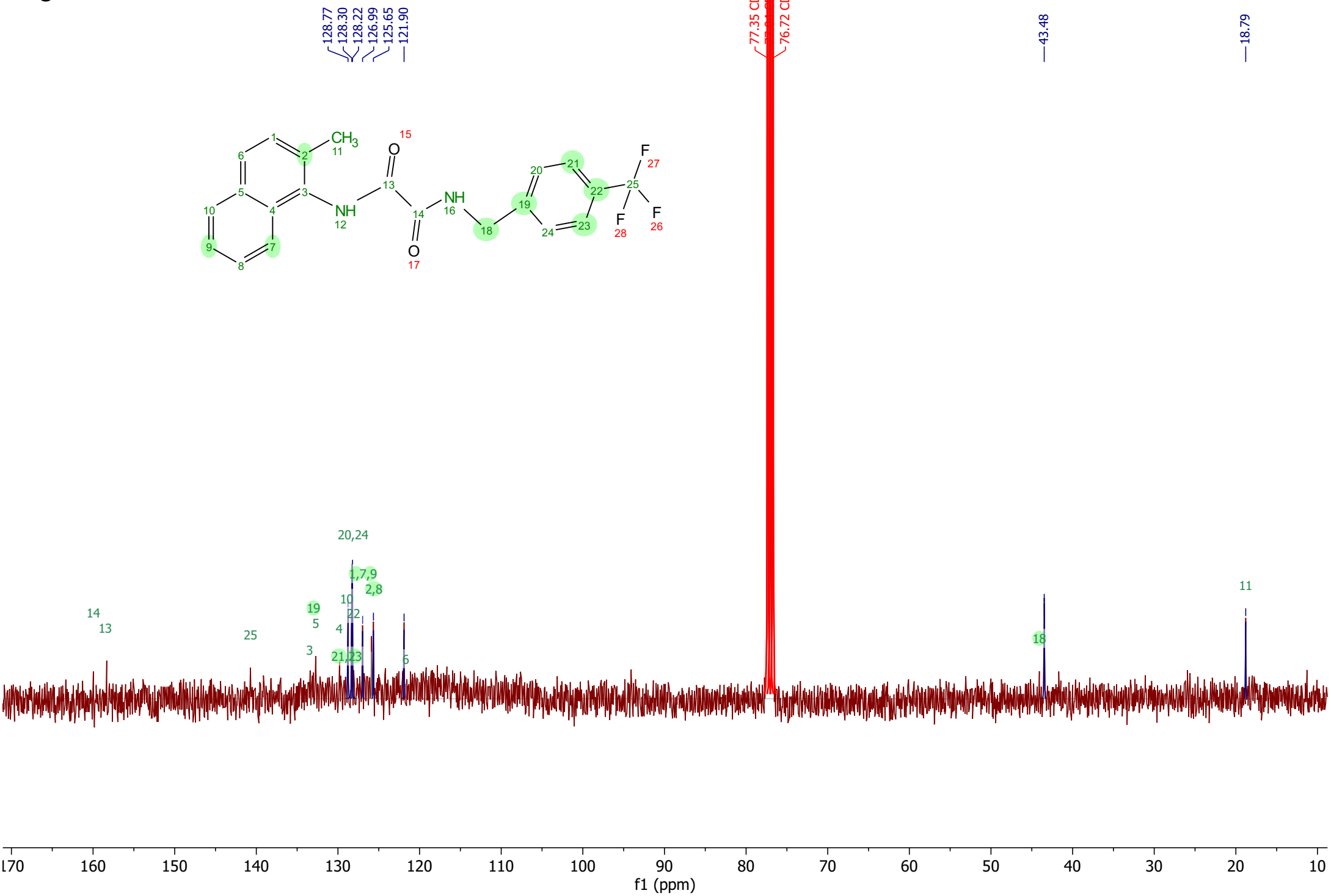


Figure S31. ¹H NMR of L41.

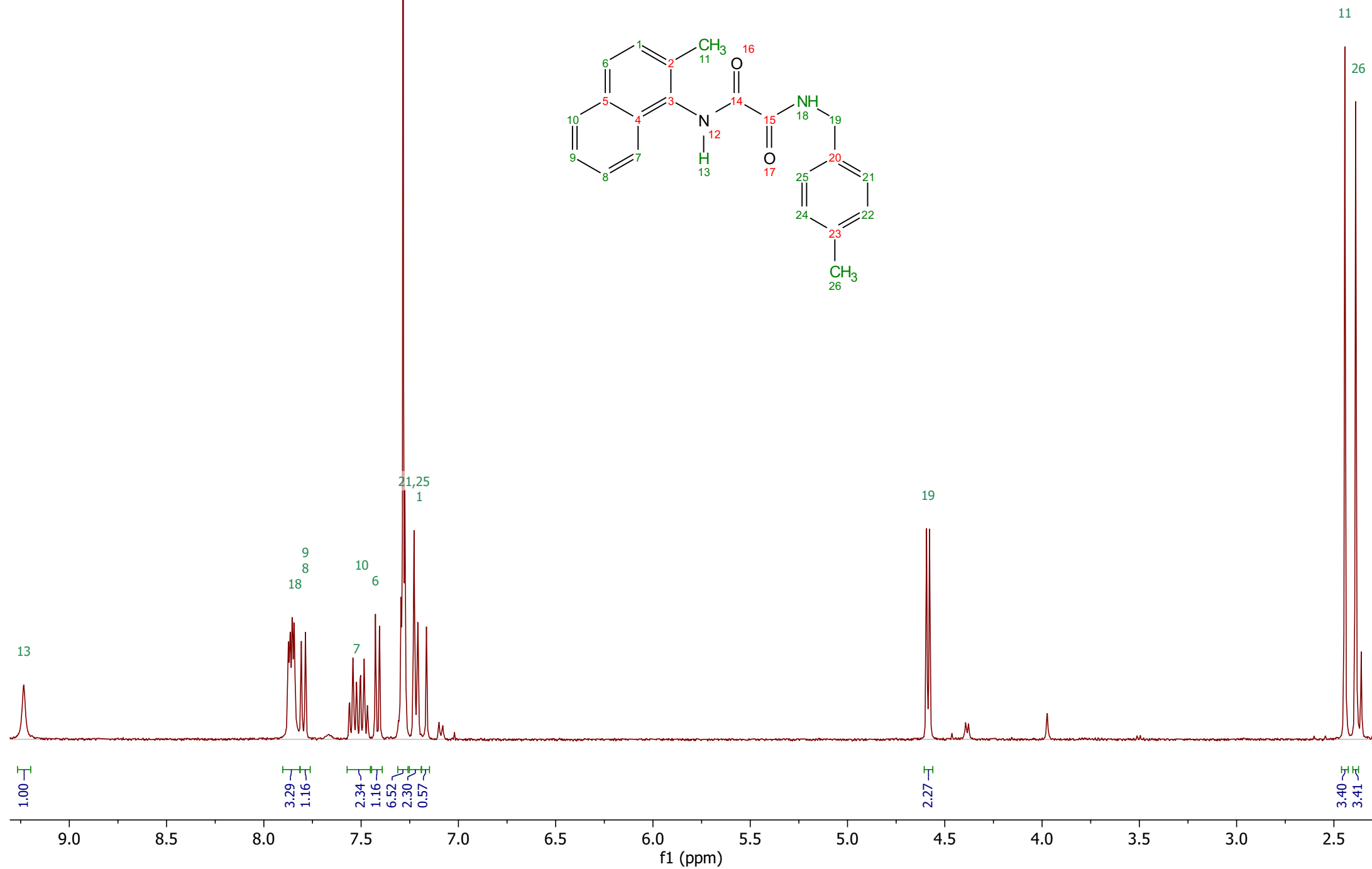
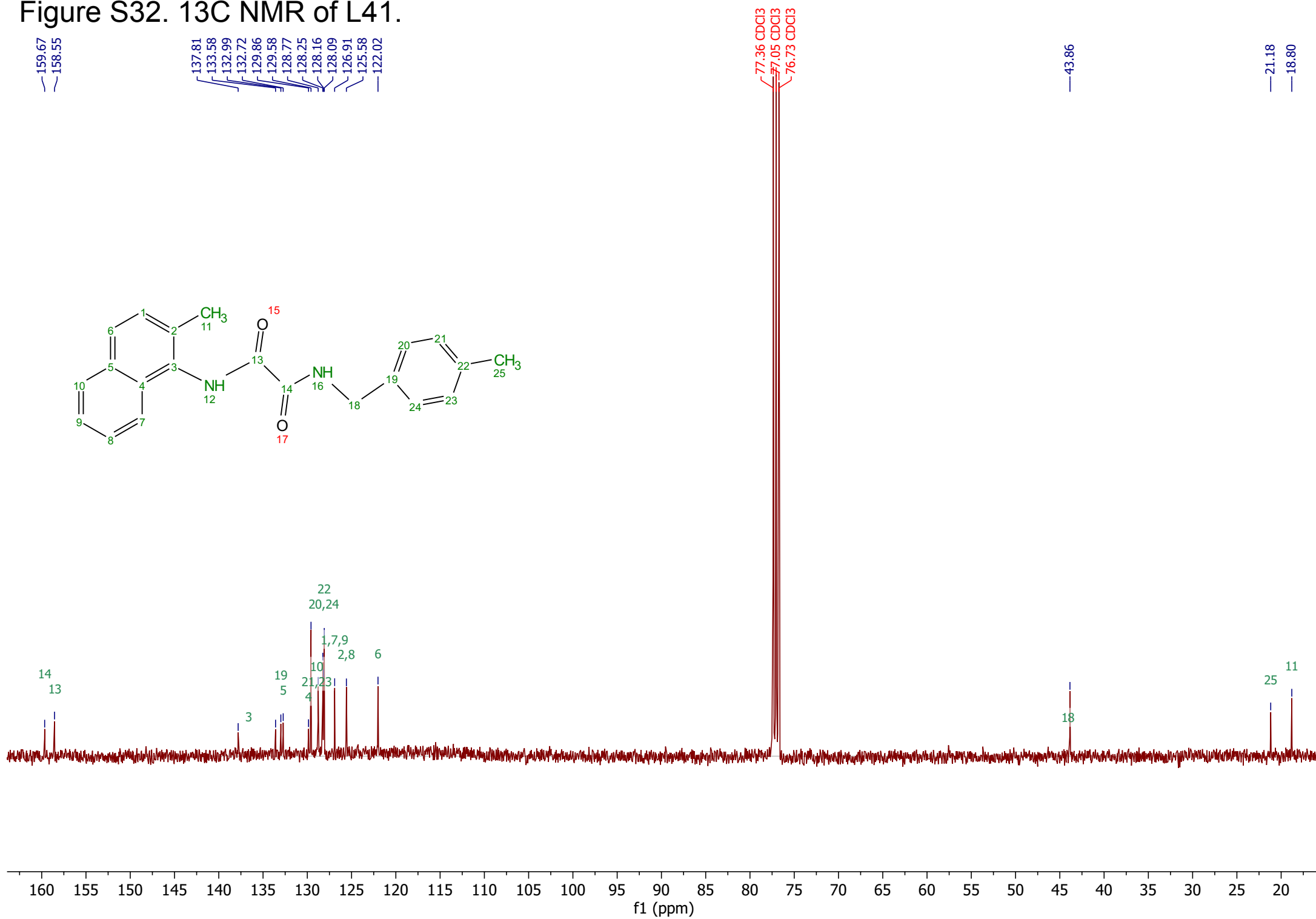
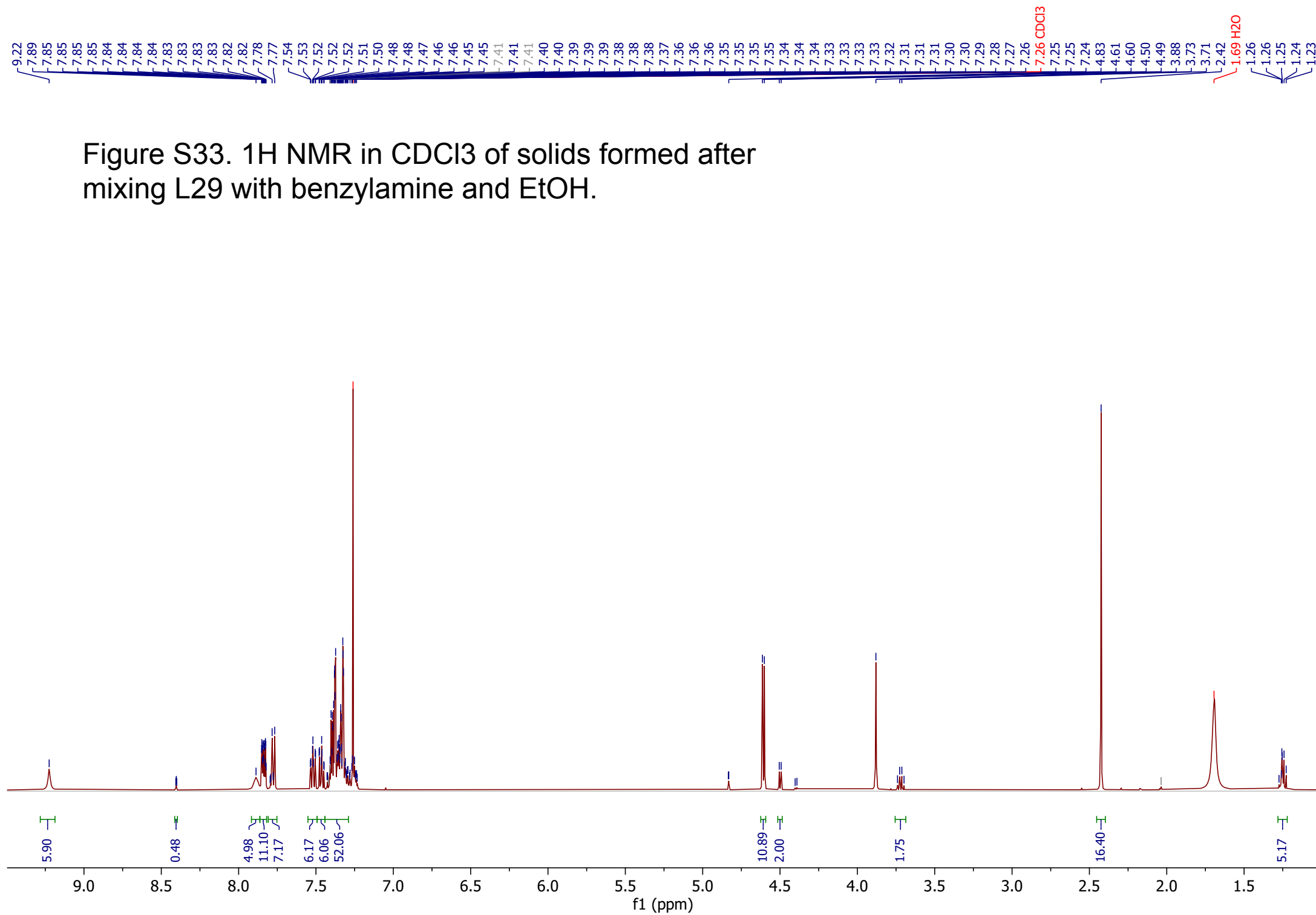


Figure S32. ^{13}C NMR of L41.





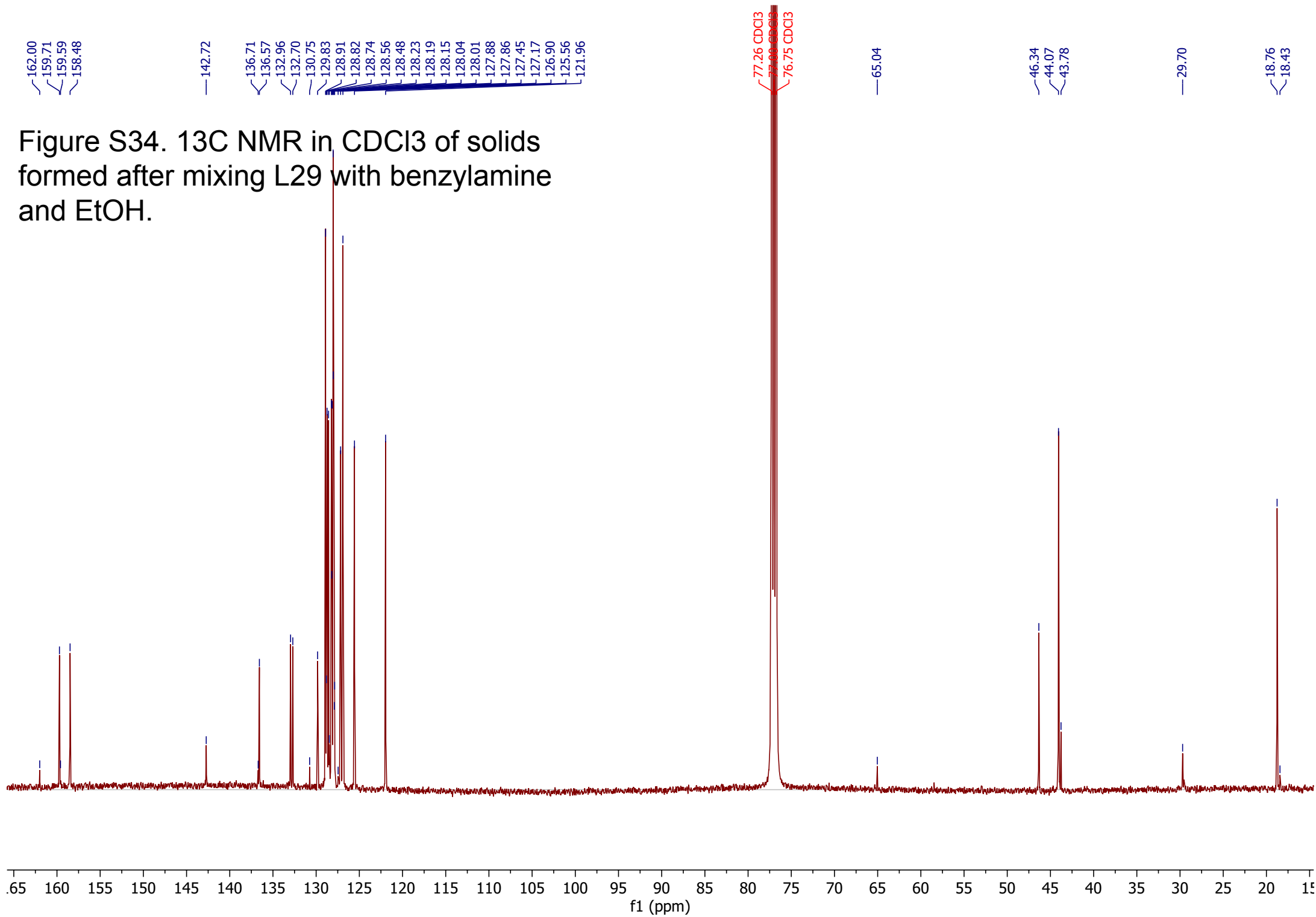


Figure S35. DOSY NMR of solids formed after mixing L29 with benzylamine and EtOH.

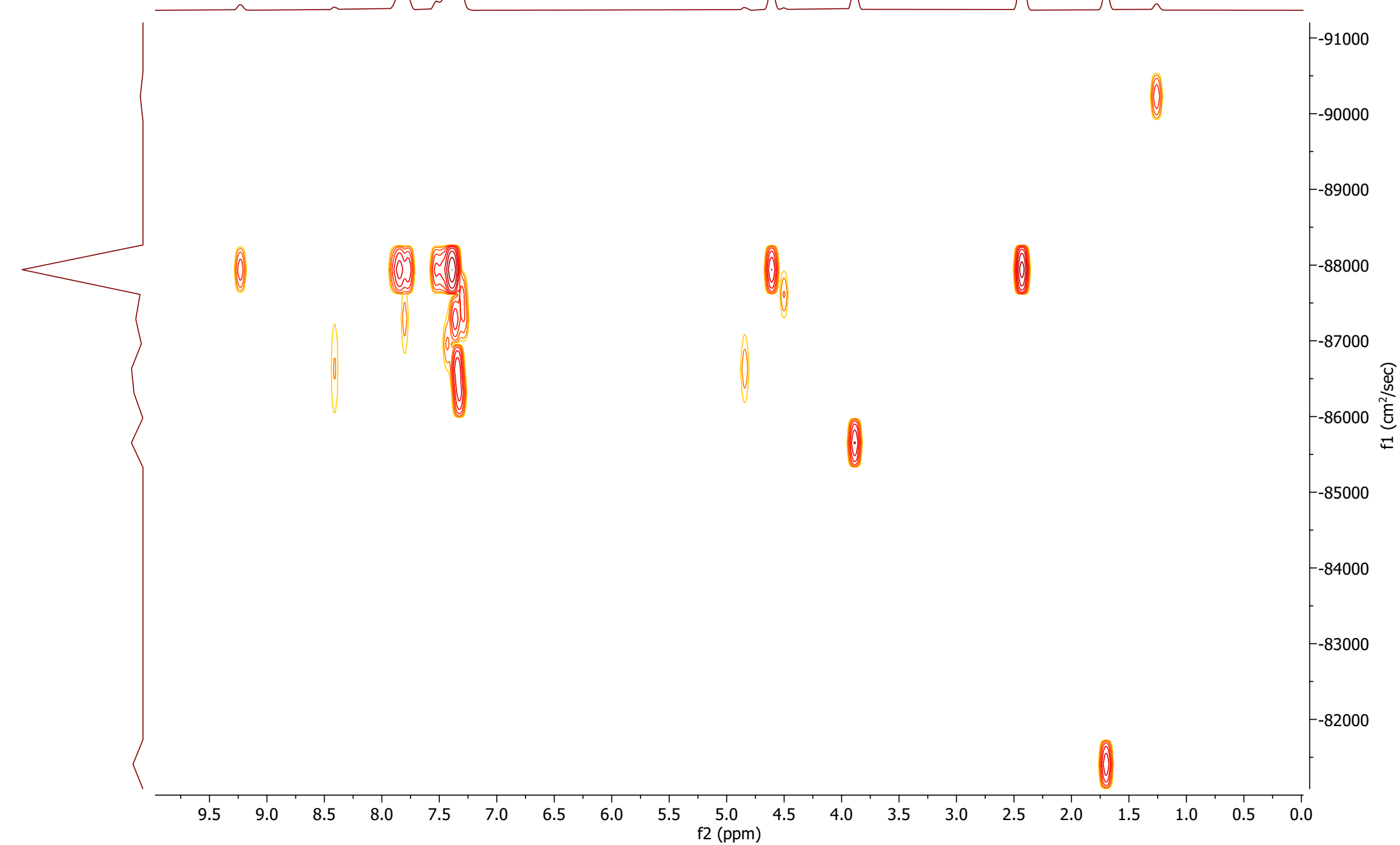


Figure S36. COSY NMR of solids
formed after mixing L29 with
benzylamine and EtOH.

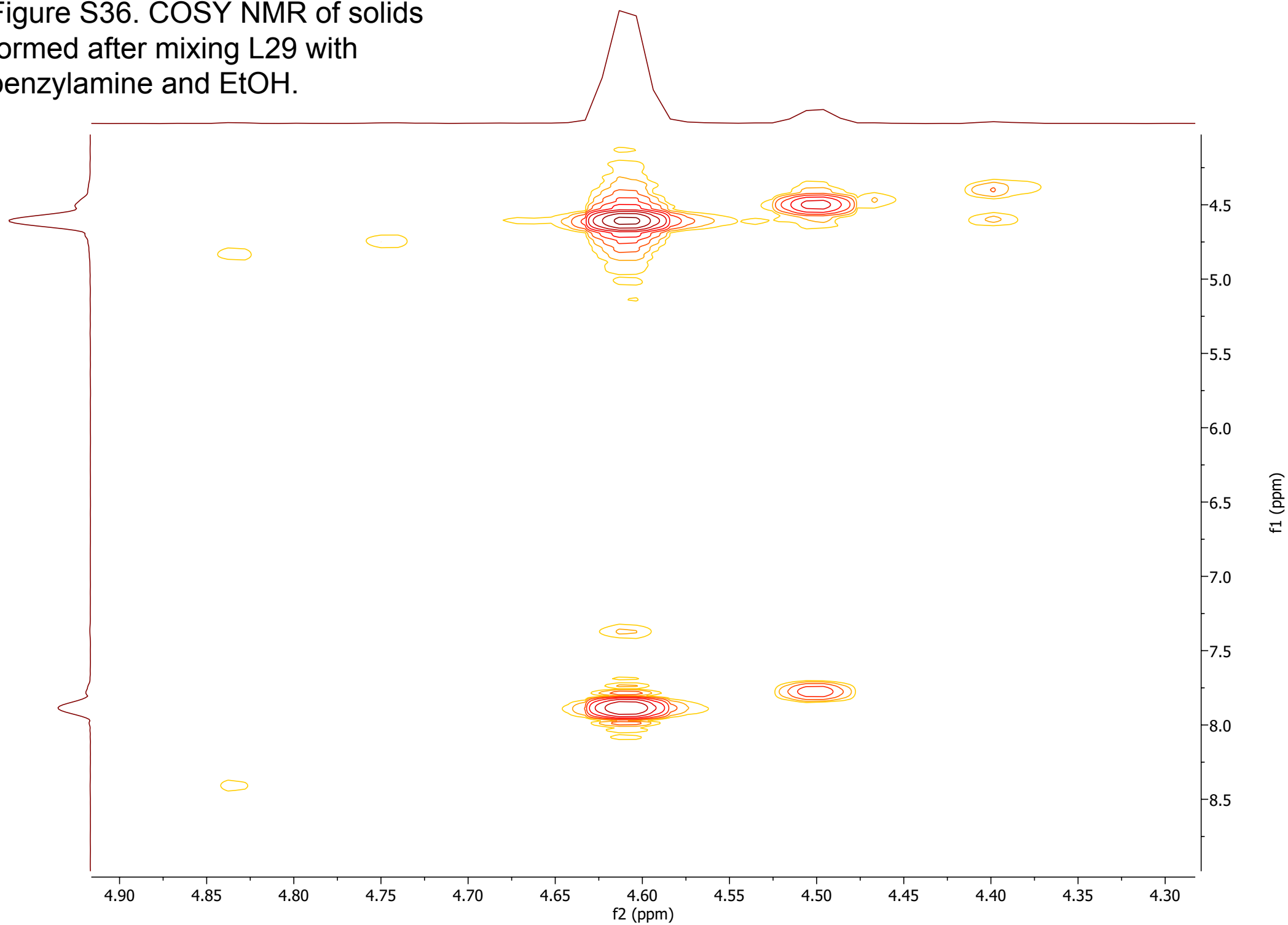
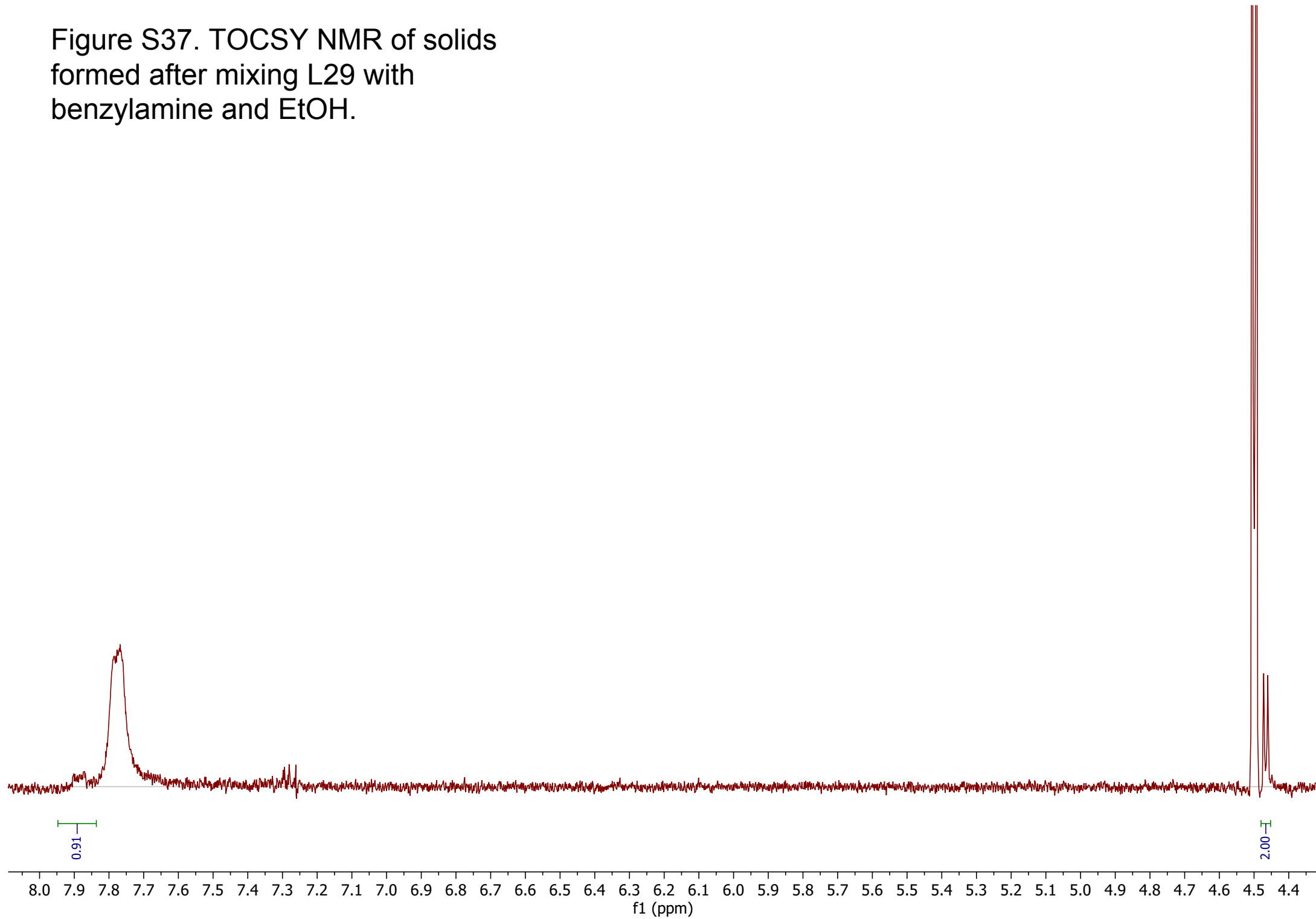


Figure S37. TOCSY NMR of solids
formed after mixing L29 with
benzylamine and EtOH.



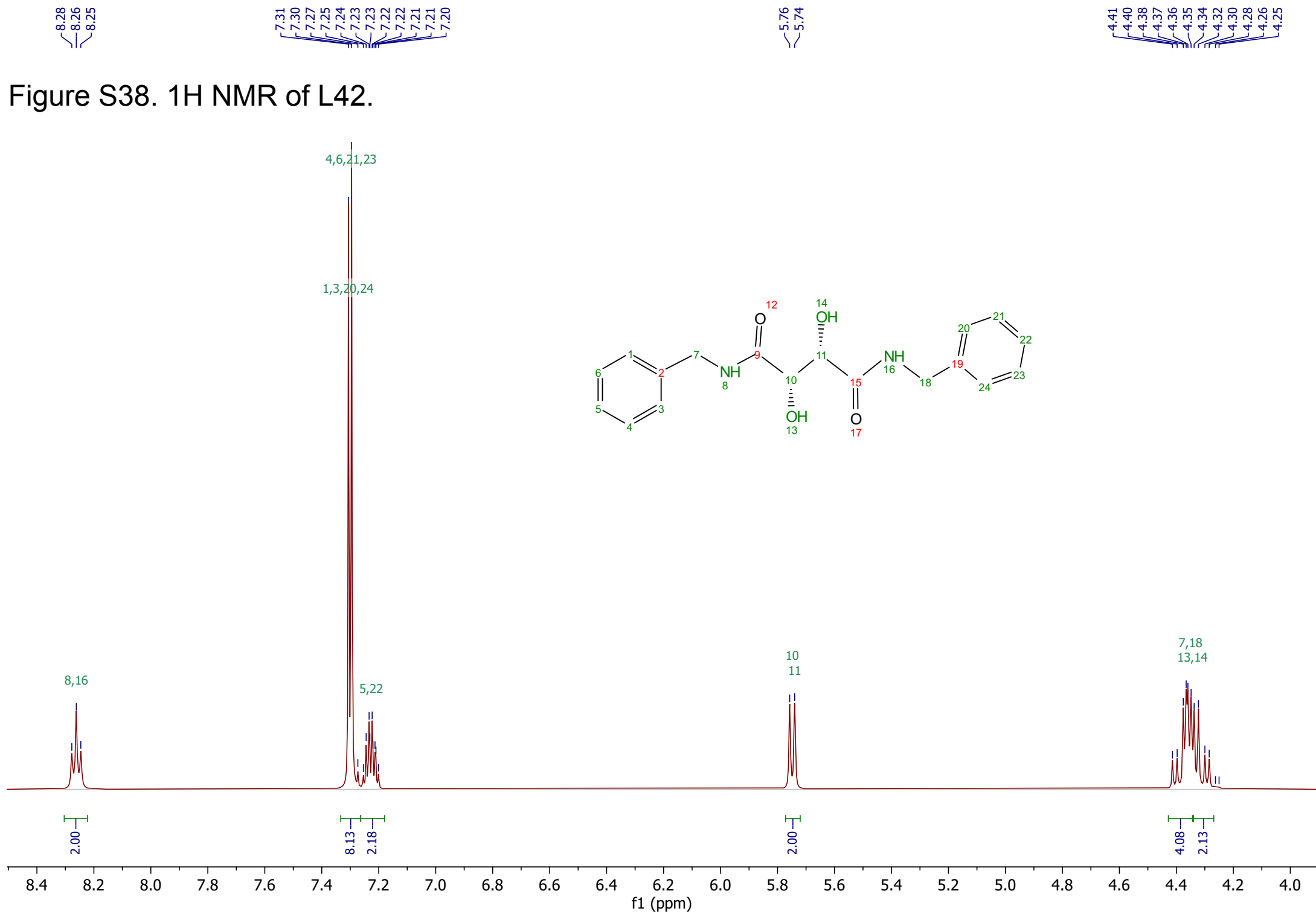
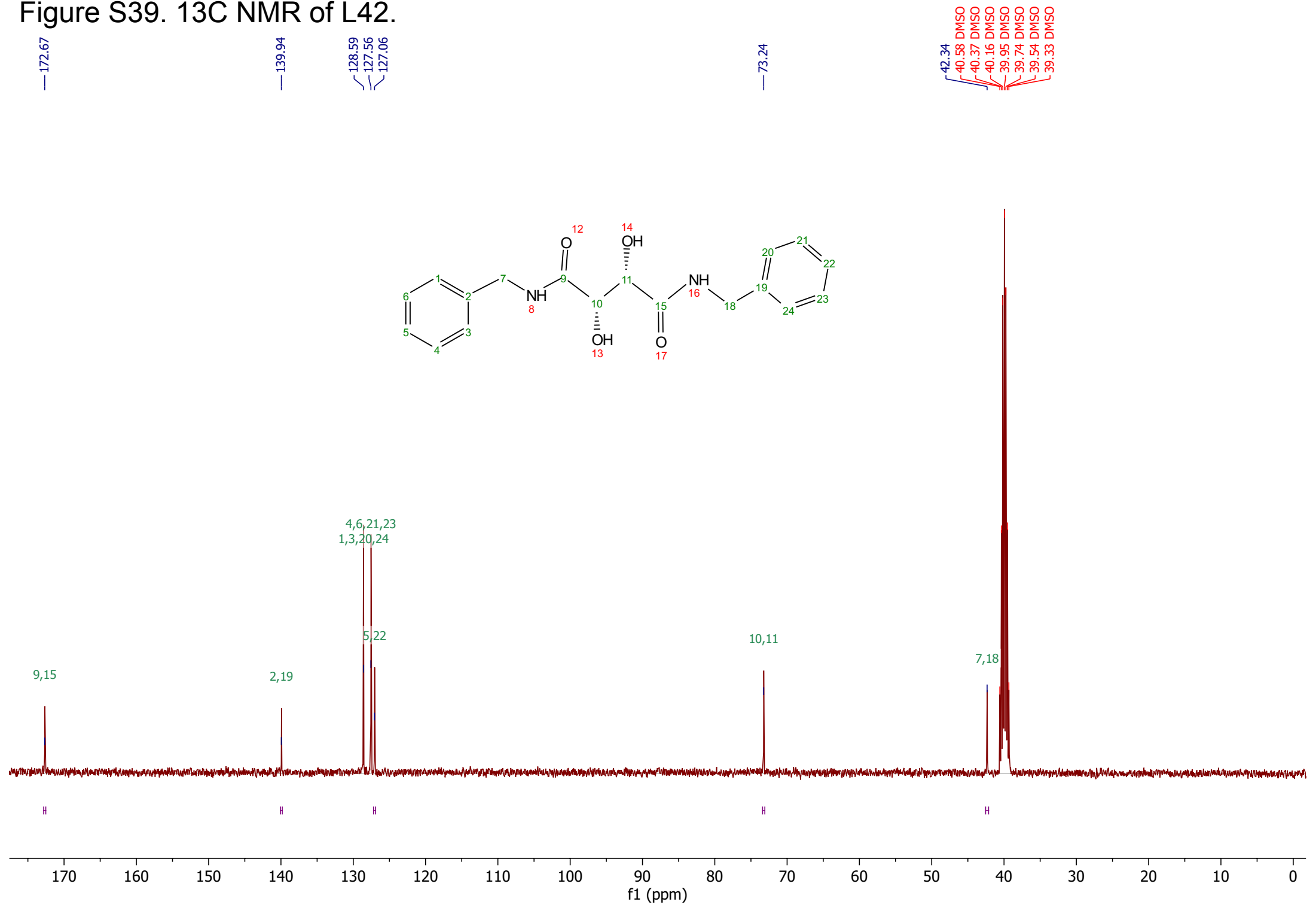


Figure S39. ¹³C NMR of L42.



8.11
8.10
8.08

7.56
7.56
7.56
7.56

6.39
6.38
6.38
6.38
6.24
6.24
6.24
6.23

5.69
5.68

4.48
4.38
4.37
4.37
4.35
4.33
4.31
4.30
4.29
4.27
4.25
4.12

Figure S40. ¹H NMR of L33.

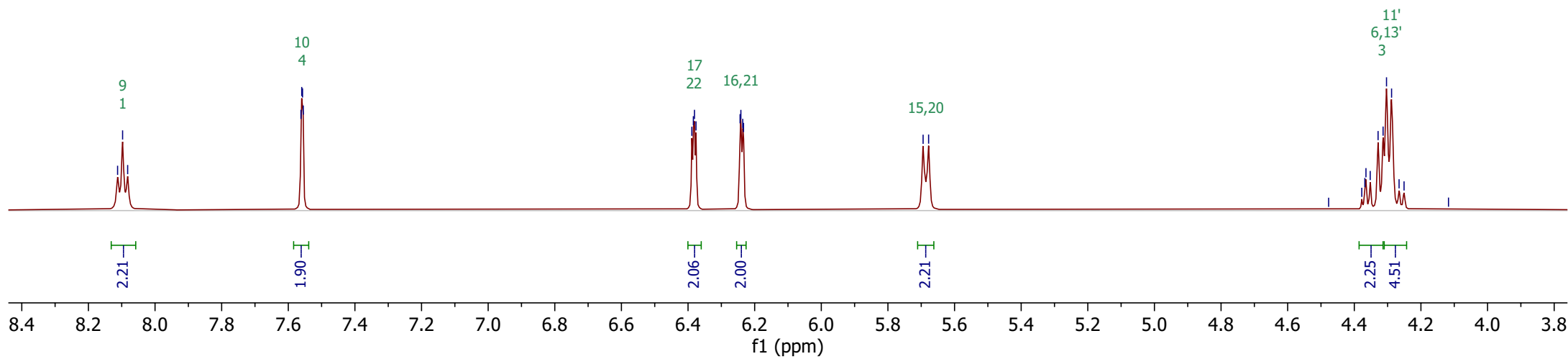
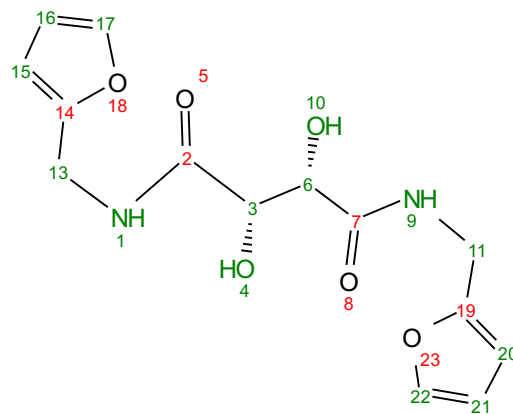
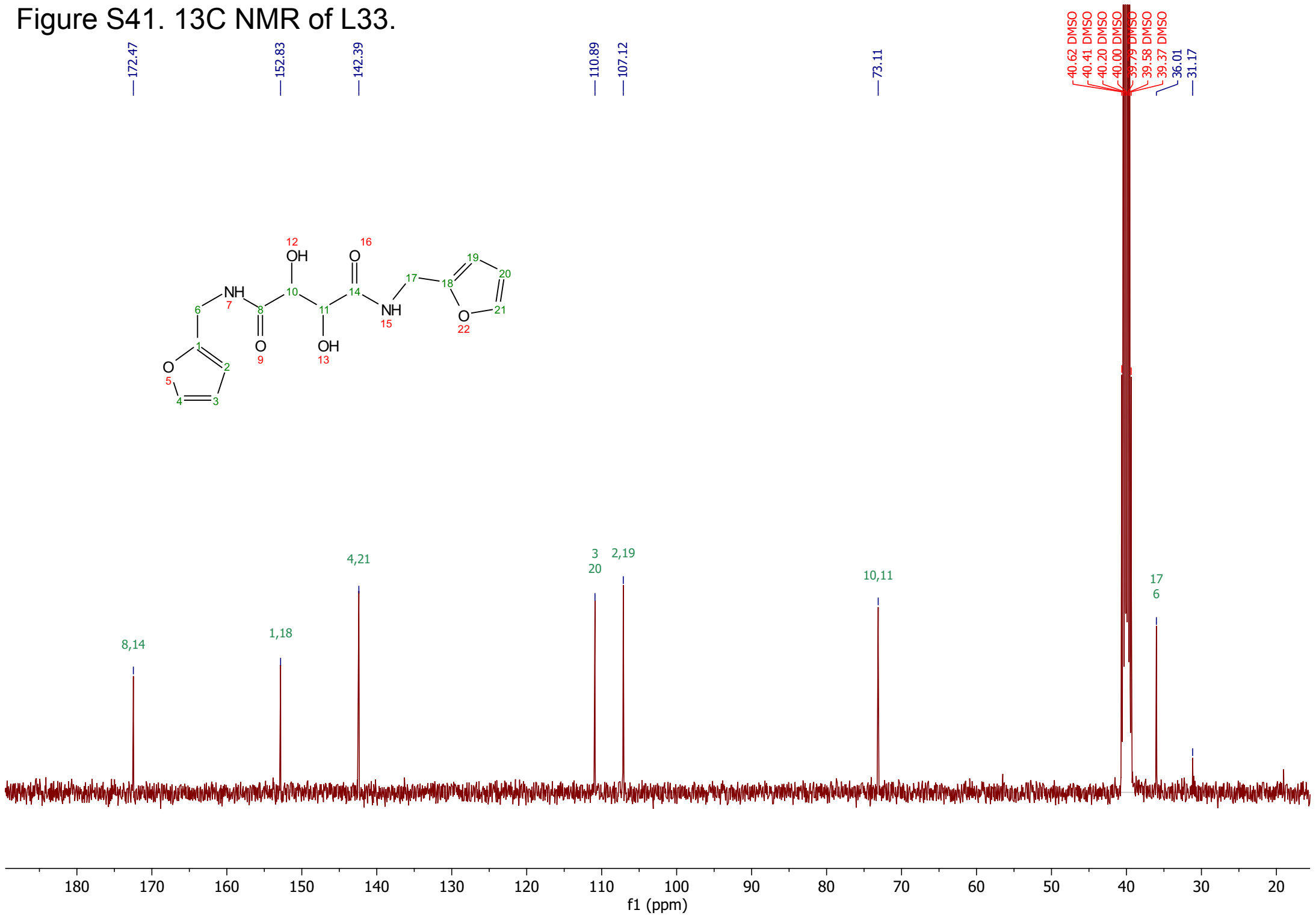


Figure S41. ¹³C NMR of L33.



— 11.29

8.56
8.55
8.54
8.54
8.53
8.53
7.89
7.89
7.88
7.87
7.87

— 3.33

Figure S42. ¹H NMR of L37.

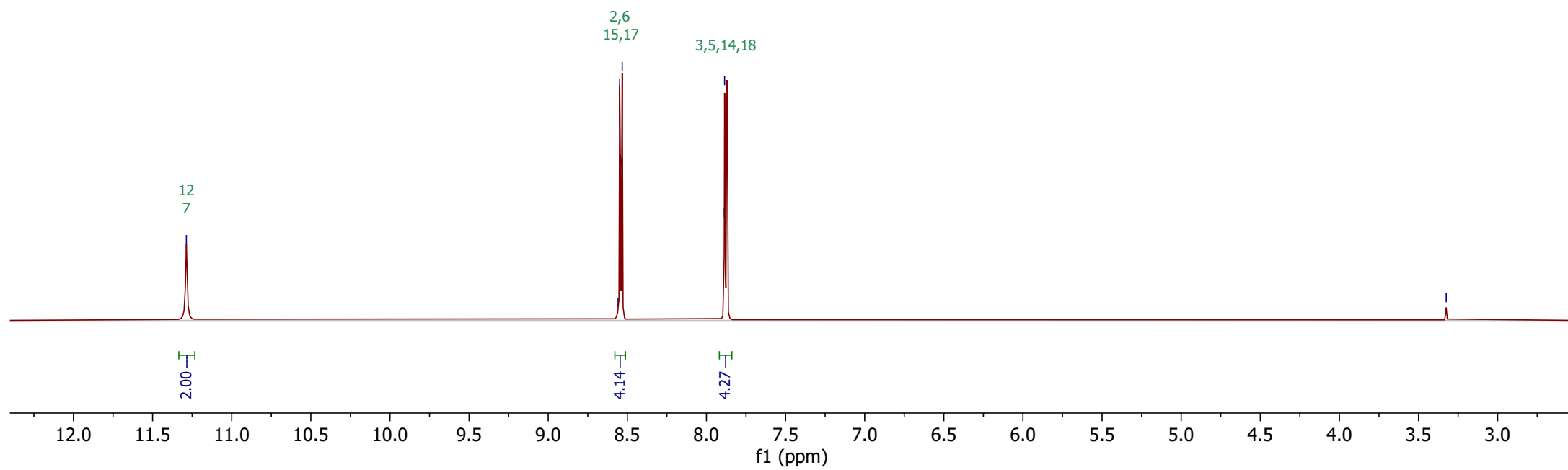
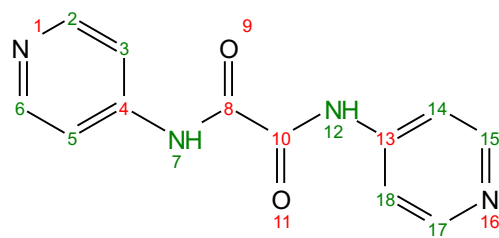


Figure S43. ¹³C NMR of L37.

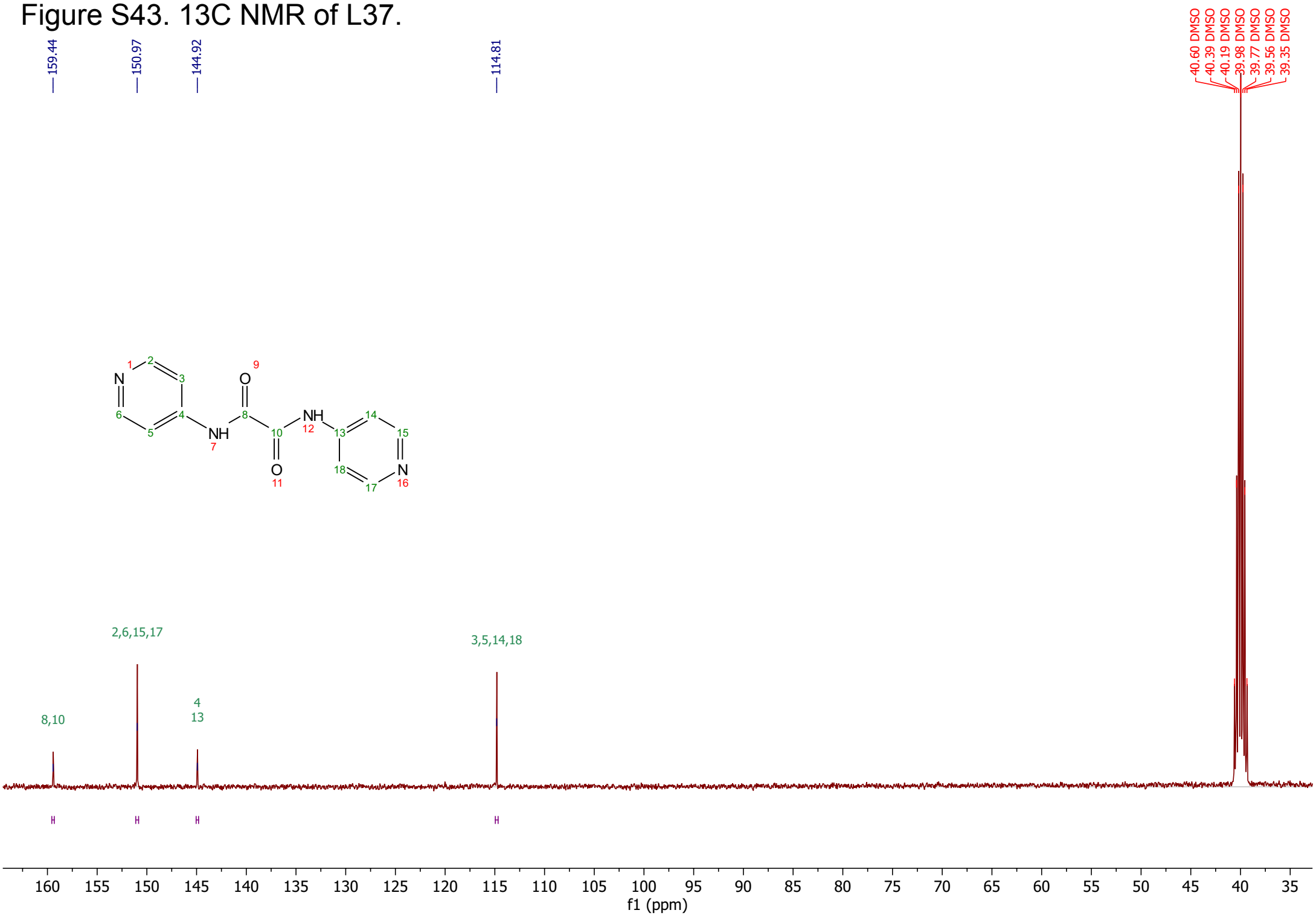


Figure S44. ^1H NMR of L45.

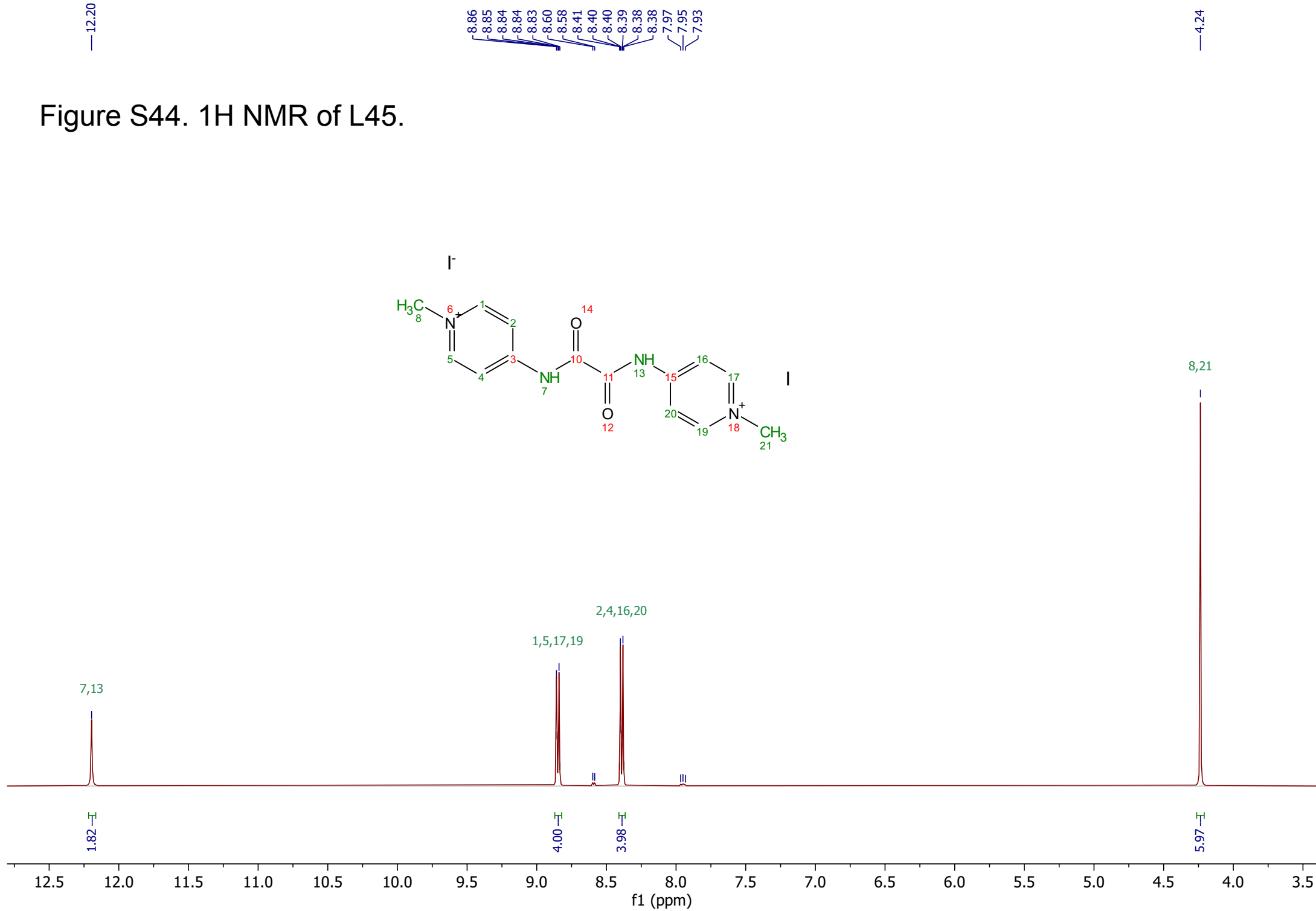
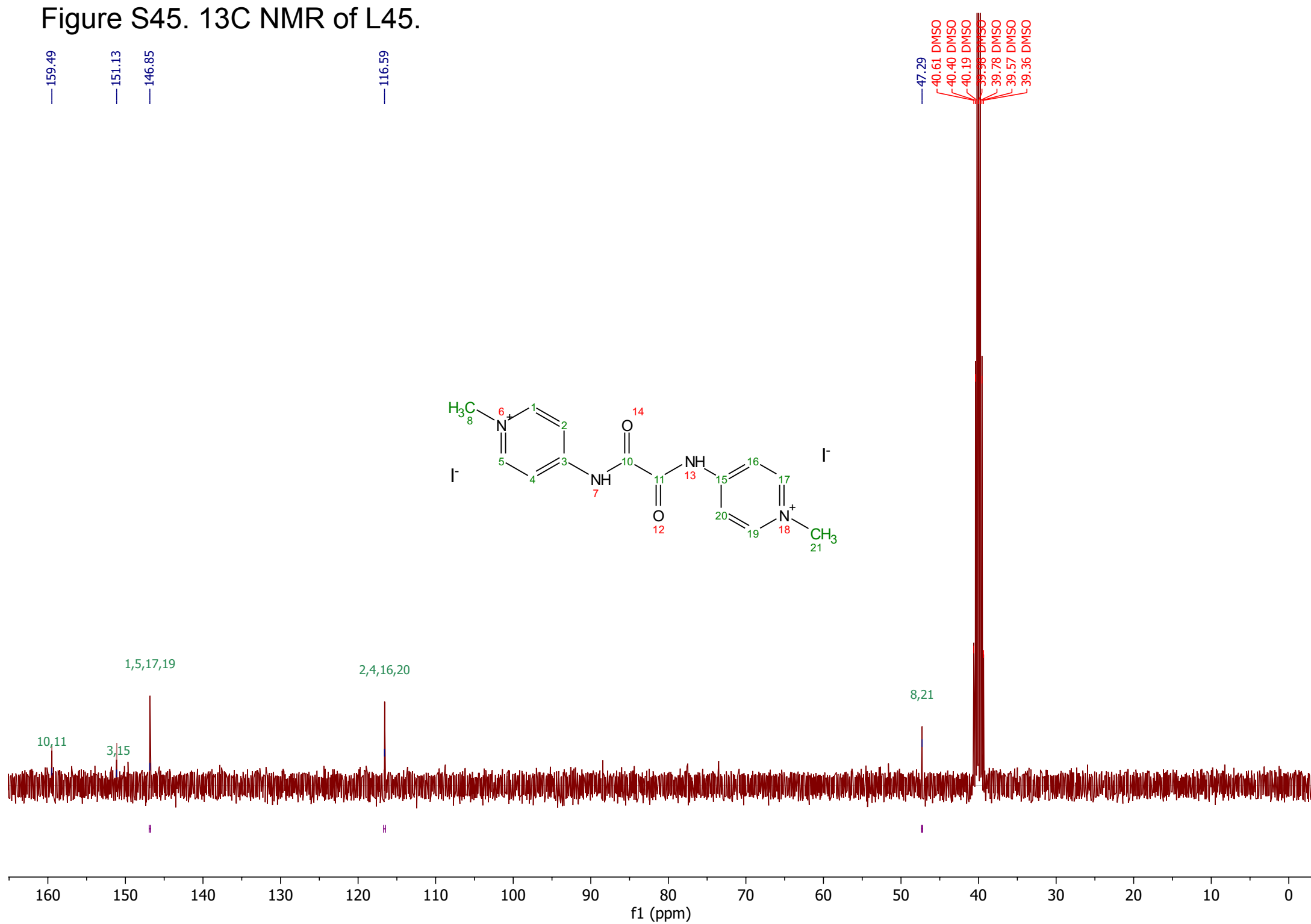


Figure S45. ¹³C NMR of L45.



9.45
9.43
9.42

7.40
7.38

7.16
6.99
6.98
6.96
6.95
6.94

4.49
4.47

Figure S46. ¹H NMR of L28.

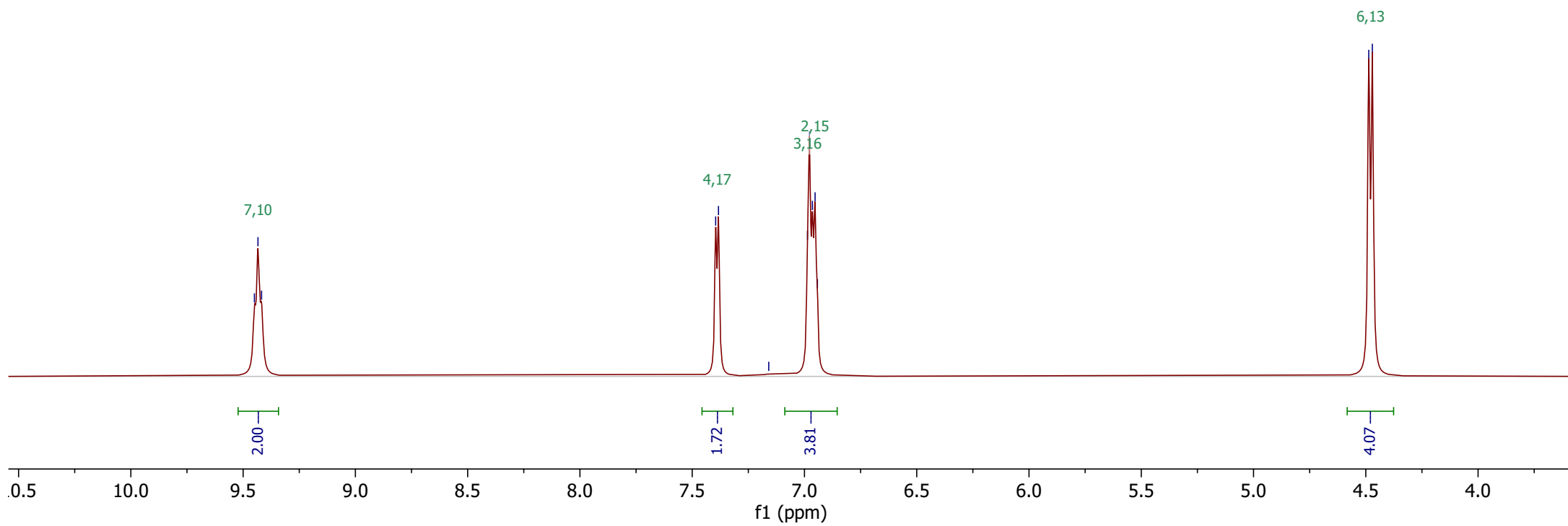
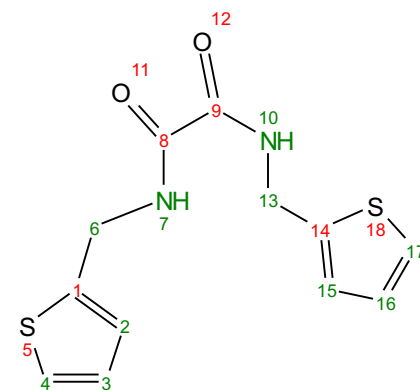


Figure S47. ¹³C NMR of L28.

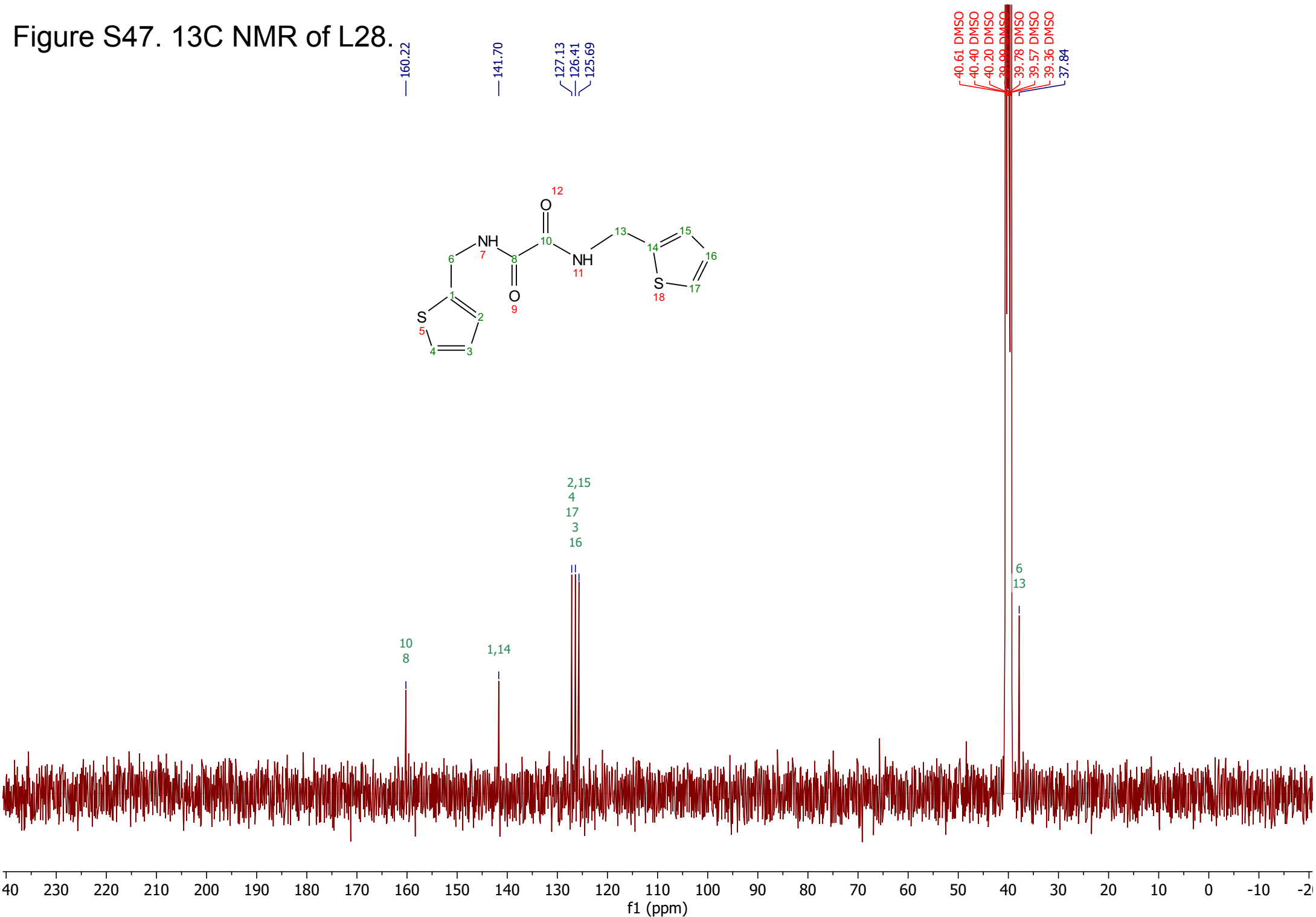


Figure S48. ¹H NMR of L46.

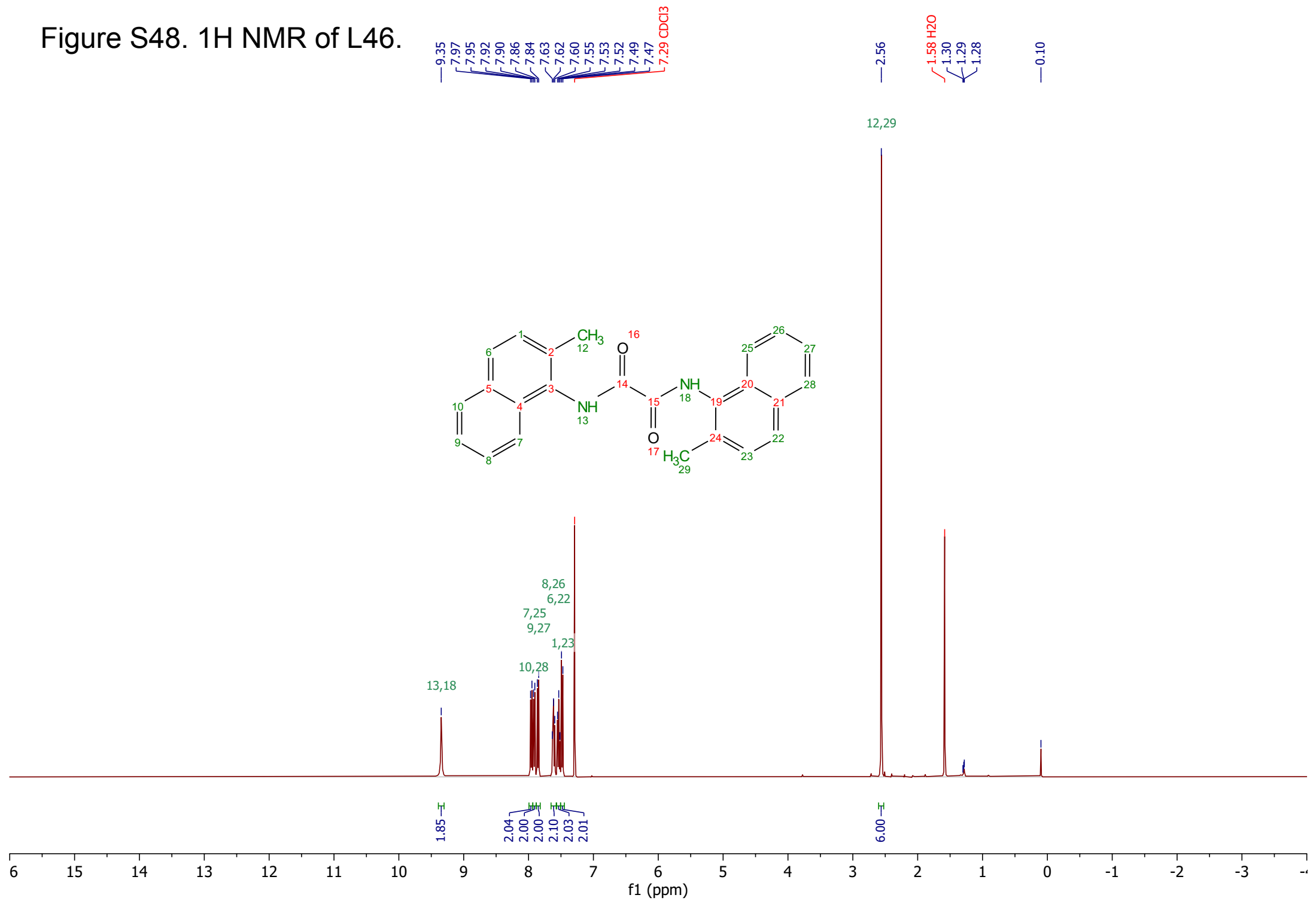


Figure S49. ¹³C NMR of L46.

