
Understanding of Cu-Catalysed Coupling Reactions for C–N Bond Formation

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Philosophy

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Declaration of Originality

The work in this thesis was carried out between October 2011 and April 2015 at the Department of Chemistry, Imperial College London and Jealott's Hill, 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

The rate of reaction for the copper-catalysed coupling reactions to form C–N bonds between aryl halides and amines can be significantly improved in the presence of various bidentate ligands. This improved reaction is often referred as the modified Ullmann amination reaction. However the intermediates and steps involved in the mechanism and the role of the ligand are not fully understood. In this work, mechanistic studies have been carried out in order to improve the current understanding of this reaction.

The role of copper(I) alkylamide complexes as potential intermediates in the modified Ullmann reaction between aryl halides and alkylamines is discussed in Chapter 2. A series of copper(I) alkylamide complexes have been synthesised and shown using single crystal X-ray crystallography to exist as tetramers in the solid state. The structures of these complexes in benzene- d_6 were determined by ^1H DOSY NMR spectroscopy which revealed equilibrating aggregates, where the equilibrium rate could be faster or slower than the NMR time scale, with average aggregation numbers between the dimeric and tetrameric forms. The complexes have been shown to react stoichiometrically with iodobenzene to give arylamine products, both in the absence and presence of 1,10-phenanthroline as an ancillary ligand. The influence of 1,10-phenanthroline on the solution structures in benzene- d_6 and DMSO- d_6 is also discussed and can be related to the stoichiometric and catalytic reactivity. Overall these results highlight the role of copper(I) alkylamide complexes as potential intermediates and show the significance of 1,10-phenanthroline in modulating the reactivity of the system.

Chapter 3 describes the improvement in product yield from utilising *O,O*- and *N,O*-chelating ligands over *N,N*-chelating ligands in the copper-catalysed C–N cross-coupling reaction between piperidine and iodobenzene. A kinetic study of this reaction using 2-acetylcyclohexanone as the added ligand demonstrated that the poorly soluble potassium phosphate base caused the reaction rate to be limited by mass transfer effects. The results provide insights into the qualitative rate dependences in the reactants and also the role of the ligand in the catalyst deactivation pathway by disproportionation.

A mechanistic study of the copper-catalysed C–N cross-coupling reaction between piperidine and iodobenzene using bis(tetra(*n*-butyl)phosphonium) malonate as a soluble base is presented

in Chapter 4. A detailed kinetic study using reaction calorimetry and the reaction progress kinetic analysis (RPKA) methodology reveals first order rate dependences in the substrates and copper catalyst concentration, and negative first order kinetics in the base concentration. NMR spectroscopic evidence suggests the malonate base simultaneously functions as an ancillary ligand and coordinates to give an off-cycle unstable species. Catalyst deactivation by disproportionation was found to be an important consequence of malonate ligand coordination, with the piperidine substrate playing a key role in mitigating the rate of catalyst deactivation. The absence of aryl radical formation suggests that the aryl halide activation mechanism occurs by an oxidative addition process. The experimental data has been successfully modelled to the proposed mechanism to give approximate equilibrium and rate constants for each step.

List of Publications

Some of the work in Chapter 2 of this thesis has been reported in the following co-written published paper:

“Synthesis, Characterisation and Reactivity of Copper(I) Amide Complexes and Studies on Their Role in the Modified Ullmann Amination Reaction”, S. Sung, D. C. Braddock, A. Armstrong, C. Brennan, D. Sale, A. J. P. White, R. P. Davies, *Chem-Eur. J.* **2015**, *21*, 7179–7192.

Table of Contents

Abstract	3
List of Publications	5
Table of Contents	6
Acknowledgements	12
Abbreviations	13
List of Numbered Compounds	16
1 Introduction	23
1.1 Transition metal catalysis	24
1.1.1 Introduction to copper	24
1.1.2 Transition metal-catalysed cross-coupling reactions	25
1.2 Importance of C–N bond formation in synthetic chemistry	27
1.3 Copper-mediated cross-coupling chemistry	30
1.4 Mechanistic studies of the Ullmann amination reaction	35
1.4.1 Oxidation state of the active copper catalyst	36
1.4.2 The role of the ligand and identification of catalyst resting states	38
1.4.3 The effects of the base and solvent	42
1.4.4 Proposed mechanisms for aryl halide activation	44
1.4.4.1 σ -bond metathesis and π -complexation mechanisms	45
1.4.4.2 Mechanisms involving aryl radical intermediates	46
1.4.4.3 Mechanisms involving oxidative addition and reductive elimination	49
1.4.4.4 Copper(III) intermediates in Ullmann reactions	57
1.5 Aims	61
1.6 References	63

2 Synthesis, Characterisation and Reactivity of Copper(I) Amide Complexes and Studies on their Role in the Modified Ullmann Amination Reaction	71
2.1 Introduction	72
2.1.1 Copper(I) intermediates in copper-catalysed C–N bond formation	72
2.1.1.1 Structurally characterised copper(I) intermediates with ancillary ligands	72
2.1.1.2 Ligand-free copper-catalysed amination reactions	79
2.2 Results and Discussion	81
2.2.1 Synthesis of copper(I) amide complexes	81
2.2.2 Solid-state structures of copper(I) amide complexes	82
2.2.3 Reaction of CuMes with piperidine	85
2.2.4 Solution behaviour of copper(I) amide complexes using ^1H DOSY NMR	89
2.2.5 Reactivity of copper(I) amides in aryl amination	95
2.2.6 Identification of solution structures of complexes 14 and 15 in the presence of 1,10-phenanthroline	98
2.2.7 Stoichiometric and catalytic reactivity in the presence of phen	104
2.3 Conclusions	109
2.4 Experimental	111
2.4.1 General Information	111
2.4.2 Preparation of copper(I) dicyclohexylamide (2.8)	112
2.4.3 Preparation of copper(I) 2,2,6,6-tetramethylpiperidide (2.9)	112
2.4.4 Preparation of copper(I) pyrrolidide (2.10)	113
2.4.5 Preparation of copper(I) piperidide (2.11)	113
2.4.6 Preparation of copper(I) benzylamide (2.12)	114
2.4.7 Isolation of the intermediate in the synthesis of copper(I) piperidide (2.13a and 2.13b)	114
2.4.8 ^1H NMR analysis of the mixture of copper(I) mesityl and dicyclohexylamine	115
2.4.9 DFT calculations to obtain r_{calc} values	115
2.4.10 ^1H DOSY NMR solutions of the copper(I) amide complexes with internal standards	116
2.4.11 Procedure for the stoichiometric C–N coupling reactions between the copper(I) amide complexes and aryl iodides	117

2.4.12	Procedure for the catalytic reactions between alkylamines and iodobenzene	117
2.4.13	Preparation of the NMR solution of 2.10 and 2.11 in the presence of phen and DOSY NMR internal standards in benzene-d ₆	117
2.4.14	Preparation of the NMR solution of 2.10 and 2.11 in the presence of phen in DMSO-d ₆	118
2.4.15	Preparation of the ESI-MS solution of 2.11 in the presence of phen in DMSO	118
2.4.16	Preparation of the ESI-MS solution of 2.11 in the presence of phen in benzene	118
2.4.17	Preparation of the NMR solution of lithium di(amido)cuprates in DMSO-d ₆ for comparison	118
2.4.18	Procedure for the stoichiometric reaction between the lithium di(piperi- dido)cuprate(I) and iodobenzene	119
2.4.19	Effect of phen loading on the catalytic C–N coupling between piperidine and iodobenzene	119
2.4.20	Crystallographic Data Tables	120
2.5	Appendix	121
2.5.1	¹ H DOSY NMR spectra of complexes 2.8 – 2.12 with internal standards with <i>D-r</i> analysis	121
2.5.2	<i>D-FW</i> analysis of ¹ H DOSY NMR data of complexes 2.10 and 2.11	131
2.5.3	¹ H NMR data of 2.10 and 2.11 at 0.05 M and 0.20 M concentration in benzene-d ₆	133
2.5.4	Linear regression analysis of <i>r_{calc}</i> vs. aggregate number, <i>n</i> , for 2.8 – 2.12	134
2.5.5	¹ H DOSY NMR spectra of complexes 2.10 and 2.11 in the presence of 1,10-phenanthroline with internal standards	135
2.5.6	ESI-MS data	137
2.6	References	139

3 The Effect of *N,N*-, *O,O*- and *N,O*-Chelating Ligands in the Modified Ullmann Am- ination Reaction and A Kinetic Investigation of the 1,3-Diketone-Ligated Copper- Catalysed *N*-Arylation of Alkylamines 144

3.1	Introduction	145
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3.1.1	<i>N,N</i> -chelating ligands in copper-catalysed cross-coupling of alkylamines and aryl halides	145
3.1.2	<i>O,O</i> - and <i>N,O</i> -chelating ligands in copper-catalysed cross-coupling of alkylamines and aryl halides	145
3.2	Results and Discussion	150
3.2.1	Ligand screening	150
3.2.2	Kinetic studies of the modified Ullmann amination reaction using L15-H as the ancillary ligand	155
3.2.2.1	Rate dependence on the equivalents of potassium phosphate base	155
3.2.2.2	Rate dependence on catalyst concentration	158
3.2.2.3	Rate dependence on diketone ligand (L15-H) concentration	160
3.2.2.4	Rate dependence on iodobenzene and piperidine concentration	162
3.2.2.5	Catalyst deactivation and inhibition	164
3.2.3	¹ H NMR spectroscopic study	170
3.2.4	Proposed mechanism	171
3.3	Conclusions	173
3.4	Experimental	174
3.4.1	General information	174
3.4.2	General procedure for screening ligands, bases and reaction temperatures in the catalytic reactions	175
3.4.3	Preparation of potassium 2-acetylcyclohexanone (L15-K)	175
3.4.4	Procedure for kinetic studies in the diketone-ligated copper-catalysed reactions between piperidine and iodobenzene	176
3.4.5	Addition of copper(I) iodide to L15-K in the presence or absence of piperidine	176
3.4.6	Preparation of solution used in ¹ H NMR spectroscopic study	177
3.5	References	178
4	Mechanistic Studies of the Copper-Catalysed <i>N</i>-Arylation of Alkylamines Promoted by Organic Soluble Ionic Bases	181
4.1	Introduction	182

4.1.1	Substrate deprotonation in the Ullmann reaction	182
4.1.1.1	Phase-transfer catalysis	182
4.1.1.2	Soluble bases	183
4.1.2	Reaction progress kinetic analysis	186
4.2	Results and Discussion	192
4.2.1	Synthesis and use of TBPM as a base	192
4.2.2	Background of reaction calorimetry	195
4.2.3	Kinetic studies of the Ullmann amination reaction using TBPM as the base	196
4.2.3.1	Rate dependence on catalyst concentration	198
4.2.3.2	“Same excess” experiments	198
4.2.3.3	“Different excess” experiments	200
4.2.3.4	Catalyst deactivation	204
4.2.4	¹ H NMR spectroscopic study	208
4.2.5	Malonate coordination and base strength	210
4.2.6	Hydrodehalogenation side reaction	213
4.2.7	Aryl halide activation mechanism	216
4.2.8	Proposed mechanism and kinetic modelling	217
4.3	Conclusions	224
4.4	Experimental	226
4.4.1	General information	226
4.4.2	Preparation of bis(tetra(<i>n</i> -butyl)phosphonium) malonate (TBPM)	227
4.4.3	Procedure for the catalytic reactions using potassium phosphate or TBPM as the base in the presence or absence of 2-acetylcyclohexanone ligand	227
4.4.4	Procedure for the deprotonation of 2-acetylcyclohexanone by TBPM	228
4.4.5	Procedure for the catalytic reaction monitored by NMR using TBPM as the base	229
4.4.6	Procedure for the kinetic studies using reaction calorimetry	229
4.4.7	“Tau”, baseline and heat of mixing corrections to raw calorimetry data	230
4.4.8	Procedure for validating the use of calorimetry as a monitoring tool using NMR analysis	231
4.4.9	Procedure for probing catalyst deactivation using multiple addition experi- ments and reaction calorimetry	232

4.4.10 Procedure for probing catalyst deactivation by using iodobenzene, TBPM and/or piperidine to initiate the reaction	232
4.4.11 Preparation of solutions used in ^1H NMR spectroscopic study	233
4.4.12 Procedure for the catalytic reaction using tetra(<i>n</i> -butyl)phosphonium mono-anionic malonic acid as the base	233
4.4.13 Procedure for the catalytic reactions using potassium phosphate as the base in the presence or absence of malonic acid as the ligand	233
4.4.14 Procedure for the catalytic reactions between pyrrolidine or piperidine with iodobenzene to determine if imine formation occurs	234
4.4.15 Procedure to test if added water affects the amount of benzene formed in the catalytic reaction	234
4.4.16 Procedure for catalytic reactions with different catalyst loadings and [Piperidine] ₀ to observe how the amount of benzene formed is affected .	235
4.4.17 Procedure for the catalytic reaction between piperidine and radical probe 2-(allyloxy)iodobenzene	235
4.4.18 Kinetic modelling using COPASI	236
4.4.19 Derivation for the $\text{p}K_{\text{a}}$ of the N–H group in intermediate 4.2	246
4.5 References	247
5 Overall Conclusions	251
5.1 Overall Conclusions	252
5.2 References	256

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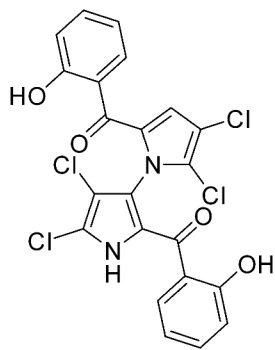
Abbreviations

[e]	Excess
°	Degree
Å	Angstrom
Ac	Acetyl
Ar	Aryl
B3LYP	Becke, three-parameter, Lee-Yang-Parr
Bu	Butyl
C	Celsius
c	Centi
<i>calc</i>	Calculated
Cy	Cyclohexyl
<i>D</i>	Diffusion coefficient
DFT	Density functional theory
DMEDA	<i>N,N'</i> -dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
DOSY	Diffusion-ordered spectroscopy
<i>E</i>	Energy
<i>E</i>	Potential
EPR	Electron paramagnetic resonance
equiv	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
EXAFS	Extended X-ray absorption fine structure
<i>F</i>	Faraday constant
<i>f</i>	Fractional conversion
FG	Functional group
FID	Flame ionisation detector
<i>FW</i>	Formula weight
<i>G</i>	Gibbs free energy

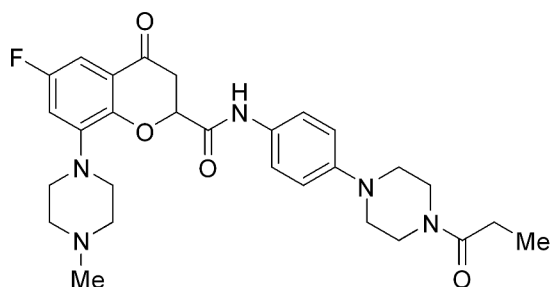
g	Gram
GC	Gas chromatography
h	Hour
h	Planck constant
<i>H</i>	Enthalpy
HAT	Halide atom transfer
Hz	Hertz
I.D.	Internal diameter
IAT	Iodine atom transfer
ⁱ Pr	<i>iso</i> -Propyl
IR	Infrared
J	Joule
<i>J</i>	Spin-spin coupling constant
k	Kilo
<i>k</i>	Rate constant
<i>K</i>	Equilibrium constant
<i>K_a</i>	Acid dissociation constant
L	Litre
LUMO	Lowest unoccupied molecular orbital
M	Molar
m	Milli
m	Meter
m	Multiplet
Me	Methyl
Mes	Mesityl
min	Mine
<i>M_n</i>	Number average molecular weight
mol	Mole
MS	Mass spectrometry
<i>MW</i>	Molecular weight
<i>n</i>	Number of moles
<i>n</i>	Aggregate number
ⁿ Bu	<i>n</i> -Butyl
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
ⁿ Pr	<i>n</i> -Propyl

Nu	Nucleophile
OAc	Acetate
obs	Observed
p	Pentet
Ph	Phenyl
Phen	1,10-Phenanthroline
ppm	Parts per million
PTFE	Polytetrafluoroethylene
q	Heat flow
r	Radius
r^2	Coefficient of determination
ROESY	Rotating frame overhauser effect spectroscopy
RPKA	Reaction progress kinetic analysis
s	Second
s	Singlet
SEM	Scanning electron microscope
SET	Single electron transfer
t	Time
t	Triplet
T	Temperature
TBPM	Bis(tetra(<i>n</i> -butyl)phosphonium) malonate
^t Bu	<i>t</i> -Butyl
THF	Tetrahydrofuran
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TMS	Tetramethylsilane
TON	Turnover number
UV-VIS	Ultraviolet-visible
V	Volt
V	Volume
XANES	X-ray absorption near edge structure
δ	Chemical shift
μ	Micro
ν	Frequency of photon

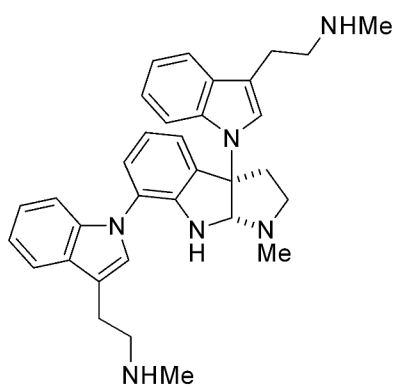
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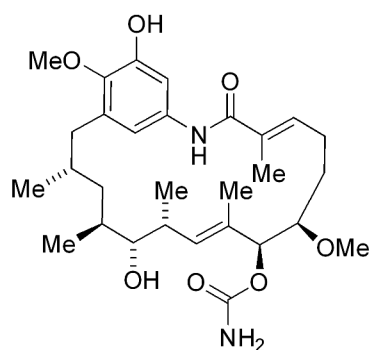
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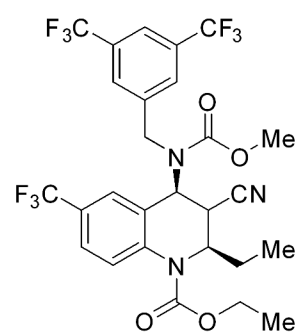
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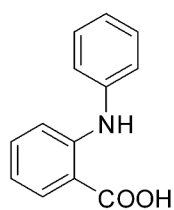
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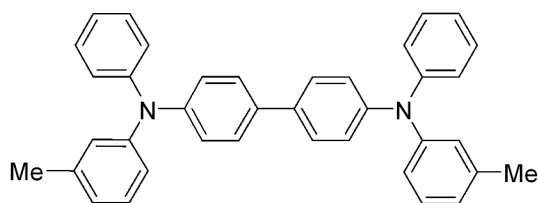
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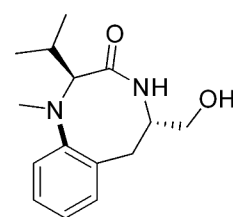
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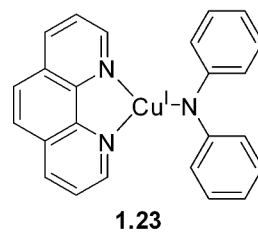
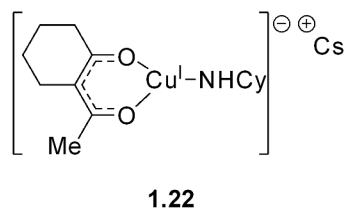
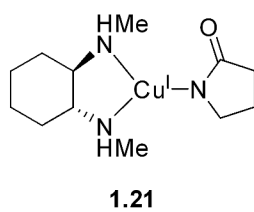
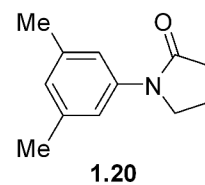
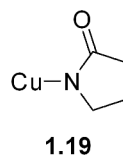
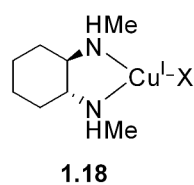
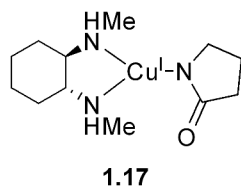
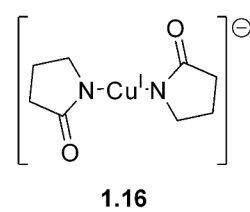
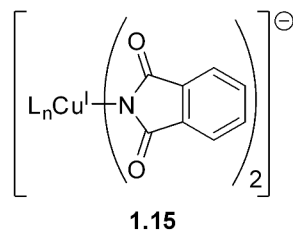
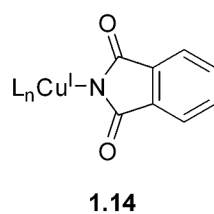
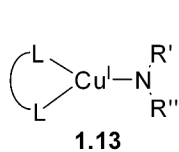
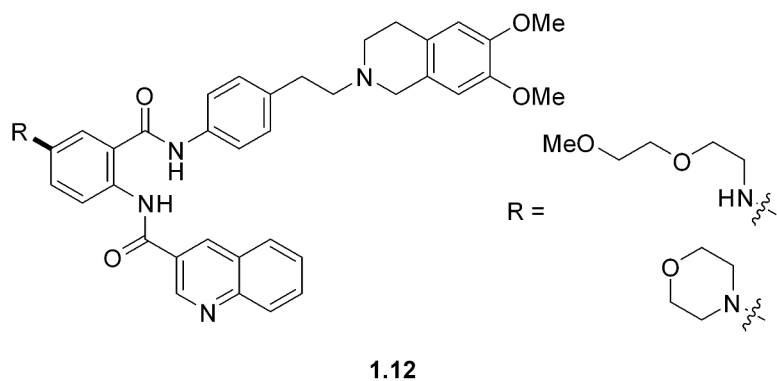
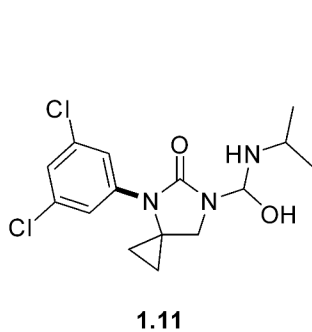
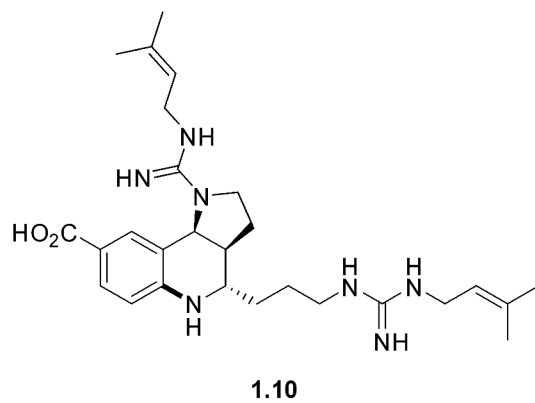
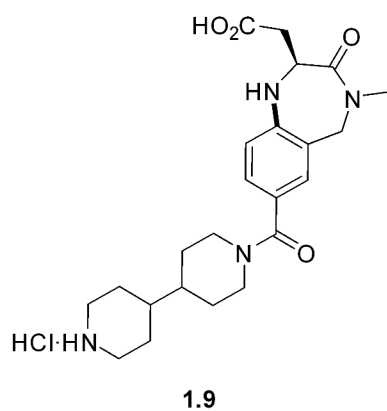
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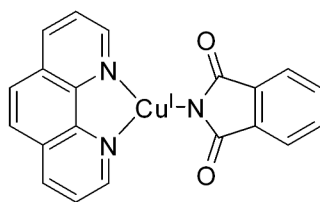


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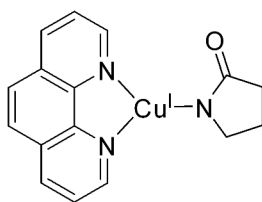


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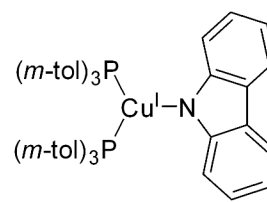




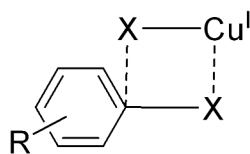
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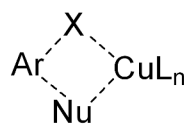
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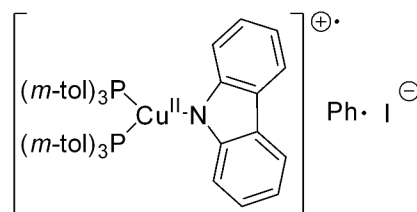
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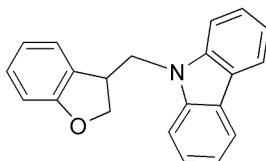
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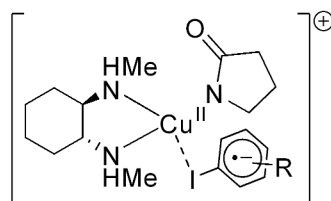
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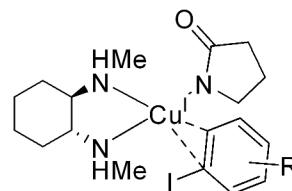
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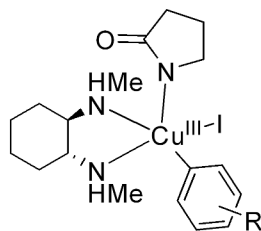
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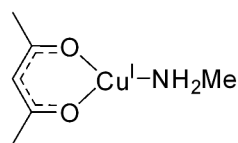
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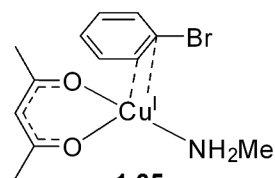
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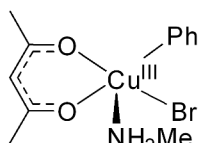
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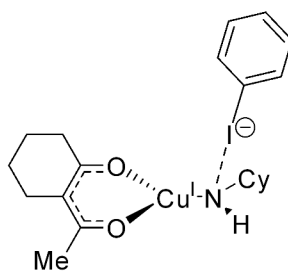
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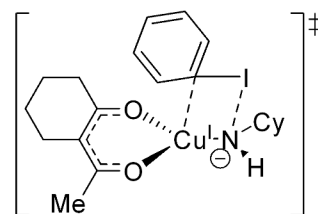
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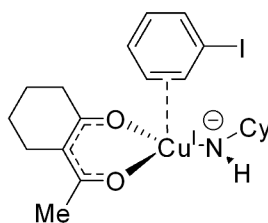
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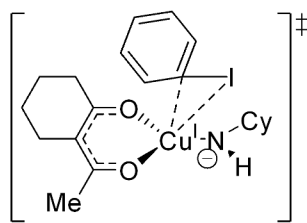
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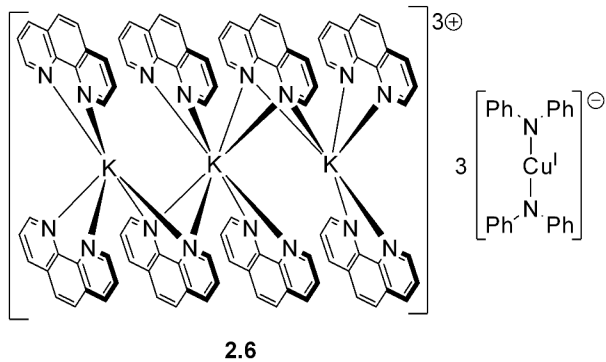
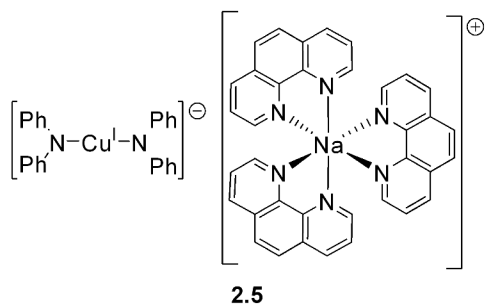
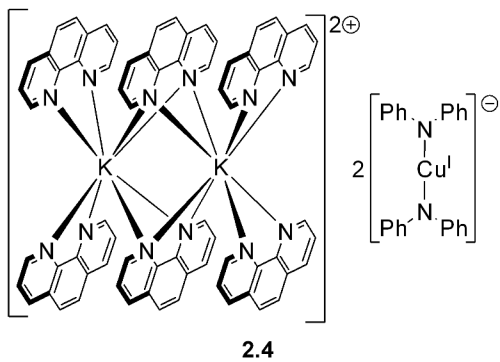
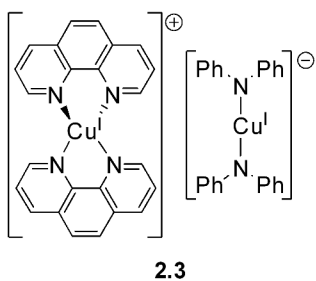
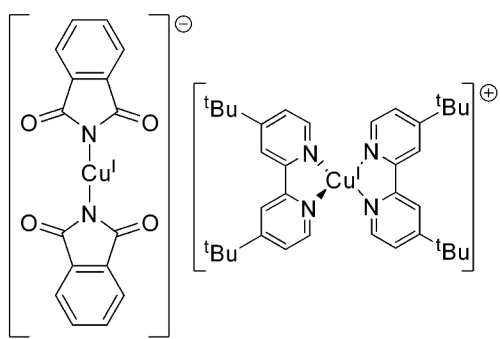
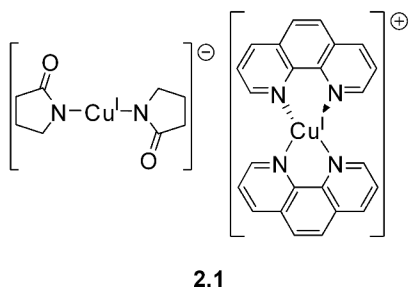
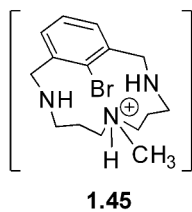
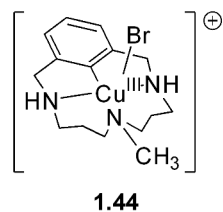
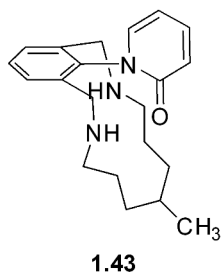
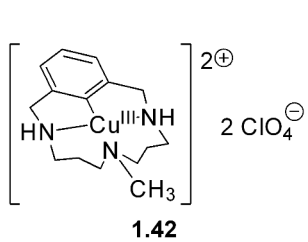


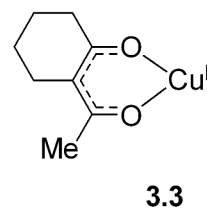
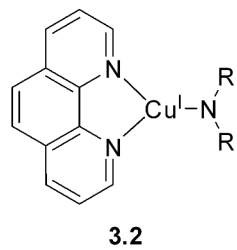
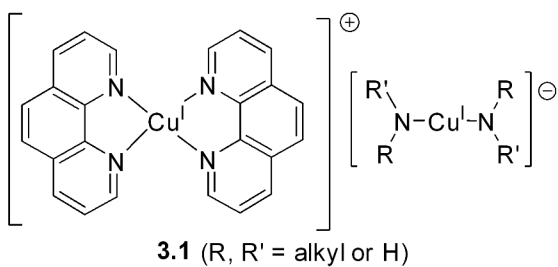
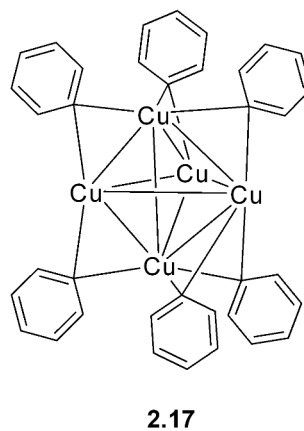
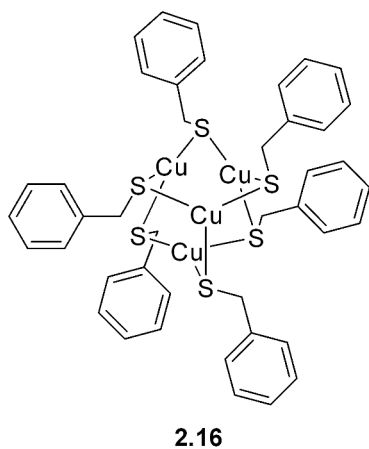
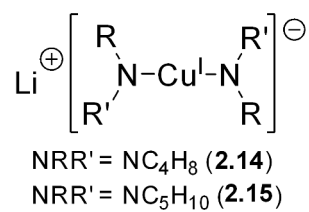
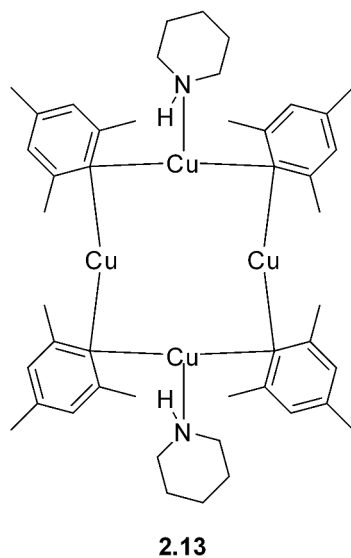
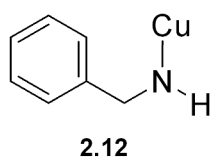
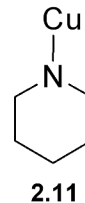
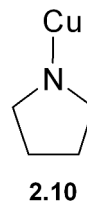
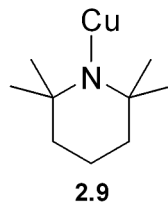
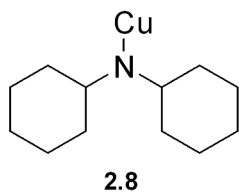
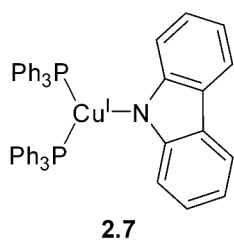
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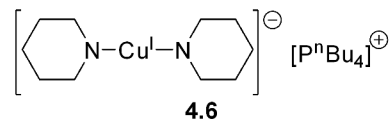
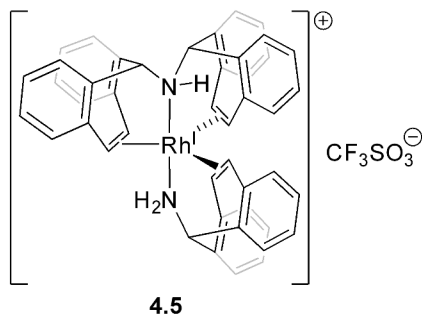
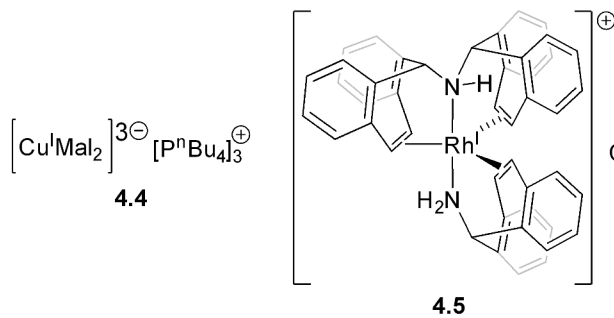
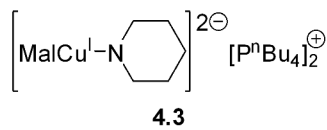
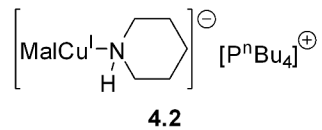
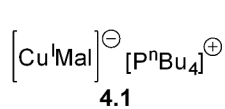
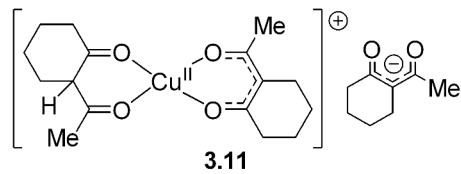
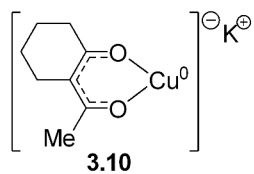
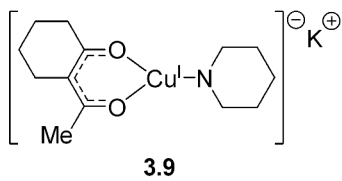
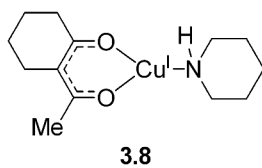
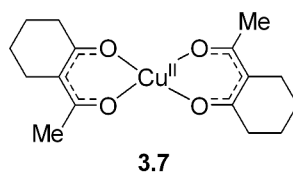
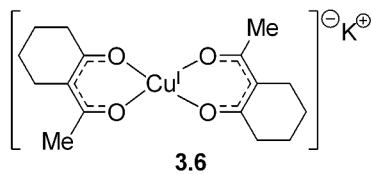
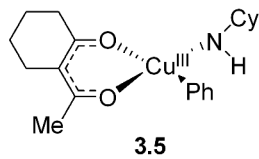
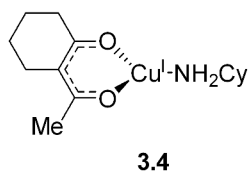


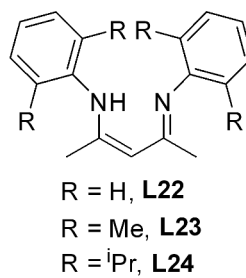
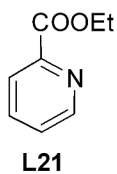
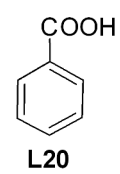
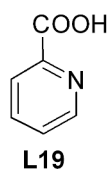
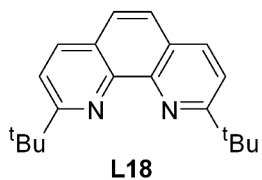
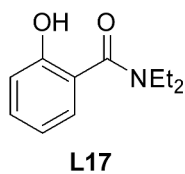
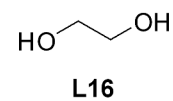
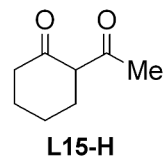
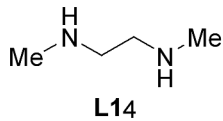
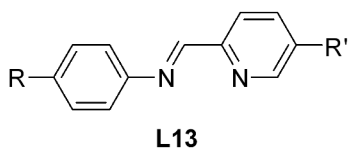
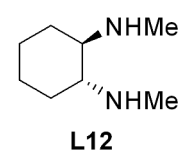
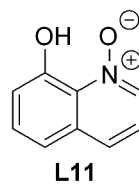
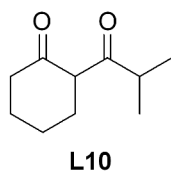
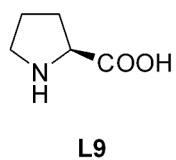
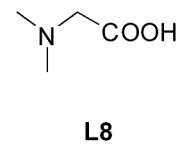
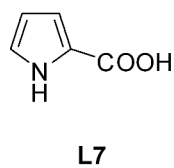
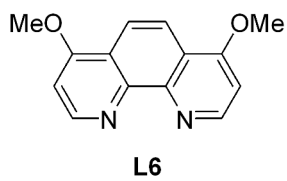
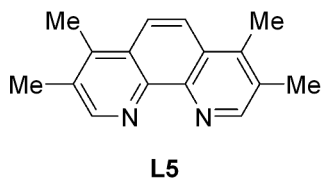
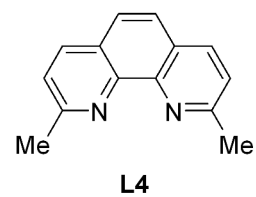
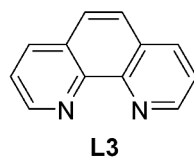
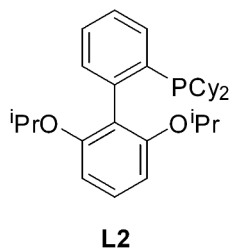
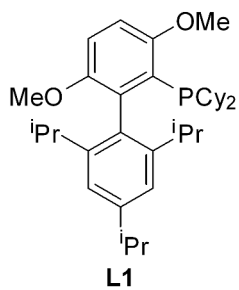
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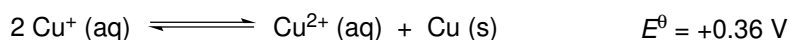
Chapter 1

Introduction

1.1 Transition metal catalysis

1.1.1 Introduction to copper

The IUPAC definition of a transition metal element is “an element whose atom has an incomplete d-sub-shell, or which can give rise to cations with an incomplete d-sub-shell”,^[1] therefore the elements in groups 3 to 12 on the periodic table are typically known as transition metals. The general electronic configuration of transition metals are $[\text{Inert Gas}]ns^{1-2}(n-1)d^{1-10}$, where the number of electrons in the outer s- and d-orbitals is dependent on the number of electrons in the element atom and which distribution is most energetically favourable. Copper has an electronic configuration of $[\text{Ar}]4s^13d^{10}$ in its elemental form and can form a wide variety of compounds in its +1 and +2 oxidation states, which are also known as cuprous and cupric. Compounds containing copper(III) are also known but are far less common owing to the high third ionisation energy of copper^[2] and also the typically short lifetimes of the complexes.^[3] This electronic configuration adopted by copper allows the 3d-orbitals to be fully filled which is energetically favoured over a partially filled 3d-sub shell configuration of $[\text{Ar}]4s^23d^9$. Although copper(I) might be predicted to have a more stable electron configuration ($[\text{Ar}]4s^03d^{10}$) than copper(II) ($[\text{Ar}]4s^03d^9$) due to the fully filled 3d-orbitals, copper(I) is actually thermodynamically unstable in the presence of water:^[4]



As the standard potential ($E^\theta = +0.36 \text{ V}$) for this reaction is positive, the change in Gibbs free energy for the overall reaction ($\Delta_r G^\theta$) will be negative according to the equation $\Delta_r G^\theta = -nFE^\theta$ where n is the number of moles of electrons transferred and F is the Faraday constant.^[5] An aspect that contributes towards the low stability of copper(I) compared to copper(0) is the relatively high ionisation energy of copper.^[2] Therefore copper(I) will spontaneously undergo disproportionation to give copper(II) and copper(0). As a result, complexes with copper(I) centres often require careful handling under dry nitrogen or argon atmospheres to prevent significant decomposition.

One of the key characteristics of most transition metals is their ability to readily adopt many different oxidation states and their ability to take on a variety of coordination geometries when combined with one or more ligands, which in turn influences their chemical, physical, electrical and magnetic properties.^[4] The ability to tune important chemical properties such as the redox

potential and steric bulk of the complexes by using various types of ligands; and also the relative ease at which ligands can be exchanged with its surroundings for some complexes have allowed transition metals to play a key role as catalysts in bond forming and breaking reactions.

1.1.2 Transition metal-catalysed cross-coupling reactions

The role of a catalyst is to provide an alternative reaction pathway for a given chemical transformation that has a lower activation energy ($\Delta G^\ddagger$) and therefore faster reaction rate, whilst not being consumed in the process.^[4] In Figure 1.1, the reaction between substrates **A** and **B** to give **P** has a higher activation energy for the uncatalysed reaction than the individual steps that are part of the catalysed reaction *via* two intermediate species, **I₁** and **I₂**. $\Delta_r G^\theta$ remains unchanged for both types of reactions as the same compounds are formed and consumed.

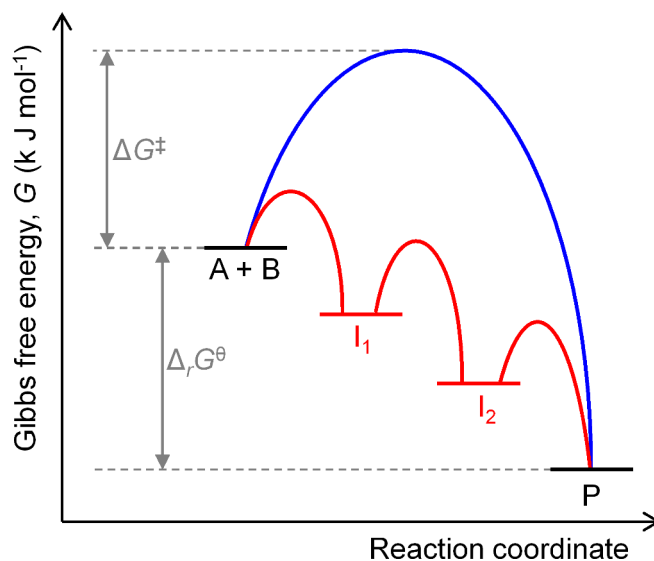


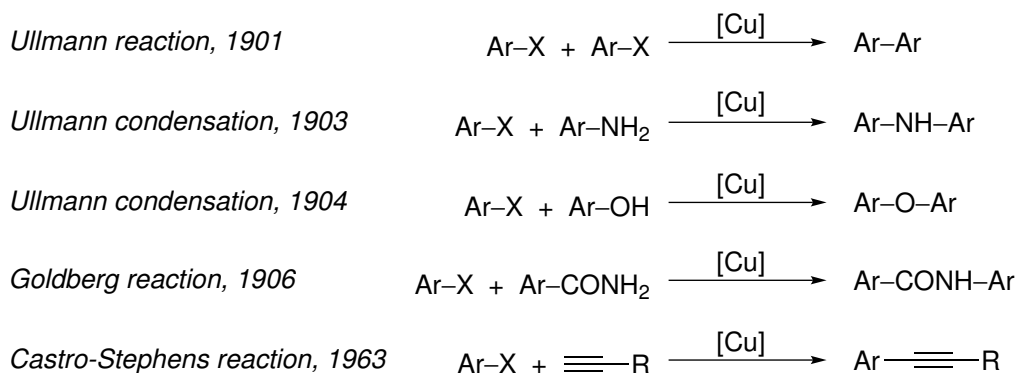
Figure 1.1: Schematic representation comparing the energetics of an uncatalysed (blue) and catalysed reaction (red).

The use of catalysts can be found in many areas such as in nature in the form of enzymes, in industries like pharmaceuticals, petrochemicals and renewables, and in academic laboratories. Overall, it is thought that approximately 90% of all chemical products have at least one hetero- or homogeneous catalytic step in their manufacture.^[6]

Cross-coupling reactions involving the formation of a new bond between two molecular fragments are notable transition metal-catalysed processes that are widely used in organic synthesis. Similar to nucleophilic substitution reactions, cross-coupling reactions typically involve

the joining of an activated carbon or heteroatom nucleophile with a carbon centre attached to a leaving group, such as a halide or triflate.^[7]

The use of palladium has seen the most development and utilisation in transition metal-catalysed reactions since the 1970s, with the most notable examples being the C–C bond forming Heck, Kumada, Sonogashira, Negishi, Stille and Suzuki reactions.^[8–12] Similar cross-coupling reactions to form C–C bonds between aromatic and alkynyl carbon centres, and C–N and C–O bonds between aromatic carbon centres and amines, amides and phenols can also be achieved through the use of copper and were first reported as long ago as the early 20th century by Ullmann, Goldberg, and Castro and Stephens (Scheme 1.1).^[13–18]



Scheme 1.1: Notable historical copper-mediated C–C, C–N and C–O cross-coupling reactions by Ullmann,^[13–16] Goldberg,^[17] and Castro and Stephens.^[18]

Although significant progress has been made in improving the substrate scope, functional group tolerance, reaction conditions and lowering of catalyst loadings for many important bond forming methodologies, progress is still required in further improving the atom economy, cost and toxicity for some reactions. This could be achieved through the improvement of existing catalytic systems or the development of new catalysts.^[19]

1.2 Importance of C–N bond formation in synthetic chemistry

Given the significant number of pharmacologically important natural products that contain aryl carbon-nitrogen bonds (see Figure 1.2 for examples **1.1** – **1.5**), the introduction of nitrogen groups to sp^2 carbon centres is an important chemical transformation in organic synthesis.^[27–31] Some examples of possible methodologies to generate arylamines are shown in Scheme 1.2.^[32] Route A shows the introduction of a C–N bond to form anilines by nitration from an aromatic C–H bond followed by reduction of the newly formed nitro group. Subsequent functionalisation of the amine group can then be performed to introduce R-groups. However, substrate scope for Route A is limited to highly stable systems due to the harsh reaction conditions typically required for nitration. An alternate method to form arylamines involves initially generating a benzyne intermediate from an aryl halide with a strong base such as NaNH_2 (Route B, Scheme 1.2). However regioisomeric mixtures are formed when unsymmetrical aryl halides are used. Nucleophilic aromatic substitution ($S_N\text{Ar}$) via a Meisenheimer intermediate can also

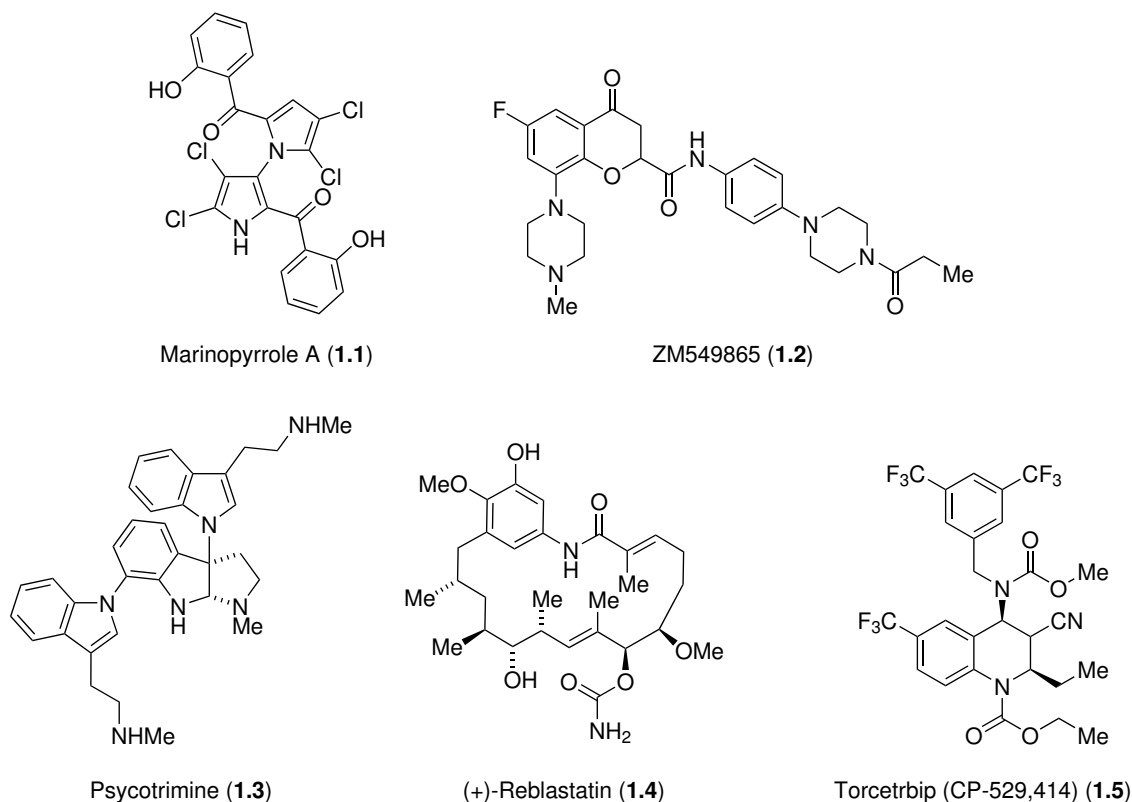
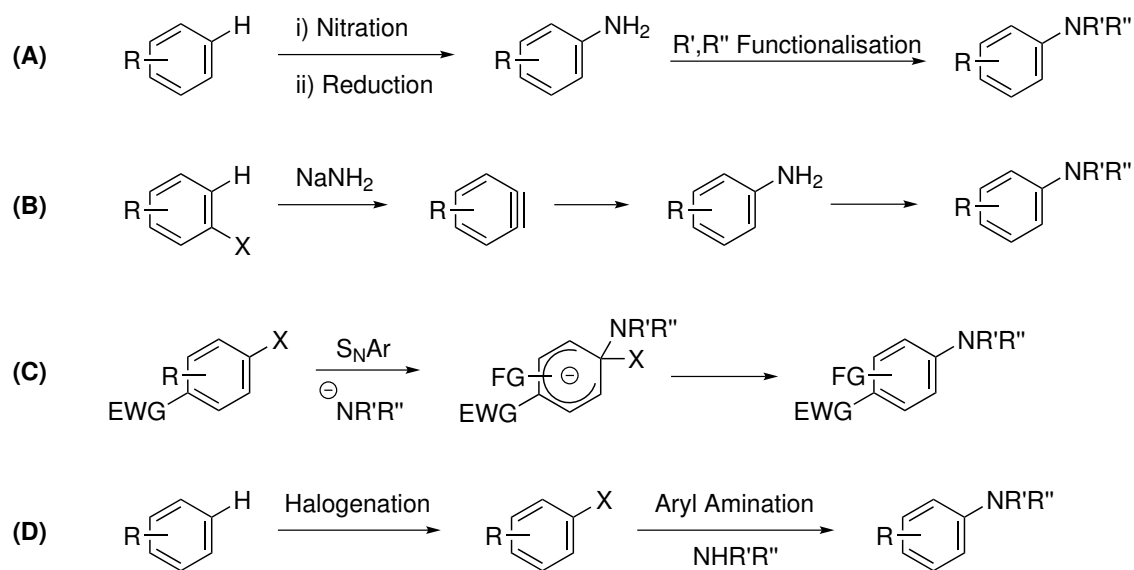


Figure 1.2: Examples of natural products that contain aromatic aryl carbon-nitrogen bonds.^[20–26]

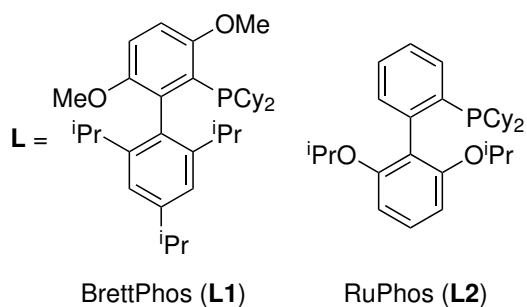
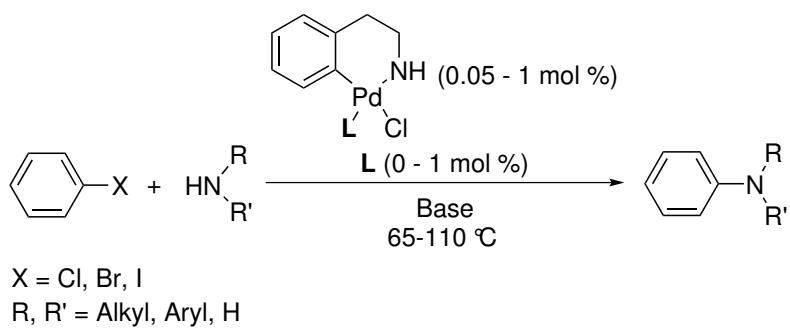


Scheme 1.2: General schemes to generate arylamines. X = halide; EWG = electron-withdrawing group.

be utilised to form arylamines (Route C, Scheme 1.2). However, this method requires using aryl halides with strong electron-withdrawing substituents at the *para*- or *ortho*- positions and/or high reaction temperatures. In contrast, Route D is superior to the three routes noted previously as halogenation followed by transition metal-catalysed reactions can produce arylamines from a wider aryl halide substrate scope and typically under milder reaction conditions (Route D, Scheme 1.2).

The palladium-catalysed Buchwald-Hartwig amination is a widely used reaction in both academia and industry for the construction of C–N bonds in the synthesis of biologically active compounds.^[33–36] Like other palladium-catalysed bond forming reactions, phosphines are typically used as ancillary ligands with dialkylbiaryl phosphines being particularly effective. For example, aryl halides including chlorides can be efficiently aminated under mild reaction conditions with primary and secondary amines using BrettPhos (**L1**) and RuPhos (**L2**) as ligands respectively (Scheme 1.3).^[37–41]

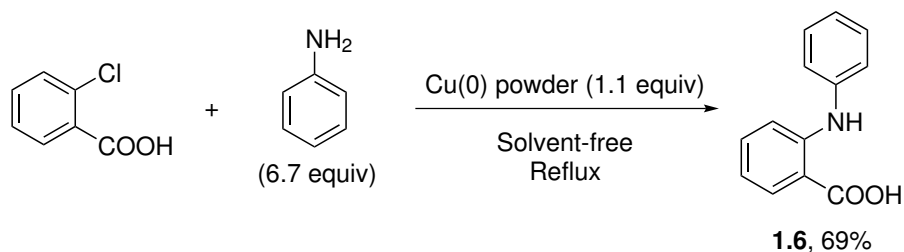
However, although palladium-catalysed amination reactions have been extensively developed, the reactions suffer from some disadvantages such as the high cost and toxicity of palladium and the high molecular weight of the typically used ligands. Recently, aryl amination reactions utilising copper catalysts have received much attention, given that the lower toxicity and cost of copper mitigates many of the disadvantages of the palladium-mediated systems.



Scheme 1.3: General reaction scheme for the palladium-catalysed Buchwald-Hartwig amination reaction with dialkylbiaryl phosphines as ancillary ligands.^[37–41]

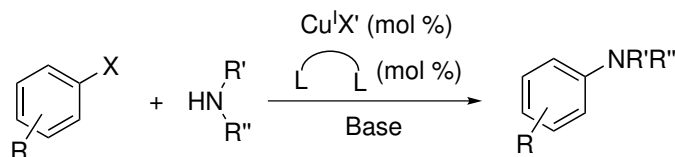
1.3 Copper-mediated cross-coupling chemistry

Copper-mediated cross-coupling chemistry was first reported over a century ago by Ullmann for the formation of $C(sp^2)-C(sp^2)$, $C(sp^2)-N$ and $C(sp^2)-O$ bonds to give biaryls, diaryl amines and diaryl ethers respectively.^[13–16] Advances and development of $C(sp^2)-N$ bonding forming Ullmann-type reactions are the most studied of these and thus will be the predominant focus of this chapter. Ullmann found that of all the metals he had tested, only stoichiometric amounts of copper metal could mediate the cross-coupling of 2-chlorobenzoic acid and aniline to form 2-(*N*-phenylamino)benzoic acid (**1.6**) (Scheme 1.4).^[14] The high reaction temperatures ($\geq 200\text{ }^{\circ}\text{C}$), long reaction times and stoichiometric amounts of copper generally required when this copper-mediated reaction was applied for future synthetic applications caused limited synthetic scope.^[42,43] As a result the Ullmann condensation reaction was not widely adopted for the synthesis of complex natural products.

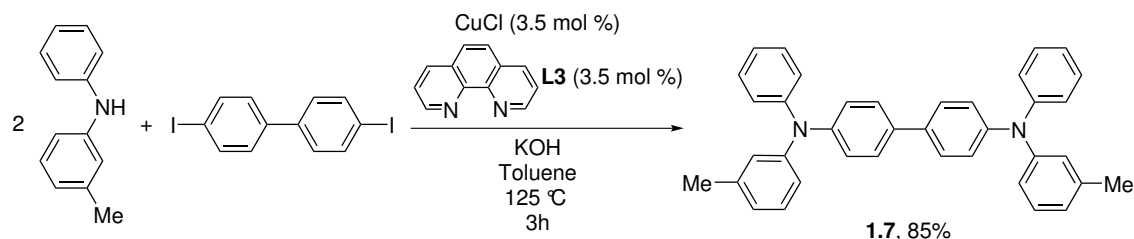


Scheme 1.4: The copper-mediated C–N bond forming reaction first performed by Ullmann.^[14]

Recently, new protocols that incorporate catalytic amounts of nitrogen- and oxygen-based bidentate ligands have partially alleviated these issues allowing milder reaction temperatures ($\leq 110\text{ }^{\circ}\text{C}$) and lower copper loadings ($\leq 10\%$) to be used.^[44–47] This improved copper-catalysed reaction is often referred to as the modified Ullmann amination reaction (Scheme 1.5). The first use of an ancillary ligand in the modified Ullmann amination reaction was reported by Goodbrand and Hu for the arylation of arylamines using catalytic quantities of 1,10-phenanthroline (phen,



Scheme 1.5: General reaction scheme of the modified Ullmann reaction.



Scheme 1.6: Example of a C–N bond forming carried out by Goodbrand with **L3** as an ancillary ligand.^[48]

L3) as the ligand.^[48] In the presence of **L3**, reaction temperatures could be reduced by 50 – 100 °C with the reactions reported to proceed more rapidly. For example, the formation of the triarylamine **1.7** in the presence of **L3** shown in Scheme 1.6 reached 85% yield after three hours at 125 °C. In comparison without the ligand, 160 °C and 6 hours were normally required to give similar yields.^[48]

Neutral 1,10-phenanthroline-type ligands with various substituents (**L4** – **L6**, Figure 1.3) have also been found to promote cross-couplings involving relatively acidic nucleophiles such as arylamines^[48–53] (pK_a in DMSO typically 20 – 30)^[54,55], aryl thiols^[56,57] (pK_a in DMSO typically less than 11)^[58], alcohols^[59,60] (pK_a in DMSO typically 10 – 30)^[61,62], imidazoles^[63] (pK_a in DMSO typically less than 20)^[64] and hydrazides^[65] (pK_a in DMSO typically less than 22)^[64]. The use of acidic pyrrole-2-carboxylic acid (**L7**, Figure 1.3) as an additive has also been reported to promote the *N*-arylation of arylamines.^[66–68] In the basic reaction mixtures, this species will deprotonate to form an anionic ligand. The substrate scope was expanded further when other acidic compounds such as α -amino acids^[69,70] (**L8** and **L9**, Figure 1.3),

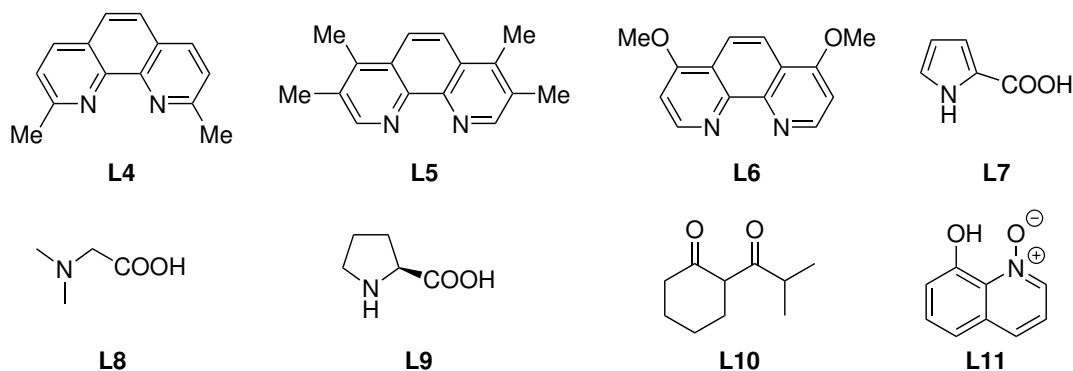


Figure 1.3: Notable examples of compounds that have been used as bidentate nitrogen- and oxygen-based ancillary ligands in the modified Ullmann reaction.

1,3-diketones^[59,71,72] (**L10**, Figure 1.3) and 8-hydroxyquinolin-*N*-oxide^[73] (**L11**, Figure 1.3) were found to be efficient promoters for the cross-coupling of less acidic alkylamine nucleophiles (pK_a in DMSO approximately 40)^[74]. These ligands have been successfully utilised in a range of synthetic endeavours including the total synthesis of natural products, analogues and other compounds with biological activity (see Figure 1.4 for examples **1.8** – **1.12**).^[75–81]

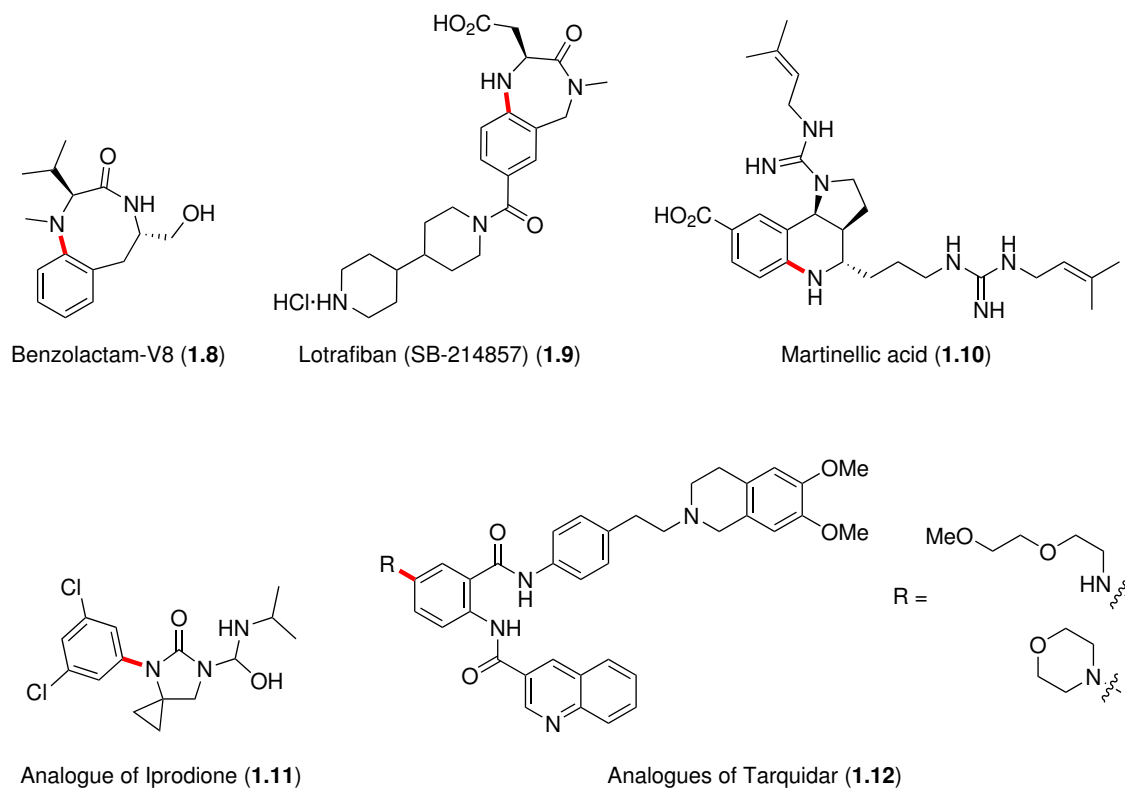
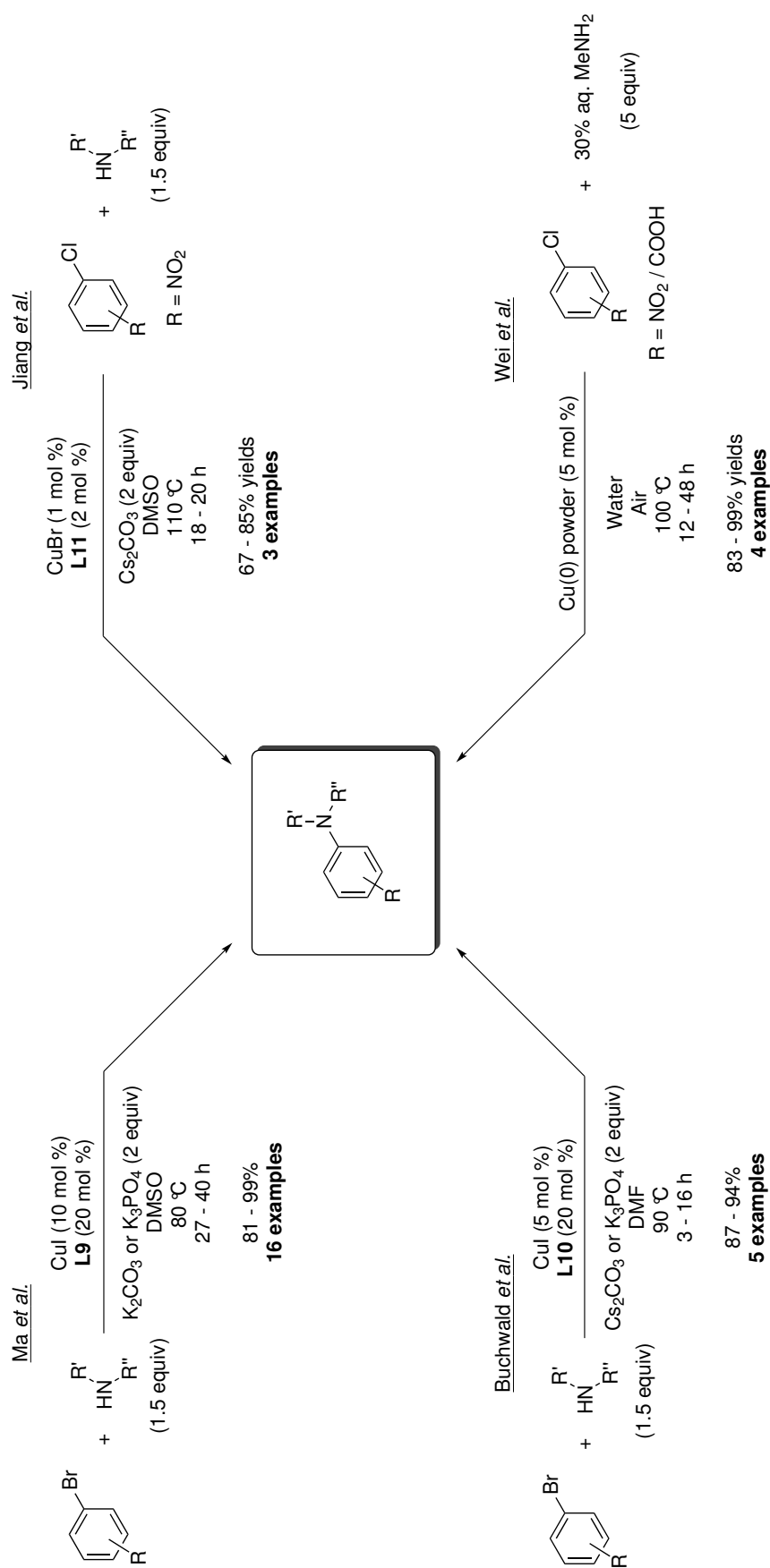


Figure 1.4: Examples of successfully synthesised biologically active natural products and analogues that include a modified Ullmann amination step.^[75–81]

The good functional group tolerance and relatively low costs of the copper and low molecular weight ligands employed make the modified Ullmann reaction an attractive and complementary method to the palladium-assisted Buchwald-Hartwig amination.^[82,83] However, poor substrate scope remains a disadvantage for this reaction. For example, reactions that involve aryl bromides and chlorides typically require relatively high reaction temperatures (≥ 80 °C) and long reaction times with additional strong electron-withdrawing substituents at the *ortho*- and/or *para*- positions (see Scheme 1.7 for examples). Furthermore, viable nucleophilic substrates are almost exclusively restricted to primary and secondary cyclic amines with secondary acyclic amines exhibiting very poor reactivity.^[70] In comparison to the extensive mechanistic studies

published about the palladium-catalysed Buchwald-Hartwig aryl amination reaction,^[84–88] the intermediates and steps involved in the reaction mechanism of the modified Ullmann reaction are not fully understood despite some recent progress in this area.^[43,82,89] Crucially, a fundamental understanding of the mechanism will provide a rational approach to improving existing catalytic systems and also aid in developing new catalysts.

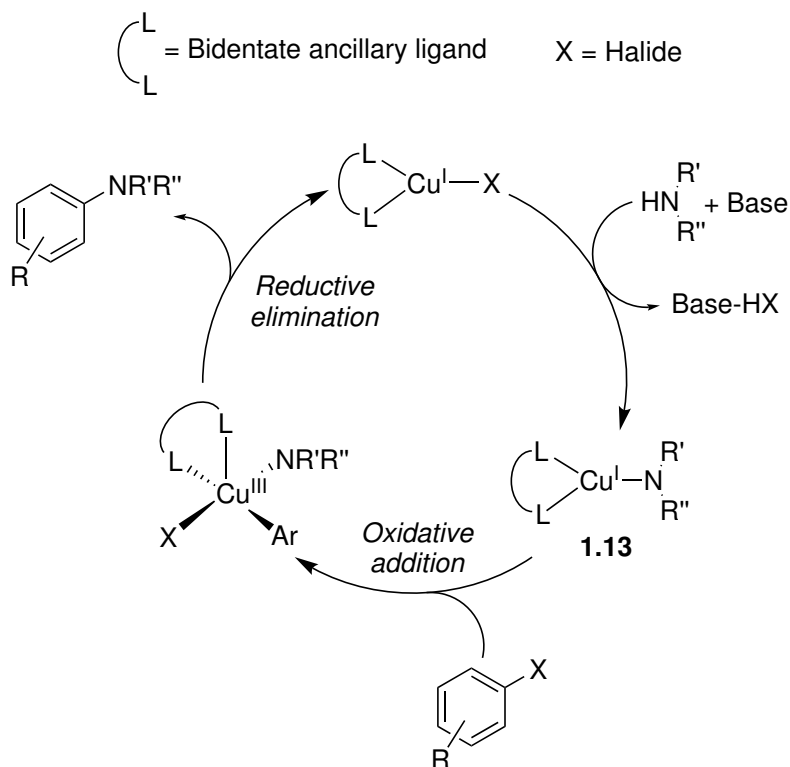


Scheme 1.7: Examples of aryl bromides and chlorides and alkylamines as substrates in the modified Ullmann amination reaction reported by Ma *et al.*^[70] Buchwald *et al.*^[71] Jiang *et al.*^[73] and Wei *et al.*^[90].

1.4 Mechanistic studies of the Ullmann amination reaction

A large number of nitrogen- and oxygen-based ligands have been reported to act as promoters for Ullmann-type cross-coupling reactions but there is generally a lack of understanding of the exact role played by these ligand and which one to use when designing a new catalytic system or how to optimise an existing one. Most reports in the literature simply choose the ligand that provides the best yield from a screening of a wide variety of *N,N*-, *N,O*- and *O,O*-type chelators (some of which are shown in Figure 1.3).^[44] However as suggested for the palladium-catalysed Buchwald-Hartwig amination^[41,82] and a recent theoretical mechanistic study for copper(I)-catalyzed C–O coupling of phenols with aryl bromides,^[91] it is likely that the choice of the base, solvent and copper source are just as crucial as the ligand to optimising a catalytic system, given that they all have important roles in the mechanism.

A general catalytic cycle for the modified Ullmann amination reaction consisting of the most commonly proposed mechanistic steps from the literature is shown in Scheme 1.8. Although the



Scheme 1.8: General catalytic cycle for the modified Ullmann amination reaction that contains the most commonly proposed mechanistic steps.

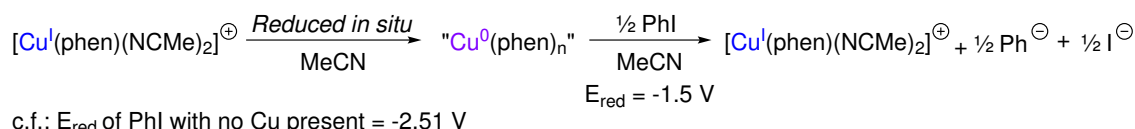
precise nature and order of the steps is not universally agreed on in the literature, it is generally accepted that the first step involves coordination of the amine nucleophile to copper(I) prior to deprotonation by the relatively weak bases due the low acidity of the coordinating amine N–H group.^[82,92] Aryl halide activation *via* oxidative addition is then frequently proposed to occur from the generated complex **1.13** to form a short-lived copper(III) intermediate.^[43,89] However, experimental evidence for aryl halide activation *via* the formation of free aryl radicals in a photoinduced Ullmann cross-coupling reaction by Fu, Peters and co-workers has recently been obtained too.^[93,94] If aryl halide activation proceeds by oxidative addition, reductive elimination would then occur to give the cross-coupling product and restart the cycle.

The significant findings reported in the literature about the mechanism such as the copper catalyst oxidation state, the roles of the ligand, base and solvent and the aryl halide activation mechanism will be discussed in greater detail in the following subsections.

1.4.1 Oxidation state of the active copper catalyst

Early work by Adkins found that many copper sources of different oxidation states, such as copper(0) metal, copper(I) and copper(II) oxides and halides, copper(II) acetate and copper(II) sulphate, were all capable of mediating the reaction of phenyl bromide and *N*-acetyl-*p*-toluidine to give *N*-phenyl-*p*-toluidine in similar yields.^[95] The similarity in yields was later proposed to be due to copper in its the +1 oxidation state facilitating the reactions, regardless of whether copper(0), copper(I) or copper(II) is loaded into the reaction.^[96–98] For example, Paine found that when catalysis using a diphenylamide nucleophile was attempted in the presence of either copper(II) bromide or copper(II) acetylacetonate, reduction to copper(I) *via* formation of tetraphenylhydrazine occurred immediately.^[98] Using SEM imaging, Paine also found that if copper(0) powder was used, adventitious copper(I) oxide on its surface could be dissolved with the aid of the amine present and in turn initiate the catalysis.^[98]

More recent reports that incorporate the ancillary ligand **L3** by Jutand and co-workers have shown that the *in situ* formation of copper(I) species from copper(0) and copper(II) precursors can occur.^[99] By using cyclic voltammetry, an electrogenerated “Cu⁰(phen)_n” complex was found to be capable of reducing aryl iodides and bromides at a reduction potential lower than their inherent reduction potentials in acetonitrile. In the example shown in Scheme 1.9 with iodobenzene as the substrate, the [Cu^I(phen)(NCMe)₂]⁺ species added was initially reduced *in situ* to give a “Cu⁰(phen)_n” complex. This complex then in turn reacted with iodobenzene at a



Scheme 1.9: Reaction scheme of the electrochemistry experiment conducted by Jutand and co-workers that was used to confirm the *in situ* oxidation of copper(0) precursors to copper(I) species.^[100]

reduction potential of -1.5 V to produce an aryl anion and regenerate the $[\text{Cu}^{\text{I}}(\text{phen})(\text{NCMe})_2]^+$ complex. In the absence of copper, iodobenzene required a more negative reduction potential of -2.51 V and therefore “ $\text{Cu}^0(\text{phen})_n$ ” was thought to promote the reduction. Thus given its reducing capability, it was proposed that catalytic reactions which use copper(0) precursors initially involve *in situ* oxidation by reaction with the aryl iodide or bromide substrate to generate the copper(I) catalyst.^[100]

By using UV-Vis spectroscopy (Figure 1.5), the transformation of a $[\text{Cu}^{\text{II}}(\text{phen})_2]^{2+}$ complex to $[\text{Cu}^{\text{I}}(\text{phen})_2]^+$ could be followed over time after addition of benzylamine and caesium carbonate.^[101] The mechanism for this conversion was proposed to first involve coordination of the amine to $[\text{Cu}^{\text{II}}(\text{phen})_2]^{2+}$ followed by deprotonation by caesium carbonate and then β -hydride elimination to give $[\text{Cu}^{\text{II}}\text{H}(\text{phen})_2]^{2+}$ (Scheme 1.10). This species was proposed to react with more base to give a copper(0) species. The β -hydride elimination and deprotonation were

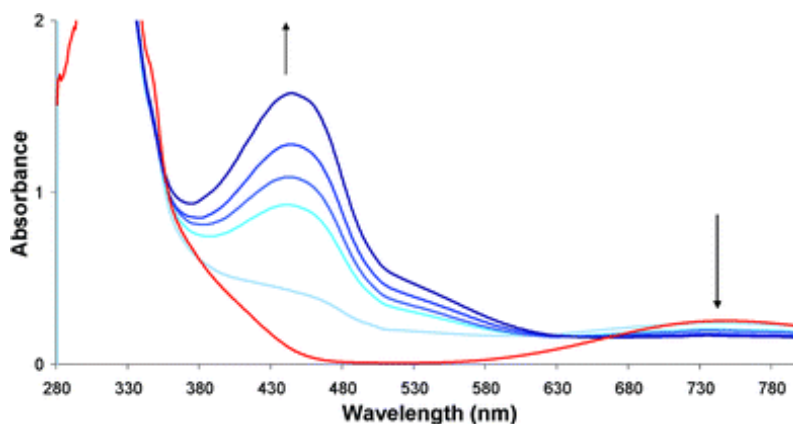
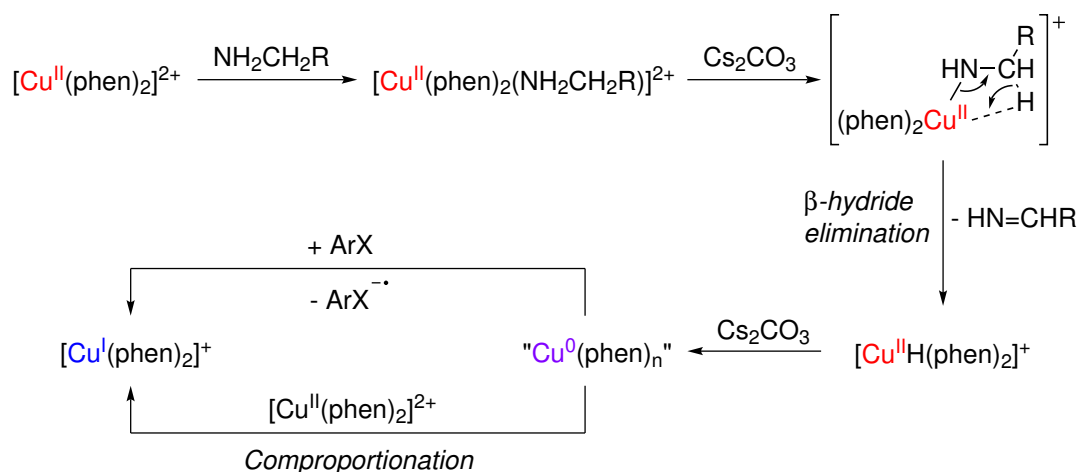


Figure 1.5: UV-Vis absorption spectra showing the conversion of copper(II) to copper(I). A solution of CuBr_2 and **L3** (1 : 2 ratio) in DMF (red curve) was treated with benzylamine and Cs_2CO_3 (13.3 equiv. each) to give formation of $[\text{Cu}^{\text{I}}(\text{phen})_2]^+$ (blue curves) over time. Image taken from reference [101].



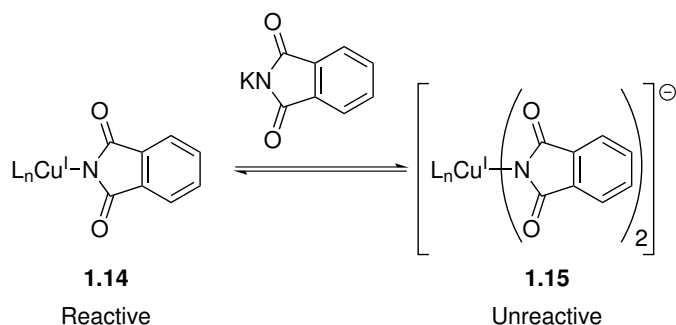
Scheme 1.10: Proposed pathway for the conversion of copper(II) to catalytically active copper(I) species in the presence of phen.^[101]

proposed to be fast because the complexes formed from these steps were not detected by UV-Vis spectroscopy. As mentioned previously, the generated copper(0) species is then able to oxidise to copper(I) by reaction with any aryl iodide or bromide present as shown in Scheme 1.9. This process was proposed to also occur simultaneously with a comproportionation with the initial $[\text{Cu}^{\text{II}}(\text{phen})_2]^{2+}$ complex to give the corresponding copper(I) complex, $[\text{Cu}^{\text{I}}(\text{phen})_2]^+$.^[101]

Overall, there is a significant amount of evidence from Adkins, Paine and Jutand and co-workers that suggests copper(I) is the predominant oxidation state in the reaction solutions and therefore it likely facilitates the Ullmann-type coupling reactions.

1.4.2 The role of the ligand and identification of catalyst resting states

Identification of the reaction intermediates, in particular the catalyst resting states, has been the subject of numerous investigations in the literature, with one of the first reports by Bacon and Karim.^[102] Prior to when ancillary ligands were used in the Ullmann reaction, their study of the copper-catalysed reaction between aryl halides and phthalimides found that the most reactive system employed a Cu : phthalimide ratio of less than one and that it became less reactive as the phthalimide quantity increased.^[102] This was one of the first examples in the literature to support a mechanism where a copper(I) nucleophile species (**1.14**) is reactive and a di(nucleophile)cuprate species (**1.15**) is unreactive (Scheme 1.11). Further evidence for the intermediacy of a copper(I) nucleophile species was provided by Paine for a reaction catalysed by copper(I) iodide between lithium diphenylamide and iodobenzene. From this mechanistic

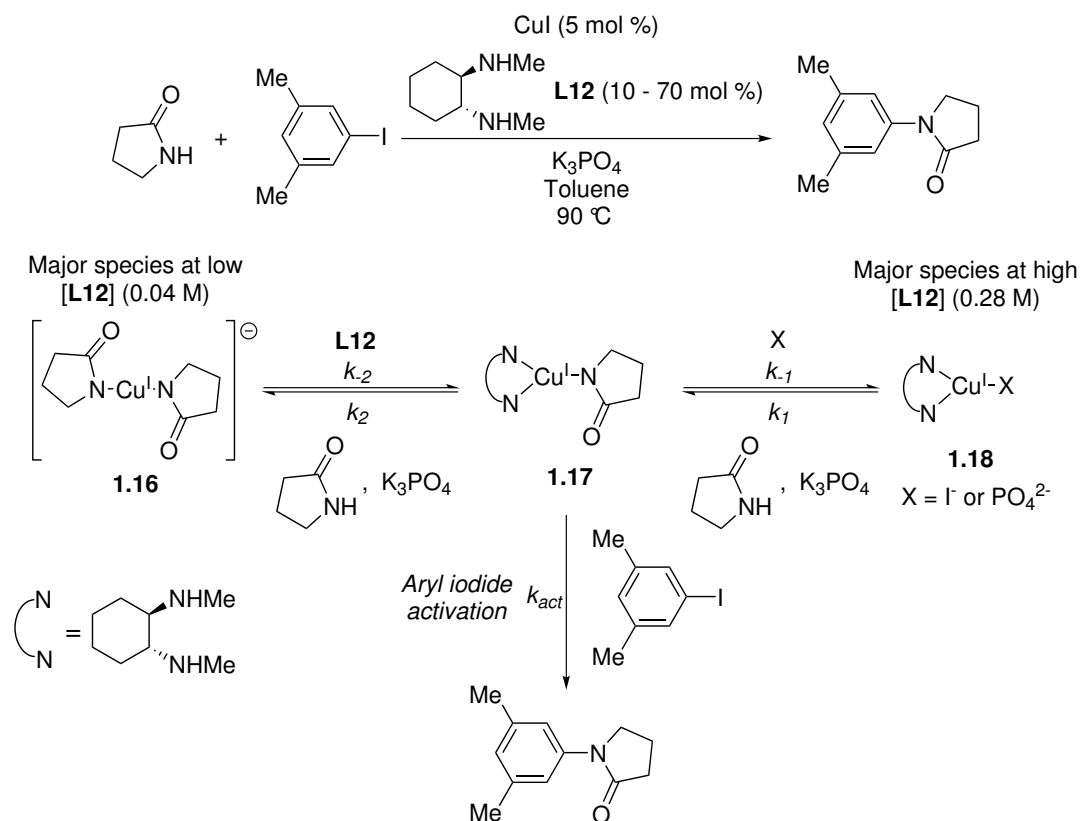


Scheme 1.11: Proposed equilibrium in the copper-catalysed reaction between aryl halides and phthalimides. L represents other possible ligands such as dimethylacetamide solvent used in the study by Bacon and Karim.^[102]

investigation, the rate determining step was found to be the activation of iodobenzene by a copper(I) diphenylamide species.^[98] Taken together, the ancillary ligand-free investigations by Bacon, Karim and Paine suggest that a copper(I) species ligated by one deprotonated nucleophile ligand is a likely catalyst resting state.

The significant reactivity enhancement induced by adding ligands has led to several investigations into how they might give rise to an increase in reaction rate and what effect they have on the solution equilibria. A study involving the phen-enhanced coupling between aryl halides and imidazoles was one of the first to propose possible roles for how ancillary ligands could improve catalytic reactivity.^[63] It suggested that the ancillary ligand could possibly improve catalyst stability, prevent aggregation, improve catalyst solubility and/or prevent multiple ligation of the imidazole substrate, which can be related to the mechanistic work by Bacon noted previously in identifying the catalyst resting state.

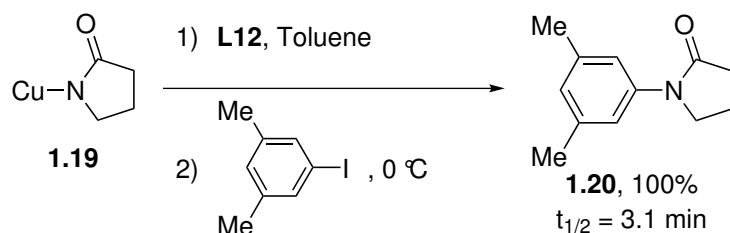
More recently, a kinetic, spectroscopic and stoichiometric study by Buchwald and co-workers on the role of the chelating 1,2-diamine ligands in the *N*-arylation of amides proposed that the role of the diamine was to control the coordination environment by preventing multiple ligation of the amide on the copper(I) centre (Scheme 1.12).^[103,104] The authors propose that when a low concentration of diamine ligand **L12** is used, an equilibrium between an unreactive di(amide)cuprate **1.16** and the active diamine-ligated copper(I) amide **1.17** is skewed towards the unreactive complex. This was confirmed by the inverse rate dependence on amide concentration with low diamine concentrations ($[\text{L12}] = 0.04 \text{ M}$). Conversely, when a higher diamine concentration ($[\text{L12}] = 0.28 \text{ M}$) is used, the major species in solution is the diamine-ligated copper(I) halide complex **1.18**, which can readily convert to the active



Scheme 1.12: A proposed mechanism for the copper-catalysed cross-coupling between aryl iodides and amides that shows the effect of **[L12]** on the equilibrium between reactive and unreactive intermediates. Typical amounts used in the reactions: [Arl]₀ = 0.4 M, [Amide]₀ = 0.8 M, K₃PO₄ = 2.4 mmol, **[L12]**₀ = 0.04 – 0.28 M, [CuI]₀ = 0.04 M in 2.0 mL toluene. Kinetic parameters: $K_1 = k_1/k_{-1} = 0.85 \pm 0.05$, $K_2 = k_2/k_{-2} = 2.0 \pm 0.2$, and $k_{act} = 12 \pm 3 \text{ M}^{-1} \text{ min}^{-1}$.^[104]

amidate complex. To confirm that complex **1.17** was the catalyst resting state, copper(I) pyrrolidinonate (**1.19**) was first synthesised. Complex **1.19** in the presence of the **L12** was then reacted stoichiometrically with 3,5-dimethyliodobenzene and yielded the coupling product **1.20** which therefore confirmed the chemical and kinetic competency of complex **1.17** (Scheme 1.13).^[103,104] DFT calculations by Guo and co-workers confirmed the relative reactivities of complexes **1.16** and **1.17**.^[105]

In addition to the catalyst resting state proposed by Buchwald and co-workers (**1.21**, Figure 1.6), Jutand and co-workers have recently identified the same general structure for the catalyst resting state where the ratio of ligand, copper(I) and deprotonated nucleophile was 1 : 1 : 1 (**1.22**) in a NMR spectroscopy, electrochemistry and DFT study of the reaction between iodobenzene and cyclohexylamine in the presence of an ancillary 1,3-diketone ligand.^[99,106,107] Other



Scheme 1.13: Reaction between copper(I) pyrrolidinonate (**1.19**) and 3,5-dimethyliodobenzene in the presence of **L12** which confirmed the chemical and kinetic competency of complex **1.17**.^[103,104]

publications by Hartwig, Fu, Peters and co-workers that predominately studied the stoichiometric reactivity of phen-ligated copper(I) diphenylamides (**1.23**),^[108] phthalimides (**1.24**),^[109] pyrrolidinonates (**1.25**),^[109] and photoluminescent phosphine ligated copper(I) carbazoles (**1.26**)^[94] also determined that the catalyst resting state had the same general trigonal planar coordination geometry (Figure 1.6). Overall, these published findings suggest that one of the primary roles of the ligand is to prevent multiple-ligation by the nucleophile and therefore ensure the catalyst resting state is present in high concentration.

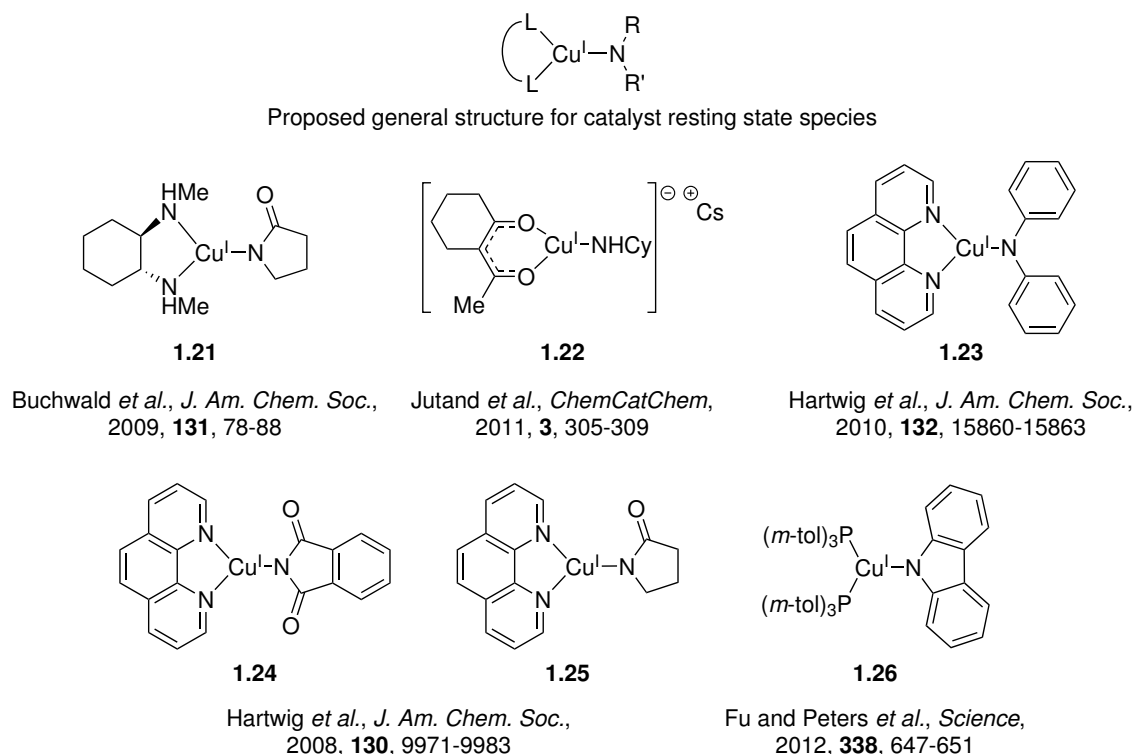
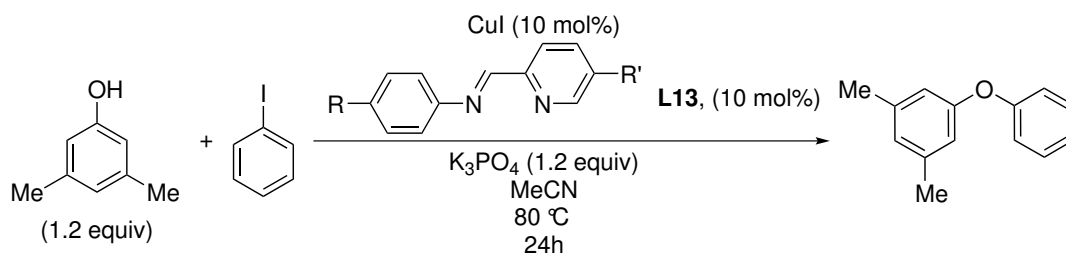


Figure 1.6: Proposed catalyst resting state intermediates from the literature.

In addition to controlling nucleophile coordination, a rare example from the literature by Taillefer and co-workers studied the copper-catalysed *O*-arylation of phenols and identified a relationship between the yield obtained and the electronic characteristics of the *N,N*-type imino-pyridine ancillary ligands (**L13**) used (Scheme 1.14).^[110] The authors proposed that the electronic characteristics of the imine unit and pyridine unit of **L13** could affect the rate of oxidative addition and reductive elimination involving copper(I) and copper(III) species. They observed that a more electron-rich pyridine unit on the ligand improved the catalytic activity and therefore proposed it would produce a more electron-rich copper(I) intermediate, which would in turn undergo faster oxidative addition to generate a copper(III) species. When the phenyl group of the imine unit was functionalised in the *para*-position with electron-withdrawing substituents, the catalytic activity increased. This was proposed to be due to a reduction in the electron-density of the copper(III) and therefore in theory would enhance the reductive elimination rate. However, an important issue to consider with this work is that the authors are proposing a structure-activity relationship without kinetic data for the reaction. Therefore care should be taken when applying their findings to other proposed mechanisms.



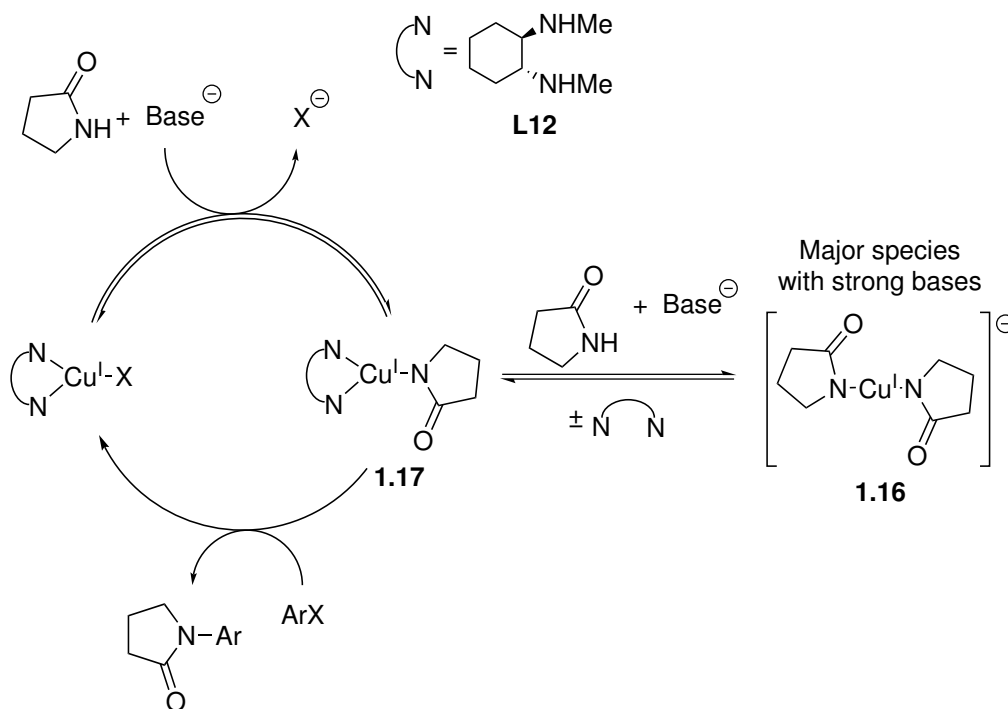
Scheme 1.14: Copper-catalysed *O*-arylation of phenols that demonstrates relationship between the yield and electronic characteristics of the *N,N*-type imino-pyridine ancillary ligand (**L13**).^[110]

1.4.3 The effects of the base and solvent

The most commonly used bases in modified Ullmann amination reactions are moderately basic and poorly soluble alkali metal carbonates and phosphates such as potassium carbonate, potassium phosphate and caesium carbonate. Although they are not basic enough to appreciably deprotonate the free amines, they are thought to be able to act as deprotonation reagents after the amine nucleophile coordinates to the copper source.^[82] Studies that investigate how the base affects the mechanism are rarely reported in the literature. Therefore like ancillary ligands,

they are usually selected empirically as opposed to from a rational understanding of their effects on the mechanism.

A notable exception was a study by Buchwald and co-workers regarding the same copper-catalysed amidation of aryl halides mentioned previously in Section 1.4.2.^[111] In addition to the effect of diamine ligand concentration ([**L12**]) on the equilibrium between solution intermediates as noted in Scheme 1.12, the strength of the base was also found to significantly affect the yield. The authors proposed that the rate of deprotonation of the relatively acidic N–H amide group should be similar to or less than the rate of the aryl amidation step in the catalytic cycle.^[111] If a strong base was chosen such that the deprotonation rate was greater than the aryl amidation rate, then the excess amide formed would coordinate with **1.17** to form the unreactive di(amido)cuprate **1.16** and therefore inhibit the desired aryl amidation reaction (Scheme 1.15).



Scheme 1.15: Simplified catalytic cycle for the copper-catalysed amidation of aryl halides emphasising the effect of the base strength on the intermediates concentrations.^[111]

Given that the N–H group of amides are more acidic ($\text{p}K_{\text{a}}$ typically between 20 – 25) than that of alkylamines in DMSO ($\text{p}K_{\text{a}}$ approximately 40),^[74] the formation of this intermediate is less likely to be an issue in the amination reaction. However, the formation of unreactive di(amido)cuprate intermediates can still occur in the amination reaction due to factors other

than base strength such as when **L3** is used as the ligand, which will be discussed in greater detail in Chapter 2.

The typical solvents used in combination with these bases are polar and aprotic such as DMF, NMP and DMSO. One of the factors for the choice of solvent is the solubility of the copper(I) catalyst source (usually copper(I) halides), which is typically greater in polar coordinating solvents. Another factor is to ensure the basicity of the bases remains relatively unaffected compared to in polar, protic solvents, which would hydrogen bond and subsequently reduce basicity.^[82] However in the ancillary ligand-free copper-mediated formation of diaryl ethers, Bridger and co-workers found that the solvents should not be too strongly coordinating otherwise the catalyst becomes inactive towards substrate binding.^[112]

To alleviate potential issues caused by poor solubility of the bases, organic soluble ionic bases have been successfully utilised in C–N cross-coupling. One of the first examples was reported by Fukuyama and co-workers who utilised caesium acetate as a soluble base for the intra- and intermolecular amination of aryl iodides in DMSO.^[113–115] A recent protocol using soluble organic ionic bases with bulky ammonium or phosphonium cations and carboxylate anions such as acetate and malonate showed excellent reactivity in C–N cross-coupling of various nitrogen-based nucleophiles.^[116] In addition to the enhanced solubility, the acceleration provided by these bases was proposed to be due to the highly ionised nature of the bases in solution, which in turn provided the highest possible concentration of free basic anions.

1.4.4 Proposed mechanisms for aryl halide activation

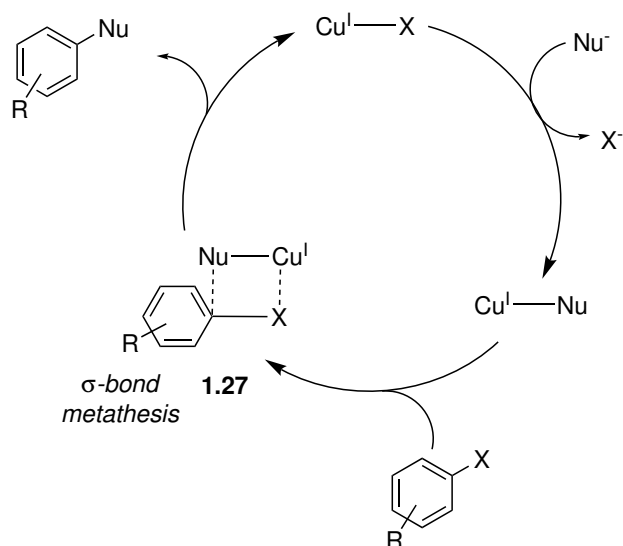
The aryl halide activation step is commonly proposed to be the rate determining step in the Ullmann reaction.^[43] As a result a better understanding of this process could allow the rational improvement of existing catalyst systems. However, different mechanisms have been proposed for similar catalytic systems and therefore no general rules regarding the mechanism currently exist. The proposed mechanisms for the aryl halide activation can be separated into four different categories depending on the nature of the reaction between the aryl halide and the copper(I) species:^[43,47]

1. σ -bond metathesis *via* a four-centre intermediate
2. π -complexation of copper(I) with the aryl halide
3. Single electron transfer or atom transfer to give a reactive aryl radical intermediate

4. Oxidative addition of the aryl halide on copper(I) followed by reductive elimination

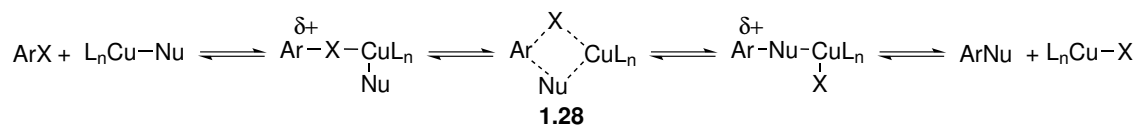
1.4.4.1 σ -bond metathesis and π -complexation mechanisms

Mechanisms that propose the activation of aryl halides *via* four-centre intermediates between aryl halides and copper species are rare in the literature. Scheme 1.16 shows a potential catalytic cycle involving a σ -bond metathesis step in an Ullmann-type reaction. After initial displacement of the halide from the initial copper(I) salt with the nucleophile, a four-centre intermediate **1.27** is formed between the aryl halide and copper(I) nucleophile species. Nucleophile substitution then occurs to give the product and reform the catalyst.



Scheme 1.16: Proposed catalytic cycle involving a four-centre intermediate **1.27** and σ -bond metathesis step.^[43]

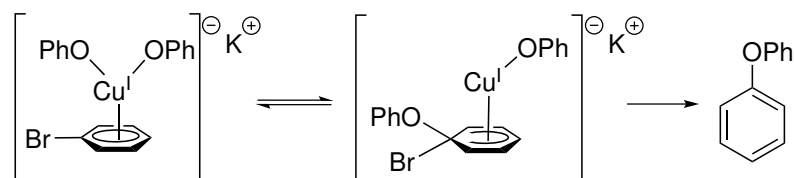
The first reported mechanism of this type was proposed by Bacon and Hill to explain their results in substitution reactions between aryl halides and cuprous salts.^[117,118] They proposed that the copper(I) centre initially formed a complex with the halogen atom of the aryl halide, which in turn polarised the C-X bond such that a partial positive charge formed on the *ipso*-



Scheme 1.17: Bacon and Hill's proposed mechanism for the reaction between aryl halides and cuprous salts.^[117,118]

carbon (Scheme 1.17). This partial charge then directed the nucleophilic attack to occur on this particular carbon *via* a four-centre intermediate (**1.28**), and then subsequently gave the product and free copper(I) species. They also reported other possible routes that involved an ionic intermediate instead of a four-centre intermediate and another that involved homolytic bond fission to give an aryl radical. However, there was not enough experimental evidence to support any of these theories.

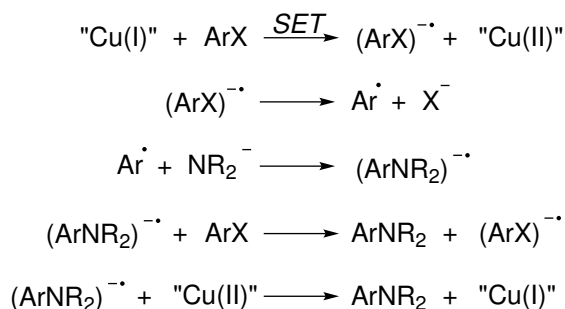
A kinetic study by Weingarten was the first to propose a mechanism that involved π -complexation by copper(I) to activate an aryl halide for substitution in a reaction between bromobenzene and potassium phenoxide.^[96] This interaction was thought to facilitate the nucleophilic attack by making the aromatic system more electron deficient and also by stabilising the build-up of negative charge during substitution (Scheme 1.18).^[119] Ma and co-workers also proposed that the mechanism for the C–N bond forming cross-coupling of α -amino acids to a range of aryl halides involved π -complexation.^[70,77] One of the main issues of the proposed π -complexation mechanism is that the reactivity order observed ($\text{ArI} > \text{ArBr} > \text{ArCl}$) was the opposite to what is usually observed for metal-free aromatic nucleophilic substitutions and also in similar η^6 -haloarenes chromium(0) complexes.^[120]



Scheme 1.18: Weingarten's proposed intermediates following π -complexation and nucleophilic attack.^[119]

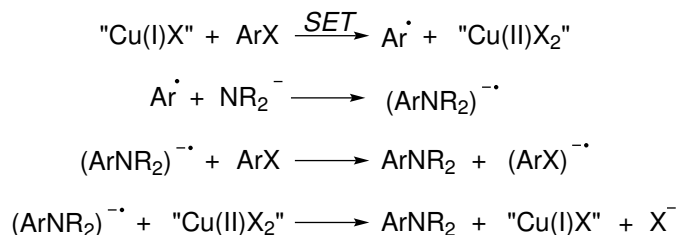
1.4.4.2 Mechanisms involving aryl radical intermediates

It should be noted that to date, no significant experimental evidence for σ -bond metathesis and π -complexation aryl halide activation in Ullmann-type reactions has been presented. In contrast, mechanisms that propose the formation of aryl radical intermediates as part of a unimolecular radical-nucleophilic substitution mechanism, $\text{S}_{\text{RN}}1$, are more common in the literature. The first step of $\text{S}_{\text{RN}}1$ typically involves the formation of an aryl halide radical by addition of an electron from a suitable source.^[121] In the case of Ullmann-type reactions, copper(I) is the most likely single electron reductant (Scheme 1.19). After single electron transfer (SET), the aryl halide



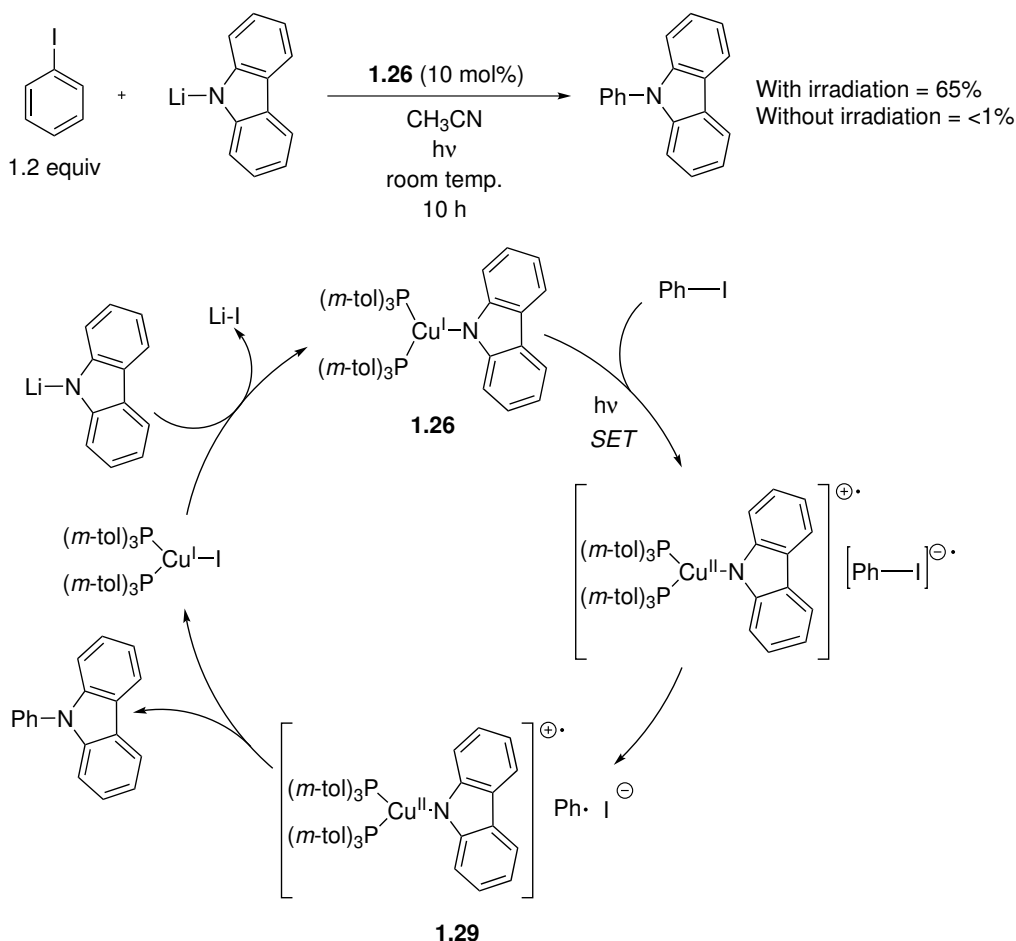
Scheme 1.19: Proposed general SET mechanism for Ullmann amination reactions.^[43]

radical anion will spontaneously dissociate to give the aryl radical and halide anion. The aryl radical is then able to react with the nucleophile to form the coupling product as a radical anion. Finally, the radical anion can transfer its electron to another aryl halide substrate molecule and thus restart the cycle. Given that copper(II) is also present, an alternate final step could involve the radical anion transferring its electron to the copper(II) to regenerate the copper(I) catalyst.^[43] A similar radical-based mechanism has also been proposed to involve the simultaneous single electron transfer from copper(I) and C-X bond cleavage to give an aryl radical and halide anion (Scheme 1.20).^[122,123] This mechanism is called a halide atom transfer (HAT).



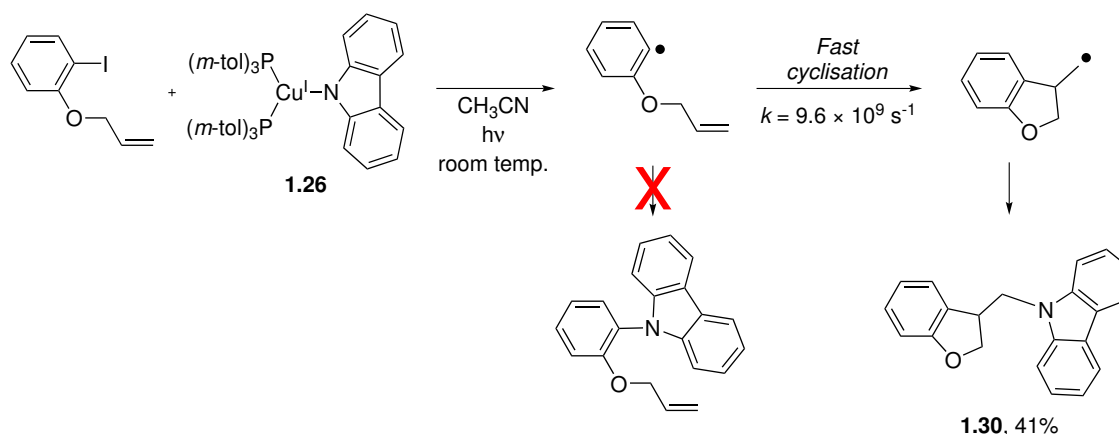
Scheme 1.20: Proposed general HAT mechanism for Ullmann amination reactions.^[122,123]

The first studies that provided experimental evidence for the formation of an aryl radical species were by Arai and co-workers from EPR experiments.^[124,125] In the reaction of 1-bromoanthraquinone (AQBr) with 2-aminoethanol catalysed by copper(I) bromide, aryl radical anions and paramagnetic copper(II) species were identified. These were thought to be produced from a SET mechanism from copper(I) to 1-bromoanthraquinone. Recently, Fu, Peters and co-workers have reported a photoinduced Ullmann cross-coupling between lithium carbazolidine and aryl halides that was found to proceed *via* photoactive copper(I) carbazolidine complex **1.26** and also an aryl radical intermediate **1.29** formed from SET or HAT (Scheme 1.21 shows the cycle for SET).^[94] A radical pathway was confirmed using EPR which was consistent with the



Scheme 1.21: Reaction scheme and a possible catalytic cycle for the photoinduced Ullmann C–N bond formation *via* a copper(I) carbazole complex.^[94]

formation of a copper radical species. Further support for a radical-based mechanism was provided through stoichiometric, photoinduced reactions between complex **1.26** and the radical probe 2-(allyloxy)iodobenzene, which exclusively yielded the cyclised compound **1.30** (Scheme 1.22). This outcome is expected for mechanisms that generate an aryl radical as they will rapidly ring close *via* a 5-*exo-trig* process using this substrate ($k = 9.6 \times 10^9 \text{ s}^{-1}$).^[126] More recently, Fu and Peters have also extended their photoinduced copper-catalysed cross-coupling studies to the formation of C–N, C–O and C–S bonds in the *N*-alkylation of carbazoles^[127] and arylation of indoles, benzimidazoles, imidazoles,^[128] amides,^[129] phenols^[130] and aryl thiols.^[131] When copper(I) species ligated with the respective nucleophiles of these reactions were isolated, they were found to be reactive only under irradiation, which confirmed the intermediacy of these types of complexes.

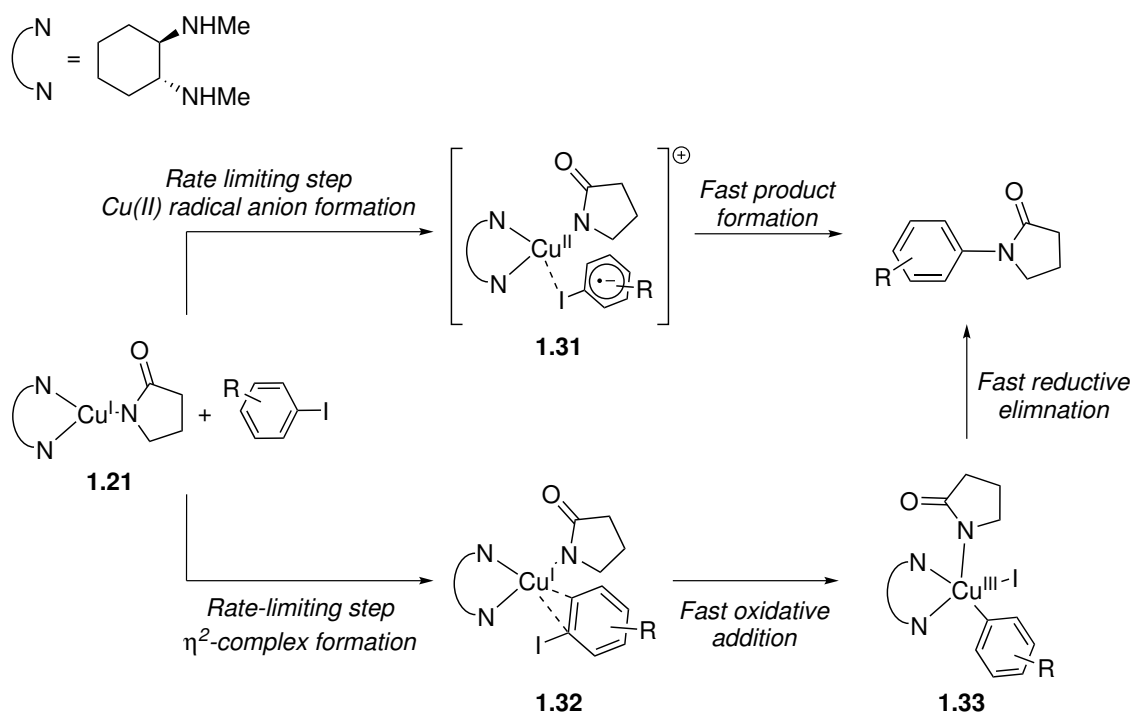


Scheme 1.22: The reaction between complex **1.26** and 2-(allyloxy)iodobenzene exclusively yielded cyclised compounds and therefore confirmed aryl radical intermediate.^[94]

1.4.4.3 Mechanisms involving oxidative addition and reductive elimination

Despite the recent comprehensive evidence for radical-based mechanisms in Ullmann-type chemistry by Fu and Peters, oxidative addition to form copper(III) intermediates from copper(I) species remains the most widely proposed aryl halide activation mechanism. It was first proposed by Cohen in 1974^[132] followed shortly after by other mechanistic pathways also involving oxidative addition.^[133–136]

As mentioned previously in Section 1.4.2, the recent mechanistic study on the *N*-arylation of pyrrolidinone by Buchwald and co-workers proposed that 1,2-diamine-ligated copper(I) pyrrolidinone **1.21** was the catalyst resting state from which aryl halide activation occurred.^[103,104] To determine if the mechanism involved a rate-limiting concerted oxidative addition, the ρ -value ($\rho = +0.48 \pm 0.14$) and enthalpy of activation ($\Delta H^\ddagger = 6.8 \text{ kcal mol}^{-1}$) for the stoichiometric reaction between the diamine-ligated copper(I) amidate and *para*-substituted aryl iodides were compared to those of the oxidative addition of palladium(0) with aryl iodides ($\rho = +2.3$, $\Delta H^\ddagger = 18.4 \text{ kcal mol}^{-1}$).^[104,137] The high ρ -value and enthalpy of activation for the palladium-mediated oxidative addition process are the result of a large amount of negative charge generated in the transition state from C-I bond breaking. Therefore the comparatively low values for the copper-mediated process suggested that the opposite was present in this case (i.e. low negative charge generated in transition state and minimal C-I bond breaking). However, the enthalpy and Gibbs free energy of activation were congruent with an oxidation addition process that is mediated by an initial η^2 -complex as determined by DFT calculations.^[105] Therefore two

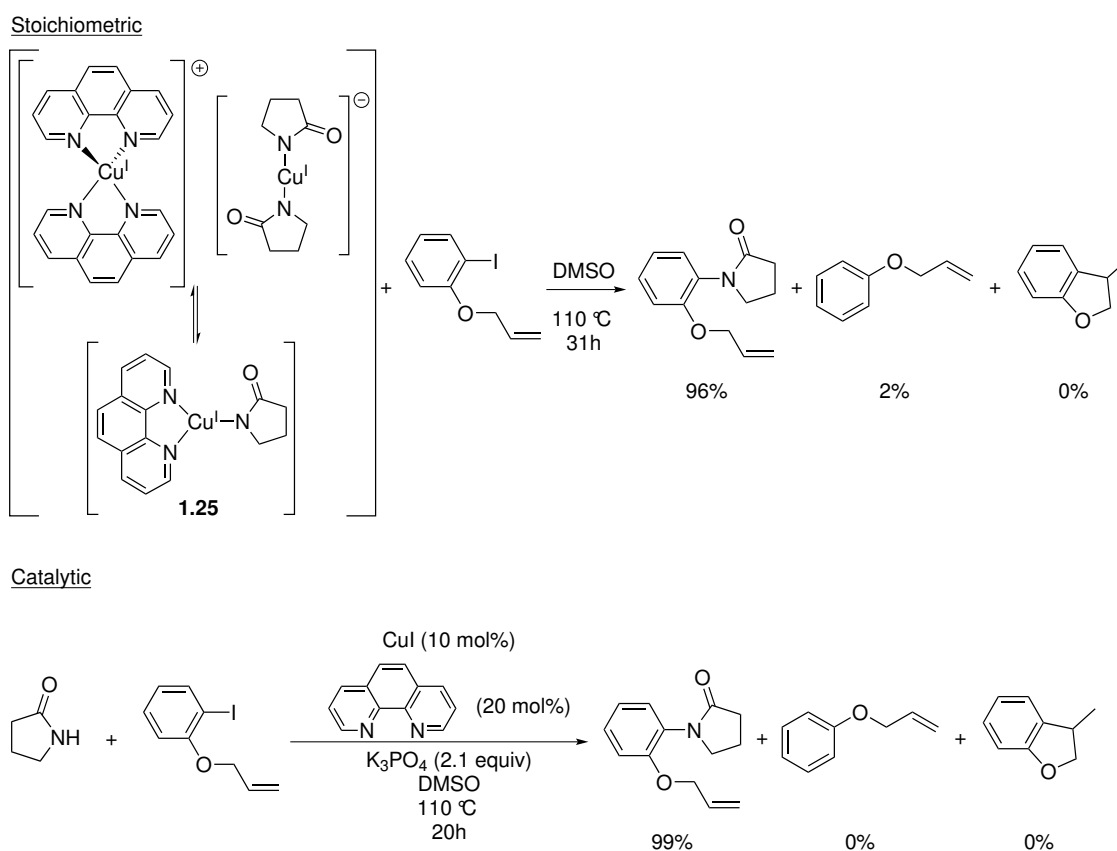


Scheme 1.23: Proposed possible mechanisms for the aryl halide activation step in the copper-catalysed *N*-arylation of amides.^[104]

possible mechanisms for this reaction were proposed and Buchwald *et al.* The first possible route involves formation of the copper(II) radical anion **1.31** by a rate-limiting inner-sphere single electron transfer to the aryl halide, which did not affect the C-I bonding significantly (top pathway, Scheme 1.23). The positive ρ -value observed was justified by the electron transfer process being facilitated by electron deficient aryl halides. The subsequent steps involved fast halide atom transfer (HAT) and then radical recombination to form a copper(III) species. These steps are so fast that no dissociation of aryl radical is able to occur. This copper(III) species will then rapidly undergo reductive elimination to give form product.

The pathway for the second possible mechanism was first suggested by Guo and co-workers and involved the initial rate-limiting formation of the η^2 -complex **1.32** between the copper(I) amide and aryl iodide to activate the C-X bond (bottom pathway, Scheme 1.23).^[105] This type of coordination ensures that the C-I bond remains minimally affected. The positive ρ -value could be explained by electron deficient arenes facilitating η^2 -complex formation by lowering the energy of the LUMO of the aromatic ring. The next steps in the mechanism consisted of fast oxidative addition to give a five-coordinate copper(III) complex **1.33** followed by reductive elimination to produce the desired *N*-arylated amide.

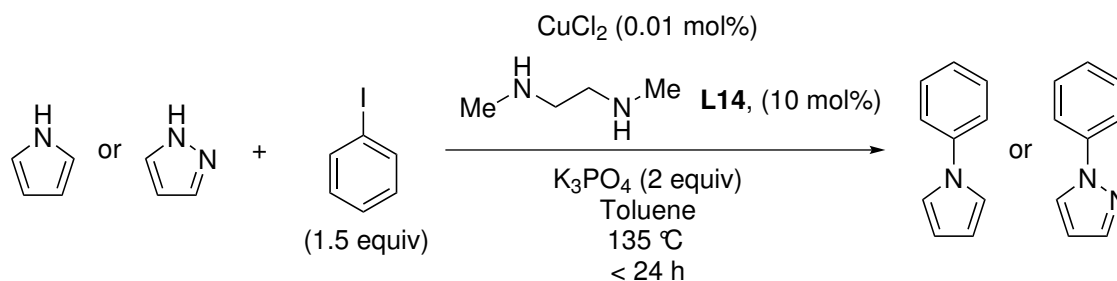
An analogous mechanism involving oxidative addition and not an electron transfer for aryl halide activation for **L3** and phen-ligated copper(I) phthalimide (**1.24**) and pyrrolidinone (**1.25**) species has also been proposed by Hartwig.^[109] They decided against an outer-sphere electron transfer mechanism because: (i) compounds that are typically obtained from radical reactions such as biaryl species were not detected; (ii) reactions proceeded with aryl bromides and iodides but not with aryl chlorides, which have less negative reduction potentials and are therefore expected to more easily accept an electron; (iii) reactions employing the radical probe 2-(allyloxy)iodobenzene as the substrate did not yield any cyclised products. For example, the radical probe was reacted stoichiometrically with a kinetically and chemically competent reaction intermediate **1.25** and also in the corresponding catalytic reaction involving pyrrolidinone as the nucleophilic substrate (Scheme 1.24). A similar study involving diphenylamine as the nucleophile instead also ruled out the presence of aryl radicals as 2-(allyloxy)iodobenzene



Scheme 1.24: Stoichiometric reaction between 2-(allyloxy)iodobenzene and **1.25** and also a catalytic reaction involving pyrrolidinone. The lack cyclised product formed in both cases confirmed the absence of long-lived aryl radical intermediates.^[109]

was aminated cleanly.^[108] Furthermore, DFT calculations suggested that a copper(I)/copper(III) oxidative addition mechanism was an energetically feasible process.^[108]

Norrby and co-workers have pioneered the copper-catalysed C–N cross-coupling between aryl iodides and pyrrole or pyrazole using submol% copper loadings (Scheme 1.25).^[138–140] From mechanistic studies, they determined that in addition to coordinating to copper(I), one of the main roles of the *N,N'*-dimethylethylenediamine (DMEDA, **L14**) ancillary ligand was to act as a mass transfer promoter to alleviate mass transfer effects caused by the heterogeneous potassium phosphate base used. In addition, a Hammett and DFT study confirmed that aryl iodide activation mechanisms involving radical intermediates or a σ -bond metathesis were not present. Instead, DFT calculations supported an oxidative addition and reductive elimination mechanism. Overall, their findings suggested that the rate was limited by the formation of the DMEDA-ligated copper(I) nucleophile intermediate due to mass transfer effects and also the subsequent aryl iodide oxidative addition.



Scheme 1.25: Copper-catalysed cross-coupling between aryl iodides and pyrrole or pyrazole using submol% catalyst loadings.^[140]

The previously mentioned studies in this section focused largely on C–N bond formation involving nucleophiles other than amines. This is because evidence for aryl halide activation mechanisms for amination reactions is less common in the literature and contradictions are often found between different reports. A theoretical study of the 1,3-diketone assisted copper-catalysed cross-coupling of bromobenzene with methylamine by Ding proposed that the neutral copper(I) species with both a diketone ligand and amine substrate was the catalyst resting state (**1.34**, Figure 1.7).^[141] Similar to the mechanism proposed by Buchwald *et al* in Scheme 1.23, the largest energy penalty in the oxidative addition was from the initial formation of a η^2 -pre-complex **1.35**. After the oxidative addition step, deprotonation of the amine from the five-coordinate copper(III) intermediate **1.36** occurs to drive the reaction forwards. This was

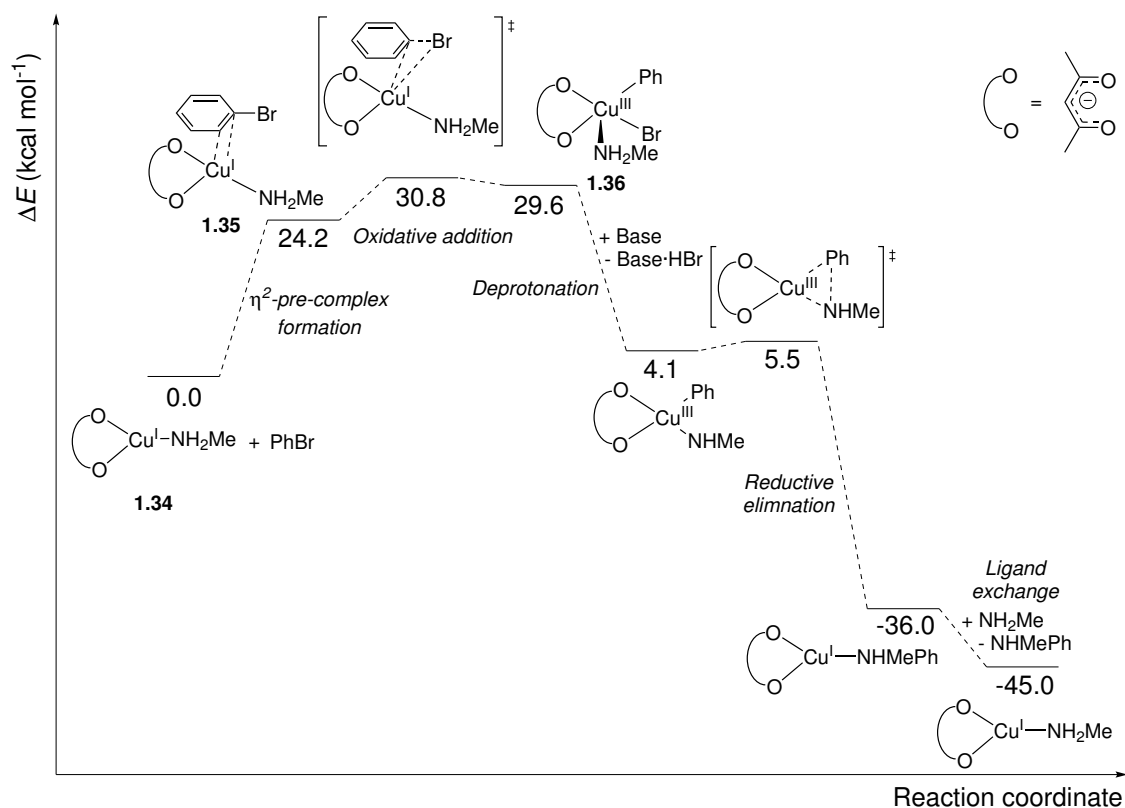
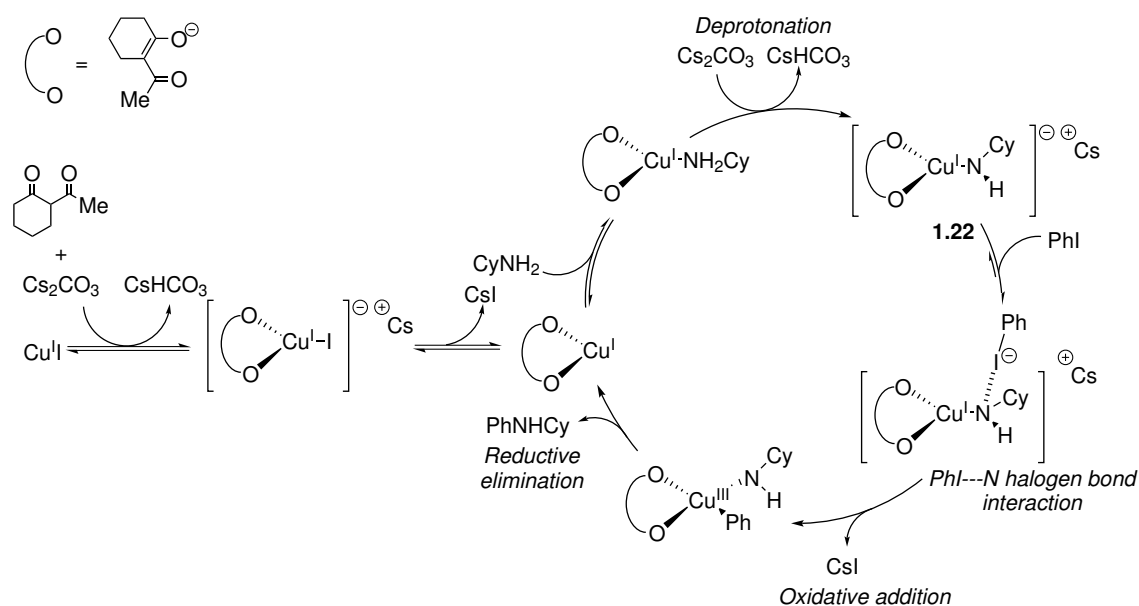


Figure 1.7: Computed oxidative addition and reductive elimination pathway for the acetylacetonate-ligated copper-catalysed amination of bromobenzene with methylamine.^[141]

followed by a facile reductive elimination to give the product. However, a comparison with a radical-based mechanism was not explored in this work.

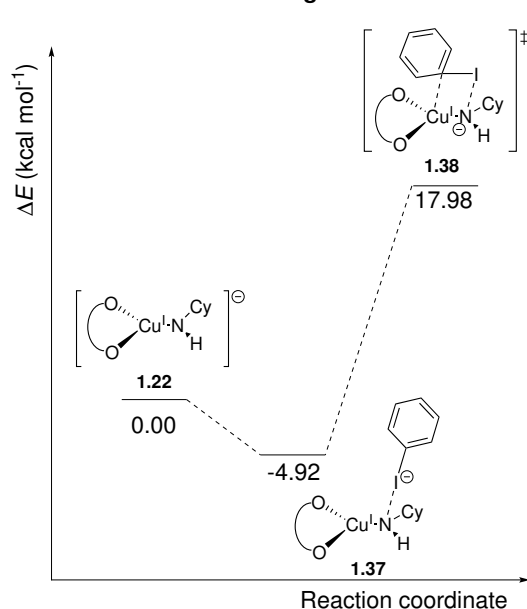
Jutand and co-workers have also explored the mechanism for the *N*-arylation of alkylamines with the 2-acetylcyclohexanone as the 1,3-diketone ancillary ligand. However through the use of cyclic voltammetry, ¹H NMR spectroscopy and DFT calculations, different key intermediates and processes in the catalytic cycle were proposed to those by Ding (Scheme 1.26).^[99,106,107] A unique feature of this mechanism was how the oxidative addition was thought to proceed. Experimental evidence and DFT calculations suggest that the oxidative addition can be mediated by a favourable halogen bonding interaction between iodobenzene and the electron-rich nitrogen atom of complex **1.22** to give intermediate **1.37** (left-hand side, Figure 1.8). An intramolecular oxidative addition then follows *via* a four-centre transition state **1.38**, in contrast to a three-centre pathway. In the alternative scenario without a halogen bonding interaction, theoretical calculations suggest a strongly endothermic η^2 -complexation of copper(I) by the aryl halide to give intermediate **1.39** is initially required instead before forming a three-centre oxidation

addition transition state **1.40** (right-hand side, Figure 1.8). The two proposed mechanisms were thought to be in competition as they had similar energy barriers towards oxidative addition, with



Scheme 1.26: Proposed catalytic cycle for the copper-catalysed *N*-arylation of cyclohexylamine with the 2-acetylcyclohexanone as the ligand.^[99,106,107]

Via *exothermic* PhI...N halogen bond interaction



Via endothermic η^2 -complexation

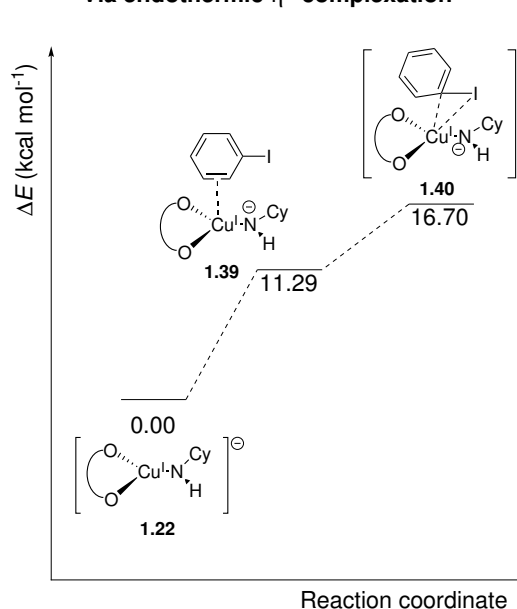
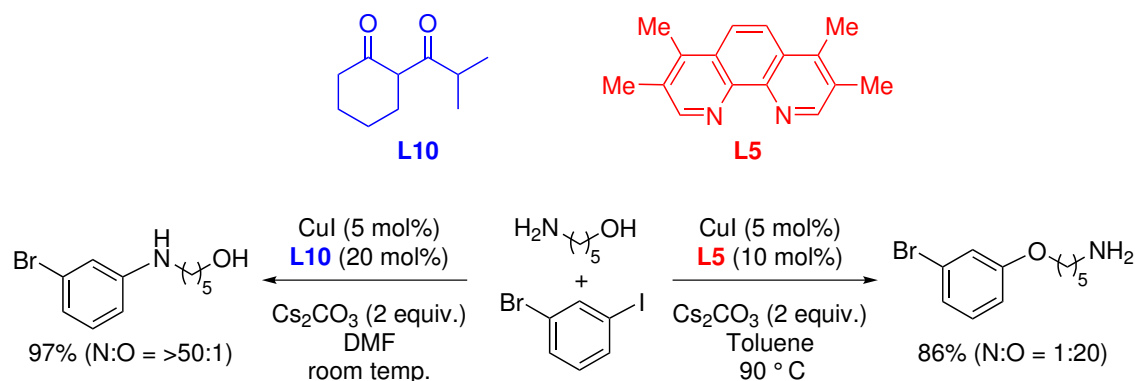


Figure 1.8: Pathways for oxidative addition *via* a halogen bond interaction (left-hand side) or η^2 -complexation (right-hand side) computed by Jutand and co-workers.^[99,106,107] The Cs⁺ counter-cation is not shown.

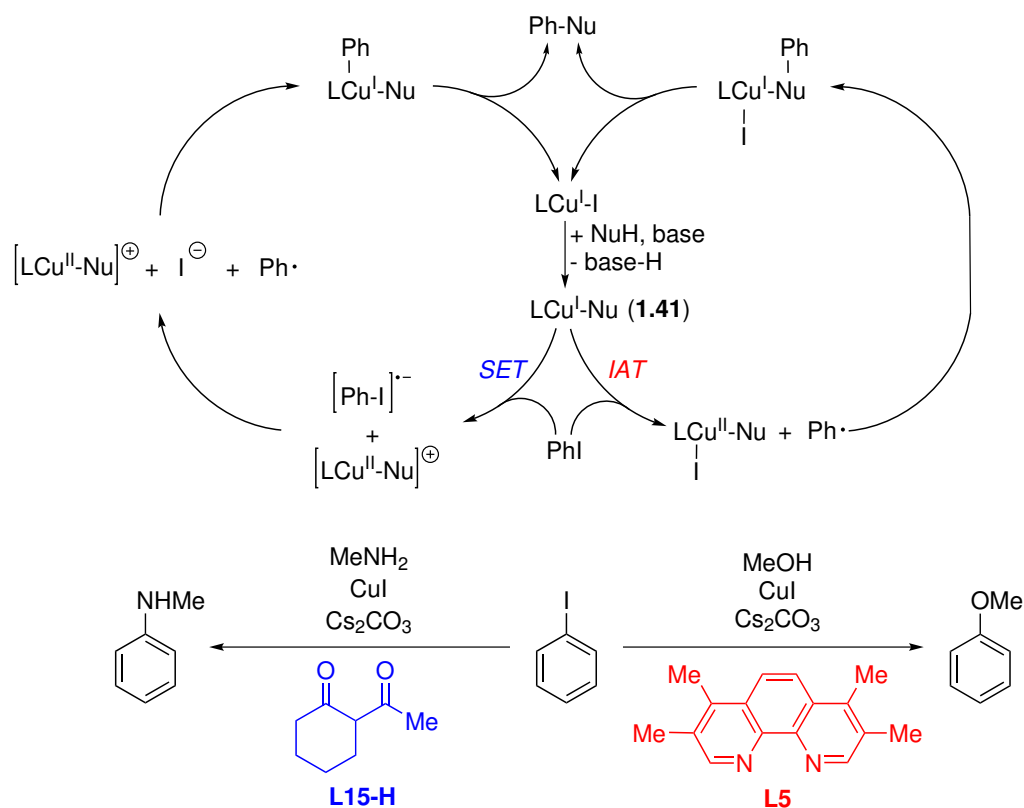
the mechanism *via* η^2 -complexation slightly favoured using the substrates shown. Subsequent reductive elimination from the copper(III) complex would then give the product but this step was not observable given the short lifetime of the complex. A radical pathway for the aryl halide activation was ruled out as cyclic voltammetry data indicated that the difference between the standard oxidation potential of the anionic catalyst resting state **1.22** and the standard reduction potential of iodobenzene was too large (≈ 3 V) to allow outer-sphere electron transfer.^[106]

Similar to the copper-catalysed *N*-arylation of alkylamines assisted by 1,3-diketone ligands, contradicting aryl halide activation mechanisms for the ligand induced *O*- and *N*-selective arylation of aminoethanol compounds (Scheme 1.27) are also present in the literature.^[59] A computational study involving a simplified system of independent methylamine and methanol nucleophiles proposed that the *O*- and *N*-arylation reactions occurred *via* iodine atom transfer (IAT) and single electron transfer (SET) aryl halide activation mechanisms respectively from the ligated copper(I) nucleophile species **1.41** (Scheme 1.28).^[142] Mechanisms involving oxidative addition for either *O*- and *N*-arylation were calculated to be less energetically favourable.

In contrast, Fu and co-workers subsequently computed that oxidative addition was present for both *O*- and *N*-arylation instead of IAT and SET mechanisms but claimed that the rate-limiting step was different in each case (Scheme 1.29).^[143] Compared to the other computational study, Fu more realistically used 5-amino-1-pentanol as the nucleophile instead of independent methylamine and methanol nucleophiles to study the *N*- and *O*-arylations. However the ligand for the *O*-arylation was simplified to phen, which would have a lower electron density than **L5**. Fu stated that the energy barriers corresponding to the aryl halide activation steps calculated in the study by Buchwald *et al* were inaccurate because the ligated copper(I) iodide species were

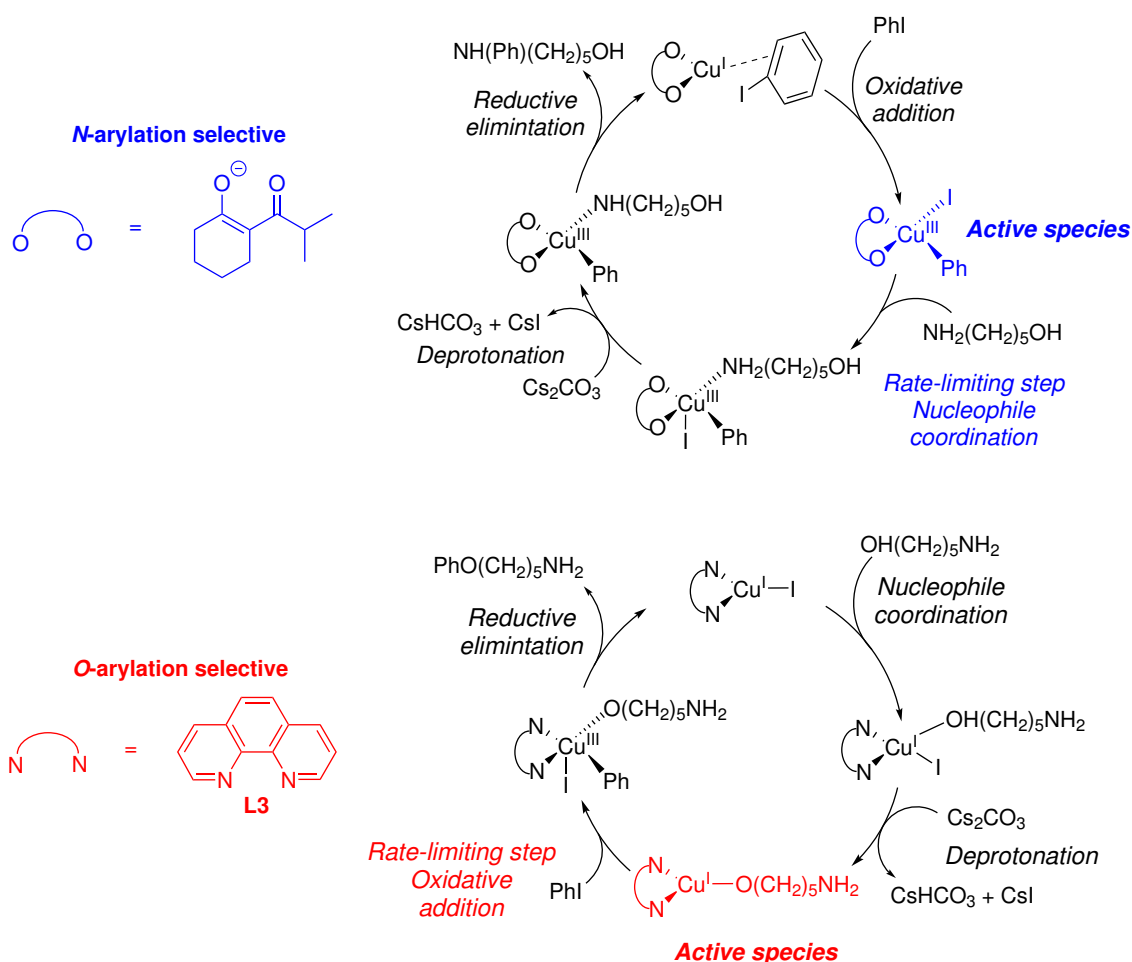


Scheme 1.27: Example of the *O*- and *N*-selectivity for the arylation of aminoethanol compounds depending on the nature of the ligand used.^[59]



Scheme 1.28: Reaction scheme showing the *O*- and *N*-arylation selectivity dependence on the type of ligand mechanisms by Buchwald and co-workers.^[142]

used to calculate the energy barriers, which according to Fu were not always the most stable complexes in the reaction solution. In addition, Fu criticised the method employed by Buchwald to calculate the energy barrier for an iodine atom transfer mechanism, which involved using the energy of the IAT product ([**L5**-Cu^{II}-I(OR)] and phenyl radical). They suggested scanning the energies of [**L3**-Cu-(OR)(I-Ph)] at different Ph-I bond distances would provide more accurate values. To complete the comparison, the energy barriers to SET, IAT and σ -bond metathesis were found to be greater than oxidative addition for both *O*- or *N*-arylation. However, it should be noted that all of the copper complexes in the *N*-arylation mechanism proposed by Fu *et al* in Scheme 1.29 have no experimental evidence to support their intermediacy whereas intermediate species **1.41** for *N*-arylation, [**L15**-Cu^I-NHMe]⁻ (Scheme 1.28), proposed by Buchwald and co-workers is similar in structure to the experimentally characterised complex **1.22**.

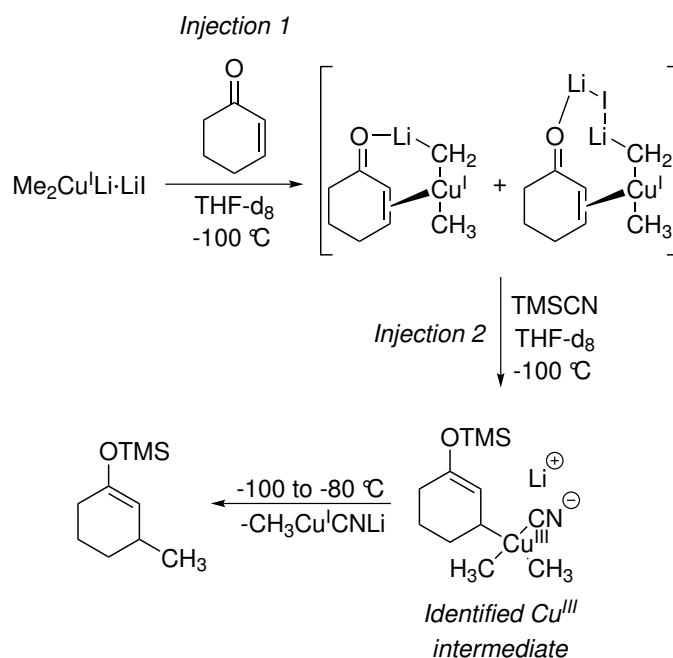


Scheme 1.29: Catalytic cycles for the ligand dependent *N*- and *O*-arylation selectivity reactions in the presence of caesium carbonate proposed by Fu *et al* in a computational study.^[143]

1.4.4.4 Copper(III) intermediates in Ullmann reactions

To summarise the mechanistic studies for the modified Ullmann reactions presented so far, oxidative addition mechanisms generally fit best when there is a lack of inhibition by free radical scavengers. Computational studies have also been employed in some cases to show that oxidative addition is the most energetically accessible aryl halide activation route compared to other mechanisms. However, copper(III) intermediates have yet to be experimentally detected in synthetically useful modified Ullmann reactions. This is likely due to the unstable and short-lived nature of copper(III) species.^[89,144,145] Nonetheless, copper(III) species have been detected before using specialised ligand systems and characterisation techniques.

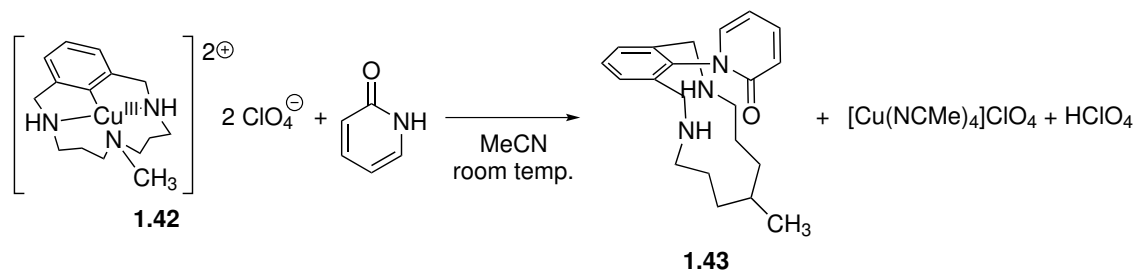
Extensive NMR studies using a technique called rapid-injection NMR (RI-NMR) carried out by Bertz and co-workers have successfully prepared and identified a copper(III) intermediate in



Scheme 1.30: The experiment carried by Bertz and co-workers used to detect copper(III) intermediates using RI-NMR.^[146]

the reaction between Gilman reagents, $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ or $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$, and 2-cyclohexenone (Scheme 1.30).^[146] Unfortunately, the insolubility of commonly used bases and the relatively high melting points of the polar aprotic solvents used in the modified Ullmann reaction preclude the use of RI-NMR for identifying copper(III) intermediates.

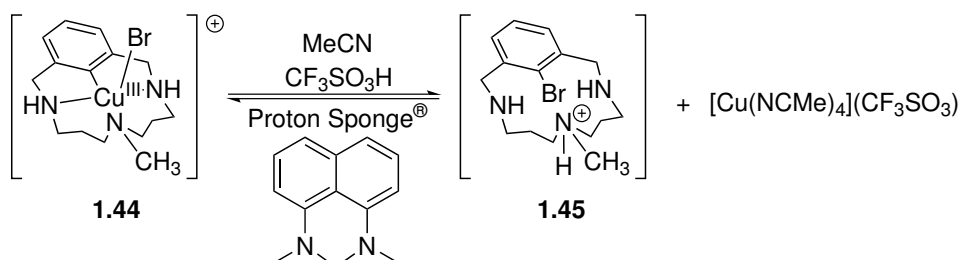
The first experimental evidence for copper(III) intermediates in Ullmann-type reactions was in the form of the isolatable and fully characterised copper(III) aryl complex **1.42** (Scheme 1.31).^[147] Stabilisation of the usually unstable copper(III) centre was attributed to the large tetradentate triazamacrocyclic ligand. The key feature of this complex was that it could rapidly



Scheme 1.31: Stoichiometric reaction between isolated triazamacrocyclic aryl copper(III) complex **1.42** and pyridone to confirm the intermediacy of copper(III) complexes.^[148]

react stoichiometrically with nitrogen nucleophiles, such as pyridone, to form a C–N bond with the aryl moiety of the macrocycle (**1.43**, Scheme 1.31).^[148]

Further evidence for the intermediacy of copper(III) species was provided when isolated aryl-copper(III) halide species (**1.44** for bromide ligated copper(III) complex, Scheme 1.32) were shown to be able to undergo reductive elimination to give the corresponding aryl halide **1.45** and copper(I) complex on addition of triflic acid. This product mixture could then also undergo oxidative addition to re-form the aryl-copper(III) halide on addition of Proton Sponge[®] without significant degradation (Scheme 1.32).^[149] A steady-state concentration of **1.44** was also remarkably detected using *in situ* NMR and UV-Vis spectroscopy in the C–N cross-coupling reaction between the triaza-aryl bromide macrocycle ligand and pyridone.^[149] This confirmed that **1.45** is an intermediate of the catalytic reaction. However, this work suggests that oxidative addition precedes nucleophile coordination, which is surprisingly the rate-limiting step. This is likely to be due to the highly stabilised copper(III) state and therefore some caution should be used when applying the findings to less well-stabilised catalytic systems. Further studies involving the reactions of other nucleophiles with this highly stable aryl-copper(III) complex have also been reported by the same authors and highlight potential copper(I)/copper(III) mechanisms within these systems.^[150–154]



Scheme 1.32: Reversible oxidative addition and reductive elimination involving aryl-copper(III) halide complex **1.44** induced by sequential protonation and deprotonation.^[149]

Mechanistic information regarding whether aryl halide activation precedes nucleophile coordination or *vice versa*, and what the aryl halide activation pathway is, have been obtained in the literature for the reactions highlighted in Section 1.4.4 after extensive mechanistic investigations. Despite advances in the understanding of aryl halide activation mechanisms, it remains difficult to predict which mechanism is present for a particular reaction that has not undergone a detailed mechanistic study. For example, other than light irradiation, the experimental conditions for the radical-driven photoinduced cross-coupling reactions by Fu and Peters are not much different

to those typically employed for other systems which exhibit no detectable radical intermediates.^[94,128] Although, information such as the standard reduction potentials and C-X bond strengths of aryl halides and standard oxidation potentials of the copper(I) intermediates should in theory be helpful for identifying the aryl halide activation mechanism, they are challenging to obtain.^[106,143]

1.5 Aims

The main reasons for the recent influx in interest in the modified Ullmann amination reaction are the cost and environmental benefits when compared to the more developed and better understood palladium-catalysed Buchwald-Hartwig amination.^[44,82] Although improvements have recently been made in the efficiency of this copper-catalysed reaction, a large number of the mechanisms proposed in the literature are contradictory.^[43] This is particularly true for copper-catalysed C–N bond formation between aryl halides and amines (see Section 1.4.4.3). Given that there is a lack of continuity in the literature for this reaction, the focus of this project is on the cross-coupling between aryl halides and alkylamines.

With the exception of the studies by Bacon and Karim,^[102] and Paine,^[98] the nature of the reaction intermediates in the absence of the ligand have rarely been investigated in detail. In comparison, three-coordinate copper(I) amide complexes ligated by ancillary ligands are much more extensively reported as active intermediates towards aryl halide activation (Figure 1.6). Furthermore direct comparison of the structure and reactivity of ligand-free or ancillary ligand coordinated copper(I) amide intermediates have only been reported for two catalytic systems in the literature,^[103,104,108] neither involving alkylamines as the nucleophilic substrate. As a result, the current understanding of the effect of the ligand on the structure and reactivity of copper(I) amide intermediates is limited in scope. Therefore the role of ancillary ligand-free and ligated copper(I) alkylamide complexes as potential intermediates in the Ullmann reaction between aryl halides and alkylamines will be explored in this work through a comprehensive structural characterisation and reactivity study. None of the proposed mechanisms in the literature for the copper-catalysed C–N bond formation between aryl halides and alkylamines have been supported by detailed kinetic studies to date.^[99,106,107,141–143] As a result, important kinetic features such as the rate dependences on the reactants and potential catalyst deactivation and inhibition modes remain unstudied. Therefore the Ullmann amination reactions performed in this work have been monitored in order to obtain kinetic and catalyst stability information, and to identify the role of the ligand and how it affects the solution equilibria of the intermediates. The mechanistic effects of using a soluble carboxylate base in the catalytic reaction have also been investigated in a detailed kinetic study that involved *in situ* reaction monitoring and the application of reaction progress kinetic analysis^[155].

Overall, this project seeks to confirm the identity and behaviour of the commonly proposed

catalytic intermediates in the modified Ullmann amination reaction formed from ancillary ligand and alkylamine coordination to copper(I), N–H deprotonation and aryl halide activation (Scheme 1.8). In addition, potential off-cycle species and catalyst deactivation pathways have not yet been incorporated into current mechanistic models. Therefore, developing an understanding of these possible aspects and studying the role of the ligand in these processes will aid in improving the performance of existing catalyst systems and help in the rational development of new improved catalytic systems.

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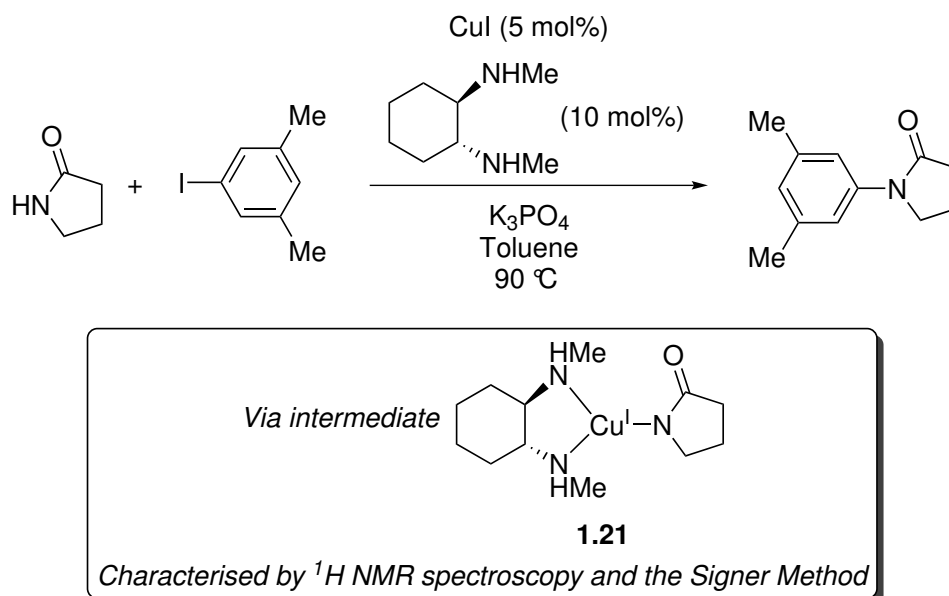
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Chapter 2

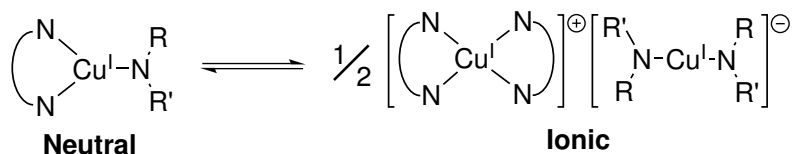
Synthesis, Characterisation and Reactivity of Copper(I) Amide Complexes and Studies on their Role in the Modified Ullmann Amination Reaction



Scheme 2.1: Reaction scheme for the copper-catalysed *N*-arylation of pyrrolidinone and the 1,2-diamine-ligated copper(I) pyrrolidinonate intermediate **1.21** identified by Buchwald and co-workers.^[2]

equivalent of 1,2-diamine ligand (*MW* 289) suggested that the two compounds form a 1 : 1 adduct in solution.^[2]

Hartwig and co-workers also determined that the intermediate active towards aryl halide activation had a 1 : 1 ratio of copper(I) imidate/amidate/amide to bidentate ligand.^[4,5] As a neutral ligand was used, this active complex was overall neutral with a formula of [LCu(NRR')] (Scheme 2.2), where L is the neutral *N,N*-chelating bidentate ligand. However, Hartwig found that the active complex can be in equilibrium with an ionic form, [CuL₂]⁺[Cu(NRR')₂][−] (Scheme 2.2), where the position of the equilibrium depends upon the nucleophile and bidentate ligand present. For example in Figure 2.2 with 1,10-phenanthroline (phen) as the bidentate ligand, the complex with phthalimide as the nucleophile ligand adopts the neutral form (**1.24**) in the solid



Scheme 2.2: Equilibrium between neutral or ionic forms of copper(I) imidate/amidate/amide complexes with neutral *N,N*-chelating bidentate ligands.

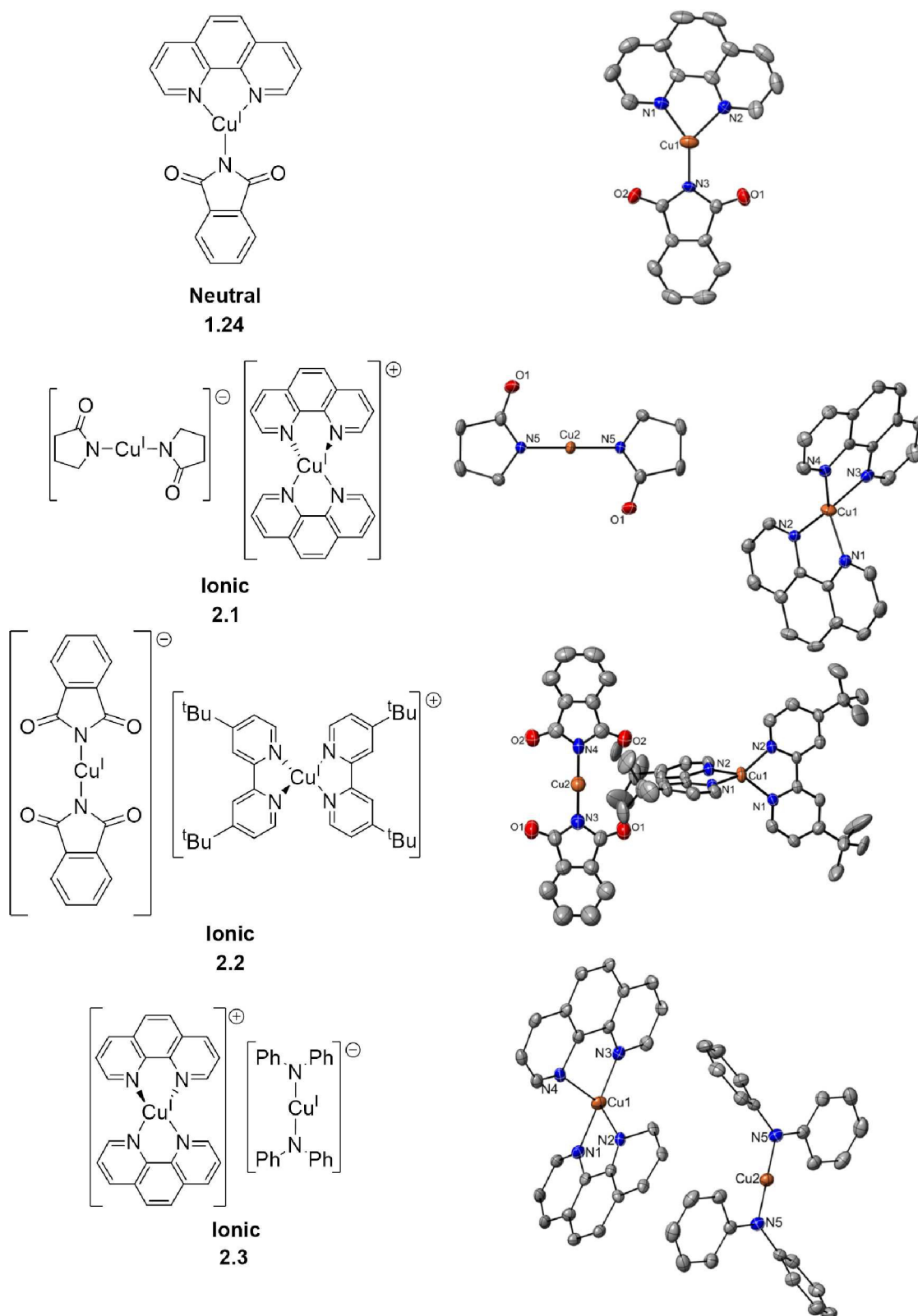
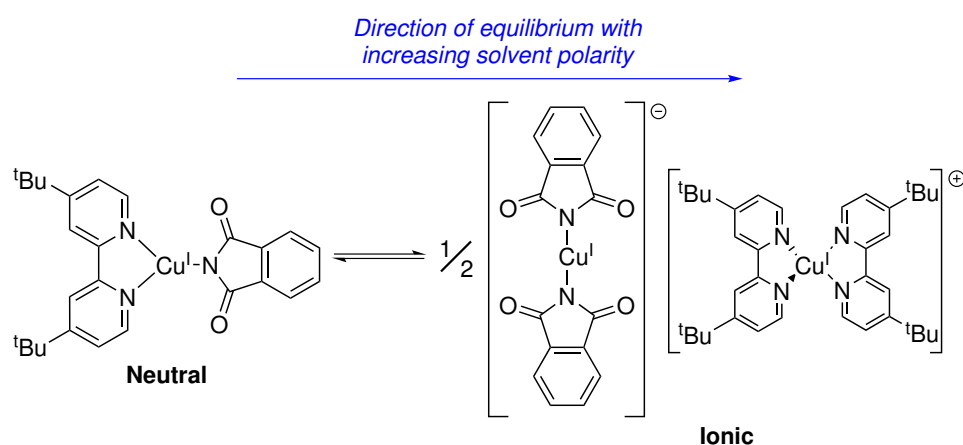


Figure 2.2: Structures of isolated phen-ligated ionic and neutral complexes characterised by Hartwig and co-workers.^[4,5] Crystal structures shown with thermal ellipsoids set at 50% probability. Hydrogen atoms are omitted for clarity.

state, whereas with pyrrolidinonate the ionic form (**2.1**) is favoured. In contrast to the neutral complex **1.24**, the solid-state structure of the copper(I) complex with phthalimide and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) ligands was ionic (**2.2**).^[4] On performing conductivity measurements on solutions of complex **2.2**, the predominant solution structure was found to be strongly affected by the polarity of the solvent (Scheme 2.3). In highly polar solvents such as DMSO, the molar conductivity was high which is indicative of the ionic form being predominantly present. When less polar solvents such as THF and benzene were used, the molar conductivity decreased with decreasing solvent polarity which indicated the equilibrium had shifted towards the neutral form. In comparison, the ionic form was always the predominant species when diphenylamide was the nucleophilic ligand (**2.3**, Figure 2.2), with the equilibrium between the ionic and neutral forms not as strongly affected by the solvent polarity of DMSO or THF as when amidate ligands were used.^[5]



Scheme 2.3: Solvent polarity dependent equilibrium between the neutral and ionic forms of complex **2.2**.^[4]

Hartwig and co-workers determined that the neutral form of ligated copper(I) complexes **2.3** is active towards aryl halide activation and not the ionic form by testing the stoichiometric reactivity of various di(amido)cuprate compounds. The authors found the stoichiometric reactivity of phen-free cuprates [(18-crown-6)K][Cu(NPh₂)₂] and K[Cu(NPh₂)₂] with aryl iodides to be relatively poor compared with [Cu(phen)₂][Cu(NPh₂)₂] (**2.3**). The phen-ligated ion pair was thought to be more reactive as the phen ligand allowed it to equilibrate to a reactive neutral [phenCu(NPh₂)] species whereas the potassium di(amido)cuprates were unable to equilibrate to analogous reactive neutral complexes.^[5]

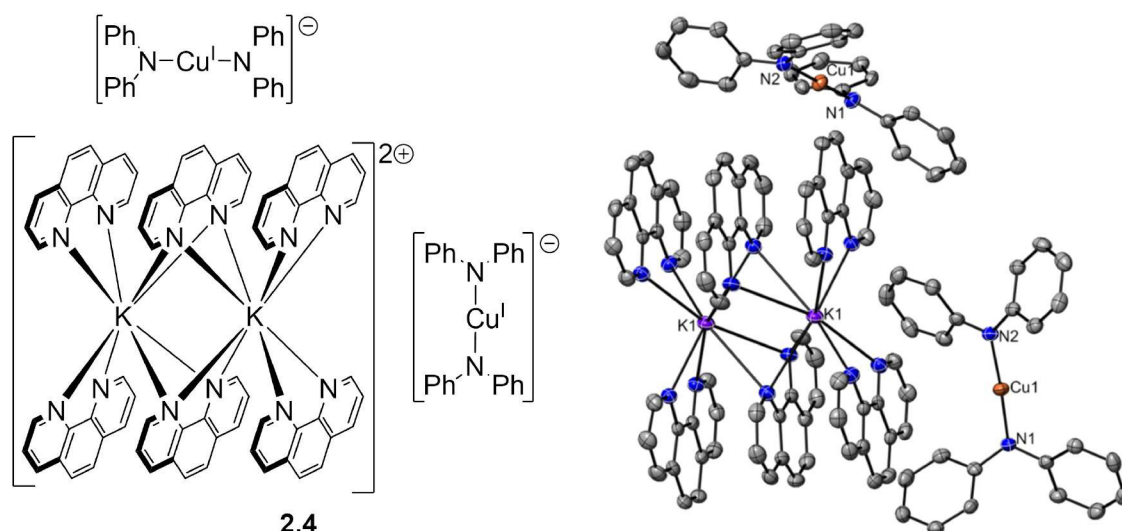


Figure 2.3: Crystal structure of complex **2.4** determined by Hartwig and co-workers. Crystal structure shown with thermal ellipsoids set at 50% probability.^[5] Hydrogen atoms are omitted for clarity.

Complexes with a general formula of $[M_2(\text{phen})_6][\text{Cu}(\text{NPh}_2)_2]_2$ were also synthesised and structurally characterised using X-ray crystallography by Hartwig and co-workers (see Figure 2.3 for an example where $M = \text{K}$, **2.4**).^[5] Although the solution structure of **2.4** was not reported, this complex was found to react stoichiometrically with aryl iodides to give the C–N coupled product and therefore was proposed to be able equilibrate to the reactive neutral $[\text{phenCu}(\text{NPh}_2)]$ species. By reacting copper(I) iodide, phen, sodium/potassium *tert*-butoxide, and diphenylamine together in toluene solvent, Shyu and co-workers successfully isolated the similar complexes $[\text{Na}(\text{phen})_3][\text{Cu}(\text{NPh}_2)_2]$ (**2.5**) and $[\text{K}_3(\text{phen})_8][\text{Cu}(\text{NPh}_2)_2]_3$ (**2.6**) (Figure 4.4).^[6,7] Although the solid-state structures were determined for complexes **2.5** and **2.6**, the structures adopted in solution were not studied by the authors. Similar to **2.4**, complexes **2.5** and **2.6** were able to react stoichiometrically with aryl halides to give C–N coupled products. When Shyu and co-workers performed *in situ* analysis using ESI-MS of the stoichiometric reaction between complex **2.5** and 4-iodotoluene^[7] or of the copper-catalysed reaction between diphenylamine and 4-iodotoluene^[6], copper(I)-containing fragments $[\text{Cu}(\text{NPh}_2)_2]^-$ and $\{\text{Na}[\text{Cu}(\text{NPh}_2)_2(p\text{-tolyl})]\}^+$ were detected in both experiments. The detected copper(III) complex $\{\text{Na}[\text{Cu}(\text{NPh}_2)_2(p\text{-tolyl})]\}^+$ was thought to be formed from oxidative addition of 4-iodotoluene to $[\text{Cu}(\text{NPh}_2)_2]^-$ to give $[\text{CuI}(\text{NPh}_2)_2(p\text{-tolyl})]^-$ (exchange of Na^+ for I^- occurred during the positive-ion mode ESI-MS measurement process). Therefore the $[\text{Cu}(\text{NPh}_2)_2]^-$ anion was proposed by Shyu to be an important component of the

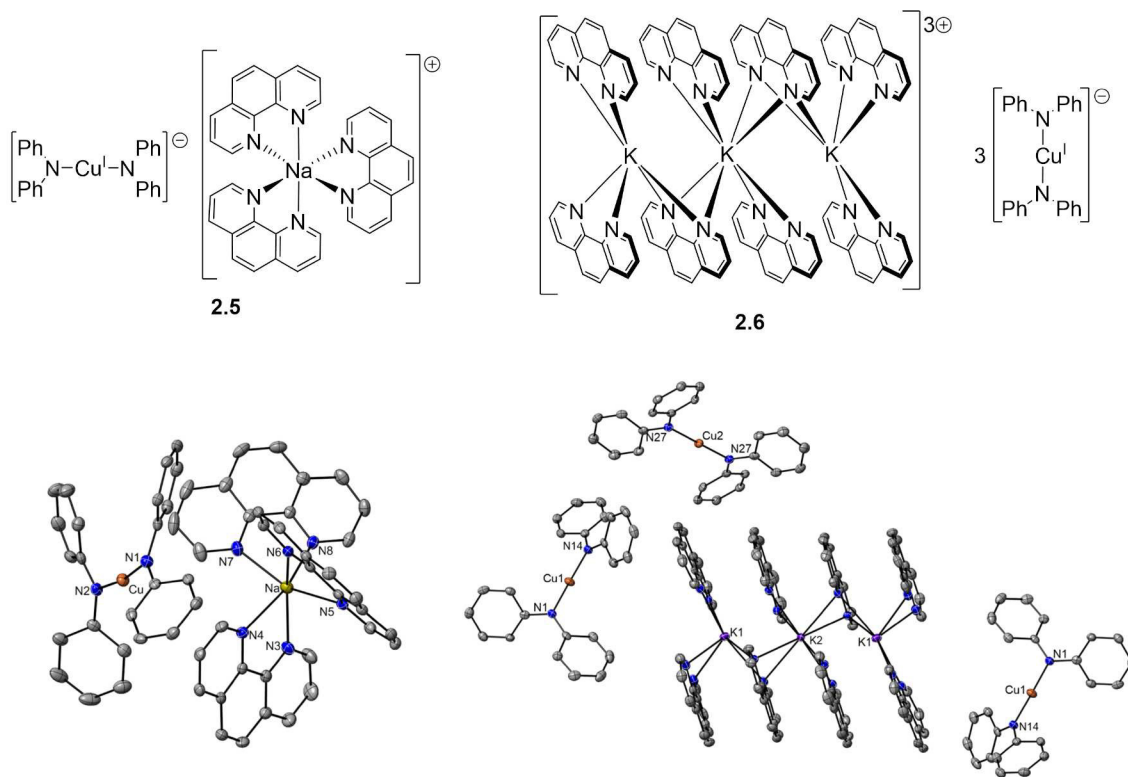


Figure 2.4: Crystal structures of complexes **2.5** and **2.6** determined by Shyu and co-workers. Crystal structures shown with thermal ellipsoids set at 50% probability.^[6,7] Hydrogen atoms are omitted for clarity.

active catalyst species.^[6]

Overall, Hartwig and Shyu have proposed conflicting accounts for the reactivity of di(amido)-cuprate complexes in modified Ullmann reactions albeit using different reaction temperatures, solvents, bases and reactant concentrations. However, the evidence presented by Shyu and co-workers is based solely on ESI-MS data which exposes the complexes to a harsh environment during the ESI-MS measurement where ions can be added or removed as suggested by the exchange of Na^+ for I^- in the detected copper(III) complex. Therefore, it is possible that the detected ions may not actually exist in the reaction solution and this weakens their mechanistic study.

A particularly notable example of a structurally characterised Ullmann reaction intermediate is the bis[tri(*m*-tolyl)phosphine] copper(I) carbazolidine complex (**1.26**, Figure 2.5) reported by Fu, Peters and co-workers.^[8] Similar to **1.21** and **1.24**, complex **1.26** exhibits a three-coordinate copper(I) centre in the solid state.^[8] Although solution structure studies of **1.26** were not carried

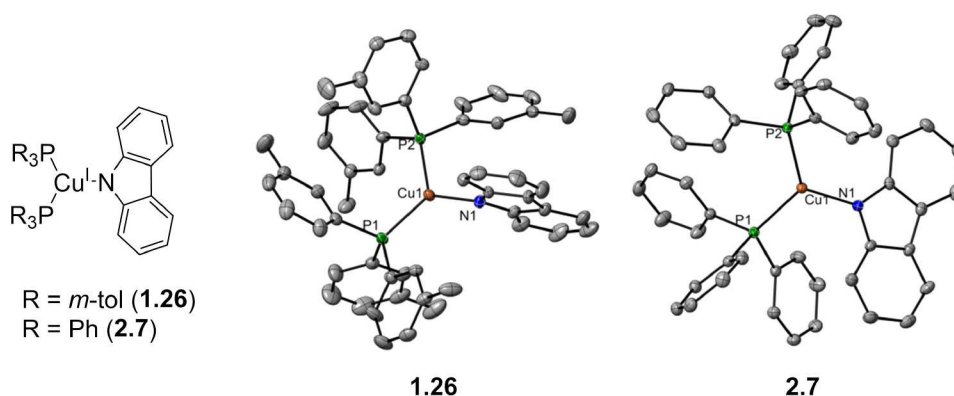
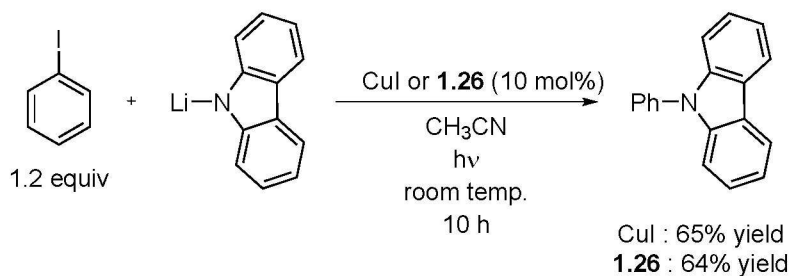


Figure 2.5: Crystal structures of complexes **1.26** and **2.7** from the literature.^[8,9] Crystal structures shown with thermal ellipsoids set at 50% probability. Hydrogen atoms are omitted for clarity.

out, the structure of the analogous triphenylphosphine-ligated copper(I) complex (**2.7**, Figure 2.5) was preserved in benzene solution at room temperature, unlike complexes **1.24** and **2.1** – **2.3** which are in equilibrium between neutral and ionic forms in solution.^[9] Reactivity studies conducted using complex **1.26** showed it was reactive towards aryl iodides only when irradiated in the near ultraviolet region.^[8] When 10 mol % of **1.26** was utilised as the catalyst in the cross-coupling between lithium carbazolidine and iodobenzene, the product yield (65%) was very similar to when copper(I) iodide was used as the catalyst in the absence of an ancillary ligand (64% yield) (Scheme 2.4). Although the similarity between the yields was not discussed by the authors, this suggests that the phosphine ligand may not be essential for the observed reactivity at least when a coordinating solvent such as acetonitrile is used.^[10] Fu, Peters and co-workers also found that the photochemically induced copper-catalysed *N*-arylation of indoles, benzimidazoles and imidazoles can be achieved in the absence of an ancillary ligand in acetonitrile solvent.^[11]



Scheme 2.4: Reaction scheme for the copper-catalysed cross-coupling of lithium carbazolidine and iodobenzene using copper(I) iodide or complex **1.26** as the catalyst.^[8]

In summary, with the exception of the ESI-MS studies by Shyu and co-workers, the key structural features of the reactive intermediate in Ullmann-type reactions in the presence of ancillary ligands has been shown to be a three-coordinate copper(I) centre ligated by a deprotonated nucleophile substrate with the two remaining coordination sites occupied by the ancillary ligand(s). This reactive intermediate has also been reported to be in equilibrium with an unreactive form where the position of the equilibrium is affected by the nature of the nucleophile, ancillary ligand and solvent.

2.1.1.2 Ligand-free copper-catalysed amination reactions

As shown in recent work by Fu, Peters and co-workers,^[8,11] copper-catalysed cross-coupling reactions between nitrogen-based nucleophiles and aryl halides can be achieved in the absence of any ancillary ligand. Although ancillary ligands have been shown to enhance the reactivity of many non-photochemically induced systems in the literature,^[12–15] some efficient ligand-free protocols for copper-catalysed aryl amination reactions have been reported in the literature.^[16–22] In general, the ligand-free aryl amination protocols employ high reaction temperatures with coordinating solvents such as DMSO, DMF and NMP. It is also possible that the amine substrate may act as an ancillary ligand in these systems. As mentioned in Section 1.4.2, Chapter 1, mechanistic studies of copper-catalysed cross-couplings suggest that copper(I) amide complexes ($[\text{Cu}(\text{NRR}')_n]$) (Figure 2.6) are the catalyst resting state when ancillary ligands are not present.^[23,24] However, relatively few studies on the synthesis and structural characterisation of copper(I) amides have been reported in the literature.^[25–32] Furthermore, the stoichiometric cross-coupling reactivity of these species with aryl halides has seldom been investigated, with no reported successful reactions in the absence of ancillary ligands.^[1,2,5] Current ligand-free studies are limited in scope with only copper(I) pyrrolidinonate^[1,2] and copper(I) pyrrolidide^[5] investigated. Therefore the intermediacy of these species warrants further study.

To improve the current understanding of the role of copper(I) amide complexes in the

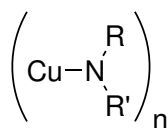


Figure 2.6: General structure for copper(I) amide complexes ($[\text{Cu}(\text{NRR}')_n]$) in the absence of ancillary ligands.

Ullmann amination reaction, a detailed study of the synthesis and structural characterisation of these species was performed. As the reactivity of well-defined copper(I) amide intermediates is currently limited to arylamido ligands in the literature, alkylamido ligands have been studied. Given that the effect of the amido ligand on the stoichiometric reactivity with aryl iodides has not been reported in the literature, a series of complexes with different alkylamido ligands were synthesised and used in this work. Characterisation of these complexes focused on their solid-state structures and solution equilibria in benzene and DMSO solutions. Stoichiometric reactions between these complexes and aryl iodides have also been investigated. The observed reactivity was correlated to the solution structures and compared to the corresponding catalytic reactions between the respective amines and aryl iodides. In addition, the influence of added phen on the solution structures, and stoichiometric and catalytic reactivity has been examined.

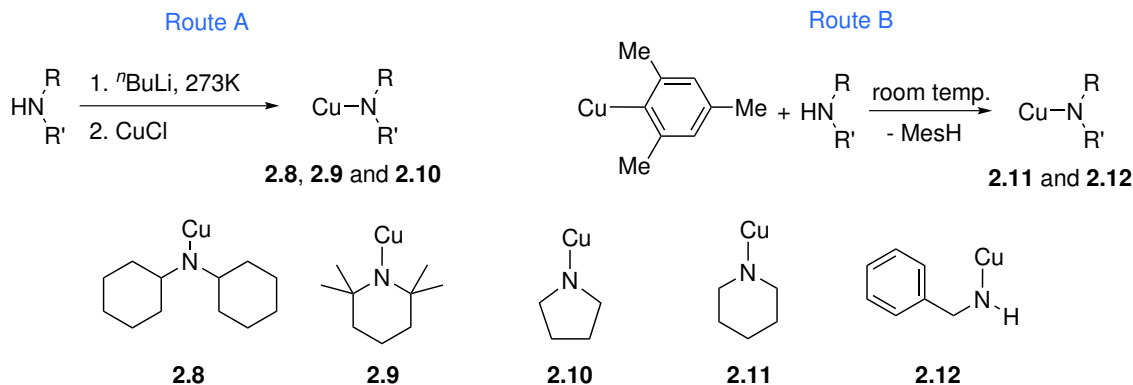
2.2 Results and Discussion

2.2.1 Synthesis of copper(I) amide complexes

As mentioned previously in Section 2.1.1.2, relatively few synthetic and structural characterisation studies of copper(I) amide complexes have been reported in the literature,^[25–32] despite the fact that the first copper(I) amide complexes were reported approximately a century ago.^[33] This can partly be attributed to the high air and moisture sensitivity of most reported copper(I) amides.

The amines used in this study (dicyclohexylamine, 2,2,6,6-tetramethylpiperidine (TMP), pyrrolidine, piperidine and benzylamine) were chosen to provide a range of steric bulk, and also according to their copper-catalysed cross coupling performance with iodobenzene, where primary amines are known to exhibit better reaction rates and produce higher yields than acyclic secondary amines.^[15]

Copper(I) dicyclohexylamide (**2.8**), copper(I) 2,2,6,6-tetramethylpiperidide (**2.9**) and copper(I) pyrrolidide (**2.10**) were prepared using a metathesis reaction between copper(I) chloride and the corresponding lithium amides of the parent amines (Route A, Scheme 2.5). Although the preparation of **2.10** has been reported using a similar synthetic route,^[31] **2.8** and **2.9** are new complexes not previously reported in the literature. Copper(I) piperidide, **2.11**, and copper(I) benzylamide, **2.12**, were prepared using a different method that involved reacting the parent amine with the copper metalation reagent copper(I) mesityl (CuMes) (Route B, Scheme 2.5).^[26,27,34] Compared to Route A, Route B allowed the preparation of copper(I) amides in high purity whilst avoiding the formation of halide salt by-products. However, despite several



Scheme 2.5: Synthesis of copper(I) amide complexes **2.8** – **2.12**.

attempts, Route B was unsuccessful in the syntheses of complexes **2.8** and **2.9**. A study of the mechanism for the reaction between CuMes and piperidine to prepare complex **2.11** gave an insight into why sterically bulky complexes **2.8** and **2.9** could not be formed using this method (see below in Section 2.2.3).

2.2.2 Solid-state structures of copper(I) amide complexes

Single-crystal X-ray diffraction was used to characterise the solid-state structures of complexes **2.8**, **2.9** and **2.11**. Complex **2.12** rapidly decomposes in solution to give an unknown orange solid and therefore it was not possible to obtain structural data for this complex. Single-crystal X-ray diffraction of complex **2.10** has been previously reported by Floriani and co-workers who found that it exists as a tetramer, $[\text{Cu}(\text{NC}_4\text{H}_8)]_4$ in the solid state.^[31] Complexes **2.8**, **2.9** and **2.11** were all found to be present as analogous tetramers in the solid state, containing bridging amido-nitrogen atoms between copper(I) ions to form eight-membered Cu_4N_4 rings (Figure 2.7). However, structural features which differ in complexes **2.8**, **2.9** and **2.11** are the planarity of the Cu_4N_4 unit and linearity of the N–Cu–N bond angles.

Selected bond lengths and bond angles in the structures of all new complexes are listed in Table 2.1. The Cu_4N_4 rings in **2.8** and **2.11** adopt butterfly confirmations where the torsion angles between opposite N–Cu–N sides of the rings are greater than 0° (**2.8**, N1–N2–N4–N3 torsion angle = $31.20(8)^\circ$; **2.11**, N1–N11–N31–N21 torsion angle = $58.9(2)^\circ$). Although the amido ligands in **2.8** and **2.11** have different steric properties, the N–Cu–N bond angles are also similar in both (**2.8**, range $170.31(8)^\circ$ – $173.09(8)^\circ$; **2.11**, range $171.68(14)^\circ$ – $173.20(14)^\circ$). However the Cu–N bond lengths in **2.8** lie in the range $1.902(2)$ – $1.940(2)$ Å (mean 1.921 Å) which are slightly longer than in **2.11** (range $1.890(4)$ – $1.907(5)$ Å, mean 1.897 Å). In contrast to **2.8** and **2.11**, the eight-membered Cu_4N_4 ring in **2.9** is planar which results in a tetramer with C_{4h} symmetry. The Cu_4N_4 ring is also nearly perfectly square such that the coordination environment of the copper(I) ions in **2.9** are close to the preferred linear geometry with N–Cu–N bond angles of $178.46(5)^\circ$ (N1–Cu1–N2A) and $178.23(5)^\circ$ (N2–Cu2–N1), all the Cu–N–Cu bond angles are also close to right-angles at $88.37(4)^\circ$, and the Cu–N bond lengths are all similar in the narrow range between $1.9326(11)$ Å and $1.9447(11)$ Å. The solid-state structure of **2.9** is therefore similar to the previously reported structure of **2.10**, which was also determined to adopt a nearly planar Cu_4N_4 ring.^[31] Although no relationship between the N–Cu–N and Cu–N–Cu bond angles and ligand steric size was observed, a positive correlation between the

steric properties of the ligand and Cu–N bond distance was clear, with the C–N bond length increasing in the order **2.10** > **2.11** > **2.8** > **2.9** (Table 2.2).

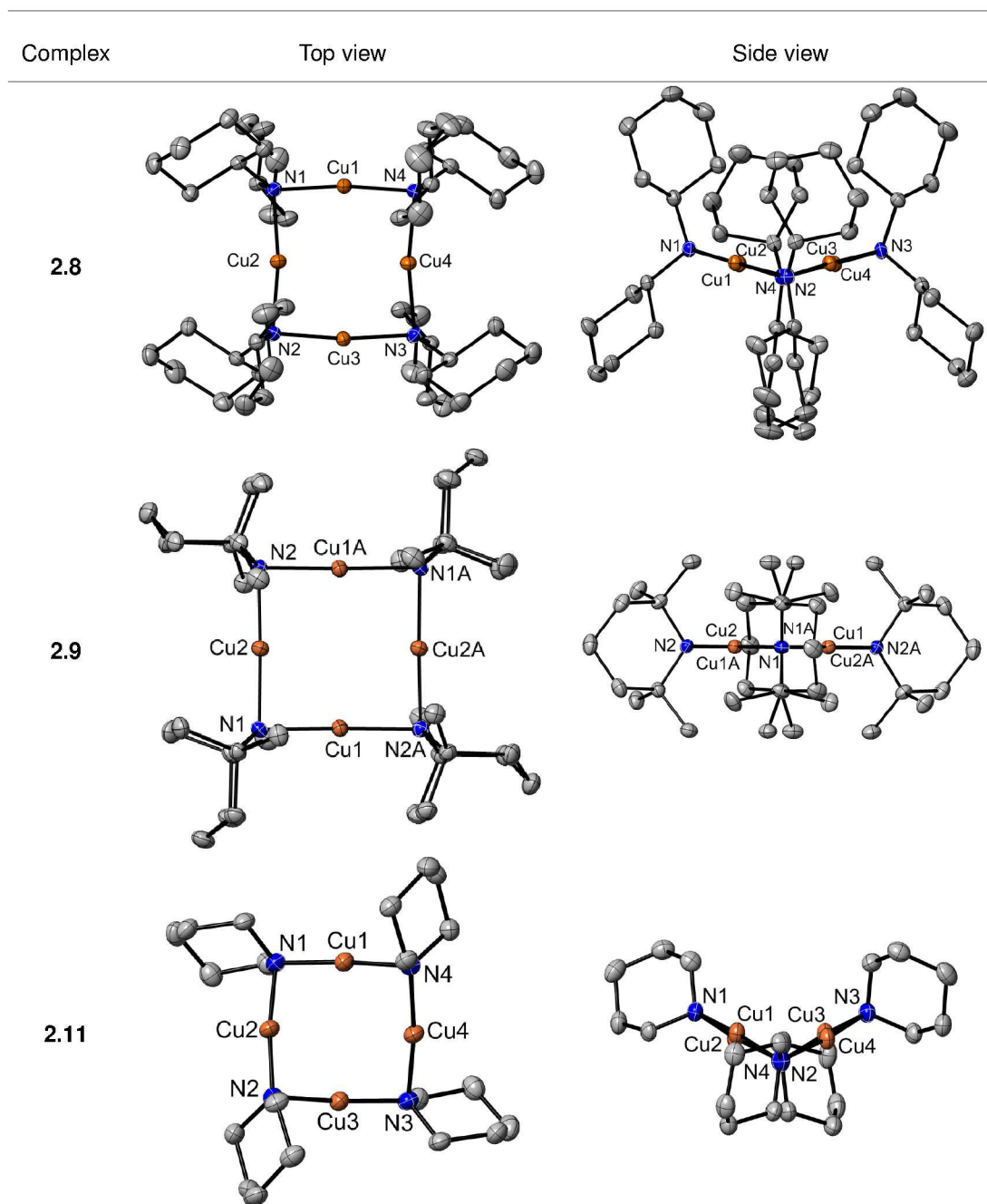


Figure 2.7: Views of solid-state structures of complexes **2.8**, **2.9** and **2.11** from orthogonal directions (50% probability ellipsoids). Hydrogen atoms are not shown for clarity.

<i>Complex 2.8</i>			
Cu1–N1	1.902(2)	N1–Cu1–N4	173.09(8)
Cu1–N4	1.902(2)	N2–Cu2–N1	171.85(9)
Cu2–N2	1.9347(19)	N2–Cu3–N3	172.62(8)
Cu2–N1	1.940(2)	N3–Cu4–N4	170.31(8)
Cu3–N2	1.9020(19)	Cu1–N1–Cu2	86.90(8)
Cu3–N3	1.9108(19)	Cu3–N2–Cu2	87.81(8)
Cu4–N3	1.9355(19)	Cu3–N3–Cu4	86.49(8)
Cu4–N4	1.939(2)	Cu1–N4–Cu4	86.83(8)
<i>Complex 2.9</i>			
Cu1–N1	1.9366(11)	N1–Cu1–N2A	178.46(5)
Cu1–N2A	1.9402(11)	N2–Cu–N1	178.23(5)
Cu2–N2	1.9326(11)	Cu1–N1–Cu2	88.37(4)
Cu2–N1	1.9447(11)	Cu1A–N2–Cu2	88.38(5)
Cu1A–N2	1.9402(11)		
<i>Complex 2.11</i>			
Cu1–N1	1.894(4)	N1–Cu1–N4	172.87(18)
Cu1–N4	1.904(5)	N2–Cu2–N2	171.66(19)
Cu2–N2	1.891(5)	N2–Cu3–N3	173.18(18)
Cu2–N1	1.898(4)	N3–Cu4–N4	171.8(2)
Cu3–N3	1.893(4)	Cu1–N1–Cu2	87.8(1)
Cu3–N2	1.907(5)	Cu2–N2–Cu3	87.2(2)
Cu4–N4	1.890(4)	Cu3–N3–Cu4	87.5(1)
Cu4–N3	1.902(4)	Cu4–N4–Cu1	87.3(2)

Table 2.1: Selected bond lengths (Å) and angles (°) in complexes **2.8**, **2.9** and **2.11**.

Complex	Cu–N (Å)	N–Cu–N (°)	N–Cu–N (°)
2.8	1.921	171.97	87.01
2.9	1.939	178.35	88.38
2.10 ^[a]	1.885	177.05	92.22
2.11	1.897	172.38	87.50

Table 2.2: Comparison of mean Cu–N bond lengths, N–Cu–N and Cu–N–Cu bond angles in the solid-state tetrameric copper(I) amide structures. ^[a] Taken from Reference [31].

2.2.3 Reaction of CuMes with piperidine

The reaction between CuMes and amines to give copper(I) amides was investigated to identify why sterically bulky complexes **2.8** and **2.9** could not be formed using this method (Route B, Scheme 2.5). In the preparation of complex **2.11**, when a solution of CuMes in THF is treated with piperidine a yellow precipitate initially formed. With prolonged stirring at room temperature the yellow precipitate then dissolved to give a clear solution, from which a white precipitate of the desired complex **2.11** formed. The ^1H NMR spectrum in benzene- d_6 of the initial yellow precipitate revealed a 2 : 1 ratio of CuMes and piperidine with the piperidine N–H proton still present at $\delta = 0.47$ ppm. Compared to free piperidine, the piperidine proton resonances in the ^1H NMR spectrum had shifted upfield and therefore suggested that the isolated material was an intermediate with the amine coordinated to a copper(I) centre. Structural data of this intermediate was obtained by growing suitable yellow crystals from the initial reaction mixture and then analysing using single-crystal X-ray diffraction. The analysis showed that the intermediate was the organocopper species $[\text{Cu}_4(\text{Mes})_4(\text{HNC}_5\text{H}_{10})_2]$ and that it was present as two

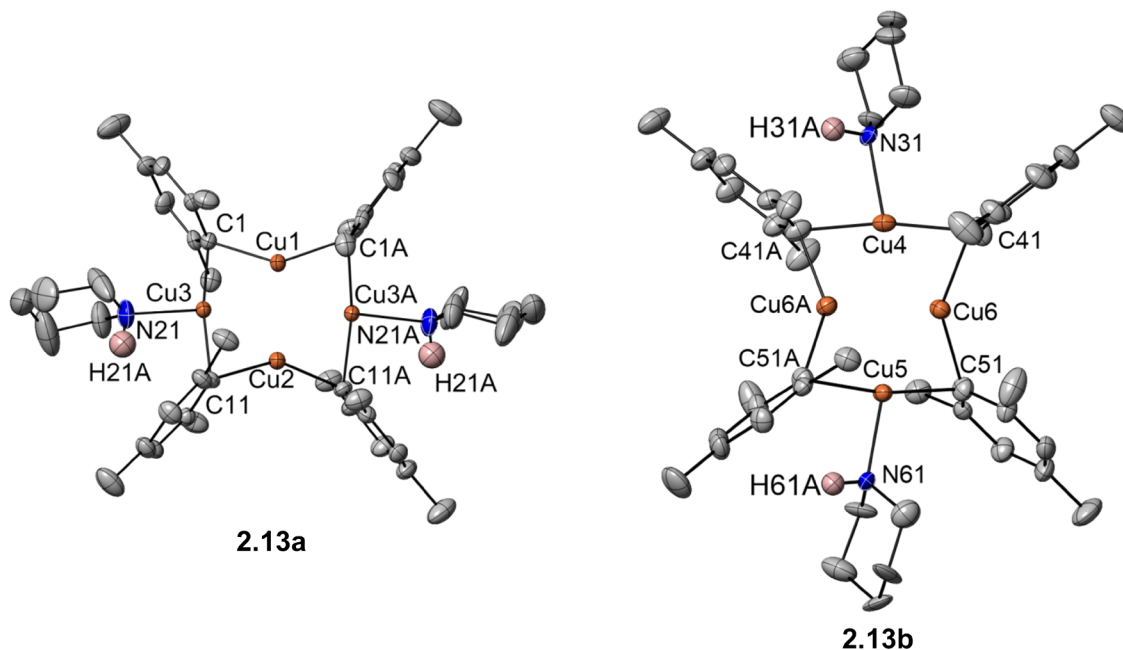


Figure 2.8: Solid-state structures of the two crystallographically independent molecules of **2.13** that differ by the orientation of the C_2 axis determined by X-ray crystallography (50% probability ellipsoids). The N–H hydrogen atoms could not be located by X-ray crystallography and so were added in idealised positions at an N–H distance of 0.90 Å.

crystallographically independent molecules **2.13a** and **2.13b** (Figure 2.8). NMR spectroscopy data of a crystallised sample of **2.13a** and **2.13b** is identical to that of the previously isolated precipitate which confirmed they were the same species. The two independent molecules with C_2 symmetry can be differentiated by the orientation of the C_2 axis, with it either passing through the short diagonal between Cu1 and Cu2 of the Cu₄ rhombus in **2.13a** or long diagonal between Cu4 and Cu5 in **2.13b**. Other than this, the bond lengths and angles of **2.13a** and **2.13b** in Table 2.3 are similar in both independent molecules.

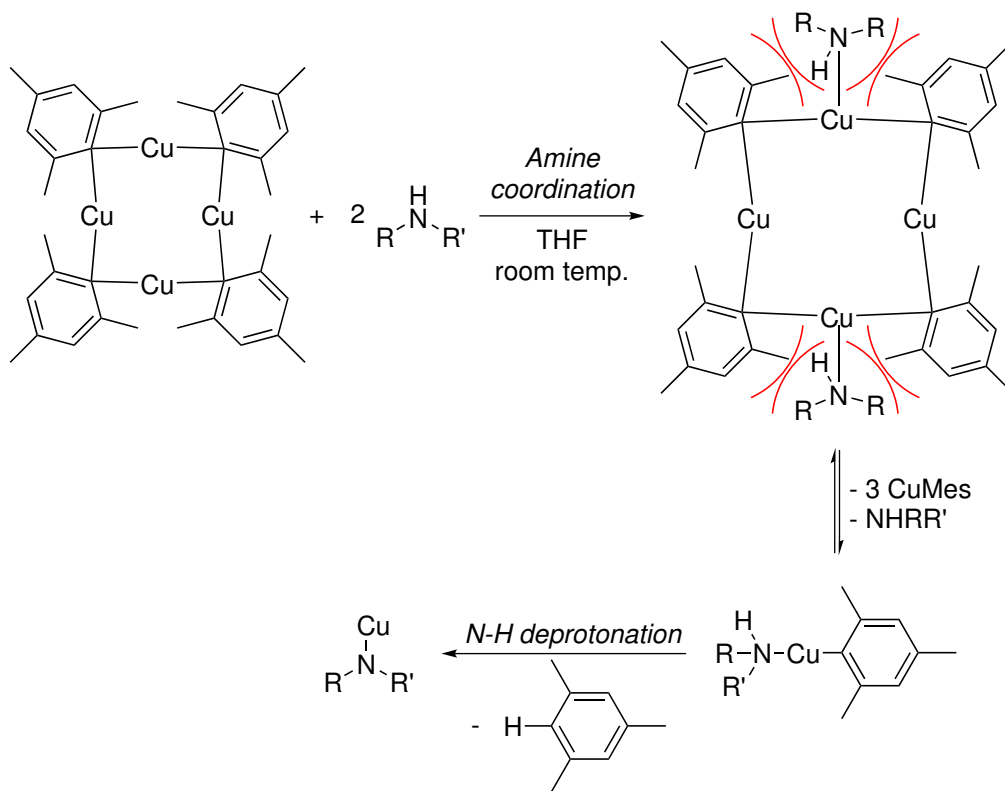
<i>Complex 2.13a</i>			
Cu1–C1	2.029(6)	Cu1–C1–Cu3	73.64(19)
Cu1–C1A	2.029(6)	Cu2–C11–Cu3	73.74(18)
Cu2–C11	2.010(6)	C1–Cu1–C1A	143.3(3)
Cu2–C11A	2.010(6)	C1–Cu3–C11	170.2(2)
Cu3–C1	2.050(6)	C11A–Cu2–C11	142.0(3)
Cu3–C11	2.079(6)		
Cu3–N21	2.133(5)		
<i>Complex 2.13b</i>			
Cu4–C41	2.059(6)	Cu6–C41–Cu4	73.9(2)
Cu4–C41A	2.059(6)	Cu6–C51–Cu5	74.4(2)
Cu5–C51	2.059(6)	C41A–Cu4–C41	169.9(3)
Cu5–C51A	2.059(6)	C51A–Cu5–C51	168.4(4)
Cu6–C41	2.006(6)	C51–Cu6–C41	142.8(3)
Cu6–C51	1.997(7)		
Cu4–N31	2.133(9)		
Cu5–N61	2.155(8)		

Table 2.3: Selected bond lengths (Å) and angles (°) in complex **2.13a** and **2.13b**.

X-ray crystallographic data of CuMes show that it exists as either a tetramer or pentamer in the solid state, with eight-membered Cu₄C₄ or ten-membered Cu₅C₅ rings respectively.^[35] Previous studies involving the addition of coordinating sulphur-based compounds, such as tetrahydrothiophene,^[36] allyl methyl sulphide or 2,5-dithiahexane,^[37] have been shown to give complexes with a general formula of [Cu₄Mes₄L₂], where L is the added monodentate ligand. In these structures, the neutral sulphur ligands coordinate to copper(I) ions on opposite sides of the eight-membered Cu₄C₄ ring. Therefore, the structures of these reported [Cu₄Mes₄L₂]

complexes are in agreement with the observed structure of **2.13a** and **2.13b** where L is $\text{HNC}_5\text{H}_{10}$. **2.13** also represents the first structurally characterised organocopper(I) complex with secondary amine coordination.

The nitrogen donors in **2.13a** and **2.13b** adopt tetrahedral conformations with significantly longer Cu–N bond lengths than those reported in complex **2.11** (**2.13a** and **2.13b**, range 2.133(5) – 2.155(8) Å; **2.11**, range 1.890(4) – 1.907(5) Å). Like the $[\text{Cu}_4\text{Mes}_4\text{L}_2]$ complexes ligated by sulphur-based compounds,^[36,37] slight puckering of the Cu_4C_4 ring is observed in **2.13a** and **2.13b**, which contrasts with the square Cu_4 arrangement in $[\text{Cu}_4\text{Mes}_4]$.^[35] The mean Cu–C bond length exhibited by the three-coordinate copper(I) centres (Cu3, Cu3A, Cu4 and Cu5 in Figure 2.8) in **2.13a** and **2.13b** (2.062 Å (range 2.050(6) – 2.079(6) Å)) is longer than the mean Cu–C bond length exhibited by the two-coordinate copper(I) centres (Cu1, Cu2, Cu6 and Cu6A in Figure 2.8) (mean 2.011 Å; range 1.997(7) – 2.029(6) Å). Furthermore, the Cu–C bond lengths in **2.13a** and **2.13b** are significantly longer than in the non-ligated $[\text{Cu}_4\text{Mes}_4]$ complex



Scheme 2.6: Possible reaction mechanism for the synthesis of copper(I) amide complexes from CuMes via a $[\text{Cu}_4\text{Mes}_4(\text{NHRR}')_2]$ intermediate and a possible $[\text{CuMes}(\text{NHRR}')]_2$ complex. Possible steric crowding using sterically bulky NHRR' shown in red.

(mean Cu-C distance of $[\text{Cu}_4\text{Mes}_4]$ 1.993 Å; range 1.986(10) – 1.999(9) Å).^[35]

Structural characterisation of **2.13a** and **2.13b** is therefore in agreement with the compound being an intermediate in the reaction between CuMes and piperidine to give **2.11**. Piperidine coordination to copper(I) of the $[\text{Cu}_4\text{Mes}_4]$ species initially occurs, followed by subsequent N–H deprotonation by the mesityl ligand to yield **2.11** and mesitylene. Therefore, it is likely that potentially significant steric crowding around the copper(I) centres caused by coordination of the sterically bulky dicyclohexylamine and 2,2,6,6-tetramethylpiperidine prevented the formation of similar $[\text{Cu}_4\text{Mes}_4(\text{NHRR}')_2]$ complexes (Scheme 2.6). Further evidence for this is the proton resonances in the ^1H NMR spectrum of a 1 : 1 mixture of dicyclohexylamine and CuMes in benzene- d_6 (Figure 2.9a) are present at similar chemical shifts to the pure compounds

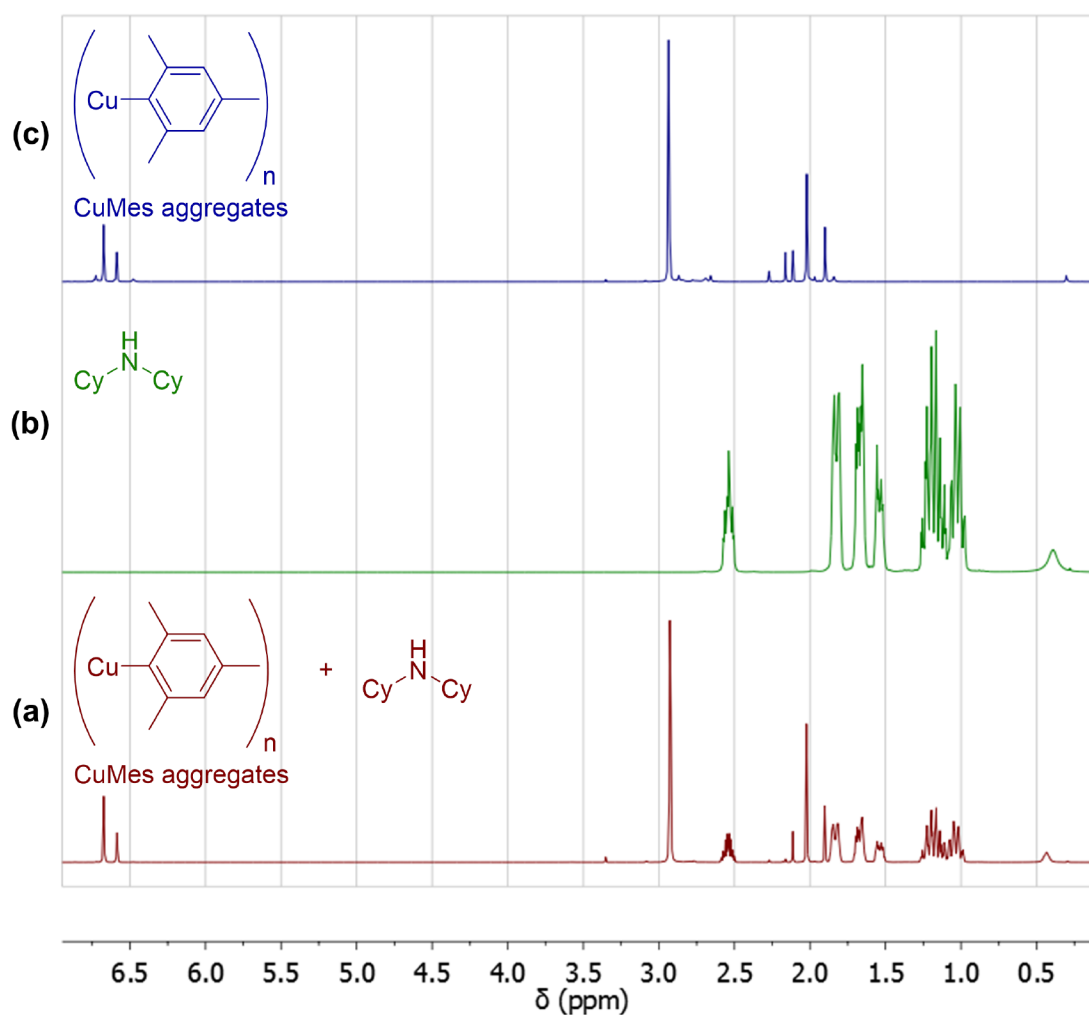


Figure 2.9: Comparison of the ^1H NMR spectra in benzene- d_6 of (a) a 1 : 1 mixture of CuMes and dicyclohexylamine, (b) pure dicyclohexylamine and (c) CuMes alone.

(Figure 2.9b and c). This confirms that significant amine coordination to $[\text{Cu}_4\text{Mes}_4]$ to give $[\text{Cu}_4\text{Mes}_4(\text{NCy}_2)_2]$ does not occur when using sterically bulky dicyclohexylamine and therefore explains the failure of Route B, Scheme 2.5 to prepare the sterically bulky complexes **2.8** and **2.9**. If $[\text{Cu}_4\text{Mes}_4(\text{NHRR}')_2]$ was the only intermediate in this reaction, the product yield would be restricted to a maximum of 50%. However as greater than 50% yield of complexes **2.11** and **2.12** were obtained using Route B, Scheme 2.5, the $[\text{Cu}_4\text{Mes}_4(\text{NHRR}')_2]$ complex is likely in equilibrium with a short-lived reactive complex that may be $[\text{CuMes}(\text{NHRR}')]_4$ (Scheme 2.6).

2.2.4 Solution behaviour of copper(I) amide complexes using ^1H DOSY NMR

Characterisation of the solution behaviour of copper(I) amide complexes, in addition to the solid-state structures, is crucial to understanding the role of these complexes in the Ullmann amination reaction. ^1H diffusion-ordered NMR spectroscopy (^1H DOSY NMR) has been successfully used in the recent characterisations of various organometallic aggregates.^[38–44] and was predominantly used to identify the aggregate species that are present in solution for these complexes. Reported methods in the literature typically involve determining the diffusion coefficients (D) of the aggregate species in solution by DOSY NMR spectroscopy and then correlating the D values to empirical formula weights (FW_{obs}) or observed radii (r_{obs}) of the solution aggregates. The aggregate species can then be identified by comparing FW_{obs} or r_{obs} to the predicted formula weights (FW_{calc}) or calculated radii (r_{calc}) of possible solution species respectively (see Section 2.4.9 for full details). These methods have been reported to work well with approximately spherical organometallic complexes containing lighter metals, such as lithium,^[40] which tend to have consistently low densities of approximately 1 g cm^{-3} . Given that D can be affected by factors such as viscosity and temperature, internal standards (1,2,3,4-tetraphenylnaphthalene, 1-phenylnaphthalene and tetramethylsilane) were used to correct for these effects.

In the ^1H DOSY NMR spectra for complexes **2.10** and **2.11**, three sets of amido ligand resonances with different D values are present in the ^1H DOSY NMR spectra for both complexes (for example, see Figure 2.10a for complex **2.10**). This suggests that the equilibrium between aggregation states was slower than the NMR time-scale at room temperature. In comparison for complexes **2.8**, **2.9** and **2.12**, only one D value was observed for the amido ligand resonances in each case (for example, see Figure 2.10b for complex **2.8**). This suggests that either there is only one aggregation state present in solution, or the equilibrium between aggregates was faster

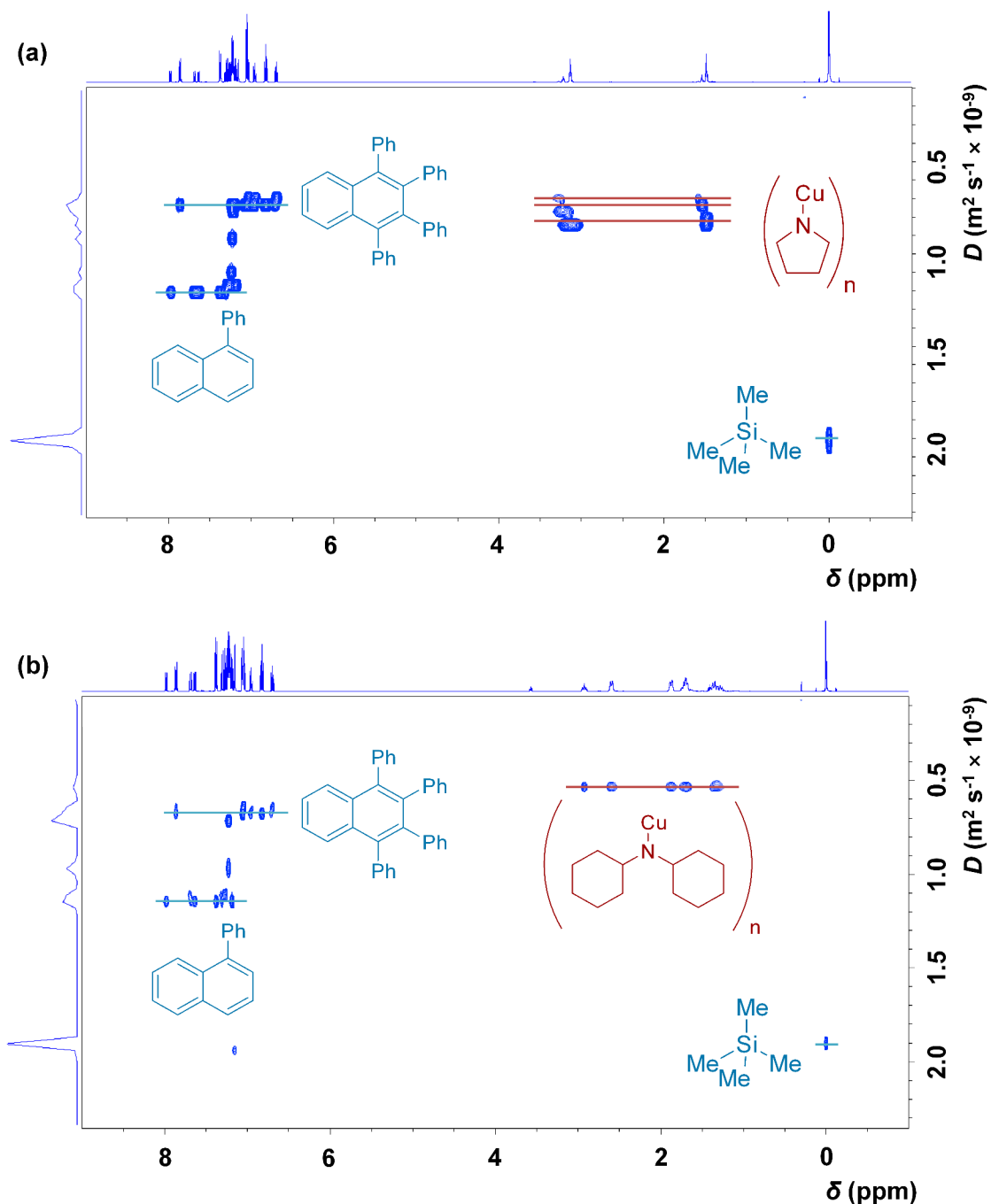


Figure 2.10: ^1H DOSY NMR spectrum of a) complex **2.10** (0.05 M) and b) complex **2.8** (0.05 M) in benzene- d_6 in the presence of 1,2,3,4-tetraphenylnaphthalene, 1-phenylnaphthalene, and tetramethylsilane as internal standards.

than the NMR time-scale at room temperature. When the concentration of **2.8**, **2.9** and **2.12** was increased, the D value from the ^1H DOSY NMR spectra for each complex decreased (increase in $FW_{\text{obs}} / r_{\text{obs}}$) which suggests that the latter of these possibilities was correct, i.e. fast solution

equilibrium between aggregates. Overall, these spectra indicate that the equilibrium rates between the three distinct aggregation states with different FW_{obs} / r_{obs} values for complexes **2.10** and **2.11** are significantly slower than those observed for **2.8**, **2.9** and **2.12**.

The FW_{obs} values for the solution aggregates of the relatively slow equilibrating complexes **2.10** and **2.11** determined from the ^1H DOSY NMR spectra are shown in Table 2.4. Using this method the dimer, trimer and tetramer aggregate states for **2.10** and **2.11** fit best with the experimental data but there is a large difference between the FW_{obs} and FW_{calc} values (between -15.4% and +37.5%) in some cases.^[45] Therefore this method is not suitable for identifying the copper(I) amides aggregates in solution. As noted previously, employing ^1H DOSY NMR spectroscopy to relate FW to D has been predominantly used for identifying approximately spherical organolithium complexes which typically have low and consistent densities of approximately 1 g cm^{-3} . However, organocopper(I) complexes incorporating the heavier copper element leads to larger variation in density, where they range from 1.324 to 1.659 g cm^{-3} for complexes **2.8** – **2.11**.^[46] This is likely the cause of the large error when using this method for identifying the solution aggregates of **2.10** and **2.11**.

Complex		FW_{calc}	FW_{obs} at 0.05 M	FW_{obs} at 0.20 M
2.10	Tetramer	535	474 (- 11.3%)	453 (- 15.4%)
	Trimer	401	406 (+ 1.3%)	417 (+ 3.9%)
	Dimer	267	352 (+ 31.6%)	333 (+ 24.6%)
2.11	Tetramer	591	570 (- 3.5%)	570 (- 3.5%)
	Trimer	443	476 (+ 7.4%)	477 (+ 7.6%)
	Dimer	295	376 (+ 27.4%)	406 (+ 37.5%)

Table 2.4: Comparison of the predicted and observed FW 's of the distinct copper(I) amide aggregates for complexes **2.10** and **2.11** in benzene- d_6 solutions determined using ^1H DOSY NMR spectroscopy. Percentage differences from expected FW_{calc} values for the FW_{obs} values are shown in parentheses.

In contrast when the method that relates aggregate radii to D was used to determine the solution aggregates of complexes **2.10** and **2.11**, all observed r_{obs} values were within $\pm 6\%$ of the r_{calc} values of the trimer, tetramer and pentramer states (Table 2.5),^[47] which is well within the error margins reported for structure identification by DOSY NMR spectroscopy in the literature.^[38] Therefore this method is more suitable for characterising the solution aggregates of copper(I) amides. By integrating each aggregates' proton resonances in the ^1H NMR spectra

Complex		r_{calc} (Å)	r_{obs} at 0.05 M (Å)	r_{obs} at 0.20 M (Å)
2.10	Pentamer	6.04	5.88 (- 2.7%)	5.80 (- 4.0%)
	Tetramer	5.65	5.65 (+ 0.1%)	5.68 (+ 0.7%)
	Trimer	5.15	5.45 (+ 6.0%)	5.38 (+ 4.4%)
2.11	Pentamer	6.37	6.16 (- 3.3%)	6.16 (- 3.4%)
	Tetramer	5.98	5.89 (+ 0.0%)	5.89 (+ 0.0%)
	Trimer	5.38	5.55 (+ 3.2%)	5.65 (+ 5.2%)

Table 2.5: Comparison of the calculated and observed radii of the distinct copper(I) amide aggregates for complexes **2.10** and **2.11** in benzene- d_6 solutions determined using ^1H DOSY NMR spectroscopy. Percentage differences from expected r_{calc} values for the r_{obs} values are shown in parentheses.

of **2.10** and **2.11**, the relative abundance of the aggregates can be determined for a certain concentration. From these values, the mean aggregation state can then be estimated. When the monomer concentration is 0.05 M, the mean aggregation numbers for **2.10** and **2.11** were calculated to be 3.2 and 3.1 respectively. On increasing the concentration to 0.20 M, the same three aggregation states with similar r_{obs} values were still detected (Table 2.5). However, in both **2.10** and **2.11** the integrals of the tetramer and pentamer ^1H NMR resonances had increased relative to those of the trimer resonances. For example, the relative integrations of the trimer : tetramer : pentamer aggregates of **2.10** changed from 1.00 : 0.25 : 0.07 at 0.05 M to 1.00 : 0.31 : 0.11 at 0.20 M. ^[48] Overall, increasing the concentration from 0.05 to 0.20 M resulted in the mean aggregation number of **2.10** increasing from 3.2 to 3.3 and that of **2.11** from 3.1 to 3.3.

The solution aggregate data for the rapidly equilibrating complexes **2.8**, **2.9** and **2.12** are shown in Table 2.6. The average aggregate number, n , for these complexes were estimated by assuming the radii increases linearly between aggregation states. This approximation is valid because the r_{calc} values of the DFT optimised aggregates for **2.8** – **2.12** are almost directly proportional to the aggregate number, where linear regression analysis of r_{calc} vs. n charts produce r^2 values greater than 0.97.^[49] At 0.05 M concentration, the r_{obs} values of 6.28 and 5.77 Å for complexes **2.8** and **2.9** respectively correlate to average aggregation numbers of 2.5 for complex **2.8** and 2.4 for complex **2.9**. This indicates that the equilibrium is predominantly between the dimeric ($n = 2$) and trimeric ($n = 3$) aggregation states in complexes **2.8** and **2.9** at 0.05 M concentration. The r_{obs} value of 5.88 Å and aggregation number of $n = 3.5$ determined

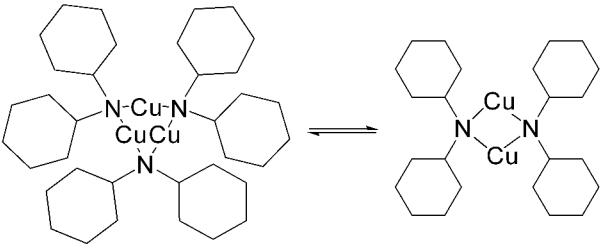
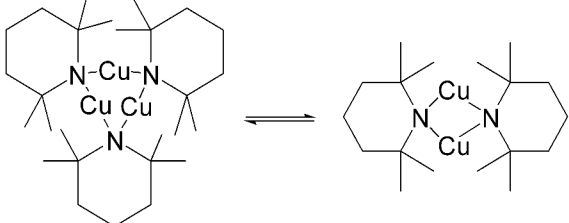
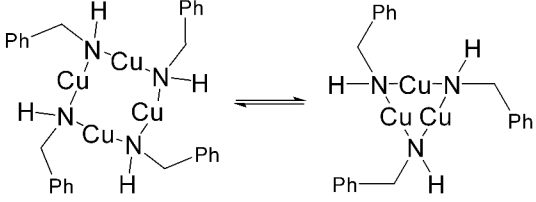
Complex	Conc. (M)	r_{obs} (Å)	Average aggregation number, n	Predominant equilibria inferred from r_{obs}	
2.8	0.05	6.28	2.5		Trimer $r_{calc} = 6.65 \text{ Å}$ Dimer $r_{calc} = 5.89 \text{ Å}$
	0.15	6.31	2.6		
2.9	0.05	5.77	2.4		Trimer $r_{calc} = 6.21 \text{ Å}$ Dimer $r_{calc} = 5.50 \text{ Å}$
	0.10	5.89	2.5		
2.12	0.01	5.78	3.3		Tetramer $r_{calc} = 6.15 \text{ Å}$ Trimer $r_{calc} = 5.62 \text{ Å}$
	0.05	5.88	3.5		

Table 2.6: Comparison of calculated and experimentally determined radii of copper(I) amide aggregates of **2.8**, **2.9** and **2.12** in benzene- d_6 solutions determined using ^1H DOSY NMR spectroscopy.

for complex **2.12** at 0.05 M concentration indicates that it exists in equilibrium predominantly between trimeric and tetrameric forms. A positive correlation between the copper(I) amide concentration and the r_{obs} values was observed, although the usable concentration range was restricted by the limited solubility of the complexes in benzene- d_6 at the higher end and the resolution of the NMR spectrometer at the lower end.

The different equilibrium rates between solution aggregates of the copper(I) amide complexes could be a result of different Cu–N bond strengths. From Table 2.2, the shorter, stronger Cu–N bonds in **2.10** and **2.11** may have resulted in slow equilibrium rates and thus caused observable

distinct aggregates by NMR spectroscopy. This is in contrast to **2.8** and **2.9** which have longer, weaker Cu–N bonds and therefore resulted in faster equilibrium rates. The steric bulk of the amido ligands in **2.8** – **2.12** can also be related to the observed aggregation numbers by using the mean cone angles of the ligands, where the cone angle is defined with the copper(I) ion at the vertex and the perimeter of the cone passing through the centre of the outermost hydrogen atoms.^[50] The cone angles for **2.8** – **2.12** were measured from the tetrameric solid-state structures from X-ray crystallography and also the DFT optimised structures (Table 2.7). The small range of Cu–N bond lengths in the [Cu(NRR')]₄ solid-state and DFT optimised

Complex	Mean cone angle of [Cu(NRR')] ₄ from solid-state (°)	Mean cone angle of DFT optimised [Cu(NRR')] ₄ (°)	Mean aggregation number, <i>n</i>
2.8	130.6	135.2	2.5
2.9	129.9	136.4	2.4
2.10	83.0 ^[a]	86.2	3.2
2.11	87.1	90.3	3.1
2.12	N/A	63.1	3.5

Table 2.7: Comparison of cone angles of the ligands in the tetrameric copper(I) amide structures as determined from solid-state structures and also measured from DFT optimised structures with the aggregation numbers determined in benzene-d₆ solution at 0.05 M concentration.

^[a] Taken from reference [31].

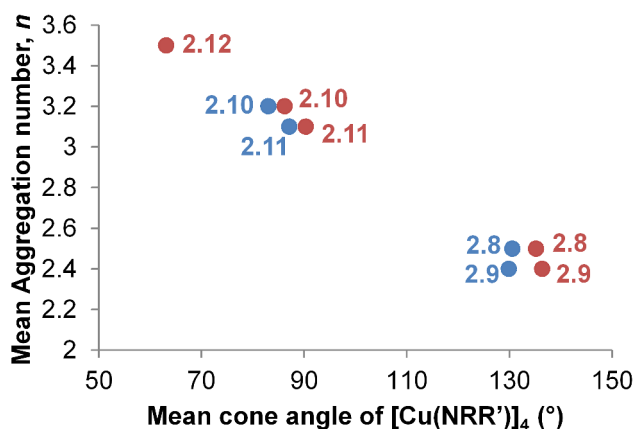


Figure 2.11: Plot of aggregation numbers in benzene-d₆ solution at 0.05 M concentration against measured cone angles of the solid-state and DFT optimised tetrameric copper(I) amide structures. Red circles: solid-state; Blue circles: DFT.

structures for complexes **2.8** – **2.12** (mean Cu–N bond length range 1.885–2.028 Å) ensure that comparison of the cone angles measured directly from these structures is valid. As shown in Figure 2.11, the complexes with more sterically bulky amido ligands such as NCy₂ and TMP (**2.8** and **2.9** respectively) have larger cone angles than complexes with less sterically bulky amides such as N(H)CH₂Ph in **2.12**, and are present in lower aggregation states.

To summarise, although copper(I) amide complexes have been found to be present exclusively as tetramers in the solid state, NMR spectroscopy studies have shown that they adopt different aggregation states in benzene-d₆ with mean aggregation numbers between 2.4 and 3.5 depending upon the concentration. The equilibrium rate between aggregation states in solution was proposed to be related to the Cu–N bond strength, with shorter, stronger bonds resulting in lower rates and longer, weaker bonds giving higher rates. Unfortunately, due to the insolubility of copper(I) amide complexes in DMSO-d₆, similar NMR spectroscopy studies could not be carried out in this solvent.

2.2.5 Reactivity of copper(I) amides in aryl amination

To ascertain the intermediacy of ancillary ligand-free copper(I) amides in the Ullmann amination reaction, complexes **2.8** – **2.12** were reacted stoichiometrically with iodobenzene at 80 °C in

Complex **2.8** - **2.12** + $\xrightarrow[80\text{ }^{\circ}\text{C}, 18\text{ h}]{\text{Benzene-d}_6 \text{ or DMSO-d}_6}$

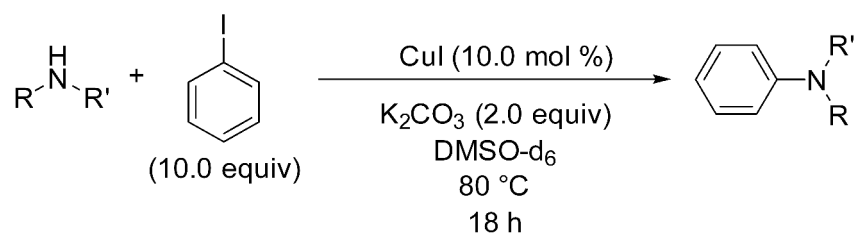
(1.5 equiv)

Complex	Benzene-d ₆ solvent % Yield	DMSO-d ₆ solvent % Yield
2.8	0	0
2.9	0	0
2.10	48	75
2.11	96	87
2.12	7	77

Table 2.8: Yields obtained in ancillary ligand-free stoichiometric reactions according to the scheme above. Yields were determined by ¹H NMR spectroscopy using mesitylene as an internal standard.

both benzene-d₆ and DMSO-d₆ to investigate their reactivity (Table 2.8). The copper(I) amides **2.8** and **2.9** failed to give any product when heated with iodobenzene in either solvent. Steric hindrance caused by the bulky amido ligands was the likely cause for the lack of reactivity. The less bulky complex **2.10** exhibited coupling reactivity in both solvent systems with higher yields in DMSO-d₆ (75%) than in benzene-d₆ solvent (48%). As well as the C–N coupled product, the β -hydride elimination product, 1-pyrroline, was also formed as a side-product in 10% yield in benzene-d₆ and 6% yield in DMSO-d₆. A significant amount of unidentified black solid was also produced, which likely accounts for the remaining amine mass balance. Benzene-d₆ solutions of **2.10** at the same concentration were observed to be sensitive to thermal decomposition at room temperature and above to give pyrrolidine, 1-pyrroline, and an unknown black solid even under a nitrogen atmosphere. Therefore, the side products in the stoichiometric reaction were likely formed due to thermal decomposition. Complex **2.11** has significantly better thermal stability than **2.10** and therefore underwent almost quantitative conversion to give the desired product in benzene-d₆ (96% yield). In comparison, the reaction with iodobenzene in DMSO-d₆ gave a slightly reduced arylamine yield of 87% with some piperidine side-product also observed (8% yield). Although **2.12** is the least sterically hindered of the studied copper(I) amides, its reaction with iodobenzene in benzene-d₆ yielded only 7% product. This was due to the instability of **2.12** in benzene-d₆ solutions, where it rapidly undergoes thermal decomposition to give benzylamine and an unidentified insoluble red precipitate as side-products. For example, experiments revealed benzene-d₆ solutions of **2.12** at the same concentration as that used in the stoichiometric reaction had only 68% of **2.12** remaining with 5% conversion to benzylamine after one hour at room temperature. After one hour at 80 °C, the decomposition is more substantial with only 24% of **2.12** remaining with 24% benzylamine. The remaining 27% and 52% undetected amine at room temperature and 80 °C respectively is likely accounted for by the unidentified insoluble red precipitate that forms by thermal decomposition. However when DMSO-d₆ was used as the reaction solvent, the coupling yield using **2.12** improved significantly to 77% with only small quantities of benzylamine formed (6%).

As previously reported by Hartwig^[5] and Ribas^[51], the formation of amine side-products from the stoichiometric reactions likely originated from abstraction of a proton from adventitious water or a solvent molecule. The mass balance between the arylamine product yield and iodobenzene conversion differed by less than 7% in both solvents and so was generally quite good. As stated in Section 2.2.4, the solubility of the studied copper(I) amide complexes are poor in DMSO-d₆,



Entry	HNRR'	% Yield
1		0
2		0
3		68
4		51
5		89

Table 2.9: Yields obtained in the catalytic reactions according to the scheme above. Yields were determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

which in turn makes it difficult to identify if the stoichiometric reactions occurred hetero- or homogeneously using this solvent.

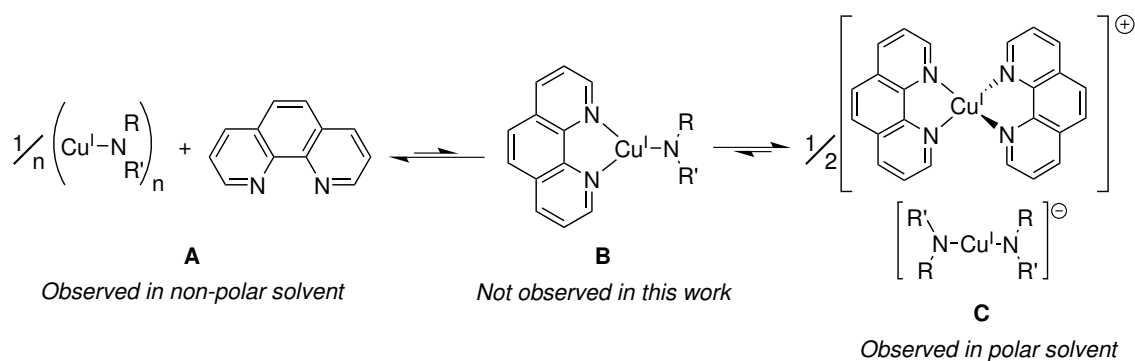
Catalytic reaction between the corresponding amines of copper(I) amides **2.8** – **2.12** and iodobenzene were also performed using 10.0 mol % of copper(I) iodide as the catalyst and two equivalents of potassium carbonate as the base. When benzene- d_6 was used as the solvent, no catalytic reactivity was observed in all cases. This was likely due to the insolubility of the base and copper(I) iodide catalyst in this solvent. Polar aprotic solvents such as DMSO^[17,20,52–55] and DMF^[56–60] are commonly used in literature Ullmann amination protocols to aid in the dissolution of the base and catalyst. The copper(I) iodide catalyst employed in this work is soluble in DMSO- d_6 and as a result catalytic reactivity between the amines and iodobenzene was observed in most cases using this as the reaction solvent (Table 2.9).

Analogous to the stoichiometric reactions of **2.8** and **2.9** with iodobenzene, the sterically hindered dicyclohexylamine and 2,2,6,6-tetramethylpiperidine substrates gave no cross-coupled product (Table 2.9, entries 1 and 2). The best reactivity was observed using the least sterically bulky primary benzylamine (89% yield, Table 2.9, entry 5), whereas moderate yields of 68% and 51% had formed using the cyclic secondary amines pyrrolidine and piperidine respectively (Table 2.9, entries 3 and 4). Overall, the similar or slightly higher yields obtained from the stoichiometric reactions compared to the catalytic reactions using the corresponding amines is consistent with the copper(I) amide complexes being competent intermediates in the Ullmann amination reaction. The stoichiometric reactivity observed with complexes **2.10** – **2.12** are also the first reported examples of ancillary ligand-free copper(I) amides reacting with aryl halides. In addition, the lack of reactivity shown by complexes **2.8** and **2.9** provides evidence that the poor catalytic reactivity exhibited by secondary acyclic amine substrates may be due to inhibition of the aryl halide activation step rather than hindered copper(I) amide formation.

2.2.6 Identification of solution structures of complexes **14** and **15** in the presence of 1,10-phenanthroline

As shown in Section 1.3, Chapter 1, many different ancillary ligands have been used for improving the reaction rate in the modified Ullmann reaction. One of the most utilised and mechanistically studied ligands is phen.^[4–7,61–64] Despite this, previous studies in the literature all focus on phen as the ancillary ligand in the *N*-arylation of arylamines and not alkylamines, which typically employ α -amino acid^[52,53] or 1,3-diketone^[56,65,66] ligands. Therefore in order to understand the potential influence of phen on the structure and catalytic reactivity of alkylamines with aryl halides, the interactions between phen and copper(I) amides were investigated.

Copper(I) amide complexes **2.10** and **2.11** were selected to be studied with phen as they are relatively stable in solution and also demonstrated the best stoichiometric reactivity with iodobenzene. Attempts to isolate phen-ligated copper(I) amide species synthesised from 1 : 1 mixtures of phen and **2.10** or **2.11** from THF or toluene by evaporation all resulted in decomposition. Furthermore, attempts to crystallise the phen-ligated copper(I) amide species also failed. Therefore, the studies herein focus on understanding the solution behaviour of these species generated *in situ* after addition of phen to **2.10** or **2.11**. When complexes **2.10** or **2.11** were treated with one equivalent of phen in benzene- d_6 , the colourless copper(I) amide solutions immediately turned deep-blue in colour. Although the colour change on addition of

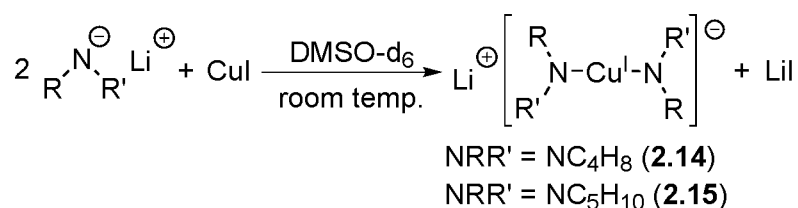


Scheme 2.7: Equilibrium between the neutral catalyst resting state **B** and an ionic species **C** when phen is used as an ancillary ligand with **2.10** or **2.11**.

phen suggests that coordination to copper(I) had occurred,^[67] the copper(I) amide resonances in the ^1H NMR spectra of the resultant solutions were unchanged. Furthermore, the chemical shifts of the phen resonances had increased by less than 0.05 ppm compared to free phen. ^1H DOSY NMR analyses also revealed r_{obs} values that were consistent with the ligand-free aggregates of **2.10** or **2.11** and uncoordinated phen ($r_{\text{obs}} = 4.51 \text{ \AA}$, cf. $r_{\text{calc}} = 4.40 \text{ \AA}$).^[68] Ionic species of general formula $[\text{Cu}(\text{phen})_2]^+[\text{Cu}(\text{NRR}')_2]^-$ (**C**, Scheme 2.7), analogous to those observed by Hartwig and co-workers (Figure 2.2), have previously been proposed to be in equilibrium with neutral $[(\text{phen})\text{Cu}(\text{NRR}')]_2$ complexes (**B**, Scheme 2.7) (see Section 2.1.1.1 for more details)^[4,5], but ionic species from phen mixtures of **2.10** or **2.11** were also not detected by NMR spectroscopy in this solvent. Overall, the NMR spectroscopy results indicate that the equilibrium for binding phen lies almost exclusively on the side of the ligand-free copper(I) amide and free phen in non-polar benzene- d_6 solvent (**A**, Scheme 2.7). The solutions of **2.10** or **2.11** in the presence of phen were also found to be unstable over time at room temperature. For copper(I) amide **2.11** two hours after the addition of phen, 81% of the complex remained and after 18 hours, only 46% remained with noticeable amounts of copper(0) also now present. Conversely, the quantities of **2.10** and **2.11** alone in benzene- d_6 remained virtually unchanged after similar storage for 19 hours.

Although complexes **2.10** and **2.11** are insoluble in DMSO- d_6 , the addition of one equivalent of phen allowed complete dissolution of the copper(I) amide to give deep-red coloured solutions. ^1H NMR spectra of these DMSO- d_6 solutions contained one set of phen resonances which had shifted significantly compared to free phen and therefore suggested that phen coordination had occurred to give either the neutral $[(\text{phen})\text{Cu}(\text{NRR}')]_2$ or an ionic $[\text{Cu}(\text{phen})_2]^+[\text{Cu}(\text{NRR}')_2]^-$

species (**B** or **C** respectively in Scheme 2.7). To determine which species was likely present, the reactions between two equivalents of lithium pyrrolidide or piperidide with copper(I) iodide to prepare lithium di(amido)cuprates **2.14** and **2.15** respectively were performed (Scheme 2.8). When the ^1H NMR spectra of **2.10** with phen and **2.14** (Figure 2.12), and **2.11** with phen and **2.15** (Figure 2.13) were compared, almost identical chemical shifts for the amido ligand protons were observed. This suggests that the same di(amido)cuprate anion was present in both cases. ESI-MS analysis of complex **2.11** with phen in DMSO and benzene solvent revealed cationic $[\text{Cu}(\text{phen})_2]^+$ (423.0 m/z , positive mode) and anionic $[\text{Cu}(\text{NC}_5\text{H}_{10})_2]^-$ (230.8 m/z , negative mode) species, which is in agreement with the NMR data in DMSO-d_6 .^[69] A possible higher aggregate amidocuprate species, $[\text{Cu}_4(\text{NC}_5\text{H}_{10})_5]^-$, was also detected by ESI-MS as a set of ions around



Scheme 2.8: Reaction scheme for the synthesis of lithium di(amido)cuprates **2.14** and **2.15**.

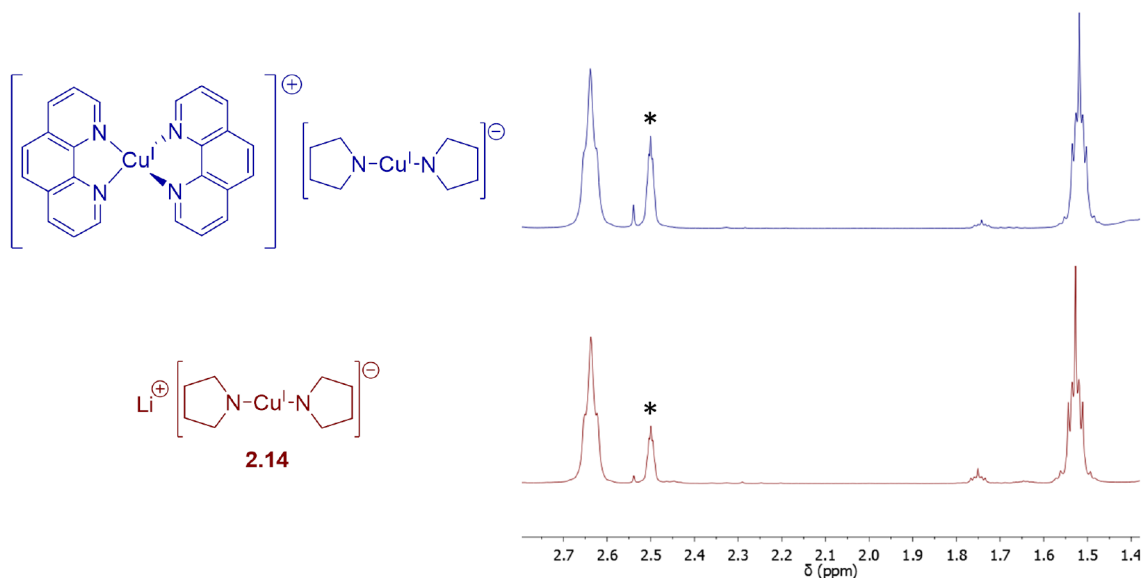


Figure 2.12: Cropped ^1H NMR spectrum of **2.10** with phen (1 : 1 equivalents) (top) in DMSO-d_6 demonstrating the similar chemical shifts of the pyrrolidide ligand resonances compared with $\text{Li}[\text{Cu}(\text{NC}_4\text{H}_8)_2]$ (**2.14**) (bottom) at $\delta = 1.52$ ppm and $\delta = 2.64$ ppm for the β - and α -protons respectively. Residual solvent resonance at 2.50 ppm is labelled with an asterisk (*).

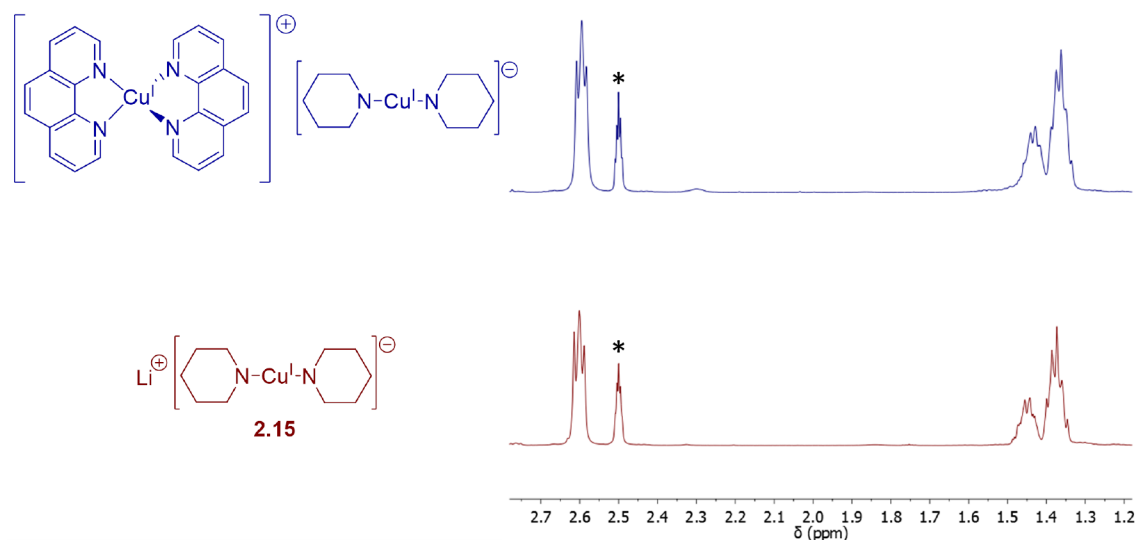


Figure 2.13: Cropped ^1H NMR spectrum of **2.11** with phen (1 : 1 equivalents) (top) in DMSO-d_6 demonstrating the similar chemical shifts of the piperidide ligand resonances compared with $\text{Li}[\text{Cu}(\text{NC}_5\text{H}_{10})_2]$ (**2.15**) (bottom) at $\delta = 1.40$ ppm for the β - and γ -protons and $\delta = 2.60$ ppm for the α -protons. Residual solvent resonance at 2.50 ppm is labelled with an asterisk (*).

674.5 m/z . Similar high FW anionic cuprate clusters such as $[\text{Cu}_4(\mu\text{-SCH}_2\text{Ph})_6]^{2-}$ (**2.16**, Figure 2.14) and $[\text{Cu}_5\text{Ph}_6]^-$ (**2.17**, Figure 2.14) have previously been reported as intermediates in other copper-catalysed reactions such as thioetherification of aryl halides and also in studies of Gilman cuprate reagents.^[70,71] In addition, ^1H - ^1H ROESY NMR spectra of 1 : 1 mixtures of **2.10** or **2.11** with phen in DMSO-d_6 contained no positive-phase cross peaks between the amide and aromatic phen resonances, which support the major species in DMSO-d_6 solution as being the ionic form with phen and amido ligands coordinated to different copper(I) centres (Figure 2.15). In Figure 2.15a for a mixture of **2.10** and phen, there are also negative-phase cross peaks involving the α - and β -protons at $\delta = 2.64$ and 1.52 ppm of $[\text{Cu}(\text{NC}_4\text{H}_8)_2]^-$ and the α - and β -protons of another $[\text{NC}_4\text{H}_8]^-$ moiety at $\delta = 2.85$ and 1.34 ppm respectively. This suggests that there may be chemical exchange of the $[\text{NC}_4\text{H}_8]^-$ ligand in the $[\text{Cu}(\text{NC}_4\text{H}_8)_2]^-$ anion with another species that is likely to be the ESI-MS detected $[\text{Cu}_4(\text{NC}_4\text{H}_8)_5]^-$. Similar negative-phase cross peaks between $[\text{NC}_5\text{H}_{10}]^-$ α -protons resonances are also present at $\delta = 2.92$ and 2.60 ppm in Figure 2.15b for a mixture of **2.11** and phen in DMSO-d_6 . The chemical exchange of the β - and γ -protons of the $[\text{Cu}(\text{NC}_5\text{H}_{10})_2]^-$ anion with the β - and γ -protons of another $[\text{NC}_5\text{H}_{10}]^-$ moiety is not visible as the resonances overlap. Overall, the results suggest that the formation of $[\text{Cu}_4(\text{NRR}')_5]^-$ anions is consistent with the data when copper(I) amides are reacted with

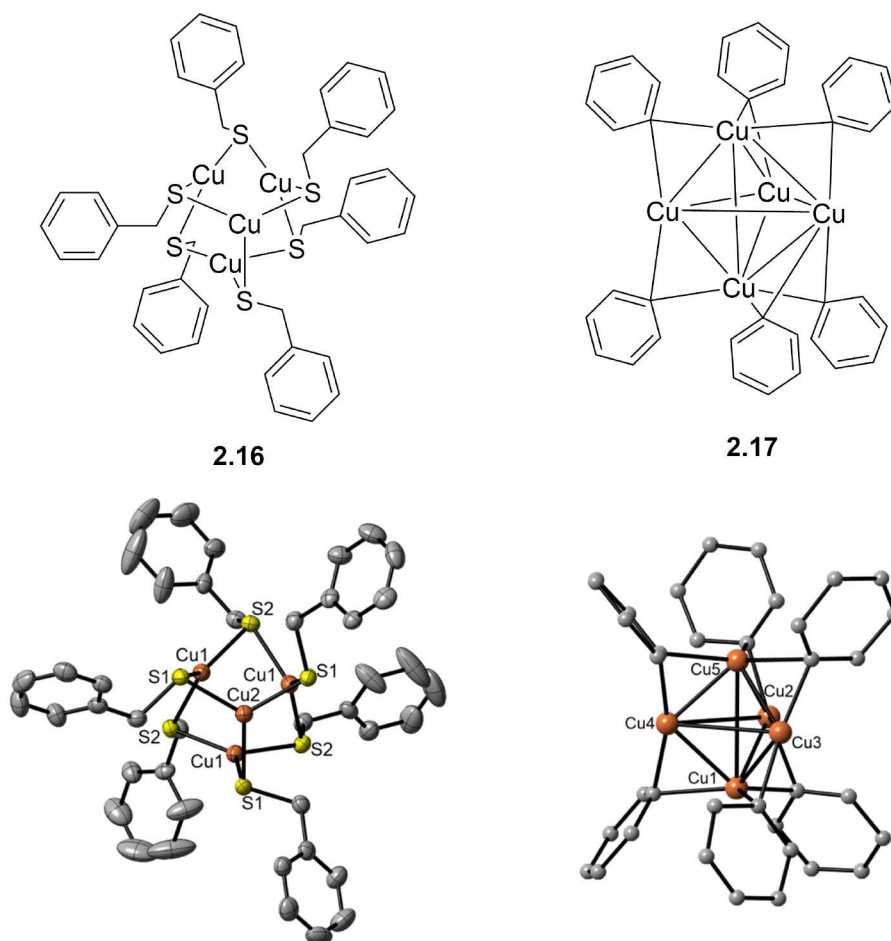


Figure 2.14: Crystal structures of anions $[\text{Cu}_4(\mu\text{-SCH}_2\text{Ph})_6]^{2-}$ (**2.16**) and $[\text{Cu}_5\text{Ph}_6]^-$ (**2.17**).^[70,72] Thermal ellipsoids shown in crystal structure of **2.16** set at 50% probability. Counter-cations and hydrogen atoms are omitted for clarity.

phen in DMSO- d_6 .

In summary, in agreement with previous work involving copper(I) phthalimide, pyrrolidinonate and diphenylamide (**1.24** and **2.1 – 2.3**) by Hartwig and co-workers as described in Section 2.1.1.1,^[4,5] mixtures of copper(I) amide and phen in polar DMSO have been found to almost exclusively form ionic species in solution. However, phen coordination to copper(I) amide species in non-polar benzene was not detectable by NMR spectroscopy and this therefore suggests that phen coordination is highly disfavoured with the alkylamide systems studied here. The examples in this work using **2.10** and **2.11** are the first reports of ligand-free copper(I) amide aggregates being directly observed in the presence of ancillary ligands. Therefore given that ancillary ligand-free copper(I) amide complexes have demonstrated high reactivity in benzene solvent (see Section 2.2.5), mechanistic studies of modified Ullmann reactions that employ

ligands should still consider the potential role that these ligand-free species may have in catalytic processes in non-polar solvent.

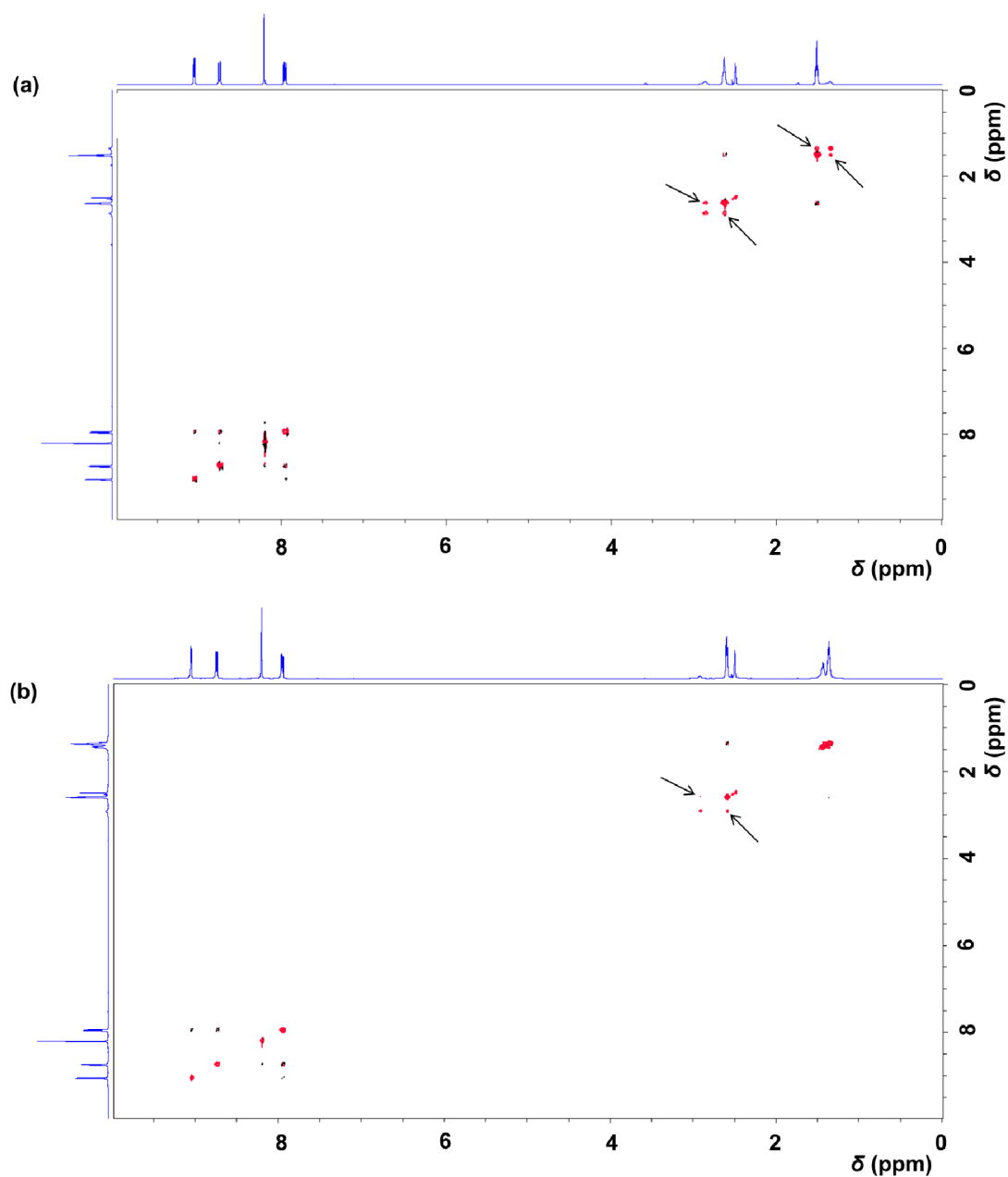


Figure 2.15: ^1H - ^1H ROESY NMR spectra of 1 : 1 mixtures of phen and (a) **2.10** or (b) **2.11** in DMSO-d_6 . Positive- and negative-phase are black and red colour respectively. Negative-phase cross peaks are indicated by black arrows.

2.2.7 Stoichiometric and catalytic reactivity in the presence of phen

Table 2.10 shows the yields of cross-coupling product from the stoichiometric reactions between copper(I) amides **2.8** – **2.12** and iodobenzene in the presence of one equivalent of phen in benzene- d_6 and DMSO- d_6 . Similar to the ancillary ligand-free reactions involving the more sterically hindered **2.8** and **2.9** (Section 2.2.5), no product was observed with **2.8** or **2.9** with phen present in either benzene- d_6 or DMSO- d_6 . Steric hindrance is likely the cause for the lack of reactivity in both cases. For complexes **2.10** and **2.12**, similar coupling yields in benzene- d_6 were obtained with phen (Table 2.10) compared to the ligand-free experiments (Table 2.8). However, the yield formed from reacting **2.11** with phen and iodobenzene in benzene- d_6 decreased from 96 to 51%. Therefore the yields after addition of phen in benzene- d_6 are similar or reduced compared to the ligand-free experiments. The studies of copper(I) amide solution structures in the presence of phen in benzene- d_6 in Section 2.2.6 show copper(I) amide aggregates with virtually no phen binding. Therefore it is likely that the ligand-free copper(I) amide aggregates are responsible for the majority of the reactivity observed in the presence of phen in benzene- d_6 . The reduced reactivity of complex **2.11** in the presence of phen compared

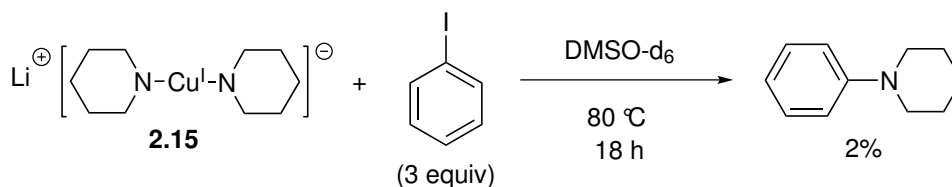
Complex **2.8** - **2.12** + (1.5 equiv) $\xrightarrow[\text{Benzene-}d_6 \text{ or DMSO-}d_6, 80^\circ\text{C}, 18\text{ h}]{\text{Phenanthroline (1.0 equiv)}}$

Complex	Benzene- d_6 solvent % Yield	DMSO- d_6 solvent % Yield
2.8	0	0
2.9	0	0
2.10	44	26
2.11	51	11
2.12	9	66

Table 2.10: Yields obtained in stoichiometric reactions in the presence of phen according to the scheme above. Yields were determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

to **2.11** alone can be attributed to lowered stability of the copper(I) amide on addition of phen (see Section 2.2.6).

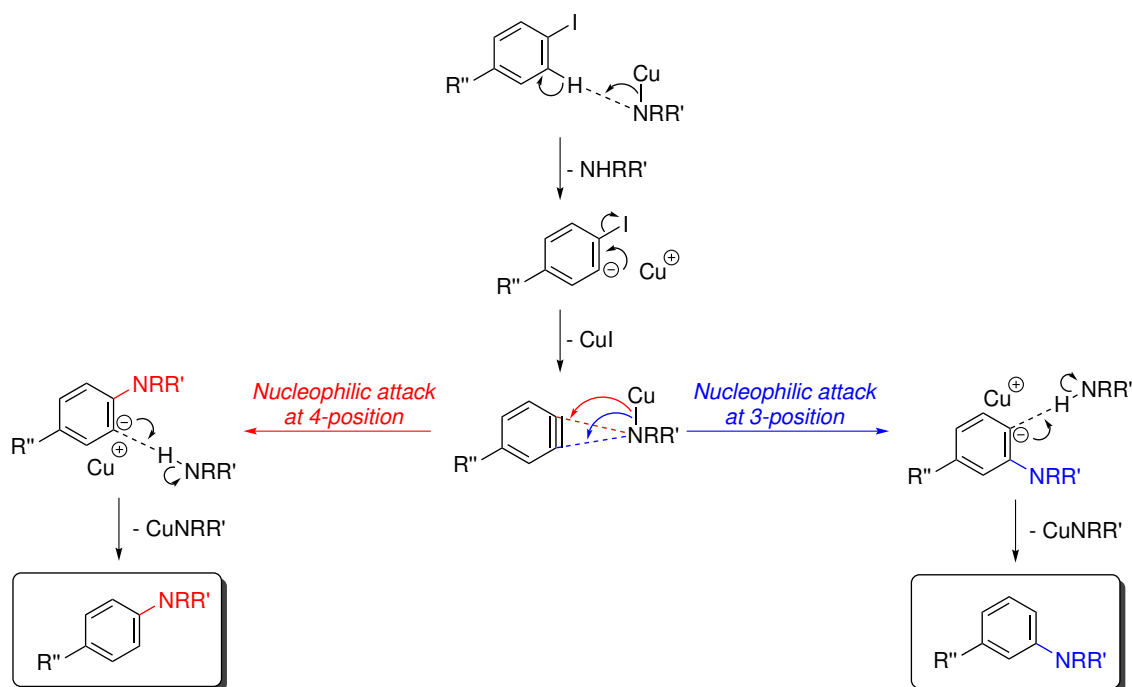
When phen was used in DMSO- d_6 as the solvent, the reactivity of **2.10** was strongly affected with the yield decreasing from 75% to 26%. Similarly, the yields using copper(I) amides **2.11** and **2.12** with phen were also lower in DMSO- d_6 compared to under ligand-free conditions (Table 2.10). The reduced reactivity could be explained by phen-ligated copper(I) amides predominantly adopting an ionic form in polar DMSO (**C**, Scheme 2.7). Previous studies by Hartwig and co-workers found that di(amido)cuprate complexes $[\text{Cu}(\text{NRR}')_2]^-$ exhibited poor reactivity in stoichiometric reactions with aryl halides.^[4,5] To verify if this was the case complex **2.15** was prepared and then treated with iodobenzene in DMSO- d_6 (Scheme 2.9). Only 2% yield of *N*-phenylpiperidine was obtained from this reaction therefore confirming that bis(dialkylamido)cuprates demonstrate relatively little C–N cross-coupling reactivity.



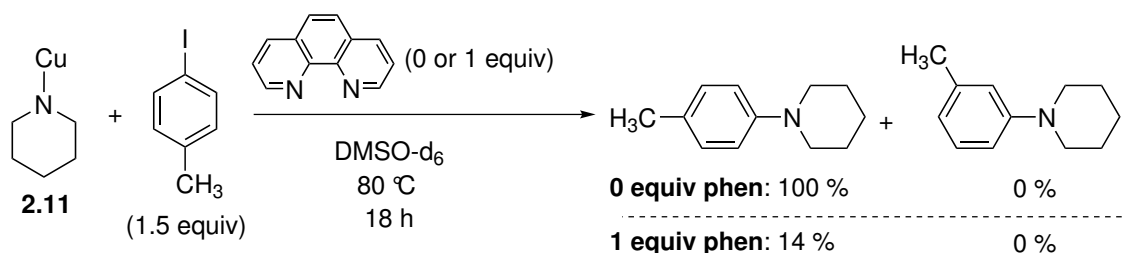
Scheme 2.9: Reaction between $\text{Li}[\text{Cu}(\text{NC}_5\text{H}_{10})_2]$ (**2.15**) and iodobenzene. Yields were determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

Given the strong basic nature of copper(I) amide complexes, the mechanism of the stoichiometric reactions mentioned previously could potentially have occurred *via* a benzyne intermediate (Scheme 2.10). Therefore a reaction between **2.11** and 4-iodotoluene in DMSO- d_6 was performed to identify if only the *para*-substituted product or if a mixture of *meta*- and *para*-substituted products are formed. Under ligand-free conditions, **2.11** and 4-iodotoluene react cleanly to give the corresponding *para*-substituted cross-coupling product in quantitative yield (Scheme 2.11). The effect of phen on the reactivity in this reaction using 4-iodotoluene was the same as observed when iodobenzene was used, with a significantly lower yield with phen present (14% yield) and for the same reason. Importantly, the *meta*-substituted product was not formed which confirmed that the reactions between the copper(I) amides and aryl iodides do not occur by benzyne formation. This provides further evidence of the potential intermediacy of these complexes in the Ullmann amination reaction.

The effect of phen on the catalytic reactivity between the corresponding alkylamines and

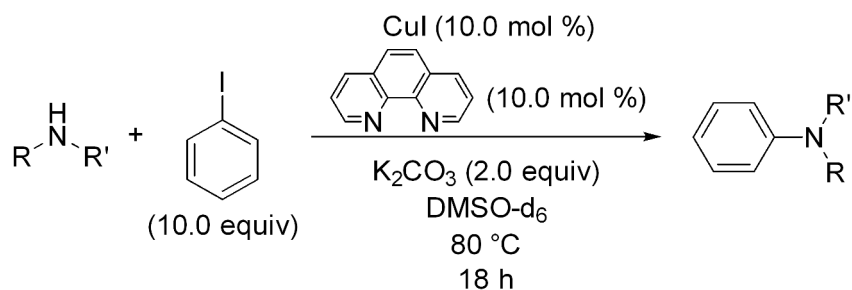


Scheme 2.10: Mechanism for the stoichiometric reaction between copper(I) amides and aryl iodides if it proceeds *via* a benzyne intermediate to give two possible product regioisomers.



Scheme 2.11: Reaction between complex **2.11** and 4-iodotoluene that demonstrate the stoichiometric reactions do not occur *via* a benzyne intermediate. Yields were determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

iodobenzene was next tested (Table 2.11). Using 10 mol % copper(I) iodide and 10 mol % phen as the catalyst in benzene- d_6 solvent yielded no product with all the tested amines. Similar to when no phen is used (Section 2.2.5), this can be attributed to the poor solubility of the catalyst and base in this solvent. In DMSO-d_6 , the sterically hindered dicyclohexylamine and 2,2,6,6-tetramethylpiperidine still yielded no cross-coupled product with iodobenzene (Table 2.11, entries 1 and 2). However, pyrrolidine, piperidine and benzylamine did react with iodobenzene to give the cross-coupling product, all in lower yields of 39%, 30% and 77% respectively than when phen is not used (Table 2.11, entries 3 – 5).



Entry	HNRR'	% Yield
1		0
2		0
3		39
4		30
5		77

Table 2.11: Yields obtained in catalytic reactions in the presence of 10 mol % phen according to the scheme above. Yields were determined by ^1H NMR spectroscopy using mesitylene as an internal standard.

The influence of phen loading on the yield in the copper-catalysed cross-coupling reaction between piperidine and excess iodobenzene was next investigated. From Figure 2.16, a negative correlation between phen loading and the product yield was observed with the highest yield obtained in the ligand-free system. This suggests that at higher phen loadings, the solution equilibrium shifts further toward the unreactive ionic species away from the reactive neutral $[(phen)Cu(NC_5H_{10})]$ species.

Although the results presented in this work appear to contradict reports from the literature which find that phen improves the copper-catalysed reactivity, it should be noted that the overall reactivity is dependent on several factors such as the position of the equilibrium, the pK_a and

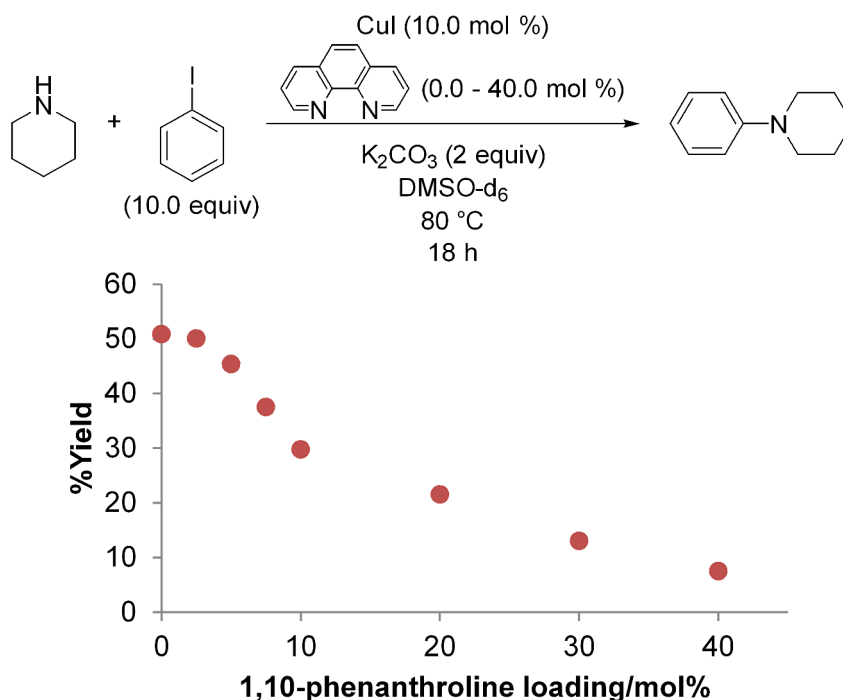


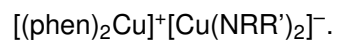
Figure 2.16: Chart showing the effect of phen on the yield of the C–N coupling between piperidine and iodobenzene. Yields were determined by ¹H NMR spectroscopy using mesitylene as an internal standard.

nucleophilicity of the amine, the reaction temperature and the solvent system. Furthermore, ligand systems described in the literature generally only report the effect of one or two ligand loading values and in many cases comparisons are not made with the baseline ligand-free reaction. Therefore it is difficult to make direct comparisons to phen-ligated catalytic systems in the literature. The results presented in this work though are in agreement with other mechanistic studies that find off-cycle di(amido)cuprates exhibiting relatively poor reactivity in C–N cross coupling with aryl iodides.^[4,5] Recent DFT calculations have also determined the activation energy for oxidative addition of iodobenzene to [(phen)Cu(NPh₂)] is greater than to an ancillary ligand-free [(DMSO)Cu(NPh₂)].^[5] Therefore in addition to affecting the aryl halide activation, this work has identified that phen and the solvent have important roles in controlling the equilibrium shown in Scheme 2.7 for the modified Ullmann reaction between aryl iodides and alkylamines.

2.3 Conclusions

Five copper(I) alkylamide complexes with a range of steric sizes were synthesised and characterised in the solid state and in solution using single-crystal X-ray diffraction and NMR spectroscopic techniques respectively. X-ray crystallographic data show that **2.8**, **2.9** and **2.11** exist as tetramers in the solid state. The solution behaviour of copper(I) amides **2.8** – **2.12** in benzene- d_6 was determined by ^1H DOSY NMR studies. Complexes **2.8**, **2.9** and **2.12** were found to rapidly equilibrate between aggregation states whereas the equilibrium rate was slower in **2.10** and **2.11** and therefore led to trimeric, tetrameric and pentameric aggregates being directly observed by NMR spectroscopy. The varying Cu–N bond strength in **2.8** – **2.12** was proposed to be the cause of the different equilibrium rates. In addition, the average aggregation numbers of the complexes were found to be inversely correlated to the steric bulk (cone angle) of the amido ligands.

Stoichiometric reactivity studies between **2.8** – **2.12** and iodobenzene with and without phen allowed new insights into the reactivity and solution structures to be obtained, which were also directly relevant to the catalytic modified Ullmann reaction. Similarities between the observed stoichiometric and catalytic reactivity suggest that copper(I) alkylamide complexes are potential intermediates in the copper-catalysed cross-coupling of aryl iodides and alkylamines. The reactions of copper(I) amides with aryl iodides presented in this work represent the first successful experiments to yield C–N coupled product in the absence of ancillary ligands. The lowered stoichiometric reactivity as a result of steric bulk in the copper(I) amides provide experimental evidence that inhibited oxidative addition of aryl halide rather than formation of the copper(I) amide complex may be the cause for the poor yields observed using bulky amine substrates in the catalytic reactions. The preferred solution structures adopted by copper(I) amides in the presence of phen have been shown to be highly dependent on the polarity of the solvent. Analysis of these solutions showed phen coordination to copper(I) amides to be highly disfavoured in non-polar benzene solvent, whereas the phen-ligated copper(I) amide species were preferably present in an ionic form, $[(\text{phen})_2\text{Cu}]^+[\text{Cu}(\text{NRR}')_2]^-$, in polar DMSO (Scheme 2.7). Therefore the role of ligand-free copper(I) amide aggregates should be considered in mechanistic studies of Ullmann reactions that incorporate phen in non-polar solvents. The reduced yields observed in stoichiometric and catalytic reactions on addition of phen in DMSO was attributed to the copper(I) species being present predominantly as the unreactive ion pair



The scope of the mechanistic information obtained so far is limited to alkylamine substrates and iodobenzene so its applicability to other nitrogen-based nucleophiles such as arylamines and amides, which have different pK_a and nucleophilicity, and other aryl halides warrants future study. Kinetic studies for the stoichiometric reactions could also be carried out to further support the conclusions drawn so far. Finally, the effect of radical probes on the reactivity could be used to identify whether the aryl halide activation occurs by oxidation addition or free aryl radical formation, similar to reported work in the literature highlighted in Section 1.4.4, Chapter 1.

2.4 Experimental

2.4.1 General Information

All experiments were conducted under a dry, nitrogen atmosphere in a glovebox or using standard Schlenk techniques. All glassware was dried for at least 12 h at a minimum temperature of 120 °C. Prior to use, toluene and *n*-hexane were dried and degassed over activated alumina using an Innovative Technologies PureSolv solvent purification system. THF was freshly distilled over sodium and benzophenone under a nitrogen atmosphere. DMSO and DMSO- d_6 were stirred over calcium hydride at room temperature under nitrogen overnight and distilled under reduced pressure and stored over 4 Å molecular sieves under a nitrogen atmosphere prior to use. Potassium carbonate base was dried by heating under vacuum for 48 h at 180 °C and phen was dried under vacuum at 85 °C for 36 h. The procedure reported by Tsuda and co-workers was used to prepare CuMes.^[27] The amines used were stirred over calcium hydride or sodium at room temperature under a nitrogen atmosphere and distilled under nitrogen for storage over 4 Å molecular sieves. All other chemicals were used as received without further purification. All products, other reagents and deuterated NMR solvents were stored in a nitrogen-filled glovebox, with liquid reagents also dried using 4 Å molecular sieves.

^1H and ^{13}C NMR spectroscopy analysis was carried out at room temperature using Bruker AV-400 spectrometers except for ^1H DOSY and ^1H - ^1H ROESY NMR spectroscopy data which were obtained using a Bruker AV-500 spectrometer. CHN microanalyses were carried out at the London Metropolitan University, UK. ESI-MS analyses were carried out using a Waters LCT Premier. Single-crystal X-ray diffraction experiments were performed on an Oxford Diffraction Xcalibur 3 (**2.8** and **2.9**), Oxford Diffraction Xcalibur PX Ultra (**2.11**), and Agilent Xcalibur 3 E (**2.13a** and **b**) diffractometers, and the structures were refined using the SHELXTL, SHELX-97, and SHELX-2013 program systems.^[73] The absolute structures of **2.8**, **2.11** and **2.13** were determined by use of the Flack parameter (0.037(9), 0.07(3) and 0.070(11) respectively). CCDC codes for **2.8**, **2.9**, **2.11** and **2.13a** and **b** are 1027216, 1027217, 1027218 and 1027219 respectively.

The yields reported in the copper(I) amide complexes syntheses are the amounts isolated after purification. ^1H NMR spectroscopy studies with mesitylene as an internal standard were used to determine the yields and conversions at the end of the catalytic and stoichiometric

reactions. The reported values are the mean of at least two independent runs. ^1H and ^{13}C NMR data were analysed using MESTRELAB MestReNova; ^1H - ^1H ROESY NMR data were analysed using Bruker TopSpin; and ^1H DOSY NMR data were processed and analysed using Bruker Dynamics Centre and TopSpin software respectively.

2.4.2 Preparation of copper(I) dicyclohexylamide (2.8)

A colourless solution of dicyclohexylamine (0.80 mL, 4.0 mmol) in THF (10 mL) was treated dropwise with *n*-butyllithium in hexanes (2.50 mL, 1.6 M, 4.0 mmol) at 0 °C and stirred for 5 min. The clear pale yellow solution was slowly transferred to a vigorously stirring white suspension of copper(I) chloride (436 mg, 4.40 mmol) in THF (5 mL) kept at 0 °C. The mixture was stirred for 2 h at room temperature, after which it was filtered through Celite to give a clear pale yellow filtrate. After reducing the amount of solvent in the filtrate by evaporation under vacuum to approximately 8 mL, the solution was stored at -25 °C. After 3 days, colourless crystals of the desired product were isolated by filtration and dried under vacuum (152 mg, 0.623 mmol, 16%). ^1H NMR (400 MHz, benzene- d_6 , 22 °C, TMS): δ =1.20 – 1.45 (m, 6H; CH_2), 1.63 – 1.78 (m, 6H; CH_2), 1.82 – 1.93 (m, 4H; β - CH_2), 2.54 – 2.65 (m, 4H; β - CH_2), 2.92 ppm (tt, $^3J_{\text{HH}}$ =11.0 Hz, $^3J_{\text{HH}}$ =3.6 Hz, 2H; α -CH); ^{13}C NMR (101 MHz, benzene- d_6 , 22 °C, TMS): δ =27.3 (s; γ - CH_2), 27.6 (s; δ - CH_2), 40.5 (s; β - CH_2), 60.5 ppm (s; α -CH); elemental analysis calcd (%) for $\text{C}_{12}\text{H}_{22}\text{CuN}$: C 59.10, H 9.09, N 5.74; found: C 59.17, H 9.22, N 5.60. Single crystals suitable for structural characterisation by X-ray diffraction were obtained by allowing slow crystallisation to occur from the filtrate at 4 °C over 3 days.

2.4.3 Preparation of copper(I) 2,2,6,6-tetramethylpiperidide (2.9)

A colourless solution of 2,2,6,6-tetramethylpiperidine (3.40 mL, 20.0 mmol) in THF (10 mL) was treated dropwise with *n*-butyllithium in hexanes (12.50 mL, 1.6 M, 20 mmol) at 0 °C and stirred for 5 min. The clear pale yellow solution was slowly transferred to a vigorously stirring white suspension of copper(I) chloride (2.178 g, 22.00 mmol) in THF (65 mL) kept at 0 °C. The mixture was stirred for 40 min at room temperature, after which it was filtered through Celite to give a clear brown filtrate. After evaporating some of the solvent under vacuum, the filtrate was stored at -25 °C for 5 days. The desired product was isolated by filtration as a crystalline white solid and dried under vacuum (1.751 g, 8.592 mmol, 43%). ^1H NMR (400 MHz, benzene- d_6 , 22 °C, TMS): δ =1.54 – 1.60 (m, 4H; β - CH_2), 1.69 – 1.81 ppm (m, 14H; CH_3 and γ - CH_2); ^{13}C NMR

(101 MHz, benzene- d_6 , 22 °C, TMS): δ =20.1 (s; γ -CH₂), 38.0 (s; CH₃), 43.3 (s; β -CH₂), 57.7 (s; α -C) ppm; elemental analysis calcd (%) for C₉H₁₈CuN: C 53.04, H 8.90, N 6.87; found: C 52.83, H 9.08, N 6.85. Single crystals suitable for structural characterisation by X-ray diffraction were obtained by allowing slow crystallisation to occur from the filtrate at 4 °C over 4 days.

2.4.4 Preparation of copper(I) pyrrolidide (2.10)

A colourless solution of pyrrolidine (1.11 mL, 13.5 mmol) in THF (10 mL) was treated dropwise with *n*-butyllithium in hexanes (5.20 mL, 2.5 M, 13 mmol) at room temperature and stirred for 10 min. The clear pale yellow solution was slowly transferred to a vigorously stirring white suspension of copper(I) chloride (1.390 g, 14.00 mmol) in THF (50 mL) at room temperature. The mixture was stirred for 25 min at room temperature, after which it was filtered through Celite to give a clear yellow filtrate. After evaporating the solvent under vacuum until a small amount of white solid had precipitated, the mixture was stored at -25 °C overnight. The desired product was isolated by filtration as a crystalline white solid, washed with *n*-hexane (2 x 5 mL) and dried under vacuum. The purified solid was stored at -25 °C to minimise thermal decomposition (917 mg, 6.86 mmol, 53%). ¹H NMR (400 MHz, benzene- d_6 , 23 °C, TMS): δ =1.44 – 1.62 (m, 4H; β -CH₂ of all solution aggregates present), 3.11 – 3.31 ppm (m, 4H; α -CH₂ of all solution aggregates present); ¹³C NMR (101 MHz, benzene- d_6 , 23 °C, TMS): δ =26.6 (s; β -CH₂), 26.8 (s; β -CH₂), 26.9 (s; β -CH₂), 54.9 (s; α -CH₂), 55.3 (s; α -CH₂), 55.5 ppm (s, α -CH₂); elemental analysis calcd (%) for C₇H₈CuN: C 35.94, H 6.03, N 10.48; found: C 35.71, H 5.85, N 10.33.

2.4.5 Preparation of copper(I) piperidide (2.11)

Piperidine (3.95 mL, 40.0 mmol) was added to a yellow solution of copper(I) mesityl (1.462 g, 8.000 mmol) in THF (10 mL) at room temperature. A yellow precipitate formed from the bright yellow reaction solution, which slowly dissolved into the reaction solvent with stirring (can take over 24 h to dissolve at room temperature). After complete dissolution of the yellow intermediate, the pale yellow solution was stirred at room temperature for 3 days until the product as a white solid had precipitated from the solution. The resultant mixture was evaporated to dryness under vacuum and *n*-hexane (10 mL) was added to suspend the product in a yellow solution. The desired product was isolated by filtration, washed with *n*-hexane (2 x 5 mL) and dried under vacuum to give a pure white powder (781 mg, 5.29 mmol, 66%). ¹H NMR (400 MHz, benzene- d_6 , 23 °C, TMS): δ =1.51 – 1.76 (m, 6H; β -CH₂ and γ -CH₂ of all solution

aggregates present), 3.14 – 3.37 ppm (m, 4H; α -CH₂ of all solution aggregates present); ¹³C NMR (101 MHz, benzene-d₆, 23 °C, TMS) δ =27.0 (s; γ -CH₂), 33.7 (s; β -CH₂), 34.0 (s; β -CH₂), 34.3 (s; β -CH₂), 56.8 (s; α -CH₂), 57.0 (s; α -CH₂), 57.2 ppm (s; α -CH₂); elemental analysis calcd (%) for C₅H₁₀CuN: C 40.66, H 6.82, N 9.48; found: C 40.61, H 6.84, N 9.36. Single crystals suitable for structural characterisation by X-ray diffraction were obtained by leaving the pale yellow solution after complete dissolution of the intermediate at room temperature over 3 days.

2.4.6 Preparation of copper(I) benzylamide (2.12)

Benzylamine (288 μ L, 2.64 mmol) was added to a yellow solution of copper(I) mesityl (439 mg, 2.40 mmol) in THF (1 mL) at room temperature and stirred for 2 min. The reaction solvent was quickly removed by evaporating under vacuum. *n*-Hexane (6 mL) was added to the resultant yellow residue and stirred for 30 min at room temperature to suspend the product as a white solid. The solid was filtered, washed with *n*-hexane (2 x 5 mL) and dried under vacuum to give the product as a white powder (304 mg, 1.79 mmol, 75%). ¹H NMR (400 MHz, benzene-d₆, 24 °C, TMS): δ =0.13 – 0.34 (m, 1H; N–H), 3.80 – 3.97 (m, 2H; CH₂), 7.04 – 7.15 (m, 1H; *p*-C₆H₅), 7.17 – 7.38 ppm (m, 4H; *o*-C₆H₅ and *m*-C₆H₅); ¹³C NMR (101 MHz, benzene-d₆, 22 °C, TMS): δ =52.6 (s; CH₂), 126.4 (s; Ph carbon), 127.8 (s; Ph carbon), 128.3 (s; Ph carbon), 146.6 ppm (s; Ph carbon); elemental analysis calcd (%) for C₇H₈CuN: C 49.55, H 4.75, N 8.25; found: C 49.39, H 4.65, N 8.35.

2.4.7 Isolation of the intermediate in the synthesis of copper(I) piperidide (2.13a and 2.13b)

Piperidine (988 μ L, 10.0 mmol) was added to a yellow solution of copper(I) mesityl (365 mg, 2.00 mmol) in THF (2 mL) at room temperature and stirred for 5 min, during which the desired intermediate had precipitated. The precipitate was filtered, washed *n*-hexane (3 x 3 mL) and dried under vacuum to give the intermediate as a yellow powder (225 mg, 0.250 mmol, 50%). ¹H NMR (400 MHz, benzene-d₆, 21 °C, TMS): δ =0.47 (p, ³J_{HH}=5.4 Hz, 2H; N–H), 1.01 – 1.20 (m, 12H; β -CH₂ and γ -CH₂), 2.04 (s, 12H; *p*-CH₃), 2.18 – 2.35 (m, 8H; α -CH₂), 2.93 (s, 24H; *o*-CH₃), 6.70 ppm (s, 8H; Ar-H); ¹³C NMR (101 MHz, benzene-d₆, 22 °C, TMS) δ =21.0 (s; *p*-CH₃), 24.7 (s; γ -CH₂), 27.1 (s; β -CH₂), 28.8 (s; *o*-CH₃), 47.0 (s; α -CH₂), 126.0 (s; Ar C-H), 138.2 (s; Ar C-CH₃), 140.1 (s; Ar C-CH₃), 152.3 ppm (s; Ar C-CH₃); Unable to acquire satisfactory

elemental analysis due to decomposition of the complex. Single crystals suitable for structural characterisation by X-ray diffraction were obtained by leaving a solution of copper(I) mesityl and piperidine in THF to stand at room temperature overnight.

2.4.8 ^1H NMR analysis of the mixture of copper(I) mesityl and dicyclohexylamine

Dicyclohexylamine (20 μL , 0.10 mmol) was added to a yellow solution of copper(I) mesityl (18 mg, 0.10 mmol) in benzene- d_6 (1.000 mL) at room temperature and stirred for 1 h. The solution was transferred to a J. Youngs tap NMR tube for analysis by ^1H NMR spectroscopy.

2.4.9 DFT calculations to obtain r_{calc} values

All calculations were performed with the Gaussian 09 package.^[74] The B3LYP DFT method^[75,76] was used for geometry optimisations with the SVP basis set^[77,78] for Cu and 6-31G(d)^[79,80] for C, H, N and Si. Solvation effects on the structures were accounted for by performing self-consistent reaction field (SCRF) calculations using the CPCM polarizable conductor calculation model with benzene set as the solvent.^[81,82] Frequency calculations at the same level of theory resulted in no imaginary frequencies and therefore confirmed the optimised geometries as energy minima. Volume calculations were performed on the fully optimised geometries with the density contour chosen as 0.002 electrons/ Bohr^3 and the number of Monte Carlo points set to 100 to minimise variation.^[83] The mean of the recommended radii from the Gaussian outputs from 10 repeated calculations were used as r_{calc} .

To identify the copper(I) amide aggregates in solution, the geometries of the three internal standards used for the ^1H DOSY NMR measurements, 1,2,3,4-tetraphenylnaphthalene, 1-phenylnaphthalene, and tetramethylsilane were optimised by DFT calculations at B3LYP/6-31g(d) level. The volume keyword in Gaussian was used to obtain the r_{calc} value for each internal standard (Table 2.12). When the $\text{Log}_{10}D$ values of the internal standards from the ^1H DOSY NMR experiments were plotted against their $\text{Log}_{10}(r_{\text{calc}})$ values, linear regression lines were produced with r^2 values typically greater than 0.99. Using the formula of these trendlines, the radii of the aggregates in solution (r_{obs}) were calculated using their experimentally determined $\text{Log}_{10}D$ values. The aggregates were identified by comparing r_{obs} with r_{calc} of DFT optimised copper(I) amide aggregates (Table 2.12).

Compound		r_{calc} (Å)
2.8	Monomer	4.79
	Dimer	5.89
	Trimer	6.65
	Tetramer	7.27
2.9	Monomer	4.55
	Dimer	5.50
	Trimer	6.21
	Tetramer	6.83
2.10	Monomer	3.73
	Dimer	4.56
	Trimer	5.15
	Tetramer	5.65
	Pentamer	6.04
2.11	Monomer	3.92
	Dimer	4.76
	Trimer	5.38
	Tetramer	5.89
	Pentamer	6.37
2.12	Monomer	4.07
	Dimer	4.97
	Trimer	5.62
	Tetramer	6.15
Tetramethylsilane		3.90
Internal standards	1-Phenylnaphthalene	4.65
	1,2,3,4-Tetraphenylnaphthalene	5.81
1,10-Phenanthroline	-	4.40

Table 2.12: r_{calc} of DFT optimised copper(I) amide aggregates of **2.8** – **2.12**, internal standards and 1,10-phenanthroline.

2.4.10 ^1H DOSY NMR solutions of the copper(I) amide complexes with internal standards

1-Phenylnaphthalene (13 μL , 0.07 mmol, 0.10 M) and tetramethylsilane (19 μL , 0.14 mmol, 0.20 M) were added to a solution of complex **2.8** – **2.12** (0.04 mmol, 0.05 M) and 1,2,3,4-

tetraphenylnaphthalene (15 mg, 0.04 mmol, 0.05 M) in benzene- d_6 (668 μ L). The solution was transferred to a J. Youngs tap NMR tube for analysis using ^1H DOSY NMR. (Amount of copper(I) amide complex was adjusted for the desired concentration).

2.4.11 Procedure for the stoichiometric C–N coupling reactions between the copper(I) amide complexes and aryl iodides

Copper(I) amide **2.8** – **2.12** (0.10 mmol), phen (18 mg, 0.10 mmol) (if required) and a magnetic stirring flea were placed in a screw-cap vial and DMSO- d_6 or benzene- d_6 (1.000 mL) was added. Mesitylene (14.0 μ L, 0.100 mmol) as an internal standard and aryl iodide (0.150 mmol) were added to the mixture. The vial was capped tightly and taken out of the glovebox. The mixtures were stirred at 80 $^\circ\text{C}$ for 18 h. The contents of the vial were filtered using a syringe filter into a NMR tube inside a glovebox or nitrogen-filled glove bag for ^1H NMR analysis to calculate the quantity of coupling product formed.

2.4.12 Procedure for the catalytic reactions between alkylamines and iodobenzene

Potassium carbonate (28 mg, 0.20 mmol) and a magnetic stirring flea were placed in a screw-cap vial and DMSO- d_6 (800 μ L) was added. Copper(I) iodide (100 μ L of 0.100 M solution in DMSO- d_6 , 0.0100 mmol), phen (100 μ L of 0.100 M solution in DMSO- d_6 , 0.0100 mmol) (if required), mesitylene (14.0 μ L, 0.100 mmol) as an internal standard, iodobenzene (111.0 μ L, 1.000 mmol) and the amine (0.100 mmol) were added to the mixture. The vial was capped tightly and taken out of the glovebox. The mixtures were stirred at 80 $^\circ\text{C}$ for 18 h. The contents of the vial were filtered using a syringe filter into a NMR tube inside a glovebox or nitrogen-filled glove bag for ^1H NMR analysis to calculate the quantity of coupling product formed.

2.4.13 Preparation of the NMR solution of **2.10 and **2.11** in the presence of phen and DOSY NMR internal standards in benzene- d_6**

Complex **2.10** or **2.11** (0.04 mmol, 0.05 M), phen (6 mg, 0.04 mmol, 0.05 M) and 1,2,3,4-tetraphenylnaphthalene (15 mg, 0.04 mmol, 0.05 M) were dissolved in benzene- d_6 (668 μ L) to give a deep-blue solution. 1-phenylnaphthalene (13 μ L, 0.07 mmol, 0.10 M) and tetramethylsilane (19 μ L, 0.14 mmol, 0.20 M) were added. The solution was transferred to a J. Youngs tap NMR tube for ^1H DOSY NMR analysis.

2.4.14 Preparation of the NMR solution of 2.10 and 2.11 in the presence of phen in DMSO-d₆

Complex **2.10** or **2.11** (0.10 mmol) was treated with a solution of phen (18 mg, 0.10 mmol) in DMSO-d₆ (1.000 mL) and stirred at room temperature. After 18 h, the resultant dark red solution was transferred to a J. Youngs tap NMR tube for analysis.

2.4.15 Preparation of the ESI-MS solution of 2.11 in the presence of phen in DMSO

A mixture of complex **2.11** (5 mg, 0.03 mmol) and phen (6 mg, 0.03 mmol) in DMSO (1.000 mL) was stirred overnight at room temperature to give a deep-red solution. The solution was passed through a syringe filter to remove any solid. 9.1 µL of the deep-red coloured filtrate was diluted to 1.000 mL using DMSO to give a 0.1 mg mL⁻¹ concentration suitable for ESI-MS analysis.

2.4.16 Preparation of the ESI-MS solution of 2.11 in the presence of phen in benzene

A mixture of complex **2.11** (5 mg, 0.03 mmol) and phen (6 mg, 0.03 mmol) in benzene (1.000 mL) was stirred for 10 min at room temperature to give a deep-blue solution. The solution was passed through a syringe filter to remove any solid. 9.1 µL of the deep-red coloured filtrate was diluted to 1.000 mL using benzene to give a 0.1 mg mL⁻¹ concentration suitable for ESI-MS analysis.

2.4.17 Preparation of the NMR solution of lithium di(amido)cuprates in DMSO-d₆ for comparison

A colourless solution of pyrrolidine or piperidine (5.5 mmol) in THF (10 mL) was treated dropwise with *n*-butyllithium in hexanes (2.00 mL, 5.0 mmol, 2.5 M) at 0 °C. After stirring at room temperature for 1 h, the solutions were evaporated to dryness to until white solids remained. After further drying under vacuum at 40 °C, the lithium amides were isolated as white powders. Copper(I) iodide solution in DMSO-d₆ (500 µL, 0.100 M, 0.0500 mmol) were added to solutions of the lithium amides (0.1 mmol) in DMSO-d₆ (500 µL) to generate the corresponding lithium di(amido)cuprates. The solutions were transferred to a J. Youngs tap NMR tubes for analysis.

2.4.18 Procedure for the stoichiometric reaction between the lithium di(piperidido)cuprate(I) and iodobenzene

A solution of lithium di(piperidido)cuprate(I) (0.05 mmol) in DMSO- d_6 (1 mL), prepared using the method described previously, was treated with mesitylene (14.0 μ L, 0.100 mmol) as an internal standard and iodobenzene (16.8 μ L, 0.150 mmol). The reaction vial was capped tightly and taken out of the glovebox. After stirring at 80 °C for 18 h, the contents of the vial were filtered using a syringe filter into a NMR tube inside a glovebox or nitrogen-filled glove bag for ^1H NMR analysis to calculate the quantity of coupling product formed.

2.4.19 Effect of phen loading on the catalytic C–N coupling between piperidine and iodobenzene

Potassium carbonate (28 mg, 0.20 mmol) and a magnetic stirring flea were placed in a screw-cap vial and DMSO- d_6 (volume required to make up to 1.000 mL total solvent) was added. Copper(I) iodide (100 μ L of 0.100 M solution in DMSO- d_6 , 0.0100 mmol), phen (25.0, 50.0, 75.0, 100, 200, 300 or 400 μ L of 0.1 M stock solution, 0.00250, 0.0050, 0.00750, 0.0100, 0.0200 or 0.0400 mmol), mesitylene (14.0 μ L, 0.100 mmol) as an internal standard, iodobenzene (111.0 μ L, 1.000 mmol) and piperidine (10.0 μ L, 0.100 mmol) were added to the mixture. The vial was capped tightly and taken out of the glovebox. The mixtures were stirred at 80 °C for 18 h. The contents of the vial were filtered using a syringe filter into a NMR tube inside a glovebox or nitrogen-filled glove bag for ^1H NMR analysis to calculate the quantity of coupling product formed.

2.4.20 Crystallographic Data Tables

Data	2.8	2.9	2.11	2.13a and 2.13b
Formula	C ₄₈ H ₈₈ Cu ₄ N ₄	C ₃₆ H ₇₂ Cu ₄ N ₄	C ₂₀ H ₄₀ Cu ₄ N ₄	C ₄₆ H ₆₆ Cu ₄ N ₂
Formula weight	975.38	815.4	590.72	901.16
Colour, habit	Colourless blocky needles	Colourless blocky needles	Colourless needles	Yellow blocks
Crystal size / mm ³	0.34 × 0.09 × 0.08	0.46 × 0.35 × 0.31	0.27 × 0.14 × 0.12	0.44 × 0.40 × 0.31
Temperature / K	173	173	173	173
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Tetragonal
Space group	C2 (no. 5)	C2/c (no. 15)	Pca2 ₁ (no. 29)	P4 ₃ 22 (no. 95)
<i>a</i> / Å	21.1288(4)	16.4470(3)	20.5083(2)	17.5541(2)
<i>b</i> / Å	15.6506(2)	16.3182(3)	5.85452(6)	17.5541(2)
<i>c</i> / Å	15.7898(3)	15.7208(3)	19.69462(18)	28.8897(6)
α / °	90	—	90	90
β / °	110.370(2)	116.481(3)	90	90
γ / °	90	—	90	90
<i>V</i> / Å ³	4894.83(16)	3776.56(16)	2364.66(4)	8902.2(3)
<i>Z</i>	4	4 [b]	4	8 [c]
ρ_{calcd} / g cm ⁻³	1.324	1.434	1.659	1.345
Radiation used	Mo-K α	Mo-K α	Cu-K α	Mo-K α
μ / mm ⁻¹	1.749	2.252	4.127	1.917
2θ max / °	65	65	145	57
No. of unique reflns measured (<i>R</i> _{int})	13409 (0.0268)	6441 (0.0236)	4385 (0.0305)	8967 (0.0209)
obs, $ F_o > 4\sigma(F_o)$	11310	5592	4085	7011
No. of variables	505	207	253	537
<i>R</i> ₁ (obs), <i>wR</i> ₂ (all) [a]	0.0321, 0.0791	0.0261, 0.0648	0.0269, 0.0707	0.0390, 0.0857

Table 2.13: Crystal Data, Data Collection and Refinement Parameters for the structures of **2.8**, **2.9**, **2.11**, **2.13**. [a] $R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$; $wR_2 = \{\Sigma [w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2]\}^{1/2}$; $w^{-1} = \sigma^2(F_o^2)$ + $(aP)^2 + bP$. [b] The complex has crystallographic *C*₂ symmetry. [c] There are two independent *C*₂-symmetric complexes.

2.5 Appendix

2.5.1 ¹H DOSY NMR spectra of complexes 2.8 – 2.12 with internal standards with *D-r* analysis

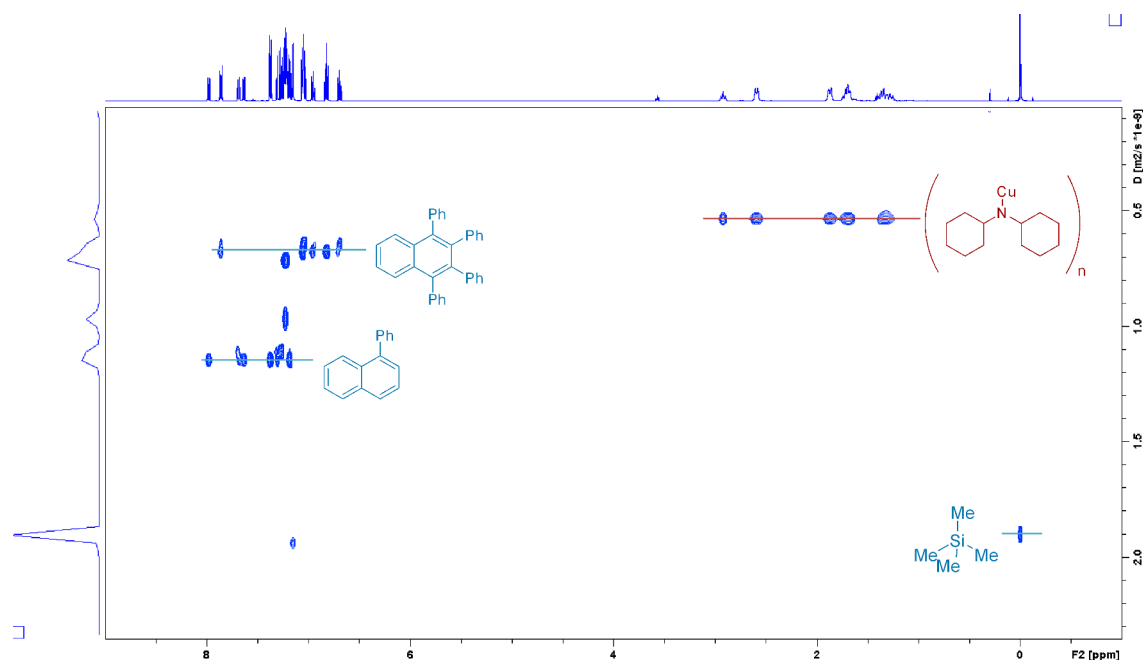


Figure 2.17: ¹H DOSY NMR spectrum of **2.8** with internal standards at 0.05 M concentration in benzene-d₆.

Compounds	r_{calc} (Å)	$\text{Log}(r_{calc}/\text{Å})$	D_{obs} (m ² s ⁻¹)	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$
1,2,3,4-Tetraphenylnaphthalene	5.81	0.764	6.67×10^{-10}	-9.18
1-Phenylnaphthalene	4.65	0.668	1.15×10^{-9}	-8.94
Tetramethylsilane	3.90	0.591	1.90×10^{-9}	-8.72
$y = -2.62x - 7.18$ $r^2 = 0.998$				
	D_{obs} (m ² s ⁻¹)	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$	Calculated $\text{Log}(r_{obs}/\text{Å})$	r_{obs} (Å)
Complex 2.8	5.36×10^{-10}	-9.27	0.798	6.28

Table 2.14: *D-r* analysis from ¹H DOSY NMR data of **2.8** with internal standards at 0.05 M concentration in benzene-d₆

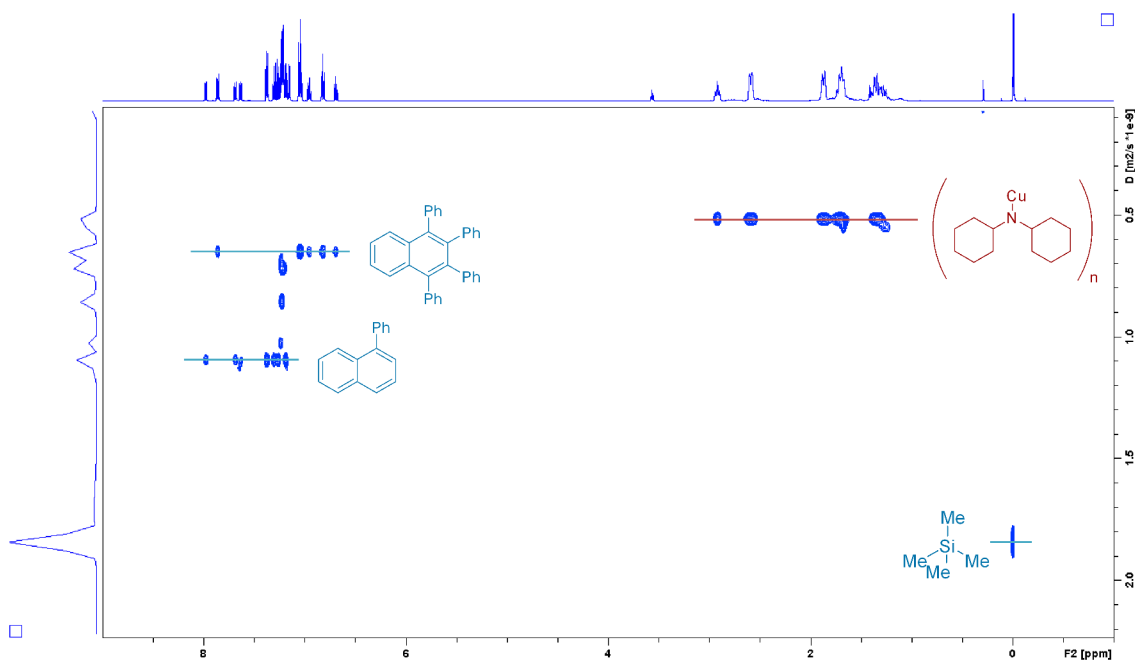


Figure 2.18: ^1H DOSY NMR spectrum of **2.8** with internal standards at 0.15 M concentration in benzene- d_6 .

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthalene	5.81	0.764	6.53×10^{-10}	-9.18
1-Phenylnaphthalene	4.65	0.668	1.10×10^{-9}	-8.96
Tetramethylsilane	3.90	0.591	1.84×10^{-9}	-8.73
$y = -2.59x - 7.21$ $r^2 = 0.996$				
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.8	5.17×10^{-10}	-9.29	0.800	6.31

Table 2.15: D - r analysis from ^1H DOSY NMR data of **2.8** with internal standards at 0.15 M concentration in benzene- d_6

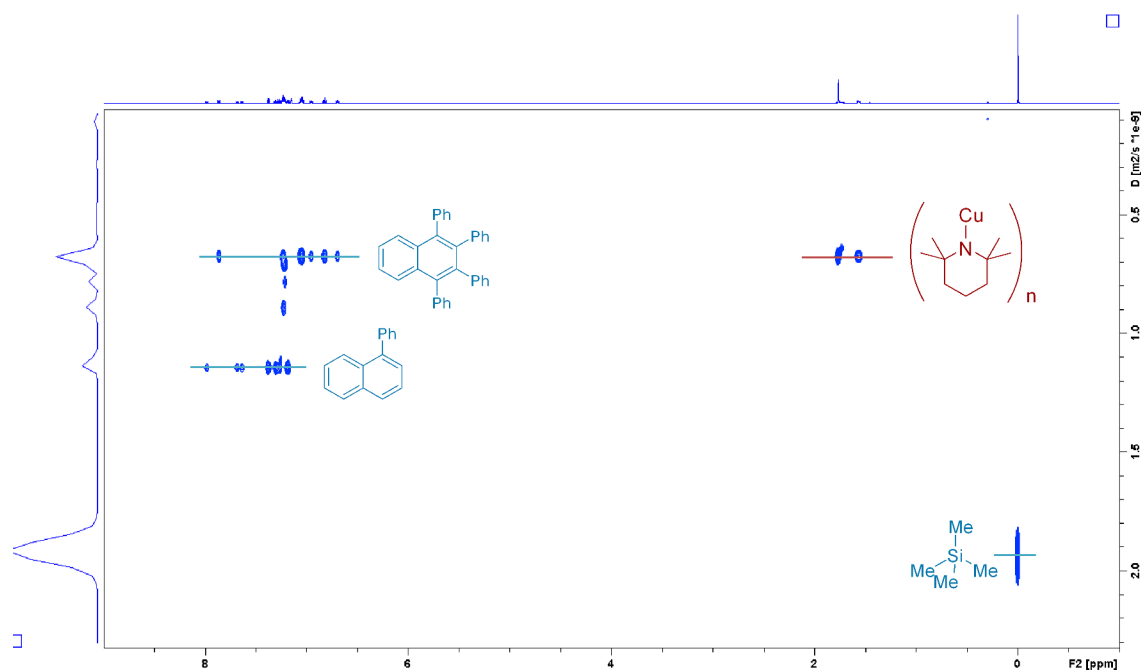


Figure 2.19: ^1H DOSY NMR spectrum of **2.9** with internal standards at 0.05 M concentration in benzene- d_6 .

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthylene	5.81	0.764	6.77×10^{-10}	-9.17
1-Phenylnaphthylene	4.65	0.668	1.15×10^{-9}	-8.94
Tetramethylsilane	3.90	0.591	1.93×10^{-9}	-8.71
$y = -2.62x - 7.18 \quad r^2 = 0.996$				
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.9	6.77×10^{-10}	-9.17	0.761	5.77

Table 2.16: D - r analysis from ^1H DOSY NMR data of **2.9** with internal standards at 0.05 M concentration in benzene- d_6

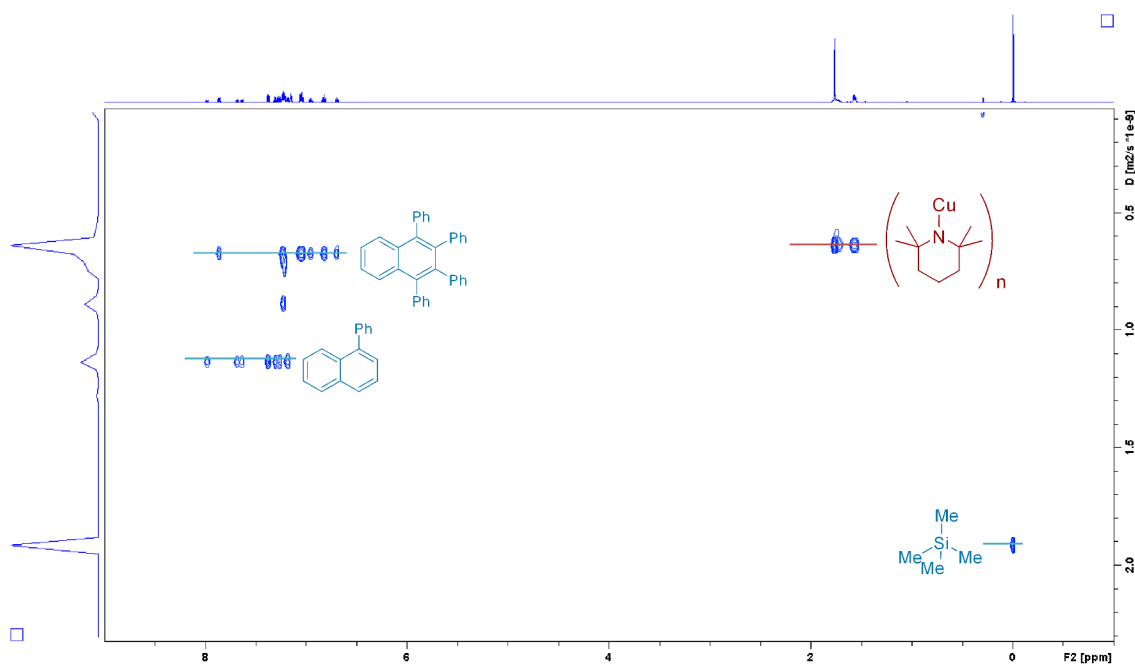


Figure 2.20: ^1H DOSY NMR spectrum of **2.9** with internal standards at 0.10 M concentration in benzene- d_6 .

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthalene	5.81	0.764	6.76×10^{-10}	-9.17
1-Phenylnaphthalene	4.65	0.668	1.14×10^{-9}	-8.94
Tetramethylsilane	3.90	0.591	1.92×10^{-9}	-8.72
$y = -2.60x - 7.19$ $r^2 = 0.996$				
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.9	6.41×10^{-10}	-9.19	0.770	5.89

Table 2.17: D - r analysis from ^1H DOSY NMR data of **2.9** with internal standards at 0.10 M concentration in benzene- d_6

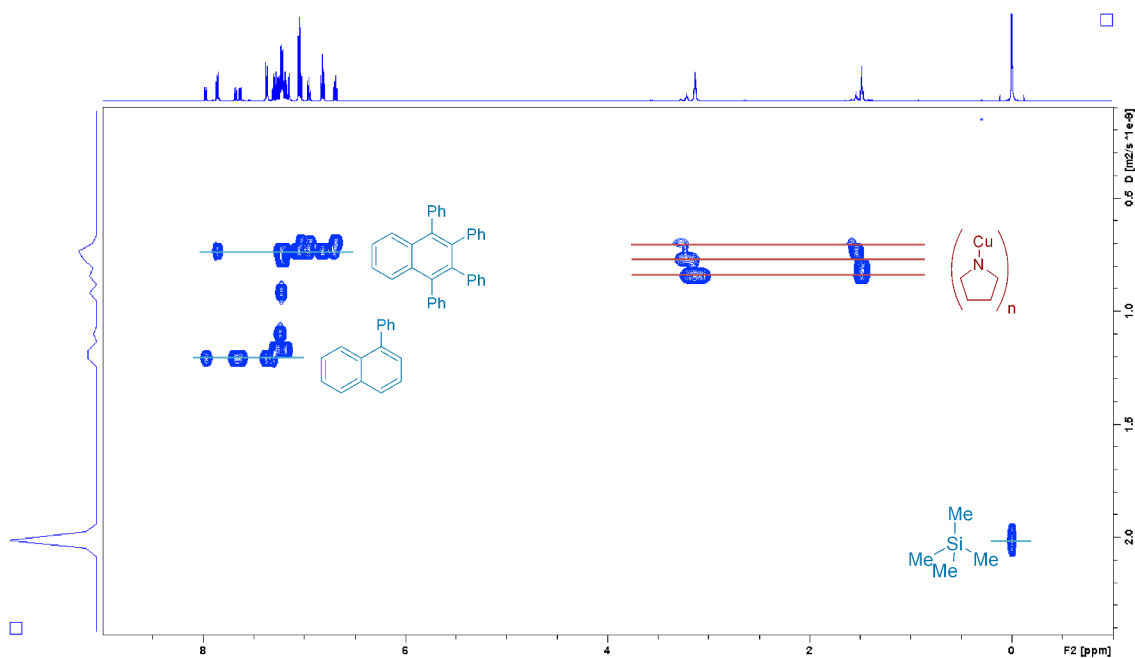


Figure 2.21: ^1H DOSY NMR spectrum of **2.10** with internal standards at 0.05 M concentration in benzene- d_6 .

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthalene	5.81	0.764	7.36×10^{-10}	-9.13
1-Phenylnaphthalene	4.65	0.668	1.21×10^{-9}	-8.92
Tetramethylsilane	3.90	0.591	2.01×10^{-9}	-8.70
$y = -2.51x - 7.22 \quad r^2 = 0.995$				
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.10	8.45×10^{-10}	-9.07	0.737	5.45
	7.72×10^{-10}	-9.11	0.752	5.65
	7.00×10^{-10}	-9.16	0.769	5.88

Table 2.18: D - r analysis from ^1H DOSY NMR data of **2.10** with internal standards at 0.05 M concentration in benzene- d_6

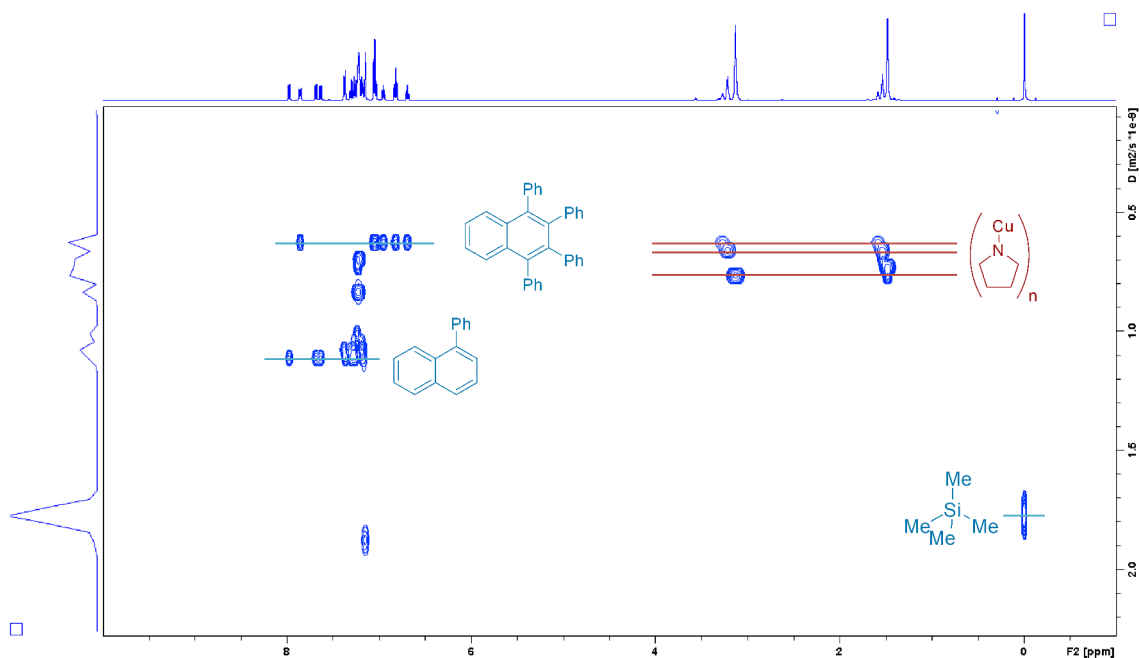


Figure 2.22: ^1H DOSY NMR spectrum of **2.10** with internal standards at 0.20 M concentration in benzene- d_6 .

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthlene	5.81	0.764	6.28×10^{-10}	-9.20
1-Phenylnaphthlene	4.65	0.668	1.11×10^{-9}	-8.95
Tetramethylsilane	3.90	0.591	1.77×10^{-9}	-8.75
$y = -2.60x - 7.21 \quad r^2 = 1.000$				
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.10	7.67×10^{-10}	-9.12	0.730	5.38
	6.63×10^{-10}	-9.18	0.755	5.68
	6.28×10^{-10}	-9.20	0.764	5.80

Table 2.19: D - r analysis from ^1H DOSY NMR data of **2.10** with internal standards at 0.20 M concentration in benzene- d_6

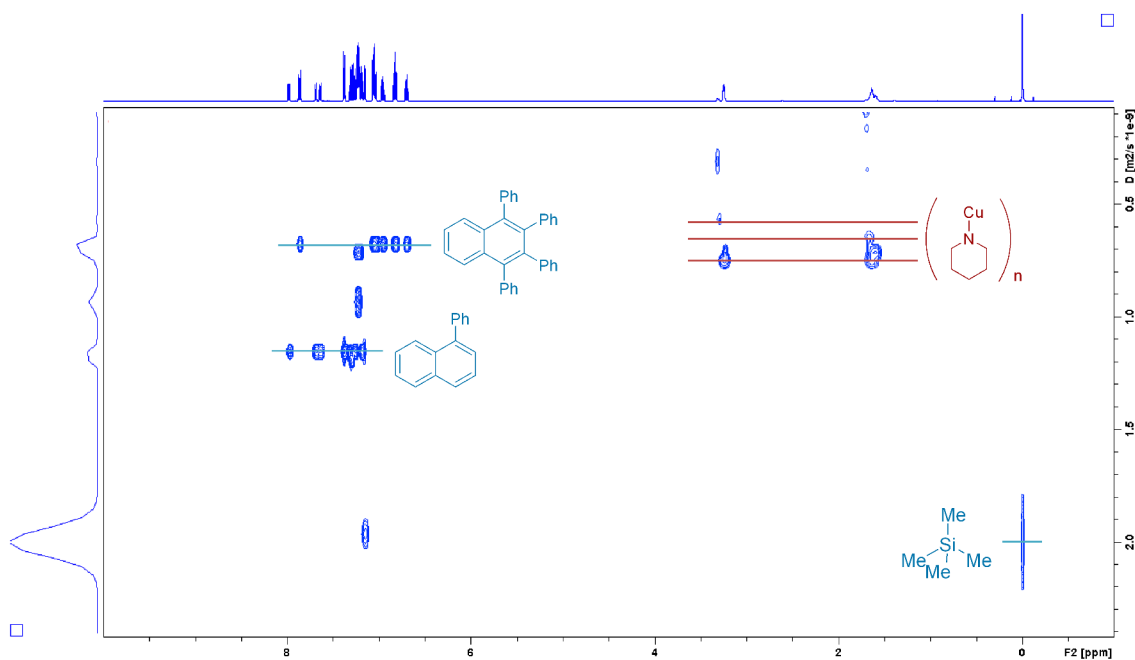


Figure 2.23: ^1H DOSY NMR spectrum of **2.11** with internal standards at 0.05 M concentration in benzene- d_6 .

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthlene	5.81	0.764	6.79×10^{-10}	-9.17
1-Phenylnaphthlene	4.65	0.668	1.16×10^{-9}	-8.94
Tetramethylsilane	3.90	0.591	2.00×10^{-9}	-8.70
$y = -2.70x - 7.12$ $r^2 = 0.995$				
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.11	7.52×10^{-10}	-9.12	0.744	5.55
	6.41×10^{-10}	-9.19	0.770	5.89
	5.67×10^{-10}	-9.25	0.790	6.16

Table 2.20: D - r analysis from ^1H DOSY NMR data of **2.11** with internal standards at 0.05 M concentration in benzene- d_6

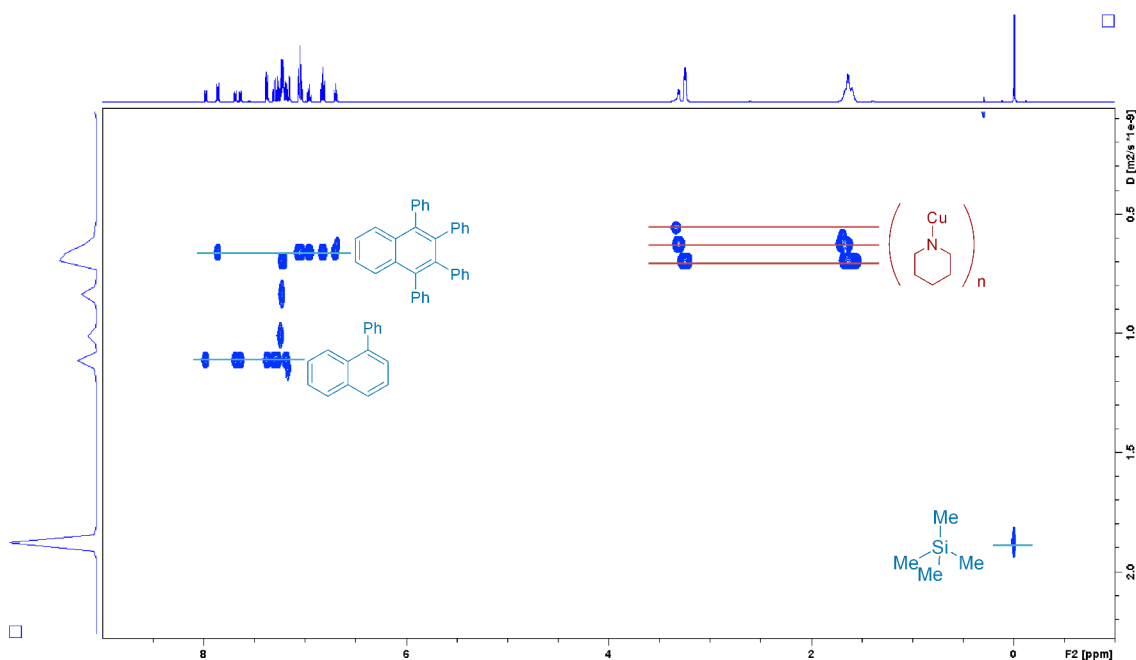


Figure 2.24: ^1H DOSY NMR spectrum of **2.11** with internal standards at 0.20 M concentration in benzene- d_6 .

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthalene	5.81	0.764	6.63×10^{-10}	-9.18
1-Phenylnaphthalene	4.65	0.668	1.12×10^{-9}	-8.95
Tetramethylsilane	3.90	0.591	1.88×10^{-9}	-8.73
$y = -2.60x - 7.20$		$r^2 = 0.996$		
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.11	6.98×10^{-10}	-9.16	0.752	5.65
	6.29×10^{-10}	-9.20	0.770	5.89
	5.59×10^{-10}	-9.25	0.789	6.16

Table 2.21: D - r analysis from ^1H DOSY NMR data of **2.11** with internal standards at 0.20 M concentration in benzene- d_6

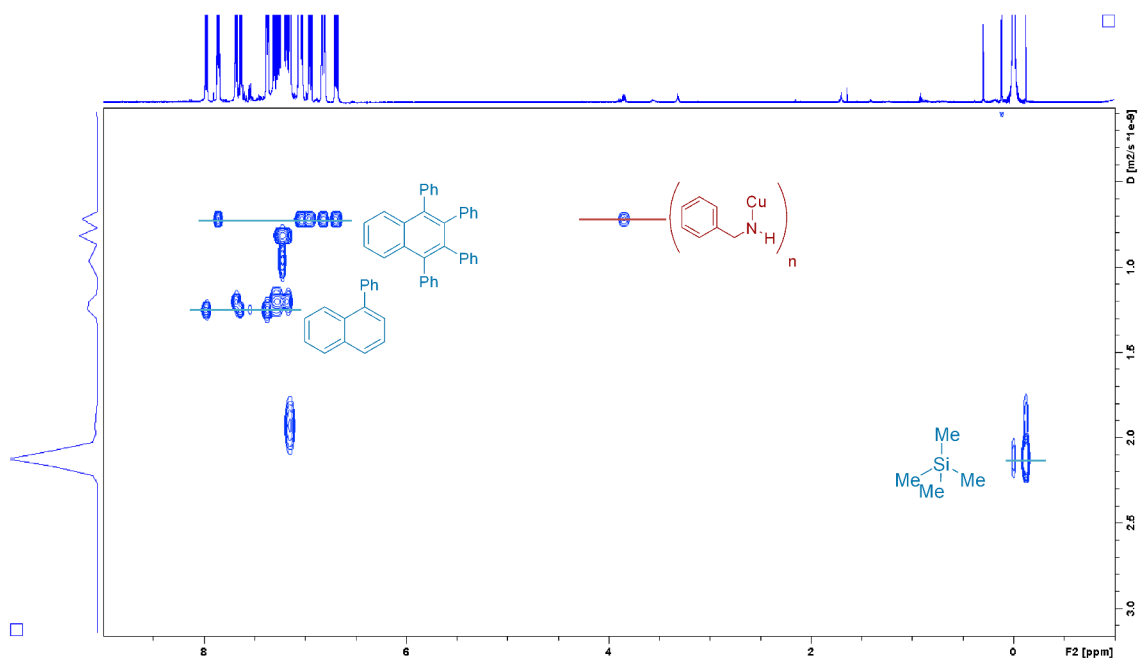


Figure 2.25: ^1H DOSY NMR spectrum of **2.12** with internal standards at 0.01 M concentration in benzene- d_6 .

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthlene	5.81	0.764	7.22×10^{-10}	-9.14
1-Phenylnaphthlene	4.65	0.668	1.25×10^{-9}	-8.90
Tetramethylsilane	3.90	0.591	2.12×10^{-9}	-8.67
$y = -2.70x - 7.09 \quad r^2 = 0.997$				
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.12	7.22×10^{-10}	-9.14	0.762	5.78

Table 2.22: D - r analysis from ^1H DOSY NMR data of **2.12** with internal standards at 0.01 M concentration in benzene- d_6

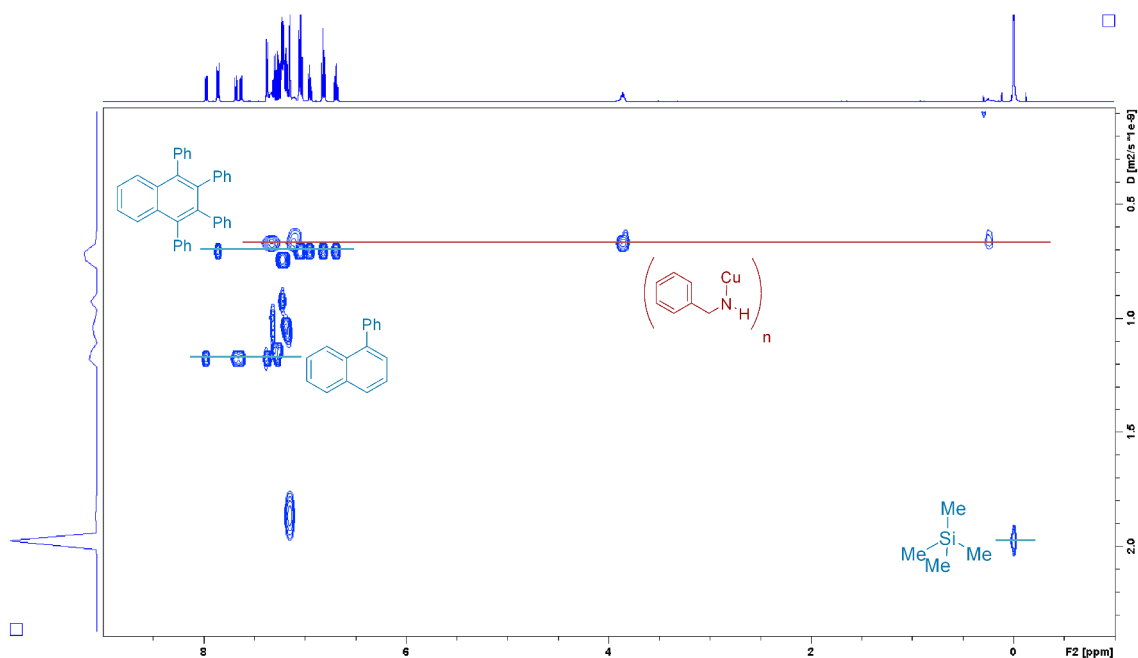


Figure 2.26: ^1H DOSY NMR spectrum of **2.12** with internal standards at 0.05 M concentration in benzene- d_6 .

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthalene	5.81	0.764	7.08×10^{-10}	-9.15
1-Phenylnaphthalene	4.65	0.668	1.18×10^{-9}	-8.93
Tetramethylsilane	3.90	0.591	1.98×10^{-9}	-8.70
$y = -2.56x - 7.20 \quad r^2 = 0.995$				
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.12	6.72×10^{-10}	-9.17	0.770	5.88

Table 2.23: D - r analysis from ^1H DOSY NMR data of **2.12** with internal standards at 0.05 M concentration in benzene- d_6

2.5.2 D-FW analysis of ¹H DOSY NMR data of complexes **2.10** and **2.11**

Compounds	FW_{calc}	$\text{Log}(FW_{calc})$	D_{obs} (m ² s ⁻¹)	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$
1,2,3,4-Tetraphenylnaphthlene	5.81	0.764	7.36×10^{-10}	-9.13
1-Phenylnaphthlene	4.65	0.668	1.21×10^{-9}	-8.92
Tetramethylsilane	3.90	0.591	2.01×10^{-9}	-8.70
$y = -0.63x - 7.46$ $r^2 = 0.999$				
	D_{obs} (m ² s ⁻¹)	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$	Calculated $\text{Log}(FW_{obs})$	FW_{obs}
Complex 2.10	8.45×10^{-10}	-9.07	2.546	351.85
	7.72×10^{-10}	-9.11	2.608	405.97
	7.00×10^{-10}	-9.16	2.676	474.39

Table 2.24: D-FW analysis from ¹H DOSY NMR data of **2.10** with internal standards at 0.05 M concentration in benzene-d₆

Compounds	FW_{calc}	$\text{Log}(FW_{calc})$	D_{obs} (m ² s ⁻¹)	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$
1,2,3,4-Tetraphenylnaphthlene	5.81	0.764	6.28×10^{-10}	-9.20
1-Phenylnaphthlene	4.65	0.668	1.11×10^{-9}	-8.95
Tetramethylsilane	3.90	0.591	1.77×10^{-9}	-8.75
$y = -0.65x - 7.47$ $r^2 = 0.999$				
	D_{obs} (m ² s ⁻¹)	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$	Calculated $\text{Log}(FW_{obs})$	FW_{obs}
Complex 2.10	7.67×10^{-10}	-9.12	2.523	333.05
	6.63×10^{-10}	-9.18	2.620	416.70
	6.28×10^{-10}	-9.20	2.656	452.59

Table 2.25: D-FW analysis from ¹H DOSY NMR data of **2.10** with internal standards at 0.20 M concentration in benzene-d₆

Compounds	FW_{calc}	$\text{Log}(FW_{calc})$	$D_{obs} \text{ (m}^2 \text{ s}^{-1}\text{)}$	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$
1,2,3,4-Tetraphenylnaphthlene	5.81	0.764	6.79×10^{-10}	-9.17
1-Phenylnaphthlene	4.65	0.668	1.16×10^{-9}	-8.94
Tetramethylsilane	3.90	0.591	2.00×10^{-9}	-8.70
$y = -0.68x - 7.37$		$r^2 = 0.999$		
	$D_{obs} \text{ (m}^2 \text{ s}^{-1}\text{)}$	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$	Calculated $\text{Log}(FW_{obs})$	FW_{obs}
Complex 2.11	7.52×10^{-10}	-9.12	2.575	376.19
	6.41×10^{-10}	-9.19	2.677	475.81
	5.67×10^{-10}	-9.25	2.756	570.18

Table 2.26: *D-FW* analysis from ^1H DOSY NMR data of **2.11** with internal standards at 0.05 M concentration in benzene- d_6

Compounds	FW_{calc}	$\text{Log}(FW_{calc})$	$D_{obs} \text{ (m}^2 \text{ s}^{-1}\text{)}$	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$
1,2,3,4-Tetraphenylnaphthlene	5.81	0.764	6.63×10^{-10}	-9.18
1-Phenylnaphthlene	4.65	0.668	1.12×10^{-9}	-8.95
Tetramethylsilane	3.90	0.591	1.88×10^{-9}	-8.73
$y = -0.66x - 7.45$		$r^2 = 0.999$		
	$D_{obs} \text{ (m}^2 \text{ s}^{-1}\text{)}$	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$	Calculated $\text{Log}(FW_{obs})$	FW_{obs}
Complex 2.11	6.98×10^{-10}	-9.16	2.609	406.12
	6.29×10^{-10}	-9.20	2.678	476.69
	5.59×10^{-10}	-9.25	2.756	570.29

Table 2.27: *D-FW* analysis from ^1H DOSY NMR data of **2.11** with internal standards at 0.20 M concentration in benzene- d_6

2.5.3 ^1H NMR data of 2.10 and 2.11 at 0.05 M and 0.20 M concentration in benzene- d_6

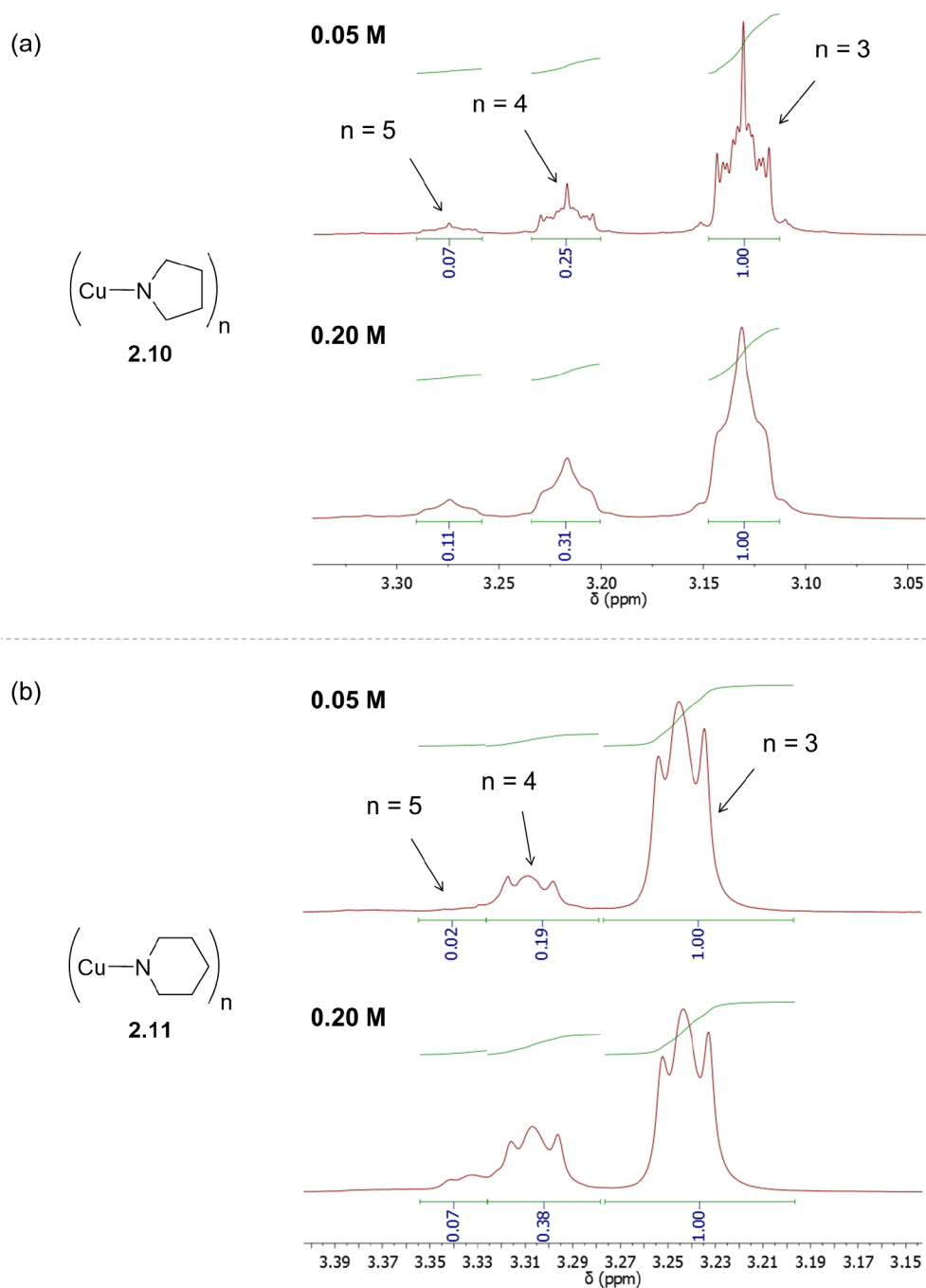


Figure 2.27: Cropped ^1H NMR spectra comparing the integrals for the $\alpha\text{-CH}_2$ protons' resonances of the trimeric ($n = 3$), tetrameric ($n = 4$) and pentameric ($n = 5$) aggregates at 0.05 and 0.20 M concentration in benzene- d_6 of (a) **2.10** and (b) **2.11**.

2.5.4 Linear regression analysis of r_{calc} vs. aggregate number, n , for 2.8 – 2.12

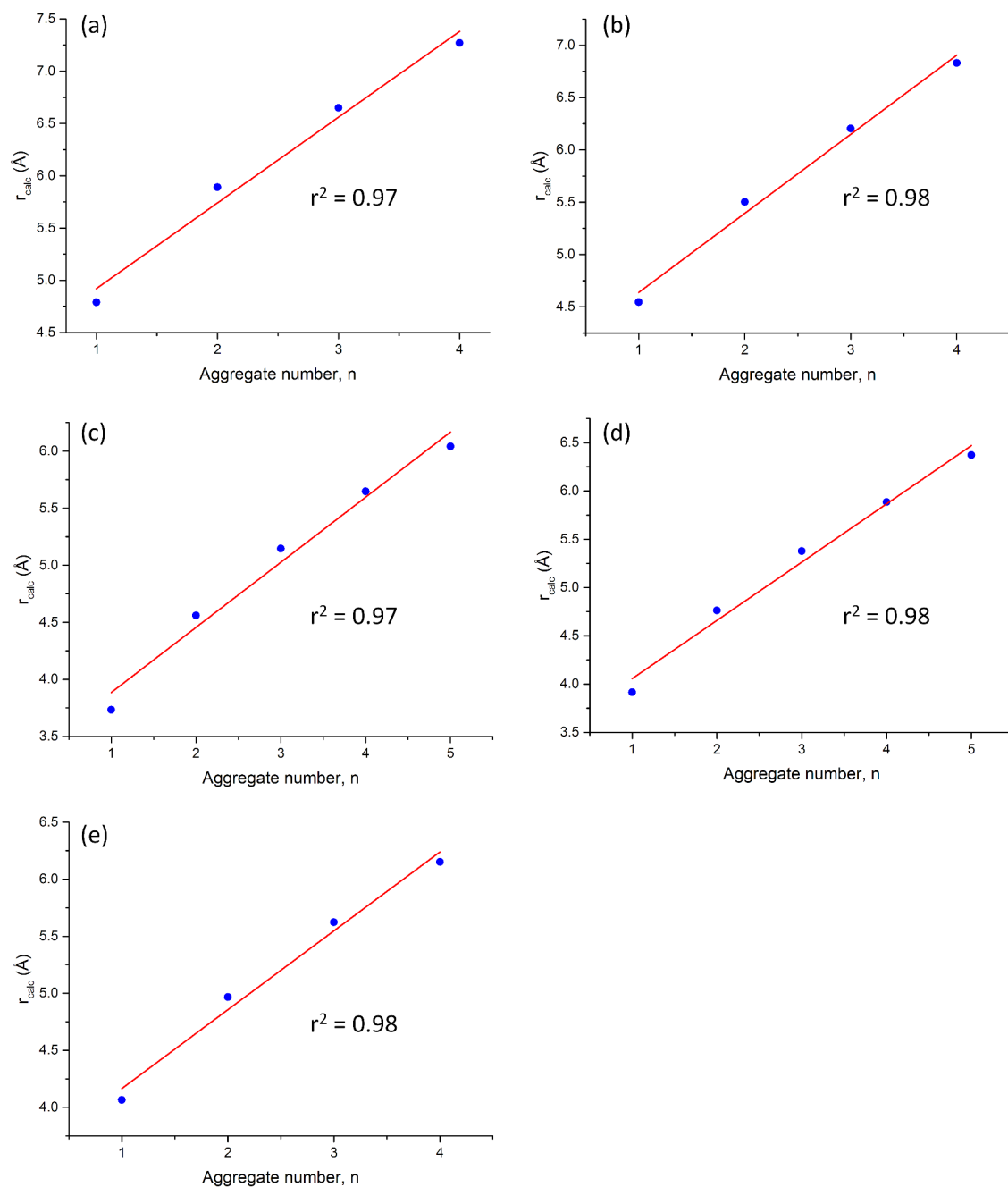


Figure 2.28: Linear regression analysis of r_{calc} vs. aggregate number, n , for complexes (a) 2.8, (b) 2.9, (c) 2.10, (d) 2.11 and (e) 2.12.

2.5.5 ¹H DOSY NMR spectra of complexes **2.10** and **2.11** in the presence of 1,10-phenanthroline with internal standards

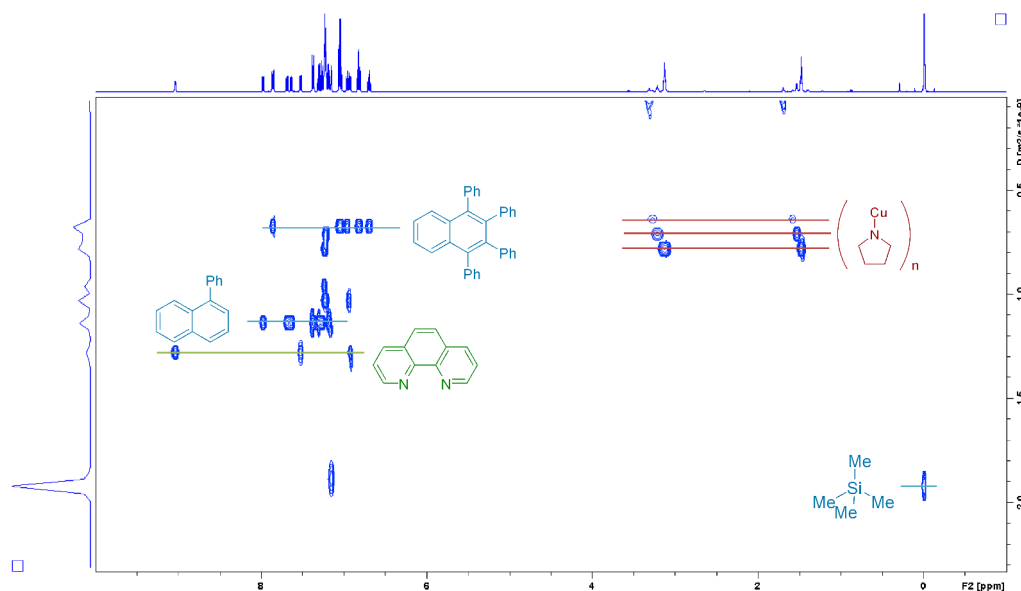


Figure 2.29: ¹H DOSY NMR spectrum of **2.10** with one equivalent of 1,10-phenanthroline and internal standards in benzene-d₆ at 0.05 M concentration

Compounds	r_{calc} (Å)	$\text{Log}(r_{calc}/\text{Å})$	D_{obs} (m ² s ⁻¹)	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$
1,2,3,4-Tetraphenyl-naphthalene	5.81	0.764	6.76×10^{-10}	-9.17
1-Phenyl-naphthalene	4.65	0.668	1.14×10^{-9}	-8.94
Tetramethylsilane	3.90	0.591	1.92×10^{-9}	-8.73
1,10-Phenanthroline	4.40	—	—	—
$y = -2.61x - 7.18 \quad r^2 = 0.996$				
	D_{obs} (m ² s ⁻¹)	$\text{Log}(D_{obs} / \text{m}^2 \text{ s}^{-1})$	Calculated $\text{Log}(r_{obs}/\text{Å})$	r_{obs} (Å)
Complex 2.10	7.83×10^{-10}	-9.11	0.737	5.45
Complex 2.10	7.12×10^{-10}	-9.15	0.752	5.65
Complex 2.10	6.41×10^{-10}	-9.19	0.770	5.89
1,10-Phenanthroline	1.28×10^{-9}	-8.89	0.655	4.51

Table 2.28: *D-r* analysis from ¹H DOSY NMR data of **2.10** with one equivalent of 1,10-phenanthroline and internal standards in benzene-d₆ at 0.05 M concentration

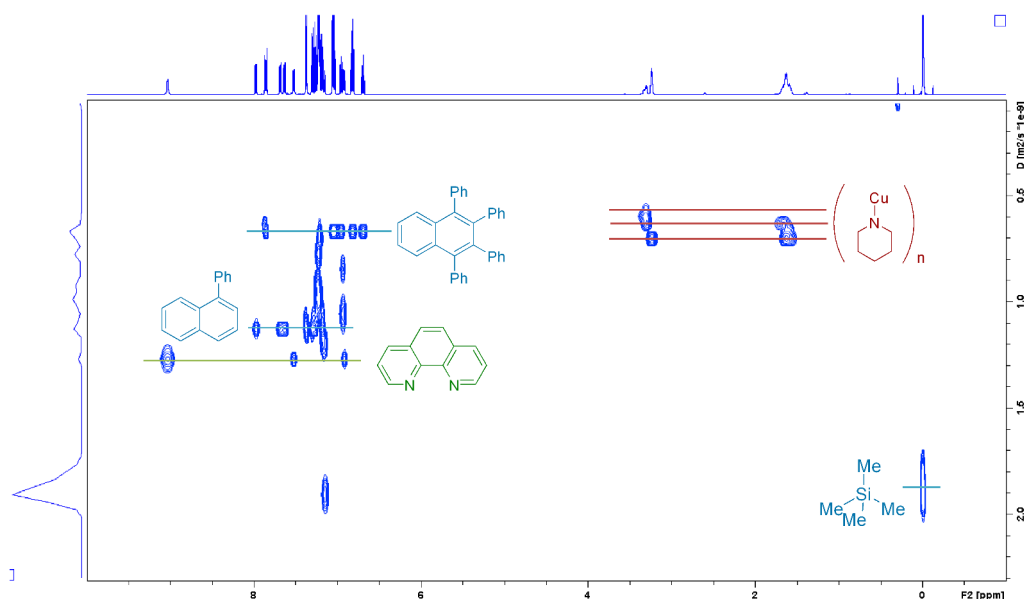


Figure 2.30: ^1H DOSY NMR spectrum of **2.11** with one equivalent of 1,10-phenanthroline and internal standards in benzene- d_6 at 0.05 M concentration

Compounds	r_{calc} (Å)	$\text{Log}(r_{\text{calc}}/\text{Å})$	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$
1,2,3,4-Tetraphenylnaphthalene	5.81	0.764	6.70×10^{-10}	-9.17
1-Phenylnaphthalene	4.65	0.668	1.13×10^{-9}	-8.95
Tetramethylsilane	3.90	0.591	1.91×10^{-9}	-8.72
1,10-Phenanthroline	4.40	—	—	—
$y = -2.61x - 7.19 \quad r^2 = 0.996$				
	D_{obs} ($\text{m}^2 \text{s}^{-1}$)	$\text{Log}(D_{\text{obs}} / \text{m}^2 \text{s}^{-1})$	Calculated $\text{Log}(r_{\text{obs}}/\text{Å})$	r_{obs} (Å)
Complex 2.11	7.06×10^{-10}	-9.15	0.752	5.65
Complex 2.11	6.34×10^{-10}	-9.20	0.770	5.89
Complex 2.11	5.64×10^{-10}	-9.25	0.790	6.16
1,10-Phenanthroline	1.27×10^{-9}	-8.90	0.654	4.51

Table 2.29: D - r analysis from ^1H DOSY NMR data of **2.11** with one equivalent of 1,10-phenanthroline and internal standards in benzene- d_6 at 0.05 M concentration

2.5.6 ESI-MS data

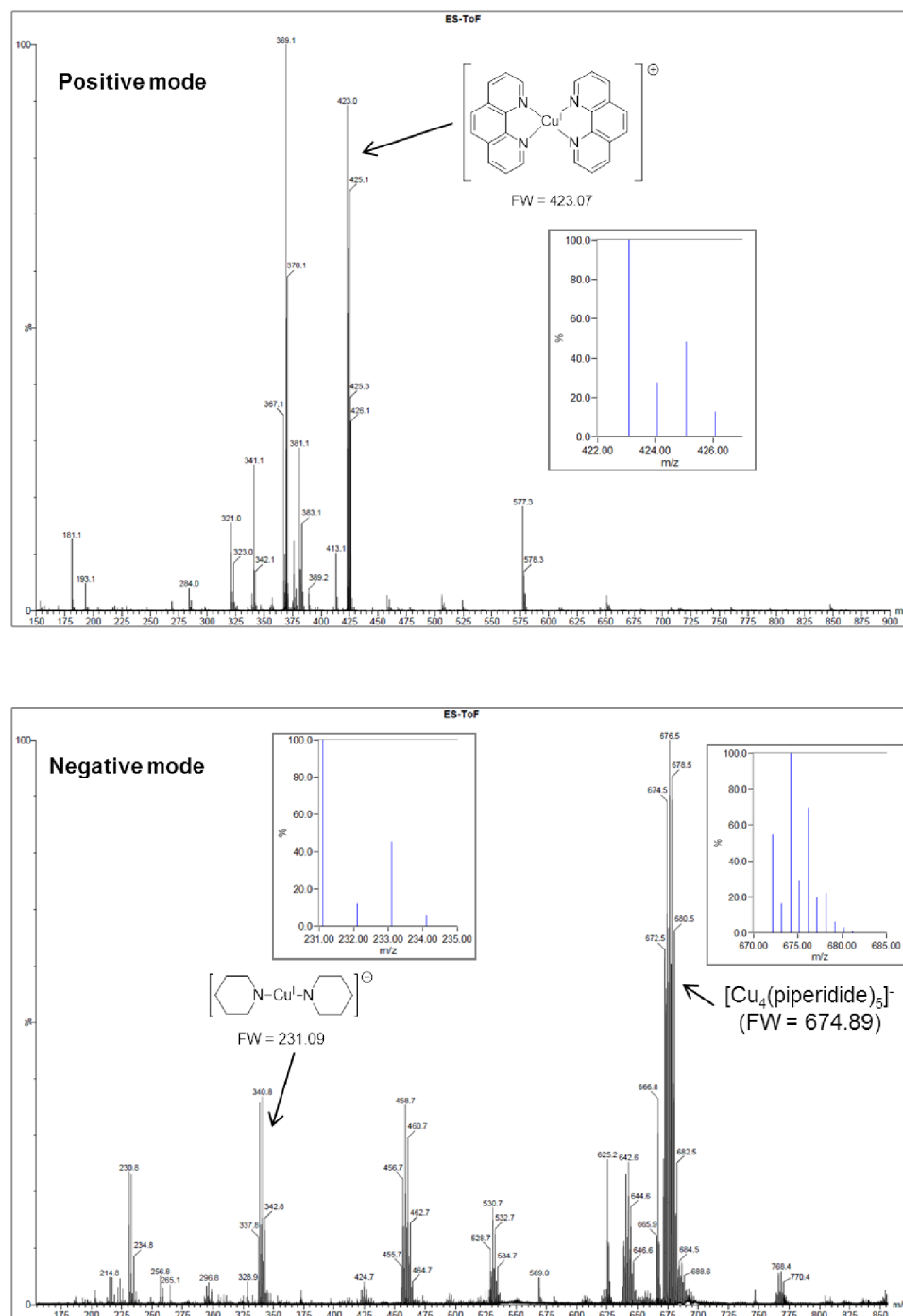


Figure 2.31: Positive and negative mode ESI-MS data of **2.11** in the presence of one equivalent of 1,10-phenanthroline in DMSO. Inset mass spectra show the expected isotope patterns for the adjacent ions.

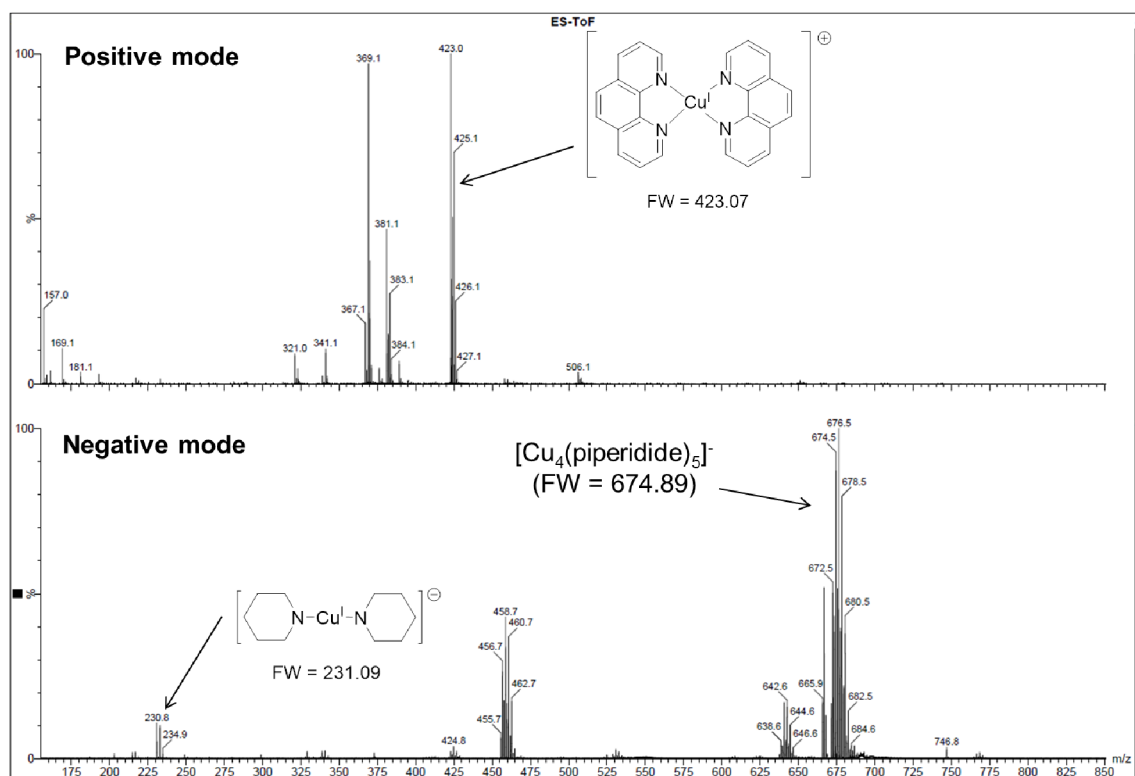


Figure 2.32: Positive and negative mode ESI-MS data of **2.11** in the presence of one equivalent of 1,10-phenanthroline in benzene.

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- [46] Densities of copper(I) amide complexes **2.8**, **2.9** and **2.11** were X-ray crystallographically determined in this work. Density of complex **2.10** taken from reference [31].
- [47] See Appendix Section 2.5.1 for the calculations involved in the *D-r* analysis of ^1H DOSY NMR data of complexes **2.8** – **2.12**.
- [48] See Appendix Section 2.5.3 for the ^1H NMR spectra of complexes **2.10** and **2.11** at 0.05 M and 0.20 M in benzene- d_6 .
- [49] See Appendix Section 2.5.4 for the linear regression analysis of r_{calc} vs. aggregate number, n , for complexes **2.8** – **2.12**.
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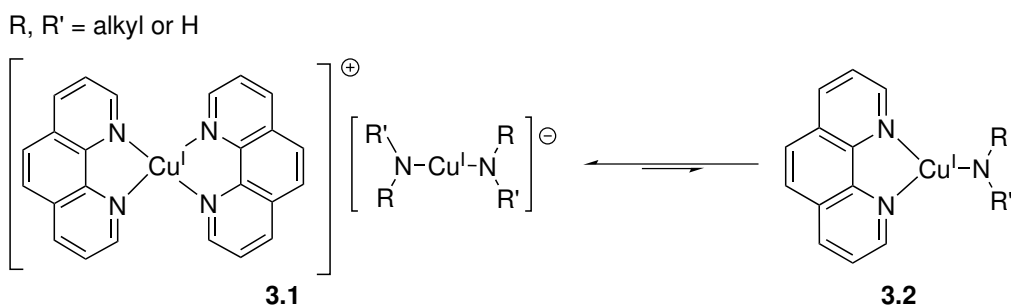
Chapter 3

The Effect of *N,N*-, *O,O*- and *N,O*-Chelating Ligands in the Modified Ullmann Amination Reaction and A Kinetic Investigation of the 1,3-Diketone-Ligated Copper-Catalysed *N*-Arylation of Alkylamines

3.1 Introduction

3.1.1 *N,N*-chelating ligands in copper-catalysed cross-coupling of alkylamines and aryl halides

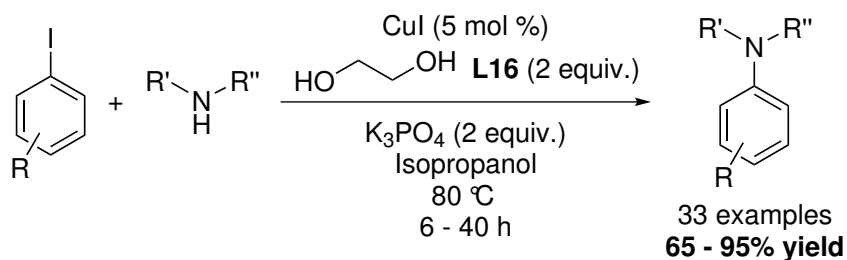
Chapter 2 explored the use of 1,10-phenanthroline (phen) (**L3**) as a *N,N*-chelating ancillary ligand in the copper-catalysed cross-coupling reactions between alkylamines and iodobenzene in polar solvent and found that it had a detrimental effect on the reactivity despite being widely used in analogous reactions for arylamine substrates.^[1–7] The poor reactivity was suggested to be due to the copper catalyst being present almost exclusively as the ionic $[\text{Cu}(\text{phen})_2]^+[\text{Cu}(\text{NRR}')_2]^-$ off-cycle species (**3.1**) in polar solvent in an equilibrium with the neutral active $[\text{Cu}(\text{phen})(\text{NRR}')]$ species (**3.2**), which was not experimentally observed (Scheme 3.1). This finding is in agreement with a mechanistic study reported by Hartwig and co-workers for the copper-catalysed arylation of arylamines where $\text{R}, \text{R}' = \text{Ph}$.^[7] Systematic investigations into influencing this equilibrium by modifying the structure or substituents on **L3** to affect the reactivity have not been reported in the literature. Copper-catalysed systems employing *N,N*-chelating ancillary ligands that can efficiently C–N cross-couple alkylamines and aryl halides have also so far not been reported in the literature. This could be attributed, at least in part, to the previously described unfavourable equilibrium in Scheme 3.1.



Scheme 3.1: Scheme showing the equilibrium in polar solvent between the unreactive ionic $[\text{Cu}(\text{phen})_2]^+[\text{Cu}(\text{NRR}')_2]^-$ complex (**3.1**) and the neutral active $[\text{Cu}(\text{phen})(\text{NRR}')]$ species (**3.2**).

3.1.2 *O,O*- and *N,O*-chelating ligands in copper-catalysed cross-coupling of alkylamines and aryl halides

In the literature, *O,O*- and *N,O*-chelating ligands have been employed more frequently than *N,N*-chelating ligands in the cross-coupling of alkylamine and aryl halide substrates.^[8–14] An



Scheme 3.2: Reaction scheme for the copper-catalysed modified Ullmann reaction between alkylamines and iodobenzene with ethylene glycol (**L16**) as the ligand as reported by Buchwald and co-workers.^[15]

early system that excelled at cross-coupling alkylamines and electron-rich and poor aryl halide substrates was reported by Buchwald and co-workers in 2002 using ethylene glycol (**L16**) as an ancillary ligand in 2-propanol solvent (Scheme 3.2).^[15] Buchwald's reaction system was found to chemoselectively *N*-arylate aliphatic amine groups over arylamine groups with a variety of functionalised aryl iodides. Primary amines were also selectively *N*-arylated over secondary amine moieties. Interestingly, although this type of catalytic system typically requires anaerobic reaction conditions, C–N cross-coupling could be performed in air using certain substrates such as piperidine, 2-aminoethanol and *n*-hexylamine which reacted cleanly with iodobenzene to give 80, 82 and 85% yields of their respective *N*-arylated products. However, C–N cross-coupling reactions involving aryl bromides were not reported. The origin of the enhancement from the use of **L16** was not mentioned by the authors. However it is interesting to speculate that **L16** was not only acting as a chelating ligand for the copper catalyst, but also as a phase-transfer catalyst to alleviate potential mass transfer limitations caused by the insoluble potassium phosphate base.

Compounds such as *N,N*-dialkylsalicylamides,^[16] α -amino acids^[9,10] and 1,3-diketones,^[11,12] which deprotonate in the basic reaction conditions to form anionic species, were first reported in 2003 to have a positive effect on reactivity when used as ancillary chelating ligands for the copper-catalysed cross-coupling between alkylamines and aryl iodides and bromides. For example, incorporating catalytic amounts of *N,N*-diethylsalicylamide (**L17**, Figure 3.1) or α -amino acids such as *L*-proline (**L9**, Figure 3.1) or *N,N*-dimethylglycine (**L8**, Figure 3.1) (2 – 4 equivalents relative to the copper loading) into cross-coupling reactions have successfully promoted the *N*-arylation of alkylamines using more difficult aryl bromide substrates at elevated temperatures.^[9,10,16] However, despite the advances made using these ligands, long reaction

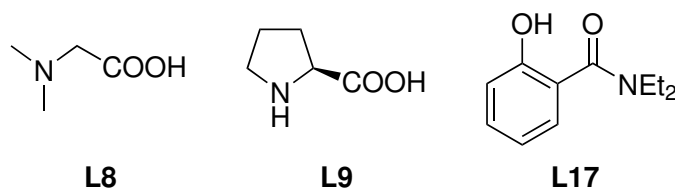
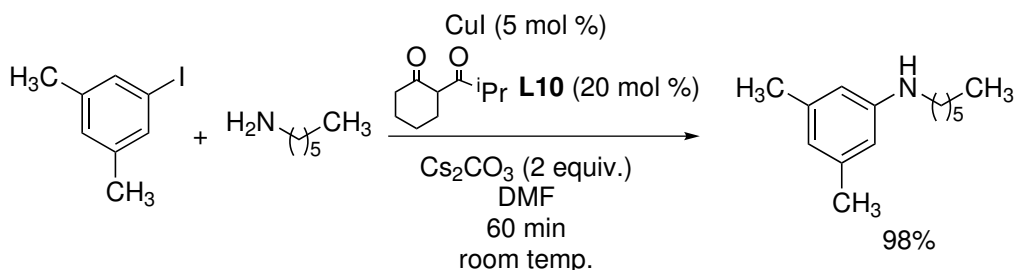


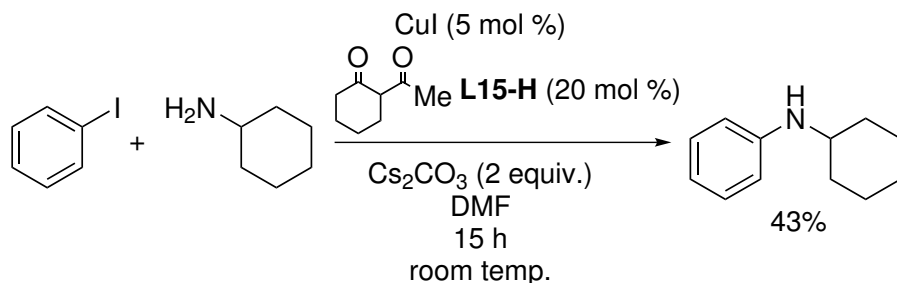
Figure 3.1: Examples of protic *O,O*- and *N,O*-chelating compounds that have been reported as bidentate ancillary ligands in modified Ullmann reactions between alkylamines and aryl bromides.^[9,10,16]

times (18 – 40 hours) and relatively high temperatures (80 – 100 °C) were still required. A breakthrough in improved reaction conditions and reaction rates came when 1,3-diketones such as 2-isobutyrylcyclohexanone (**L10**) were reported to promote the reaction between aryl iodides and alkylamines at room temperature with reaction times as short as 60 minutes (Scheme 3.3).^[11] Although a kinetic profile of the aryl iodide conversion over time for the reaction in Scheme 3.3 was produced using reaction calorimetry, an experimental mechanistic study of this catalytic system and the role of the ligand was not reported by the authors. Computational studies on the 1,3-diketone-ligated modified Ullmann amination reaction have been reported by Buchwald,^[17] Fu^[18] and Ding^[19] although there is no consensus between these reports on the overall mechanism of the reaction.

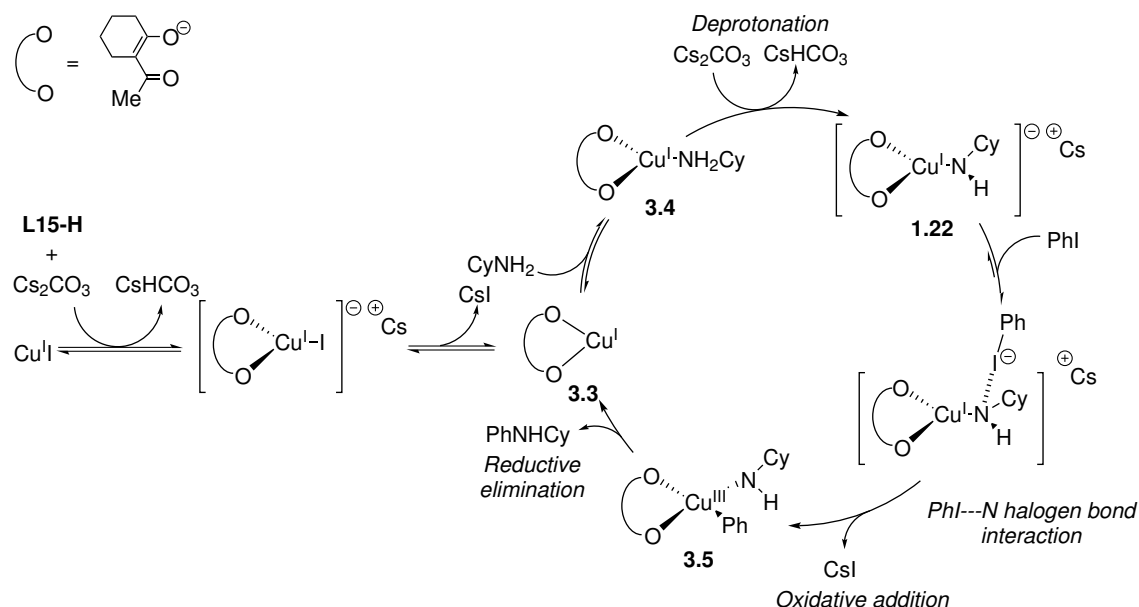


Scheme 3.3: Reaction scheme for the copper-catalysed modified Ullmann reaction between *n*-hexylamine and iodobenzene with 2-isobutyrylcyclohexanone as the ligand reported by Buchwald and co-workers.^[11]

To date, the only reported mechanistic study with experimental evidence using a protic ligand was by Jutand and co-workers for the 2-acetylcyclohexanone (**L15-H**) ligated reaction shown in Scheme 3.4.^[13,14,20] As discussed previously in Section 1.4.4.3, Chapter 1, through the use of cyclic voltammetry and ¹H NMR spectroscopy, copper intermediates in the mechanism leading up to the catalyst resting state [**L15**-Cu^I-NHCy][−] (**1.22**) were identified (Scheme 3.5).^[13,14,20]



Scheme 3.4: Reaction scheme for the copper-catalysed modified Ullmann amination reaction with 2-acetylcyclohexanone as the ligand studied by Jutand and co-workers.^[13,14,20]



Scheme 3.5: Catalytic cycle for the copper-catalysed *N*-arylation of cyclohexylamine with the 2-acetylcyclohexanone as the ligand proposed by Jutand and co-workers.^[13,14,20]

In the proposed mechanism, the initial steps involve the deprotonation of **L15-H** followed by coordination to form the on-cycle copper(I) intermediate **3.3**. This is then followed by amine coordination to give intermediate **3.4**. Formation of the catalyst resting state **1.22** was then completed after deprotonation of the N–H group in the coordinated amine. As the 1,3-diketone ligand is anionic, the catalyst resting state **1.22** is overall anionic, which is in contrast to the neutral catalyst resting state when neutral *N,N*-chelating ligands are used. DFT calculations showed that the aryl iodide activation mechanism can involve an oxidative addition *via* a halogen bond interaction between the iodine atom on the aryl iodide and the most electron-rich atom on **1.22**, which was calculated to be the nitrogen atom on the amido ligand (Scheme 3.5).

After forming the short-lived, undetected copper(III) intermediate **3.5**, reductive elimination then occurs to give the product and regenerate **3.3**. The role of the ligand was not explored in the mechanistic study but given the proposed importance of the halogen bond interaction between intermediate **1.22** and the aryl iodide, it is likely that the ancillary ligand could affect this process by changing the electronic properties of the nitrogen atom in the amido co-ligand.

To summarise, it is clear from the literature that anionic *O,O*- and *N,O*-chelating ligands have a significant role in the mechanism for the copper-catalysed cross-coupling of alkylamines and aryl halides, given the dramatic improvement in the reaction rate compared to when neutral *N,N*-chelating ligands such as **L3** are used. Although some mechanistic information using protic ligands was obtained by Jutand *et al* (Scheme 3.5), a kinetic study was not performed to confirm the proposed mechanism, determine the rate dependences in the reaction components and identify other processes such as possible deactivation pathways. Furthermore, mechanistic information regarding the role of protic ligands in this type of reaction and how it differs from when neutral *N,N*-chelating ligands are used is currently limited in the literature. For example, equilibria analogous to the one shown in Scheme 3.1 have not been observed in the literature when anionic *O,O*- and *N,O*-chelating ligands are utilised.

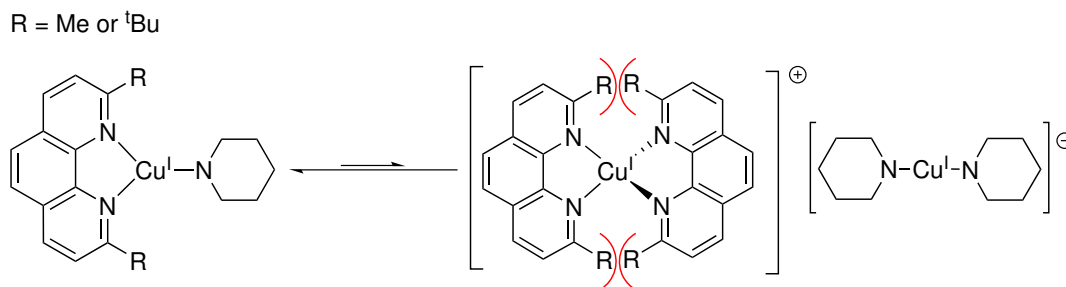
To improve the current understanding of the role of ligands in the modified Ullmann amination reaction of alkylamines and aryl iodides, a study on the kinetics of this reaction was undertaken. To minimise complications due to over *N*-arylation of amine substrates, the nucleophile used was a secondary amine. Although secondary amines typically exhibit poor reactivity,^[10] cyclic amines react better than acyclic amines therefore the reactions in this work involved coupling of piperidine with iodobenzene to give *N*-phenylpiperidine. Firstly, the ligand to be investigated in the kinetic study was selected from a screening experiment that investigated the effect of a range of *N,N*-, *O,O*- and *N,O*-chelating ligands on the coupling yield. Using this ligand, the rate dependence on the base equivalents and catalyst, ligand and substrates concentrations on the C–N cross-coupling reaction have been determined. Catalyst deactivation, inhibition and the effects of the reaction components on these processes were also investigated. Finally, solution equilibria in the catalytic cycle have been proposed using the mechanistic information obtained in this study.

3.2 Results and Discussion

3.2.1 Ligand screening

Before conducting an investigation into the role of the ligand in the mechanism, a ligand screening study was undertaken to investigate the effect of electron density, sterics and chelating ability of the ligands on the coupling yield for the model reaction between piperidine with iodobenzene to give *N*-phenylpiperidine. The reaction conditions used in the screening experiment and the product yields obtained are shown in Figure 3.2. The order of addition was found to be an important factor for catalyst stability when protic ligands pyrrole-2-carboxylic acid (**L7**), *L*-proline (**L9**), 2-acetylcyclohexanone (**L15-H**) or picolinic acid (**L19**) were used. When iodobenzene is added last to initiate the reactions, noticeable disproportionation to give copper(II) and copper(0) had already occurred in the reaction mixtures containing the ligands, copper(I) iodide, base, piperidine and solvent. Therefore, copper(I) iodide was added last to initiate the reactions instead of iodobenzene which minimised catalyst deactivation by disproportionation prior to initiation of the coupling reaction.

The added steric bulk in the 2,9-positions of *N,N*-chelating ligands neocuproine (**L4**) and 2,9-di(*tert*-butyl)-1,10-phenanthroline (*^t*Bu-phen) (**L18**) compared to phen (**L3**) has been reported to influence the equilibrium shown in Scheme 3.6 towards the neutral species by causing steric crowding in the $[\text{CuL}_2]^+$ cation of the ionic species^[21]. It was therefore postulated that using these ligands may improve the reactivity by favouring the formation of the catalytically active neutral species. However the product yields when **L4** (2%) and **L18** (5%) were used were not significantly different in comparison to when **L3** (5%) or ligand-free conditions (6%) were used.



Scheme 3.6: Scheme illustrating the potential effect of using the sterically bulky **L4** or **L18** as the ancillary ligand in driving the equilibrium from the ionic off-cycle species towards the neutral active species. Possible steric crowding shown in red.

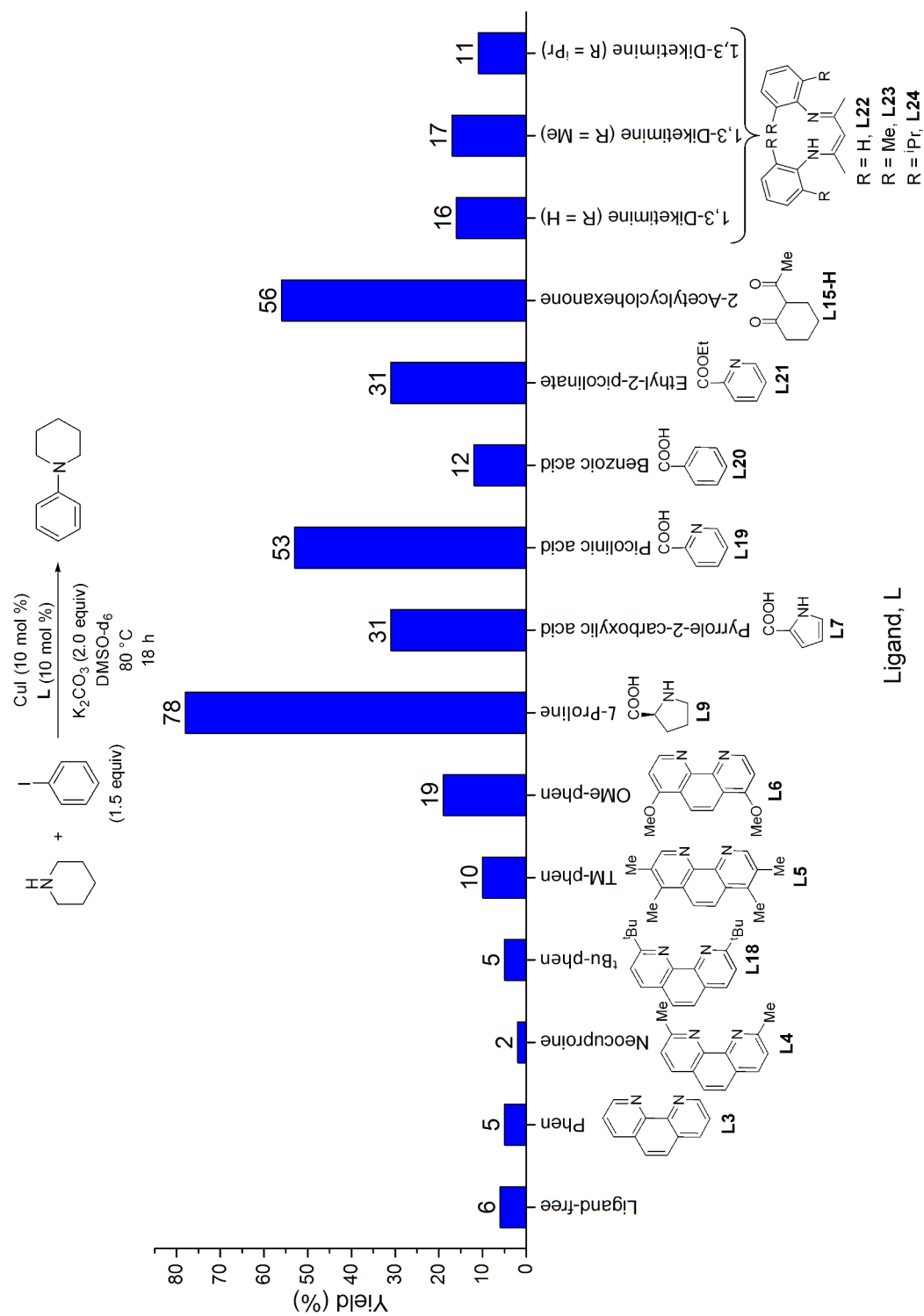


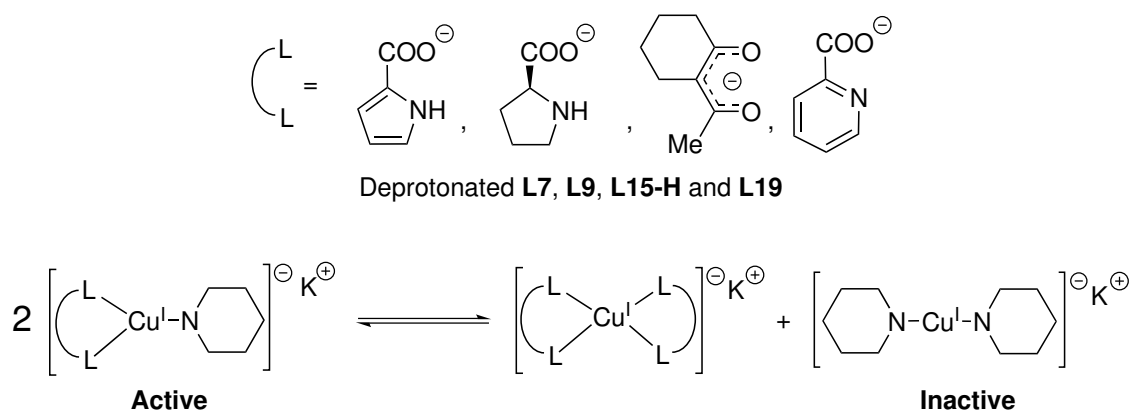
Figure 3.2: N-phenylpiperidine yields obtained from a ligand screening of the reaction shown in the scheme above.

Although the equilibrium in Scheme 3.6 would have been affected by the additional steric bulk in **L4** and **L18**, this increased steric bulk is also likely to inhibit other steps in the catalytic cycle. When the more electron-rich 3,4,7,8-tetramethyl-1,10-phenanthroline (TM-phen) (**L5**) and 4,7-dimethoxy-1,10-phenanthroline (OMe-phen) (**L6**) ligands were used, the yields marginally increased compared to phen to 10% and 19% respectively. This suggests that increasing the electron density of the copper(I) centre is advantageous, possibly favouring faster oxidative addition of the aryl halide. The increase in *N*-phenylpiperidine yield using **L5** or **L6** is in agreement with a report by Buchwald and co-workers who found that using either of these two ligands in the copper-catalysed cross-coupling between alcohols and aryl halides produced higher product yields than for **L3**.^[22]

The highest yield was achieved using *N,O*-chelating ligand *L*-proline (**L9**) (78%). Although the structure of pyrrole-2-carboxylic acid (**L7**) is similar to **L9**, the yield observed using it was lower (31%). This may be due to the unavailability of the lone pair of electrons on the nitrogen on **L7** for coordination, which in turn would make it a poorer chelating ligand than **L9**. Conversely, chelation is possible using picolinic acid (**L19**) as it has a free lone pair of electrons on the nitrogen atom, and therefore may explain why it produced a better coupling yield (53%) than **L7**. The effect of chelation on the yield is also apparent when comparing the yields obtained using *N,O*-chelating ligand **L19** and benzoic acid (**L20**) (12%). In addition, the poorer chelating ability of ethyl 2-picolinate (**L21**) in comparison to **L19**, in which an ethyl ester group that cannot be deprotonated under these reaction conditions formally replaces the carboxylic acid group in **L19**, also resulted in a lower yield (31%). The *O,O*-chelating ligand 2-acetylcyclohexanone (**L15-H**) gave moderate yields (56%). The ability of 1,3-diketimine compounds **L22** – **L24** to function as ligands was also tested as they are similar in structure to 1,3-diketones. However, poor yields were observed in all cases (yields $\leq 17\%$). This could be the result of the significantly different electronic character and large steric hindrance around the nitrogen atoms compared to **L15-H**.

Overall, it appears that the chelating ability of the ligand is crucial to giving good yields in this coupling reaction. This is in agreement with results by Chaudhari and co-workers, who suggested that the blocking of adjacent *cis* sites on the copper catalyst by a bidentate ligand would promote coordination of the amine and aryl groups in a *cis* mode in a square planar copper(III) intermediate and therefore enhance reactivity.^[23] As noted in Section 3.1.1, the poor cross-coupling yield using neutral ligand **L3** is due to an equilibrium where an inactive di(amido)cuprate species is significantly favoured over the active catalyst species (Scheme

3.1). As **L7**, **L9**, **L15-H** and **L19** are protic, they deprotonate in the reaction mixture to form anionic *O,O*- and *N,O*-chelating ligands. As a result, the three-coordinate catalyst resting state species would be negatively charged (Scheme 3.7). Therefore the better yields obtained using these anionic ligands compared to neutral phen (**L3**) could be because the equilibrium between the active catalyst species and an inactive di(amido)cuprate species (Scheme 3.7) is either no longer present or has shifted in favour of the active species. Another possible reason could be the electron density of the active complex is greater using anionic ligands than neutral ligands, which would be favourable for oxidative addition.^[22]



Scheme 3.7: Hypothetical equilibrium between the active catalyst species and an inactive di(amido)cuprate species when **L7**, **L9**, **L15-H** and **L19** are used.

Although using *L*-proline (**L9**) as the ligand produced the best yield in the ligand screening, its poor solubility in DMSO made it unsuitable for use in detailed kinetic studies. Therefore 2-acetylcyclohexanone (**L15-H**) was taken forward for use as the ancillary ligand as it is miscible with DMSO.

To ensure accuracy and reproducibility, all compounds other than the insoluble inorganic bases were added as solutions in DMSO to the reaction mixtures. ¹H NMR analysis of the reaction mixture of the **L15-H** promoted copper-catalysed reaction with potassium carbonate as the base after heating at 80 °C for 18 hours (Table 3.1, entry 1) revealed that 28% yield of water is also generated. The water was likely formed from the hydrogen carbonate by-product acting as a base. Given that this type of reaction is air and moisture sensitive, the water produced would have likely caused some irreversible catalyst deactivation. In order to avoid this catalyst deactivation, alternative commonly used inorganic bases, caesium carbonate and potassium phosphate, were tested (Table 3.1). When caesium carbonate was used, only 15% *N*-

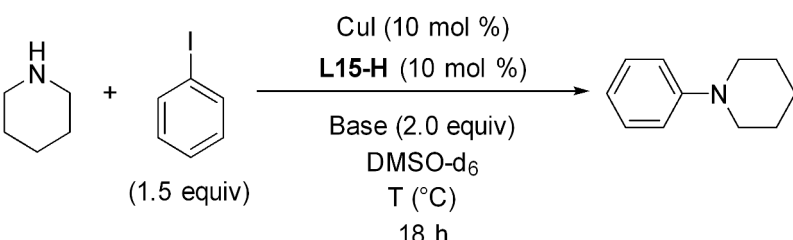
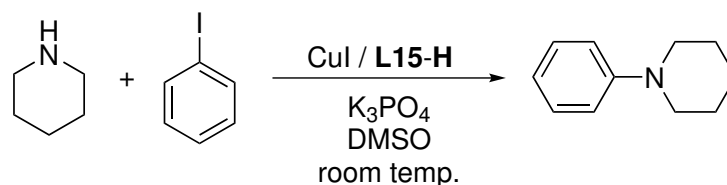
				
Entry	Base	Temperature, T (°C)	Product Yield (%)	PhI conversion (%)
1	K ₂ CO ₃	80	56	56
2	CS ₂ CO ₃	80	15	29
3	K ₃ PO ₄	80	67	69
4	K ₃ PO ₄	room temp.	56	56

Table 3.1: Product yields and iodobenzene conversions when different bases and reaction temperatures were employed in the reaction shown in the scheme above. Yields and conversions were determined by ¹H NMR spectroscopy using mesitylene as an internal standard.

phenylpiperidine yield was produced in addition to an unknown compound from a side-reaction, which accounted for the excess iodobenzene conversion (Table 3.1, entry 2). In contrast, when potassium phosphate was employed as the base, the yield improved to 67% (Table 3.1, entry 3). This reaction also had excellent mass balance between iodobenzene and the product and no water was detected in the ¹H NMR spectrum of the reaction mixture after heating at 80 °C for 18 hours. Furthermore, similar to the modified Ullmann reaction protocol for cross-coupling alkylamines and aryl iodides in DMF solvent reported in the literature,^[11] this ligand and base combination conveniently allowed the reaction to be performed at room temperature to give 56% yield after 18 hours at room temperature in DMSO-d₆ solvent (Table 3.1, entry 4).

As a result of the above studies, an ideal modified Ullmann amination system for kinetic studies that reacts at room temperature and forms no significant by-products was identified (Scheme 3.8).



Scheme 3.8: General reaction scheme for the catalytic system to be studied.

3.2.2 Kinetic studies of the modified Ullmann amination reaction using L15-H as the ancillary ligand

The primary aims of the kinetic study are to determine the rate dependences in the reaction components, propose possible off-cycle species and identify potential deactivation pathways. These will be achieved by observing changes in the reaction rates caused by different initial reactant concentrations.

3.2.2.1 Rate dependence on the equivalents of potassium phosphate base

The heterogeneous nature of the virtually insoluble potassium phosphate base in DMSO could result in a mass transfer limited deprotonation process. To identify if the reaction rate was limited by mass transfer effects, the reaction was first conducted with different equivalents of potassium phosphate base. For the reaction conditions shown in Figure 3.3, a positive reaction rate dependence in the amount of base used was observed, which indicated that the reaction may be mass transfer limited. This was confirmed by a series of experiments which showed

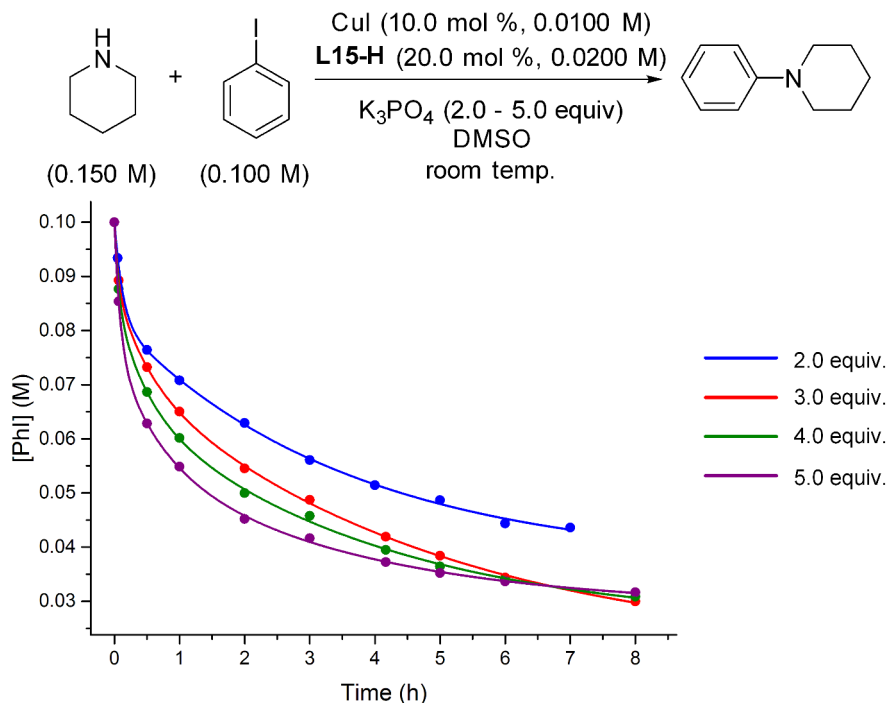


Figure 3.3: [PhI] over the course of the reactions shown in the scheme above using different equivalents of potassium phosphate base. [PhI] were determined by GC using naphthalene as an internal standard.

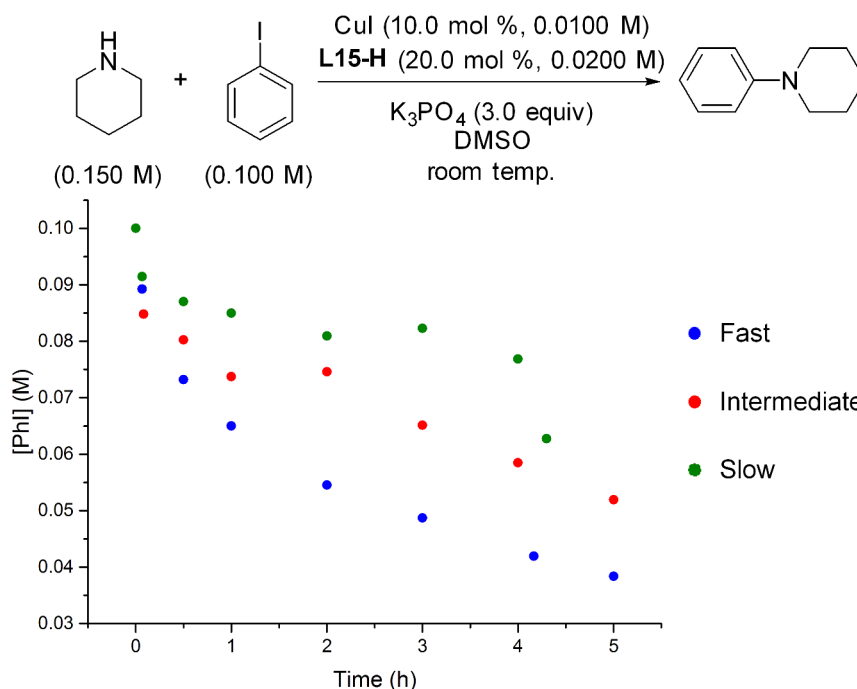


Figure 3.4: [PhI] over the course of the reaction shown in the scheme above using different stirring rates. [PhI] were determined by GC using naphthalene as an internal standard.

that the reaction rate also increases with faster stirring rates (Figure 3.4). The stirring rates used were defined as slow, intermediate or fast, where a slow stirring rate kept most of the base near the lower portion of the reaction solution; an intermediate stirring rate involved stirring the base until it reached half way up the reaction solution; and a fast stirring rate involved constant thorough mixing of the solid base throughout the solution. Stirring using slow and intermediate rates gave irregular reaction rates over time, with lower iodobenzene conversions observed at a given time compared to the fast stirring rate.

Deprotonation of **L15-H** using potassium phosphate typically takes several hours when stirred together in DMSO in the absence of any other compounds. Therefore to determine if the C–H deprotonation of **L15-H** or the N–H group of piperidine was the mass transfer limited process, the reaction was also performed using the pre-formed potassium diketonate salt (**L15-K**) as the ligand. **L15-K** was formed by treating a solution of **L15-H** in THF with potassium tert-butoxide base to give a white precipitate. After filtration, the white precipitate was washed with THF and the dried under vacuum to give pure **L15-K**. From Figure 3.5, the reactions using either the potassium salt or neutral ligand have similar [PhI]-time profiles. This indicates that C–H deprotonation of **L15-H** does not affect the reaction rate, presumably due to enhanced

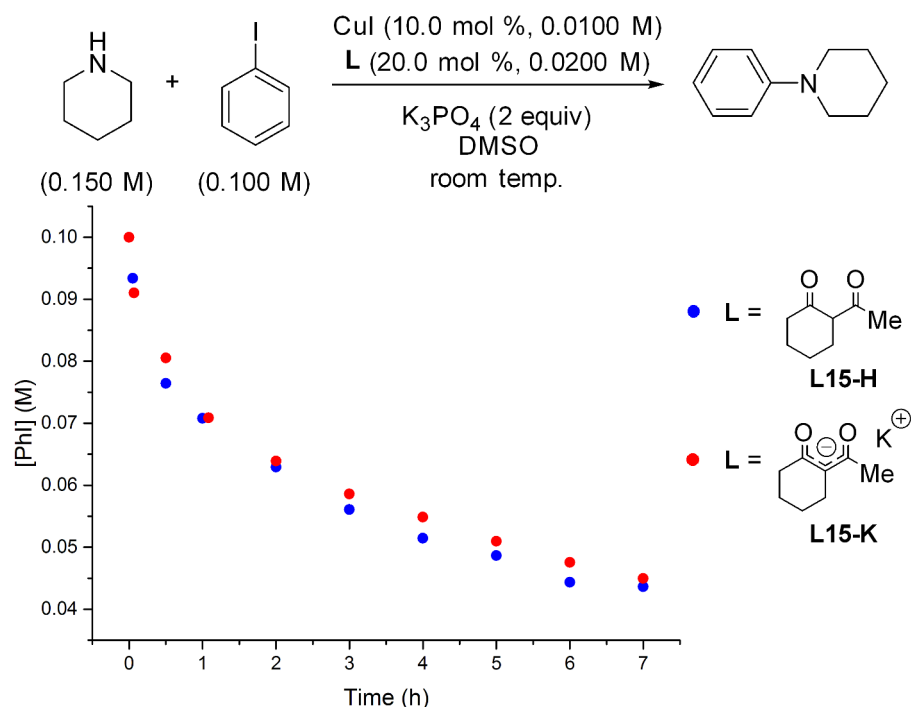


Figure 3.5: [PhI] over the course of the reactions shown in the scheme above using **L15-H** or **L15-K**. [PhI] were determined by GC using naphthalene as an internal standard.

C–H acidity caused by coordination to copper(I) prior to deprotonation. A similar effect has also been suggested for enhanced N–H amine acidity on copper(I) coordination.^[24,25] The deprotonation of the N–H group of piperidine coordinated to copper(I) therefore must be the slow deprotonation step in the reaction.

To summarise, the mass transfer limitation caused by the poorly soluble base unfortunately complicates the quantitative kinetic study due to several factors such as potential irregularities in the stirring efficiency and difficulties in modelling the kinetic data to a proposed mechanism. It may also complicate the interpretation of experiments involving different initial concentrations of the other reactants because they may aid the dissolution of the base, in addition to influencing the inherent reaction kinetics. This in turn will prevent the identification of numerical orders with respect to the substrate and reagent concentrations. Similar effects on the reaction rate caused by poorly soluble inorganic bases in palladium-catalysed Buchwald-Hartwig amination reactions have been previously reported by Meyers and co-workers so this issue is not unique to modified Ullmann reactions.^[26] However despite these issues, a qualitative understanding of the rate dependences in the reactants and also deactivation pathways can still be identified.

3.2.2.2 Rate dependence on catalyst concentration

To determine the rate dependence on catalyst concentration, a set of experiments were performed varying the concentrations of copper(I) iodide and **L15-H** simultaneously whilst maintaining a 1 : 2 ratio of copper(I) iodide and **L15-H**. As shown in Figure 3.6, a positive rate dependence on the catalyst concentration was observed which confirms that copper mediates the reaction. However, the turnover number (TON) by six hours also changed, decreasing from approximately 9.6 to 3.3 on increasing the catalyst loading from 2.0 to 20.0 mol % (Table 3.2). This indicates that a catalyst deactivation process occurs more readily with higher catalyst

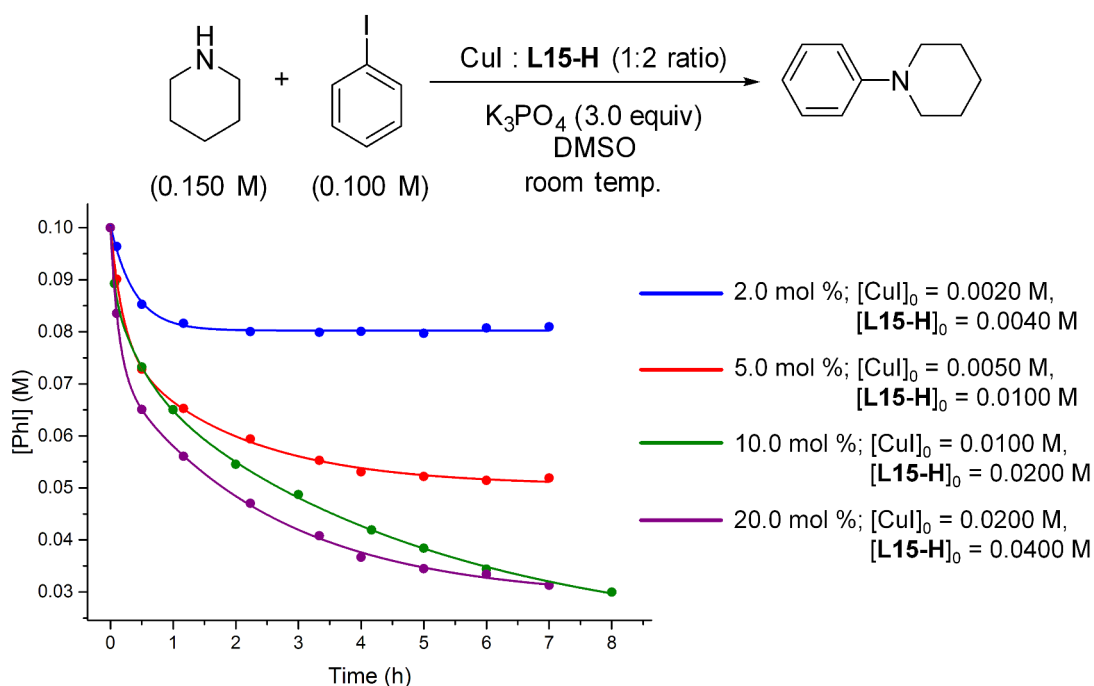


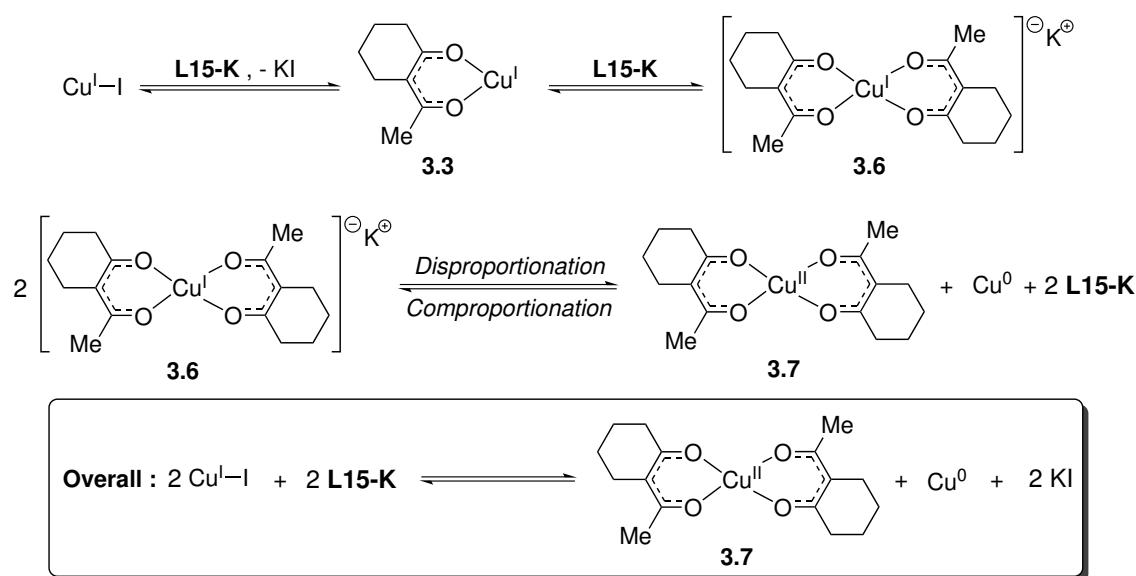
Figure 3.6: [PhI] over the course of the reactions shown in the scheme above using different catalyst loading. [PhI] were determined by GC using naphthalene as an internal standard.

Catalyst amount (mol %)	TON by six hours
2.0	9.6
5.0	9.7
10.0	7.1
20.0	3.3

Table 3.2: Turnover numbers (TON) by six hours achieved using different catalyst loadings in the copper-catalysed cross-coupling of piperidine and iodobenzene.

concentrations. The loss of the ligand by *C*-arylation at the alpha position of **L15-H** was not observed as the mass balance for iodobenzene conversion was consistent with *N*-phenylpiperidine formation. When 20 mol % catalyst was used, a red-grey precipitate, likely to be copper(0), had formed within one hour of the reaction whereas the other catalyst loadings did not produce the same precipitate. Since DMSO solutions of copper(I) iodide under a nitrogen atmosphere were found to be stable at room temperature for several days, a ligand-coordinated complex is likely to be responsible for catalyst deactivation.

Given that disproportionation of bis(diketonate)cuprate complexes ligated by 1,3-diketone enolates, 1,3-keto ester enolates, and 1,3-keto amide enolates to copper(0) and copper(II) are known processes in the literature, catalyst deactivation in this reaction is likely due to disproportionation.^[27–30] Since this disproportionation is a bimolecular reaction, it occurs more readily at higher concentrations of the disproportionating species. Therefore at higher copper concentrations, a greater concentration of off-cycle $\text{K}[\text{Cu}^{\text{I}}(\text{L15})_2]$ (**3.6**) would also be present which in turn would result in increased disproportionation to give copper(II) di(2-acetylcyclohexanonate) (**3.7**) and copper(0) (Scheme 3.9). Although no copper(0) precipitate was observed with 2.0 to 10.0 mol % of catalyst loading, a decrease in TON was still observed with higher catalyst loadings which suggests that disproportionation was still occurring. This implies that soluble copper(0) species were formed. In the literature for a ligand-free palladium-catalysed Heck



Scheme 3.9: Possible equilibria showing the series of **L15** coordination to copper(I) that ultimately leads to disproportionation from **3.6** to give copper(II) and copper(0).

reaction, it has been reported that soluble palladium(0) species are stable against nucleation to palladium black as long as the palladium(0) concentration remains low.^[31] Similarly, the absence of copper(0) precipitate using 2.0 to 10.0 mol % catalyst could have been due to the low copper(0) concentration in solution, compared to when 20.0 mol % catalyst was used.

3.2.2.3 Rate dependence on diketone ligand (L15-H) concentration

After establishing the effect of the amount of base and catalyst concentration on the rate, the rate dependence on [L15-H] was next investigated. As shown in Figure 3.7, the rate at the initial stages of the reaction increases from 10.0 to 100 mol % L15-H loading, which indicates there is a positive rate dependence on [L15-H] at this time in the reaction. This implies that

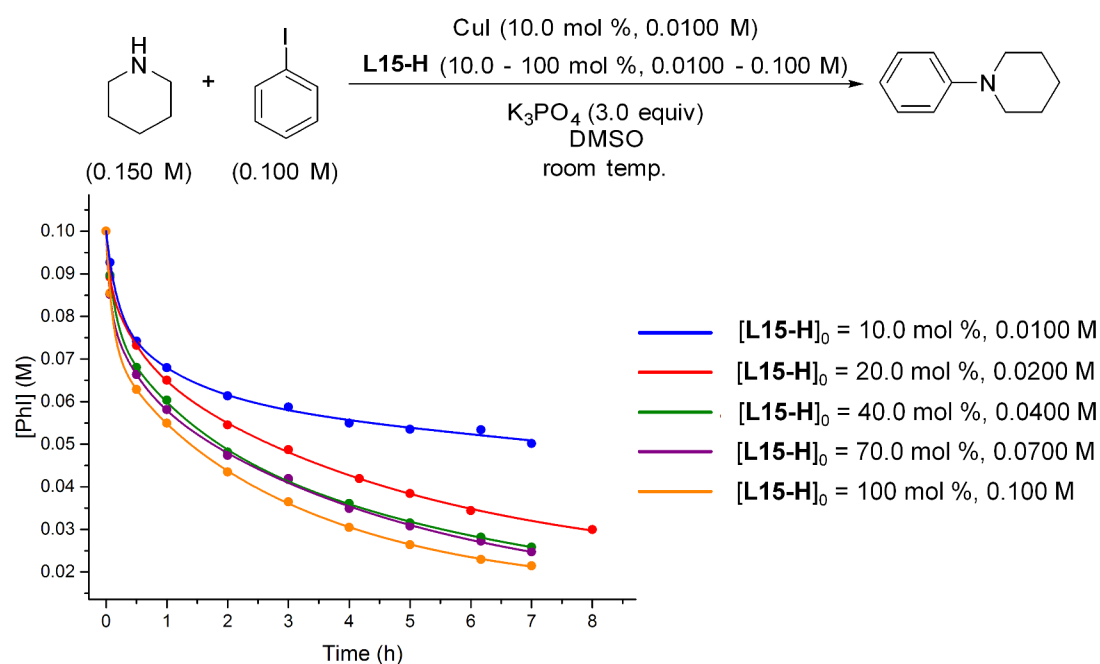
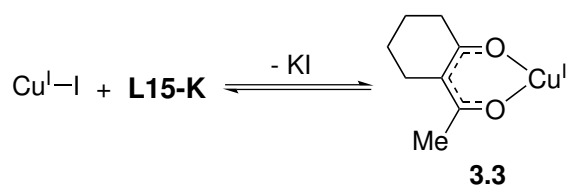


Figure 3.7: [PhI] over the course of the reactions shown in the scheme above using different [L15-H]₀. [PhI] were determined by GC using naphthalene as an internal standard.

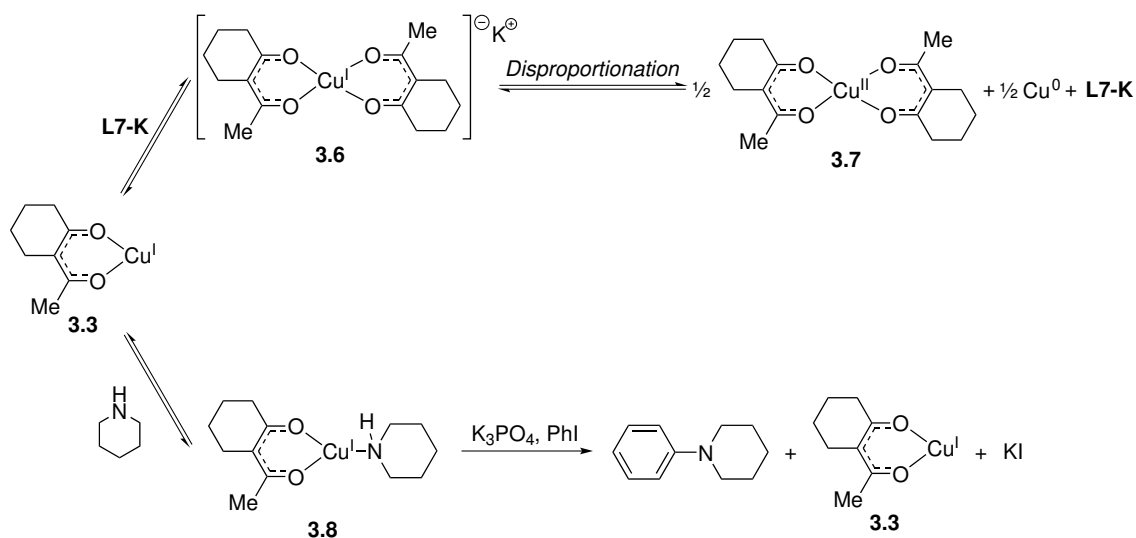


Scheme 3.10: Possible equilibrium between copper(I) iodide and a L15-ligated copper(I) intermediate **3.3**.

L15 coordination to generate copper(I) 2-acetylcyclohexanonate (**3.3**) from the copper(I) iodide pre-catalyst could be reversible and/or slow (Scheme 3.10), and/or **L15** was aiding dissolution of the poorly soluble base which in turn would mitigate the mass transfer effects, and/or the excess **L15-K** formed was acting as a soluble base for the reaction.

Although yield and rate improvements were observed using 40.0, 70.0 and 100 mol % **L15-H** loadings, copper(0) precipitate was also present after reacting for more than seven hours, which indicated that more disproportionation had occurred in these cases than the lower [**L15-H**]₀ reactions. At higher **L15-H** loadings, a greater concentration of off-cycle copper(I) di(2-acetylcyclohexanonate) (**3.6**) would be present which in turn would have resulted in more disproportionation (Scheme 3.9). Although high [**L15-H**] is conducive for catalyst deactivation, increasing initial reaction rates were still observed with increasing **L15-H** loadings. This suggests that **L15-H** has at least two roles in this catalytic system: improving the reaction rate due to the possible reasons mentioned previously and forming copper species susceptible to catalyst deactivation. This also suggests that at the initial stages of the reaction, the rate of catalyst deactivation is slow compared to product formation rate. The slow deactivation may be due to the higher substrate concentrations at the start of the reaction counteracting catalyst deactivation. As the reaction proceeds, the substrate concentrations decrease and therefore the substrates cannot provide the same degree of catalyst stability over time.

To test the effect of piperidine on catalyst stability, two experiments were conducted that involved treating copper(I) iodide with **L15-K** in the absence or presence of piperidine at the same concentrations as those used in the catalytic reaction. In the absence of piperidine, when copper(I) iodide was added to a DMSO-d₆ solution of **L15-K**, the solution immediately changed to a green colour indicative of copper(II) formation and also copper(0) precipitate formed. The ¹H NMR spectrum of the resultant solution contained very broad and poorly defined peaks. These observations indicate that disproportionation had occurred. Conversely in the presence of piperidine, copper(0) precipitation did not occur until approximately three hours after **L15-K** addition. This confirms that piperidine can stabilise copper(I) against disproportionation presumably by competitively binding to the copper(I) centre in **3.3** to form the piperidine-coordinated complex **3.8** and prevent substantial formation of unstable complex **3.6** (Scheme 3.11). Three-coordinate copper(I) 1,3-diketonate complexes ligated with stabilising Lewis bases such as phosphines, alkenes, alkynes, carbon monoxide and ammonia are known in the literature therefore the structure after piperidine coordination shown in Scheme 3.11 is certainly



Scheme 3.11: Proposed competitive coordination between **L15-K** or piperidine to complex **3.3** to give **3.6** or **3.8** respectively that shows the stabilising effect of piperidine.

viable.^[32–35]

To summarise, increasing initial reaction rates were observed with increasing **L15-H** loadings because the high piperidine concentration at the initial stages of the reaction favours coordination of piperidine to the copper(I) centre in **3.3** to form complex **3.8** and therefore prevents coordination of **L15-K** to give unstable intermediate **3.6**. This allows the uncoordinated **L15-K** to fulfil its other role in improving the reaction rate by aiding the formation of **3.3** from the copper(I) iodide pre-catalyst, and/or aid dissolution of the poorly soluble base, and/or act as a soluble base for the reaction.

3.2.2.4 Rate dependence on iodobenzene and piperidine concentration

Figure 3.8 shows piperidine concentration over time for three different reactions with different [PhI]₀. The difference in piperidine conversion within the first hour for the reactions using [PhI]₀ = 0.100 M and 0.067 M was relatively small compared to the difference when [PhI]₀ = 0.067 M and 0.033 M was used. This suggests that when using higher [PhI]₀ (0.100 M and 0.067 M), the aryl iodide activation rates from **L15**-ligated copper(I) piperidine complex **3.9** at the start of the reaction are sufficiently high such that the reaction rates are predominately limited by the prerequisite N–H deprotonation step involving complex **3.8** to form **3.9** (Scheme 3.12). In contrast, reducing [PhI]₀ to 0.033 M caused the rate of aryl iodide activation to decrease such that the overall rate of reaction was now predominately affected by this step and not

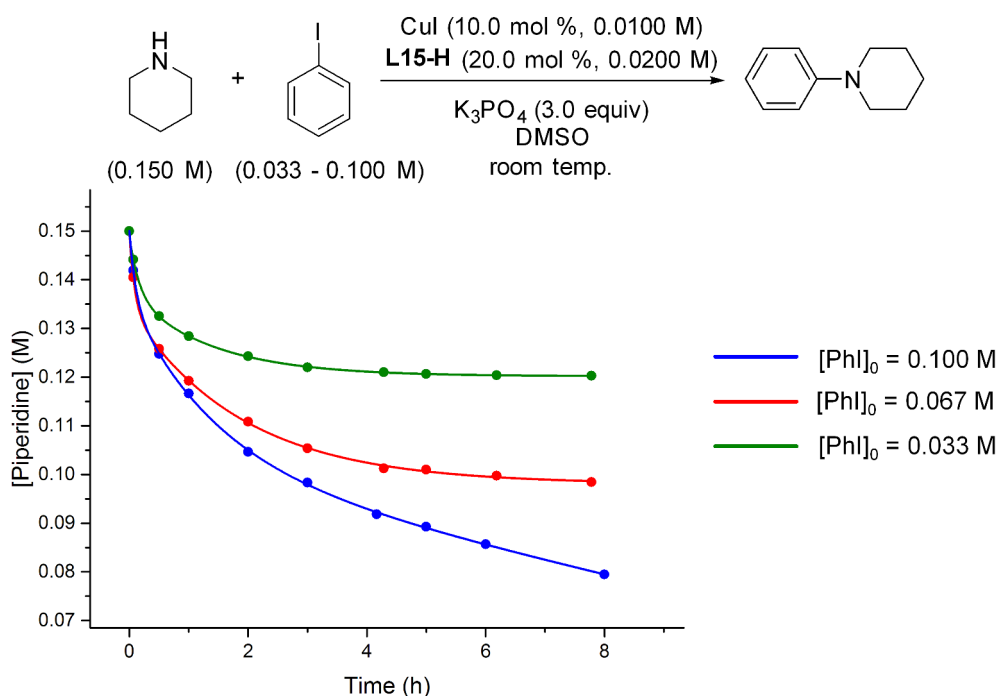
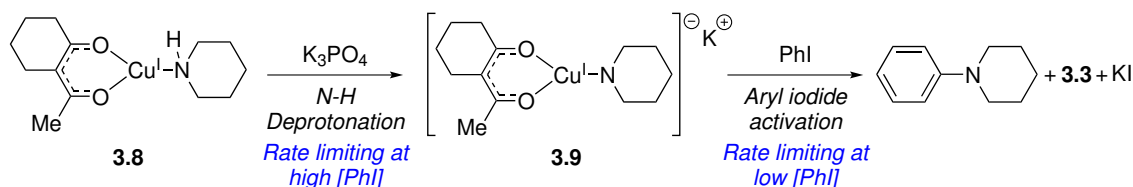


Figure 3.8: [Piperidine] over the course of the reactions shown in the scheme above using different [PhI]₀. [Piperidine] were calculated from iodobenzene conversions measured by GC.



Scheme 3.12: Proposed positions of the rate-limiting step with different [PhI].

the preceding deprotonation step. Overall, the rate dependence in [PhI] is not constant with the rate-limiting step changing from a deprotonation step involving complex **3.8** to aryl iodide activation involving complex **3.9** as [PhI] decreases (Scheme 3.12).

When [Piperidine]₀ was increased from 0.150 to 0.450 M, the rate of reaction also increased therefore there is also a positive dependence in piperidine on the observed reaction rate (Figure 3.9). The positive dependence could be due to several reasons such as increasing catalyst stability, increasing the rate of piperidine coordination to copper(I) 2-acetylcyclohexanone (**3.3**) to form **3.8** or possibly aiding dissolution of the potassium phosphate base. The final yields and thus TON after 24 – 28 hours also increased with higher [Piperidine]₀ and therefore showed that piperidine improved the catalyst stability (Table 3.3), which is in agreement with findings in Section 3.2.2.3.

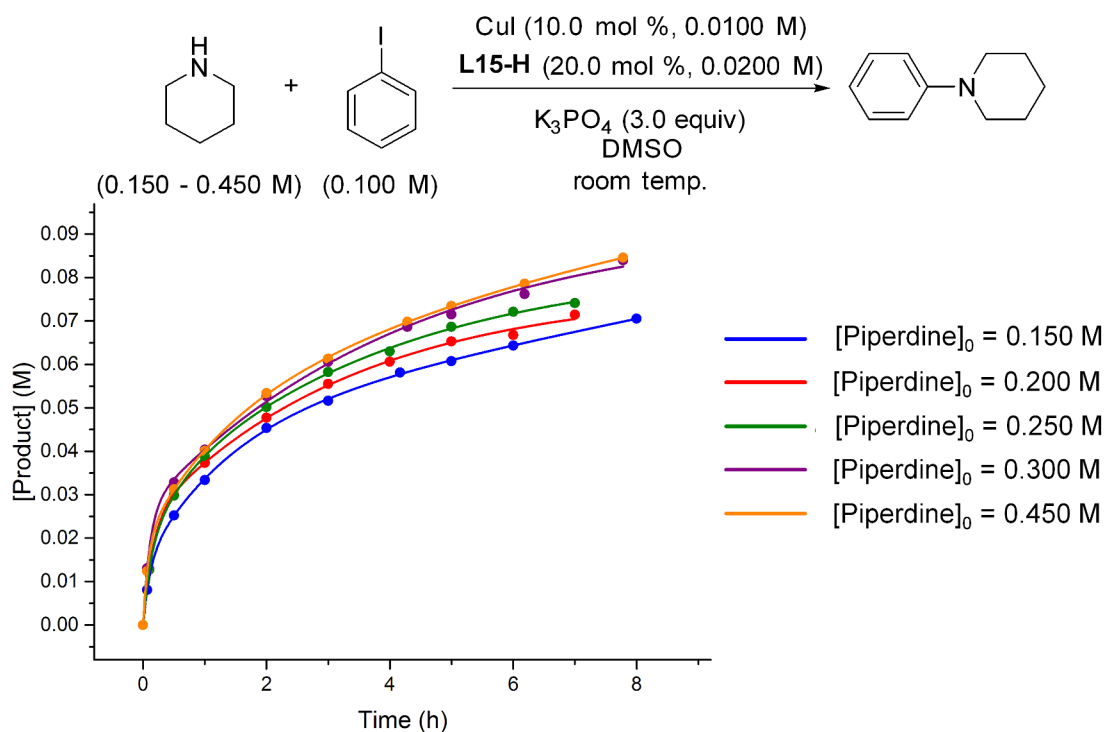


Figure 3.9: [Product] over the course of the reactions shown in the scheme above using different [Piperidine]₀. [Product] were determined by GC using naphthalene as an internal standard.

[Piperidine] ₀ (M)	Reaction time (h)	Yield (%)
0.150	26	81
0.200	28	86
0.250	28	91
0.300	24	100
0.450	24	100

Table 3.3: Product yields using different [Piperidine]₀ in the copper-catalysed cross-coupling of piperidine and iodobenzene. Yields were determined by GC using naphthalene as an internal standard.

3.2.2.5 Catalyst deactivation and inhibition

In addition to the catalyst deactivation *via* disproportionation discussed previously (see Sections 3.2.2.2 and 3.2.2.4, catalyst inhibition by-product coordination or side-effects caused by the potassium iodide and protonated base by-products were also investigated. This was done by performing the reaction shown in Figure 3.10 in the presence of 0.050 mmol of each potential

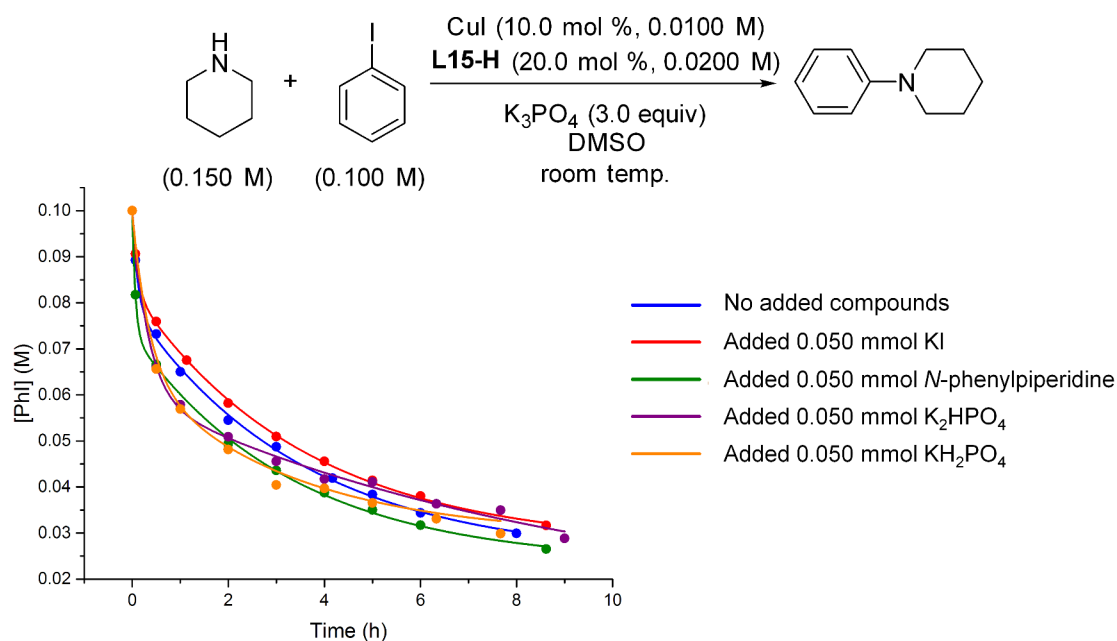


Figure 3.10: [PhI] over the course of the reaction in the scheme with different potential inhibiting compounds present. [PhI] were determined by GC using naphthalene as an internal standard.

inhibiting compound (equal to 50 mol %). From the chart in Figure 3.10, the similar reaction rates suggest that catalyst inhibition by the different added compounds is statistically insignificant in this particular cross-coupling reaction.

The substrate and ligand concentrations were next varied to verify their influence on catalyst deactivation. The 2.0 mol % catalyst loading reaction shown in Figure 3.6 was chosen as the standard reaction because the yield in this case is limited to approximately 20%. From this reaction, the substrate and ligand concentrations can be varied to easily identify changes in final yield and reaction rate (Figure 3.11). In comparison to the standard substrate concentrations reaction (Figure 3.11, blue curve), the reaction rate decreased as expected when [PhI]₀ was reduced to 0.050 M from 0.100 M (Figure 3.11, red curve). However the final yield when [PhI]₀ was reduced to 0.050 M was also lower. This can be explained by considering that these two reactions have the same rate of catalyst deactivation (which is not dependent upon [PhI]₀) and therefore the catalyst in the lower [PhI]₀ reaction would inevitably perform fewer turnovers before complete deactivation. The improved yields when [L15-H]₀ and [Piperidine]₀ were increased (Figure 3.11, green and purple curve respectively) can be explained by the increased concentration of on-cycle catalytic intermediates copper(I) 2-acetylcyclohexanonate (**3.3**) and piperidine-ligated copper(I) 2-acetylcyclohexanonate (**3.8**) (Scheme 3.11) and reduced

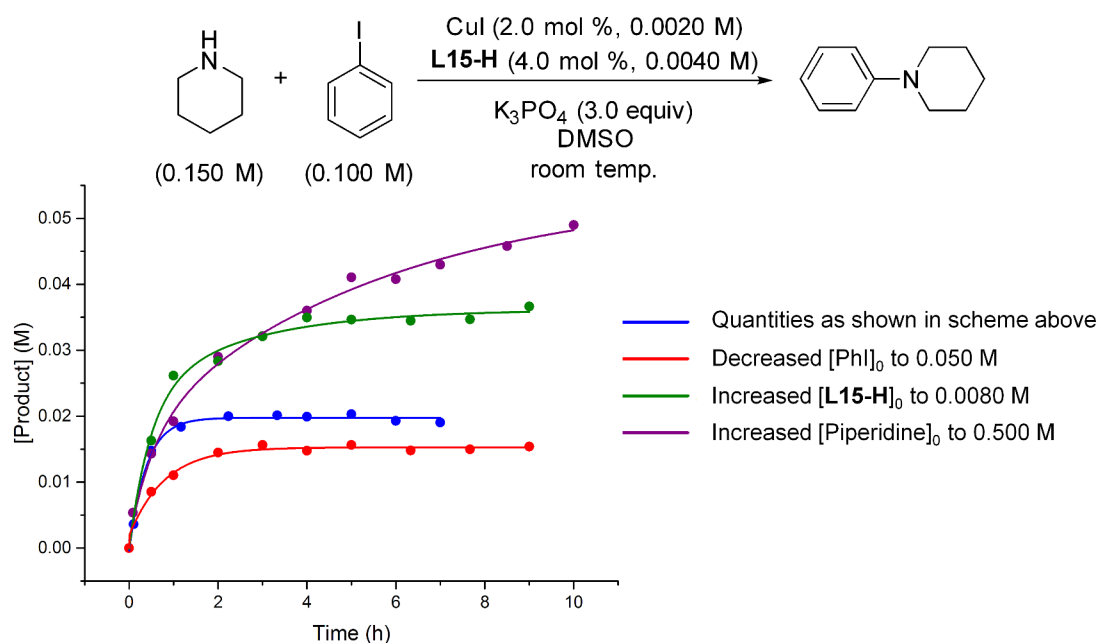


Figure 3.11: [Product] over the course of reaction with different initial substrate and **L15-H** ligand concentrations to observe for changes in yield and reaction rate. [Product] were determined by GC using naphthalene as an internal standard.

catalyst deactivation. Therefore, these experiments demonstrate how the substrates and **L15-H** ligand affect the product forming and catalyst deactivation rates and also how they affect the TON.

The nature of the copper species after deactivation was next probed to confirm it occurs by disproportionation. The experiments involved adding additional copper(I) iodide, **L15-H** ligand or piperidine during the cross-coupling reactions to observe for increases in reactivity. Firstly, after allowing sufficient time for the 2.0 mol % catalyst loading experiment to significantly decrease in reaction rate, copper(I) iodide, **L15-H** or piperidine were added (Figure 3.12). When additional piperidine was added three hours after initially starting the reaction, no change in reactivity was observed compared to when no additional compound was added (Figure 3.12, red and blue curves respectively). This result is as expected because piperidine is not directly involved in the disproportionation/comproportionation equilibrium shown previously in Scheme 3.9. This result also rules out catalyst deactivation by phosphate anion coordination because piperidine would be expected to displace any potentially coordinated phosphate. Conversely, the reactivity did increase when additional copper(I) iodide or **L15-H** were added (Figure 3.12, green and purple curves respectively). The similarities between the reaction rates after adding copper(I) iodide

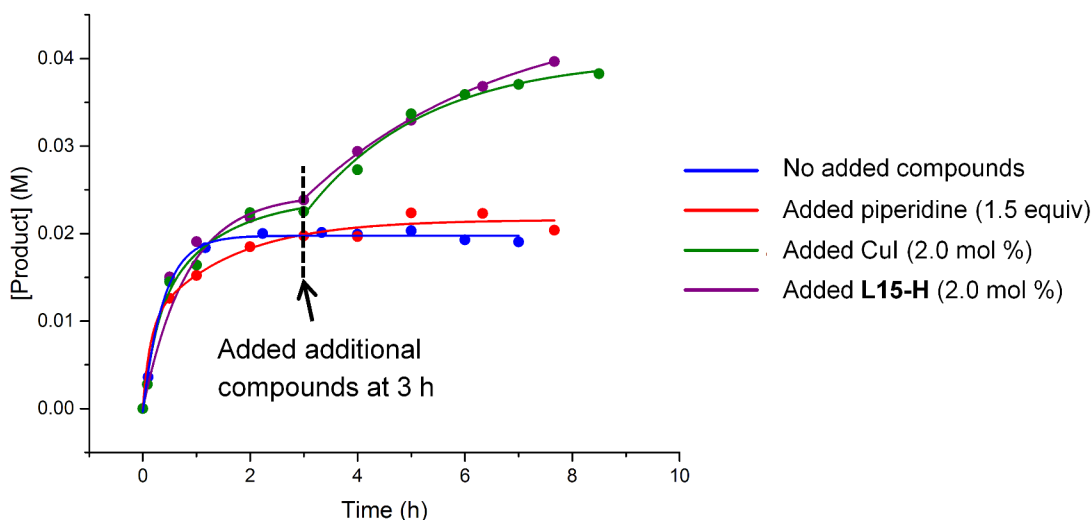
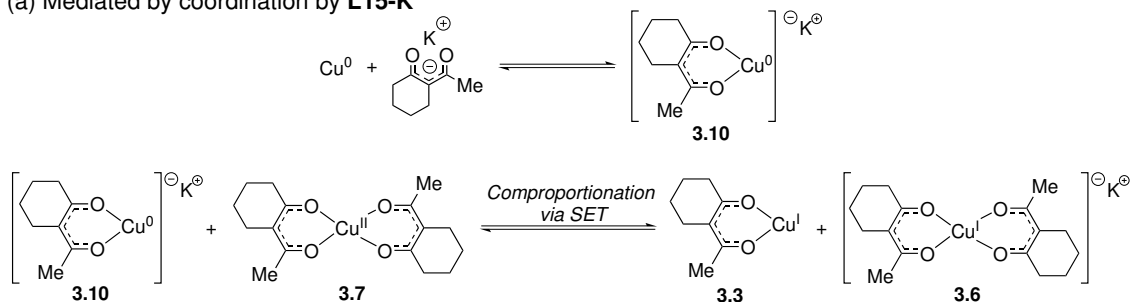


Figure 3.12: [Product] during the 2.0 mol % catalyst loading reaction (scheme shown in Figure 3.11) with copper(I) iodide, **L15-H** ligand or piperidine added during the reaction. [Product] were determined by GC using naphthalene as an internal standard.

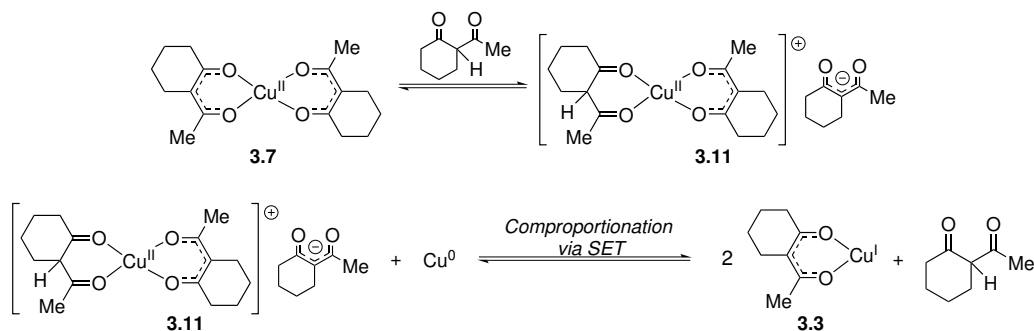
and **L15-H** suggest that approximately the same amount of active catalyst was regenerated in each case. As shown in the overall equation in Scheme 3.9, disproportionation consumes a 1 : 1 amount of copper(I) iodide and diketone. The reaction shown in Figure 3.12 utilised 0.0020 M : 0.0040 M ratio of $[\text{CuI}]_0$: $[\text{diketone}]_0$ therefore 0.0020 M **L15-H** or **L15-K** remained in solution after disproportionation. As a result, any copper(I) iodide added can coordinate with the free diketone and thus restart the reaction.

Just before additional **L15-H** was added, the predominant copper species were soluble copper(0) and copper(II) complex **3.7**. One possible explanation for the increase in reactivity caused by the additional **L15-H** could be **L15** coordination to copper(0) to form the anionic copper(0) complex **3.10** with a lower reduction potential and thus a more strongly reducing species. This would consequently enhance the likelihood for comproportionation by SET from **3.10** to copper(II) complex **3.7** (Scheme 3.13a) to give intermediates **3.3** and **3.6**. This potential mechanism is similar to the reverse order of steps for the disproportionation mechanism of copper(I) diketonate complexes reported in the literature.^[32,36] Another possible mechanism may be the acidic C–H proton of the **L15-H** could transfer to copper(II) complex **3.7** to form a cationic copper(II) species **3.11** with a higher reduction potential and thus a more strongly oxidising species. Alternatively, **L15-H** could undergo ligand exchange with **L15** in complex **3.7** to form the same cationic copper(II) species **3.11**. These processes promote comproportionation as

(a) Mediated by coordination by **L15-K**



(b) Mediated by protonation or coordination by **L15-H**

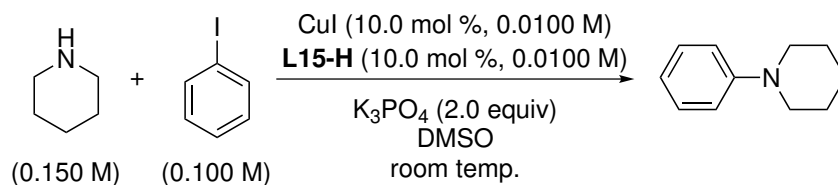


Scheme 3.13: Possible mechanisms for the increase in reactivity on adding additional diketone ligand to the reaction shown in Figure 3.12.

3.11 is more prone to reduction by copper(0) than complex **3.7**. Comproportionation by SET from copper(0) to **3.11** would generate two equivalents of intermediate **3.3** (Scheme 3.13b).

In the previous experiments employing an initial 1 : 2 ratio of copper(I) iodide to **L15-H**, additional copper(I) iodide or **L15-H** ligand were both found to improve reactivity. To confirm that free diketone ligand was responsible for the increase in reactivity when copper(I) iodide was added, analogous experiments that utilised an initial 1 : 1 ratio of copper(I) iodide and **L15-H** were also performed (Scheme 3.14). In comparison to the untreated reaction (Figure 3.13, blue curve), no increase in reactivity was observed two hours after adding 10 mol % copper(I) iodide to the reaction mixture (Figure 3.13, red curve), which is in agreement with no free diketone ligand remaining in solution. However if the same mixture was subsequently treated with 10 mol % **L15-H** ligand, an increase in reactivity did occur (Figure 3.13, red curve). An increase in reactivity was also still observed when only 10 mol % **L15-H** was added (Figure 3.13, green curve). Therefore, the observations from these experiments are in line with the proposed mechanisms mentioned previously (Scheme 3.9 and Scheme 3.13).

The formation of copper(II) and copper(0) species in other Ullmann-type reactions has



Scheme 3.14: Scheme of the reaction used to investigate loss in catalyst activity using 1 : 1 ratio of copper(I) iodide and **L15-H**.

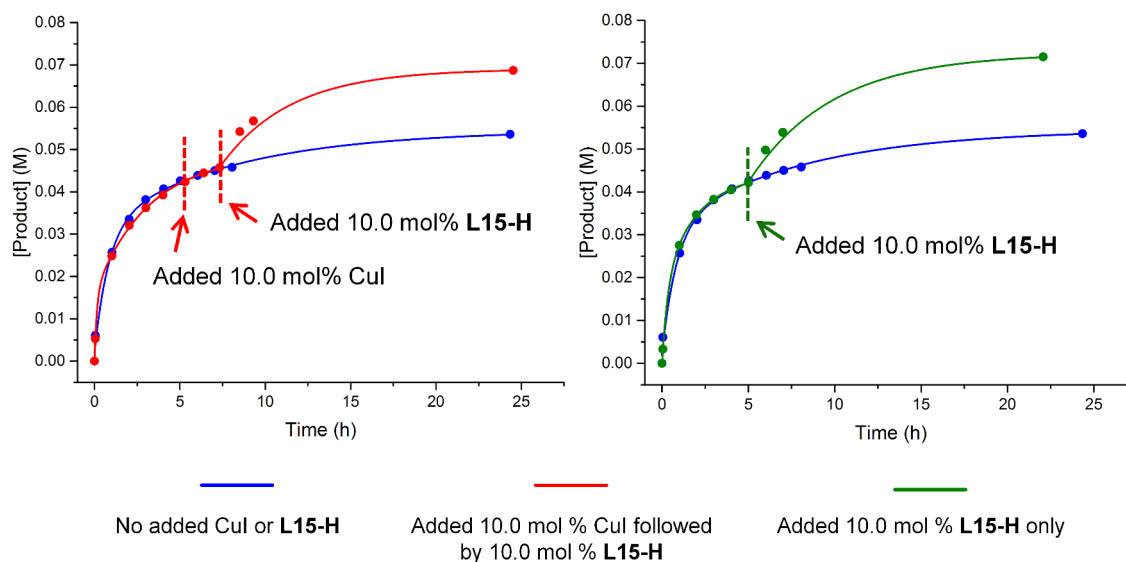


Figure 3.13: Comparison of the product formed over time when the reaction shown in the Scheme 3.14 is treated with additional copper(I) iodide or diketone **L15-H** ligand during the reaction. [Product] were determined by GC using naphthalene as an internal standard.

been reported before in the literature. Hartwig and co-workers identified that the copper(II) species $[\text{Cu}^{\text{II}}(\text{DMEDA})_2]\text{I}_2$ was one of the copper products formed in the stoichiometric aryl amidation reaction between the catalytic intermediate $[\text{Cu}^{\text{I}}(\text{DMEDA})_2][\text{Cu}^{\text{I}}(\text{phthalimide})_2]$ and 4-iodotoluene to produce *N*-phenylphthalimide.^[37] The authors proposed that $[\text{Cu}^{\text{II}}(\text{DMEDA})_2]\text{I}_2$ was formed from disproportionation of the by-product $[\text{Cu}^{\text{I}}(\text{DMEDA})\text{I}]$, which is an intermediate in the catalytic reaction between phthalimide and 4-iodotoluene. Lei and co-workers confirmed that disproportionation of the di(acetylacetonate)cuprate intermediate in the copper-catalysed C–C cross-coupling reaction between acetylacetonate and aryl iodides occurs by identifying the copper(II) acetylacetonate complex using EPR, *in situ* IR, UV-Vis, XANES and EXAFS.^[29] More recently, McGowan and co-workers have isolated and identified copper(II) products in the copper-catalysed formation of aryl ethers and suggested that they are formed from an

electron transfer process.^[38] It should be noted that a disproportionation process in modified Ullmann amination reactions has not been reported before in the literature as far as we are aware. When the results from this subsection are taken together, a disproportionation process in the **L15-H**-ligated copper-catalysed cross-coupling of piperidine and iodobenzene has been identified and determined to be the mode of catalyst deactivation.

3.2.3 ¹H NMR spectroscopic study

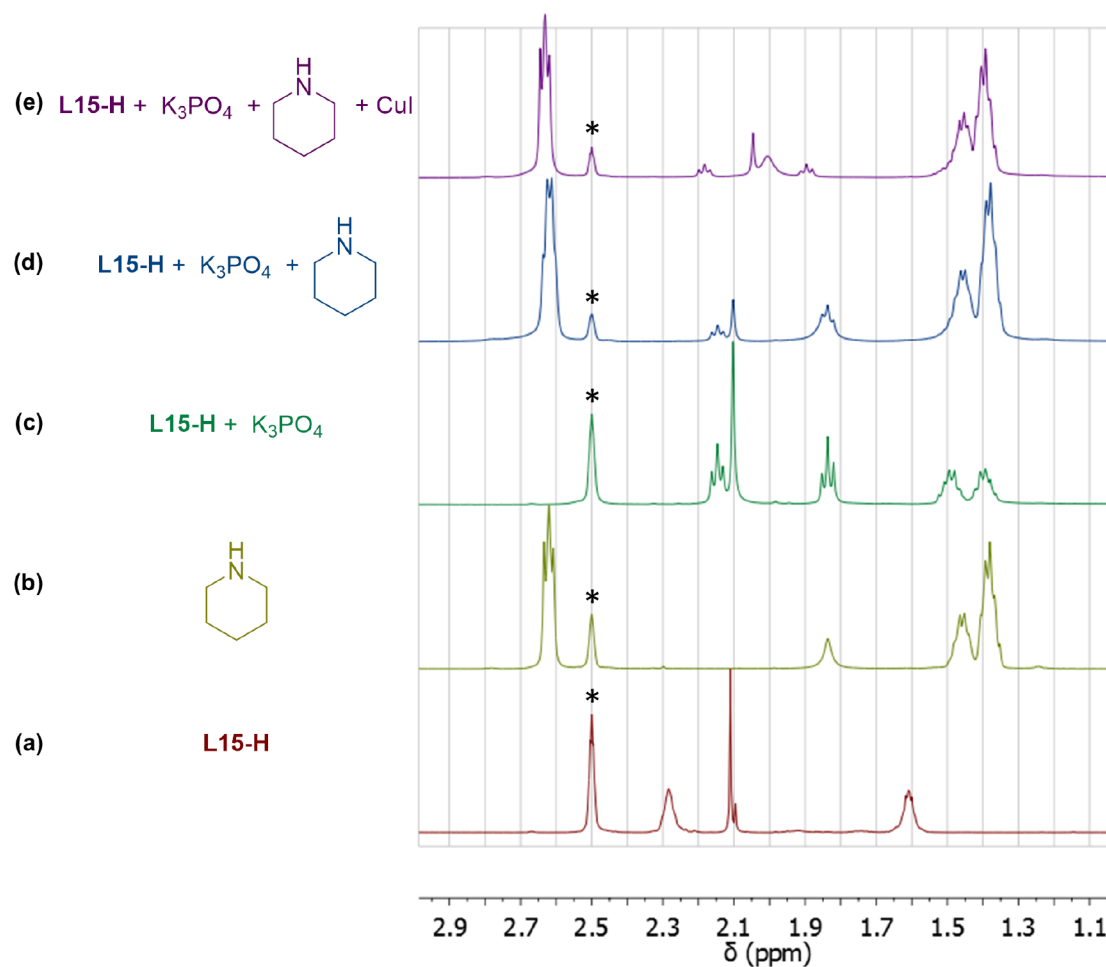
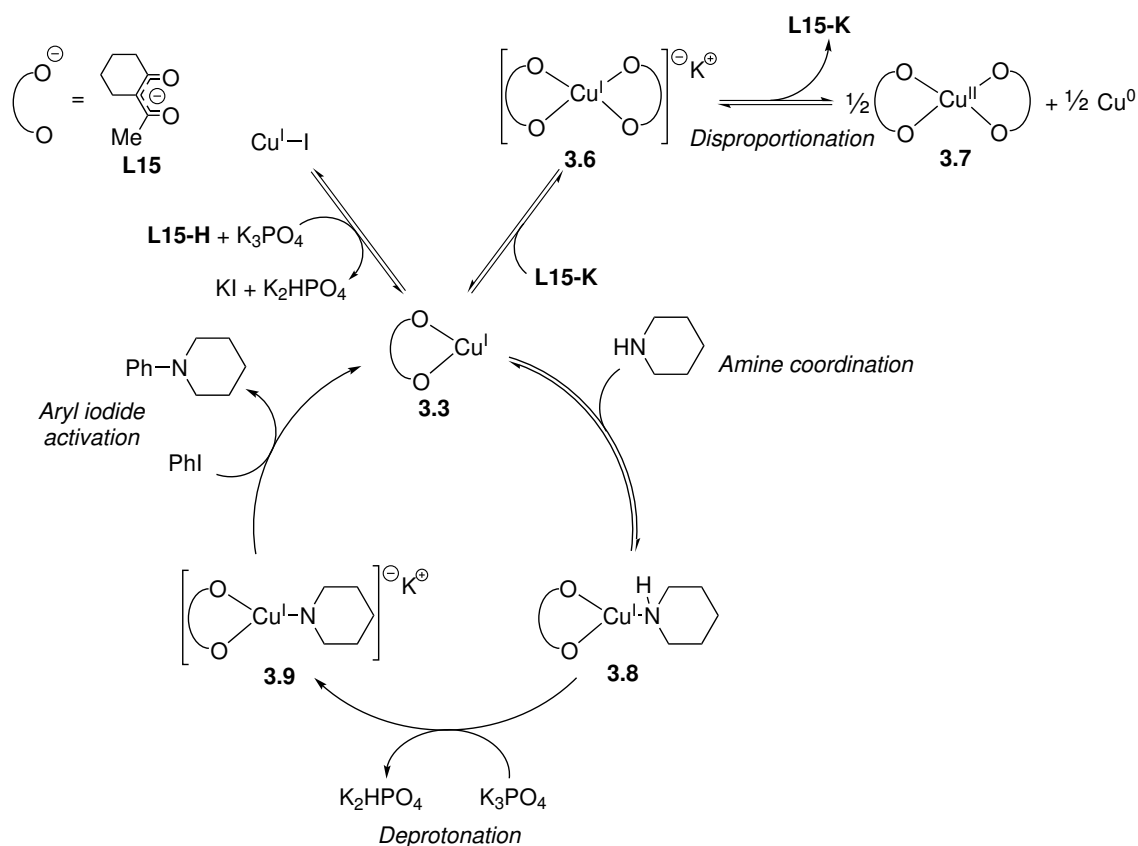


Figure 3.14: ¹H NMR spectra in DMSO-*d*₆: (a) **L15-H** (0.0200 M); (b) piperidine (0.150 M); (c) **L15-H** (0.0200 mmol) and K_3PO_4 (0.30 mmol) after six hour stir at room temperature; (d) After addition of piperidine (0.150 mmol) to the mixture of ¹H NMR spectrum (c); (e) NMR analysis immediately after addition of copper(I) iodide (0.0100 mmol) to the mixture of ¹H NMR spectrum (d). Residual solvent resonance is at 2.50 ppm labelled with asterisk (*).

From the kinetic study, possible off-cycle species and equilibria were identified. A NMR spectroscopic study was then performed to confirm the coordination of **L15** and piperidine and propose structures for intermediate species. Figure 3.14 shows ^1H NMR spectra after the reaction components were added together sequentially in the amounts that would be present in the catalytic reaction. By comparing Figure 3.14a and c, the formation of new resonances shows that **L15-H** was completely deprotonated by potassium phosphate to form **L15-K** after stirring together in DMSO-d_6 for six hours at room temperature. After addition of piperidine to the mixture, in comparison to the ^1H NMR spectrum of piperidine alone (Figure 3.14b), there is negligible change in the chemical shifts of the piperidine and **L15-K** resonances (Figure 3.14d). This confirmed there is no interaction between these species and that N–H deprotonation does not occur at room temperature (broad N–H resonance overlapping with **L15-K** resonance at $\delta = 1.84$ ppm). When copper(I) iodide is added to the mixture, the solution turned yellow which indicated that a complex had formed. The chemical shifts for the piperidine (in particular the N–H resonance) and **L15** protons in the ^1H NMR spectrum also shifted (e.g. piperidine N–H resonance shifted from $\delta = 1.84$ ppm to 2.01 ppm; **L15** CH_3 resonance shifted from $\delta = 2.10$ ppm to 2.05 ppm) (Figure 3.14e). This confirmed that both piperidine and **L15** coordinate with copper(I) to form a complex containing both ligands.

3.2.4 Proposed mechanism

From the kinetic and spectroscopic studies, a possible mechanism can be proposed (Scheme 3.15). The initial step involves coordination of the potassium 1,3-diketonate salt **L15-K** to copper(I) iodide to give the intermediate copper(I) 1,3-diketonate species **3.3** and potassium iodide. An off-cycle equilibrium involving coordination of an additional **L15-K** ligand to **3.3** gives the bis(1,3-diketonate)cuprate species **3.6** required for disproportionation to copper(II) complex **3.7** and copper(0). As piperidine was found to reduce catalyst deactivation, piperidine coordination to **3.3** to give a **L15**-ligated copper(I) piperidine complex **3.8** is proposed to be the next step in the active catalytic cycle. Coordination of the amine to copper is likely required to mediate the deprotonation of piperidine given that the $\text{p}K_a$ of the N–H group of the similarly structured pyrrolidine is 44 in DMSO .^[39] Deprotonation to give **L15**-ligated copper(I) piperide complex **3.9** from **3.8** is proposed to be an essentially irreversible process given that the dibasic and monobasic potassium phosphate by-products were found to have negligible effect on the reactivity. Intermediate **3.9** has the same general structure as proposed by Jutand



Scheme 3.15: Proposed reaction mechanism that includes a disproportionation step in the copper-catalysed cross-coupling reaction between piperidine and iodobenzene with **L15** as the ancillary ligand.

and co-workers for the species active toward aryl halide activation.^[13,14,20] According to the literature, the highest energy barrier is the subsequent aryl iodide activation with **3.9** and has been proposed to occur by oxidative addition between the aryl iodide and nitrogen atom of the complex.^[13,14,20] Finally, after this step the product is formed and **3.3** is regenerated. The presence of *N*-phenylpiperidine was found to not influence the reaction rate therefore product coordination to **3.3** is not part of the mechanism.

Overall, the proposed mechanism contains the same on-cycle intermediate species in the same order as the mechanism proposed by Jutand and co-workers (Scheme 3.5).^[13,14,20] The key difference is the off-cycle equilibrium and catalyst deactivation identified by the kinetic study performed in this work. However it should be noted that in this study DMSO solvent was employed whereas Jutand and co-workers used DMF therefore there might be some differences in the redox properties of the copper(0), copper(I) and copper(II) species.

3.3 Conclusions

Screening ancillary ligands for the copper-catalysed C–N cross-coupling reaction between piperidine and iodobenzene demonstrated that using *O,O*- and *N,O*-chelating ligands generally provides significantly better yields than *N,N*-chelating ligands in this reaction. This may be due to differences in solution equilibria that led to higher concentrations of the active catalyst species with these ligands. In addition, greater electron density on the ligated copper(I) centre may have been a factor in improving the product yield. Although limitations due to mass transfer effects in the reaction with **L15-H** as the ancillary ligand prevented a quantitative kinetic study to identify the numerical orders with respect to the reactant concentrations, new insights into a catalyst deactivation route for the copper-catalysed C–N cross-coupling reaction between piperidine and iodobenzene were obtained. Through a series of kinetic experiments, disproportionation to give copper(II) and copper(0) species was identified as the catalyst deactivation route. As noted previously in Section 3.2.2.5, formation of these species has also been proposed in other copper-catalysed reactions^[29,37,38] but this is the first report of disproportionation in the modified Ullmann amination reaction. A copper(I) species ligated with **L15** was found to have a key role in the disproportionation process. Therefore, when designing new catalytic systems, the role of the ligand in potential catalyst deactivation pathways should be considered as well as its role in improving the reaction rate.

Additional mechanistic insights could be obtained in future work by probing the proposed mechanism from the kinetic studies. For example, characterisation of the copper(II) and copper(0) species produced from disproportionation using techniques such as EPR, *in situ* IR, UV-Vis, XANES and EXAFS, as demonstrated by Lei and co-workers, would provide further proof and identification of these species in solution.^[29,30] Although the mass transfer effects and poor stability of copper(I) diketonate complexes made identifying the catalyst resting state difficult, a DFT study could provide further insight into the kinetics of the individual steps on the catalytic cycle with the base effect removed. Although oxidative addition has been proposed for the aryl halide activation mechanism, the use of radical probes may still affect the reactivity by influencing the disproportionation/comproportionation equilibrium that occurs *via* SET. Therefore future experiments employing radical probes could provide information about this off-cycle equilibrium.

3.4 Experimental

3.4.1 General information

All glassware was dried for at least 12 h at a minimum temperature of 120 °C prior to use. Anhydrous DMSO was purchased from Sigma Aldrich and stored over 4 Å molecular sieves under a nitrogen atmosphere. DMSO-d₆ was dried by stirring over calcium hydride at room temperature under nitrogen overnight and distilling under reduced pressure and storing over 4 Å molecular sieves under a nitrogen atmosphere prior to use. THF was freshly distilled over sodium and benzophenone under a nitrogen atmosphere. Potassium carbonate and potassium phosphate bases were dried by heating under vacuum for 48 and 24 h respectively at 180 °C. Piperidine was purified by stirring over calcium hydride at room temperature under a nitrogen atmosphere and distilled under nitrogen for storage over 4 Å molecular sieves. Phen (**L3**) was dried prior to use by heating to 85 °C under vacuum for 36 h. ^tBu-phen (**L18**) was prepared according to the procedure by Pallenberg and co-workers.^[21] 1,3-Diketimine ligands **L22 – L24** were synthesised according to the method reported by Feldman and co-workers.^[40] All other chemicals were used as received without further purification. All products and reagents used in the catalytic reactions were stored in a nitrogen-filled glovebox, with liquid reagents other than **L15-H** also dried using 4 Å molecular sieves.

¹H and ¹³C NMR spectroscopy analysis was carried out at room temperature using Bruker AV-400 spectrometers. CHN microanalyses were carried out at the London Metropolitan University, UK. GC analyses were performed using a Hewlett-Packard 5890 Series II GC instrument with an FID detector equipped with a 30 m x 0.25 mm I.D. (5% phenyl)-methylpolysiloxane stationary phase capillary column. The following GC oven temperature program was used when analysing the samples: (i) 70 °C upon injection, (ii) hold at 70 °C for 2 min, (iii) increase the temperature to 250 °C at a rate of 10 °C per minute, (iv) hold at 250 °C for 5 min. Injector temperature: 250 °C; Detector temperature: 250 °C.

¹H and ¹³C NMR data were analysed using MESTRELAB MestReNova; and GC data were analysed using DataApex Clarity software.

3.4.2 General procedure for screening ligands, bases and reaction temperatures in the catalytic reactions

In a nitrogen-filled glovebox, the inorganic base (0.20 mmol), DMSO- d_6 (900 μ L), ligand (0.01 mmol) (unless ligand-free), piperidine (10.0 μ L, 0.100 mmol), iodobenzene (16.7 μ L, 0.150 mmol) and mesitylene (14.0 μ L, 0.100 mmol) as an internal standard were added to a screw-cap vial and stirred. At room temperature, copper(I) iodide (100 μ L of 0.100 M solution in DMSO, 0.0100 mmol) was added to the stirring mixture and the vial was capped and taken out of the glovebox. The reaction mixture was stirred at room temperature or 80 °C for 18 h. The contents of the vial were filtered using a syringe filter into a NMR tube inside a glovebox for ^1H NMR analysis. The quantities of product and iodobenzene were measured by ^1H NMR spectroscopy by comparing the integrals of the product CH_2 resonance at $\delta = 3.06 - 3.13$ ppm (m, 4H; CH_2) and iodobenzene aromatic CH resonance at $\delta = 7.73$ ppm (d, 2H; CH) against the integral of the mesitylene internal standard CH_3 resonance at $\delta = 2.20$ ppm (s, 9H; CH_3).

3.4.3 Preparation of potassium 2-acetylcyclohexanonate (L15-K)

A stirred solution of **L15-H** (469 μ L, 3.61 mmol) in THF (5 mL) was treated slowly with a solution of potassium *tert*-butoxide (337 mg, 3.00 mmol) in THF (5 mL) at room temperature under a nitrogen atmosphere to form a white precipitate of the desire product. After stirring overnight at room temperature, the reaction mixture was filtered and the white precipitate was isolated. The precipitate was washed with THF (2 x 15 mL) and dried under high vacuum at 40 °C. The product **L15-K** was collected as a hygroscopic white powder and stored in a nitrogen-filled glovebox (437 mg, 2.45 mmol, 82%). ^1H NMR (400 MHz, DMSO- d_6 , 24 °C, TMS): δ =1.33 – 1.55 (m, 4H; CH_2), 1.84 (t, $^3J_{\text{HH}}$ =6.5 Hz, 2H; CH_2), 2.11 (s, 3H; CH_3), 2.15 ppm (t, $^3J_{\text{HH}}$ =6.5 Hz, 2H; CH_2); ^{13}C NMR (101 MHz, DMSO- d_6 , 24 °C, TMS): δ =24.9 (s; CH_2), 25.1 (s; CH_2), 26.5 (s; CH_2), 31.1 (s; CH_3), 39.4 (s; CH_2), 104.2 (s; $\text{C}(\text{O})=\text{C}-\text{C}(\text{O})\text{CH}_3$), 185.4 (s; ketone-C), 187.8 ppm (s; ketone-C); elemental analysis calcd (%) for $\text{C}_8\text{H}_{11}\text{KO}_2$: C 53.90, H 6.22; found: C 53.70, H 6.28.

3.4.4 Procedure for kinetic studies in the diketonate-ligated copper-catalysed reactions between piperidine and iodobenzene

The following is a general experimental procedure for the kinetic studies performed in Section 3.2.2. The amounts added were adjusted accordingly to obtain the desired initial concentrations and millimoles of each compound. All compounds were added as DMSO solutions to ensure accuracy and reproducibility, except for insoluble K_3PO_4 , K_2HPO_4 and KH_2PO_4 which were added as solids. In a nitrogen-filled glovebox, potassium phosphate, DMSO (volume required to make up to 2.000 mL total liquid), **L15-H** or **L15-K**, piperidine, iodobenzene and naphthalene as an internal standard were added to a screw-cap vial and stirred well. Potassium iodide, *N*-phenylpiperidine, K_2HPO_4 or KH_2PO_4 in the catalyst inhibition experiments were added at this stage. At room temperature, copper(I) iodide was added to the stirring mixture and the vial was capped and kept in the glovebox to react. For the multiple addition experiments, DMSO solutions of additional piperidine, copper(I) iodide or **L15-H** were added to the reaction mixture in the glovebox. The reaction was monitored by taking 100 μ L samples of the reaction solution and quenching at certain reaction times outside of the glovebox using a mixture of ethyl acetate (300 μ L) and water (100 μ L). The organic layer was taken and passed through a pasteur pipette containing a pad of silica gel (1.0 – 1.5 cm height of silica gel) into a clean GC vial. Ethyl acetate (3 x 200 μ L) was added wash the silica gel and ensure all of the iodobenzene and *N*-phenylpiperidine had passed through. The GC vial containing the combined organic fractions was capped and analysed by GC. Quantities of product formed and iodobenzene remaining were measured using calibrations against a naphthalene internal standard.

3.4.5 Addition of copper(I) iodide to **L15-K** in the presence or absence of piperidine

In a nitrogen-filled glovebox, a solution of **L15-K** (200 μ L of 0.10 M solution in $DMSO-d_6$, 0.020 mmol) and piperidine (14.8 μ L, 0.150 mmol, if required) in $DMSO-d_6$ (685 μ L or 700 μ L) in a J. Youngs tap NMR tube was treated with copper(I) iodide (100 μ L of 0.100 M solution in $DMSO-d_6$, 0.0100 mmol). The NMR tube was shaken well to mix and immediately formed a green coloured copper(II) solution and grey precipitate in the absence of piperidine and a clear yellow solution in the presence of piperidine. The solutions were transferred to a NMR spectrometer for analysis.

3.4.6 Preparation of solution used in ^1H NMR spectroscopic study

In a nitrogen-filled glovebox, potassium phosphate (64 mg, 0.30 mmol), DMSO- d_6 (685 μL) and **L15-H** (200 μL of 0.100 M solution in DMSO- d_6 , 0.0200 mmol) were added to a screw-cap vial and stirred for 6 h at room temperature. The contents of the vial were transferred to a J. Youngs tap NMR tube for ^1H NMR analysis. The NMR tube was returned to the glovebox, piperidine (14.8 μL , 0.150 mmol) was added, and the NMR tube was shaken to mix. After additional ^1H NMR analysis, the NMR tube was again returned to the glovebox after which copper(I) iodide (100 μL of 0.100 M solution in DMSO- d_6 , 0.0100 mmol) was added. The NMR tube was shaken well and immediately transferred to a NMR spectrometer for analysis.

3.5 References

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Chapter 4

Mechanistic Studies of the Copper-Catalysed *N*-Arylation of Alkylamines Promoted by Organic Soluble Ionic Bases

4.1 Introduction

4.1.1 Substrate deprotonation in the Ullmann reaction

Copper-catalysed systems for C–N cross-coupling aryl halides and nitrogen-based substrates such as amines, amides, and *N*-heterocycles commonly utilise virtually insoluble inorganic bases to deprotonate the nucleophilic substrate.^[1,2] As a result of the low base solubility, the rate of deprotonation can significantly affect the overall rate of reaction, as previously reported by Meyer and co-workers.^[3] Such a rate-limiting base effect was also observed in the diketone-ligated copper-catalysed cross-coupling between piperidine and iodobenzene studied in Chapter 3. In the literature, methodologies involving phase-transfer catalysts and soluble bases for copper-catalysed C–N bond formation between aryl halides and various nitrogen-based substrates have been designed and do show improved reactivity over only using poorly soluble bases in some cases. The following subsections will briefly describe these catalytic systems reported in the literature.

4.1.1.1 Phase-transfer catalysis

Phase-transfer catalysis is used to aid the reactivity of systems that have at least two phases which are separated by one interface.^[4] The process typically involves the phase-transfer catalyst assisting the transfer of an anionic reactant from its “normal” liquid or solid phase into another liquid phase where a reaction between the transferred reactant and a non-transferred reactant takes place. Commonly used phase-transfer catalysts in the literature include quaternary ammonium and phosphonium salts, crown ethers and open-chain polyethers such as poly(ethylene glycol) (PEG) (Figure 4.1). Phase-transfer is mediated by quaternary ammonium and phosphonium salts through cation exchange to form more soluble ionic pairs with the reactant anion.^[5] In comparison, neutral crown ethers and open-chain polyethers aid the dissolution

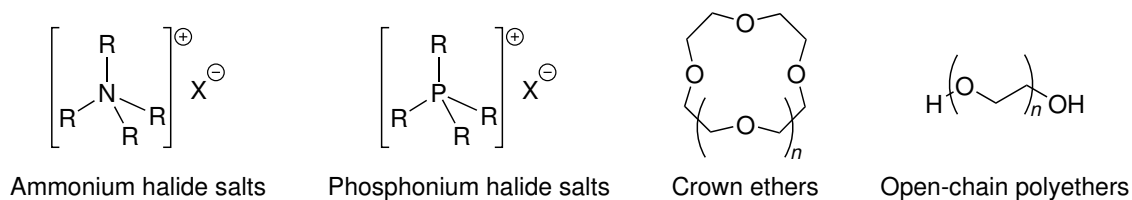
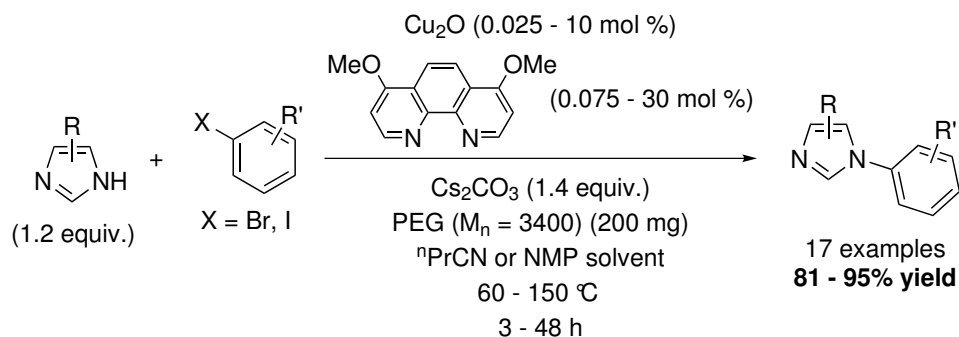


Figure 4.1: Examples of commonly used phase-transfer catalysts.

of ionic reactants into the reaction phase by coordinating to the inorganic counter cations.^[6]

In modified Ullmann reactions that utilise sparingly soluble inorganic bases such as alkali metal carbonates and phosphates, phase-transfer catalysis is typically employed to mediate the transfer of the basic anion into the reaction solvent containing the copper catalyst and substrates. For example, in the reported copper-catalysed *N*-arylation of imidazoles and benzimidazoles with caesium carbonate as the base, employing poly(ethylene glycol) (PEG) ($M_n = 3400$) as an additive caused an increase in reaction rates by 10 – 30% (Scheme 4.1).^[7] The rate increase was thought to be due to improved base solubility caused by PEG. PEG has also been utilised as a solid-liquid phase-transfer catalyst for the ligand-free copper(I) catalysed intramolecular *N*-arylation of diazoaminobenzenes with many commonly used insoluble alkali metal carbonate and phosphate bases.^[8]



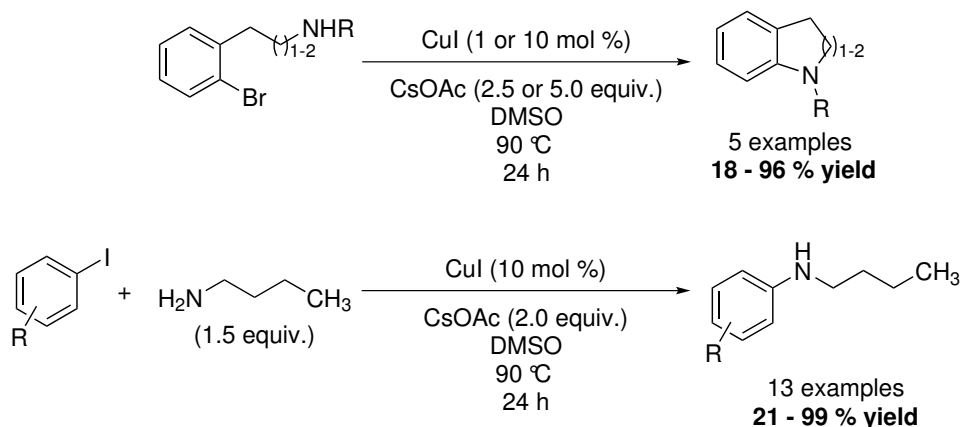
Scheme 4.1: Copper-catalysed *N*-arylation of imidazoles and benzimidazoles with PEG as an additive to improve reaction rate.^[7]

Tetra-*n*-butylammonium bromide (TBAB) has been used as a phase-transfer catalyst for microwave-assisted copper-catalysed C–N bond formation between aryl halides and amines.^[9] Phase-transfer catalysis using TBAB also extends to copper-catalysed C–C bond formation between aliphatic halides and arylboronic acids.^[10] In other more extreme cases, PEG and molten TBAB have been used as the reaction solvent in copper-catalysed *N*-arylations of amines, amides and imidazoles where similar favourable solid-liquid phase-transfer behaviour was observed.^[11,12]

4.1.1.2 Soluble bases

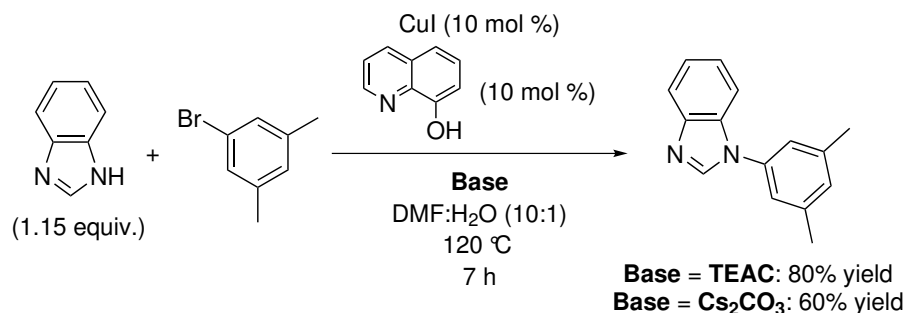
An alternate method to alleviate the solubility effects of commonly used inorganic bases has been to utilise soluble bases. Fukuyama and co-workers developed a copper-catalysed system

for intra- and intermolecular amination of aryl iodides that employed soluble caesium acetate as the base in DMSO at reaction temperatures of 90 °C (Scheme 4.2).^[13–15] This catalytic system was successfully utilised in the natural product syntheses of Duocarmycin A and SA^[16] and (+)-Yatakemycin.^[17,18] Although no ancillary ligand was added in their protocol, the authors proposed that as well as acting as a base, caesium acetate was simultaneously functioning as a ligand to copper(I) as it aided the solubility of copper(I) iodide. However no kinetic or spectroscopic evidence was obtained for the proposed acetate coordination.^[13]

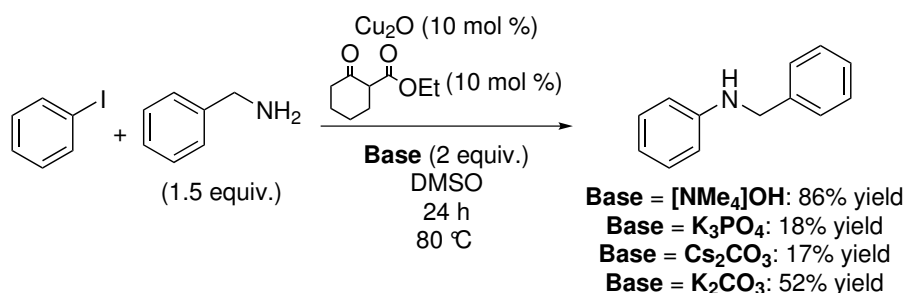


Scheme 4.2: Copper-catalysed intra- and intermolecular amination of aryl iodides using soluble caesium acetate as the base.^[13–15]

The quaternary ammonium salt bis(tetraethylammonium) carbonate (TEAC) is significantly more soluble in organic solvents than its alkali metal analogues and in turn provides virtually homogeneous reaction mixtures in DMF : water (10 : 1) solvent.^[19] TEAC has been successfully used as the base in this solvent mixture for the copper-catalysed *N*-arylation of imidazoles and benzimidazoles where rate enhancement attributed to enhanced solubility was observed. For example, the yield of the cross-coupling product in Scheme 4.3 after seven hours was 80% using TEAC as the base compared to 60% using the sparingly soluble caesium carbonate.^[19] Due to the improved yields, an advantage of using TEAC over caesium carbonate was the improvement in substrate scope to include some aryl chlorides. Another example of the use of a quaternary ammonium salt as the base was in the copper-catalysed C–N bond formation between pyrrole or alkylamines with aryl halides (see Scheme 4.4 for an example cross-coupling between benzylamine and iodobenzene).^[20] This reaction benefitted from yield and rate improvements using soluble tetramethylammonium hydroxide as the base compared to alkali metal carbonate and phosphate bases.



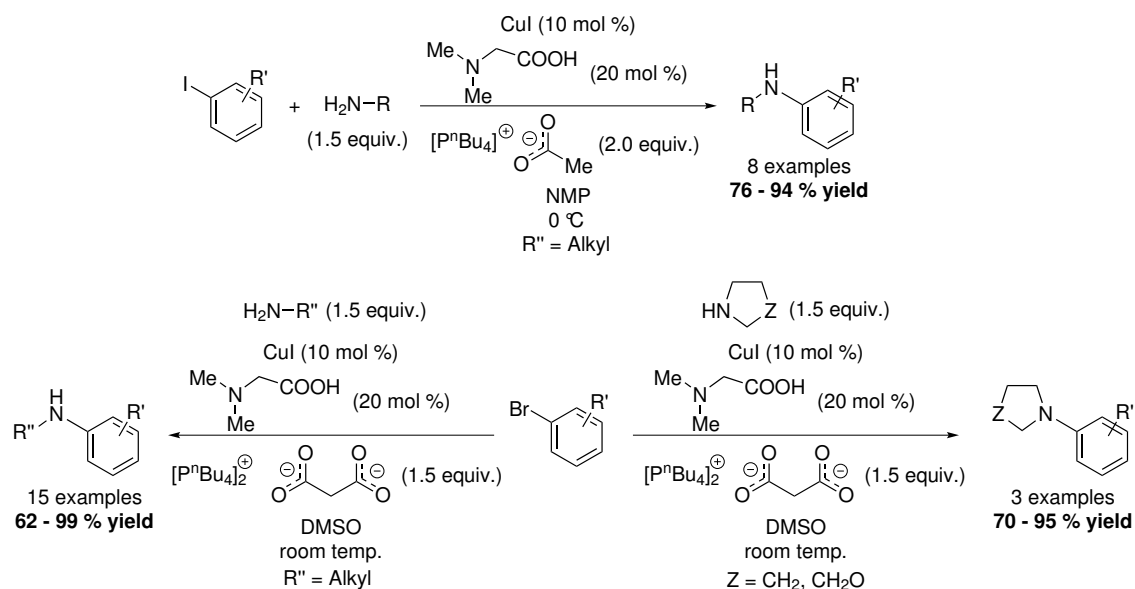
Scheme 4.3: Comparison of yields obtained using TEAC or caesium carbonate as a base in the copper-catalysed cross-coupling between 1-bromo-3,5-dimethylbenzene and benzimidazole.^[19]



Scheme 4.4: Comparison between using soluble tetramethylammonium hydroxide with alkali metal carbonate and phosphates as the base in the copper-catalysed *N*-arylation of benzylamine.^[20]

The highest reported reaction rates for copper-catalysed C–N bond formation between aryl halides and alkyl- and arylamines, *N*-heterocycles and ammonia were published by Liu and co-workers who synthesised and employed a variety of soluble organic ammonium and phosphonium bases.^[21] The coupling of alkylamines with aryl iodides and bromides were promoted at temperatures as low as 0 °C and room temperature using (tetra(*n*-butyl)phosphonium) acetate and malonate bases respectively, which are the lowest reported temperatures for successful copper-catalysed cross-couplings involving these substrates (Scheme 4.5). In addition to their high solubility, the significantly enhanced reactivity using the soluble organic ionic bases was also proposed to be due to excellent charge separation between the soft cations and hard carboxylate anions. For example, a 0.01 M solution bis(tetra(*n*-butyl)phosphonium) malonate (TBPM) in DMF has a conductivity measurement of 842 $\mu\text{S cm}^{-1}$, which is 35 times higher than caesium carbonate in DMF (24.00 $\mu\text{S cm}^{-1}$), and therefore demonstrates their excellent ionisation ability.^[21] Despite the excellent reactivity, the disadvantages of the organic ionic bases are their relatively high cost compared to commonly used inorganic bases, and that they are

hygroscopic and therefore require vigorous drying and storage under a dry atmosphere. The issues have been partially resolved by binding the ionic bases to hydrophobic polymer resins, which in turn made them stable in air and moisture.^[22]



Scheme 4.5: Copper-catalysed cross coupling of aryl halides with alkylamines using soluble organic phosphonium bases.^[21]

With organic ionic bases providing the best reactivity reported so far in the literature, understanding the cause of the dramatic acceleration is important in the rational design of better, cheaper bases and other new catalytic systems. Other than the significantly improved ionisation ability of the organic ionic bases, an understanding of the reaction mechanism has not yet been reported. Therefore a detailed kinetic study was performed using the reaction progress kinetic analysis (RPKA) methodology on the copper-catalysed cross-coupling of piperidine and iodobenzene utilising TBPM as the base. Using this methodology, kinetic information regarding possible catalyst deactivation or inhibition pathways was rapidly obtained. This was then followed by a spectroscopic study to identify potential reaction intermediates and an investigation of the aryl halide activation mechanism.

4.1.2 Reaction progress kinetic analysis

Kinetic studies carried out using RPKA involve analysing experimental data over the course of a reaction where the substrates are under synthetically relevant conditions.^[23] Another important advantage of RPKA over the classical approach is the significantly reduced number of

experiments needed to obtain reaction rate orders for substrate concentrations. In comparison, the classical approach involves performing a large number of repetitive experiments to generate enough reaction rate data over a range of substrate concentration to obtain a trend. In addition, classical approaches require one or more substrates to be at a significantly large excess at pseudo-zero order concentrations which may skew the kinetics of the catalytic cycle. This would subsequently result in a potentially incorrect understanding of the reaction when the information is extrapolated back to synthetically relevant conditions. Another key advantage of RPKA is that an understanding of how the concentrations of substrates and reagents affect the kinetics of a catalytic cycle is obtained rapidly at the outset of a mechanistic investigation.^[23,24] Performing this analysis at the start limits the number of possible reaction pathways under consideration and therefore can inform the experimental direction of subsequent structural and spectroscopic studies. This is in contrast to the often reported method where structural and spectroscopic work is initially performed and then global kinetic analysis of the reaction is used to confirm what has been proposed.

Collection of reliable RPKA data requires *in situ* monitoring of a reaction to provide a continuous rate or concentration over time profile. The data is then processed and presented in a graphical form, consisting of plots of various reaction rate functions against substrate concentration, called graphical rate equations. These plots allow easier extraction of kinetic information such as identifying orders with respect to substrates and reagents and processes such as catalyst deactivation or inhibition.^[23] For example, shown in Figure 4.2a is raw rate data obtained from a reaction over time (pink circles).^[23] This rate data can also be processed and

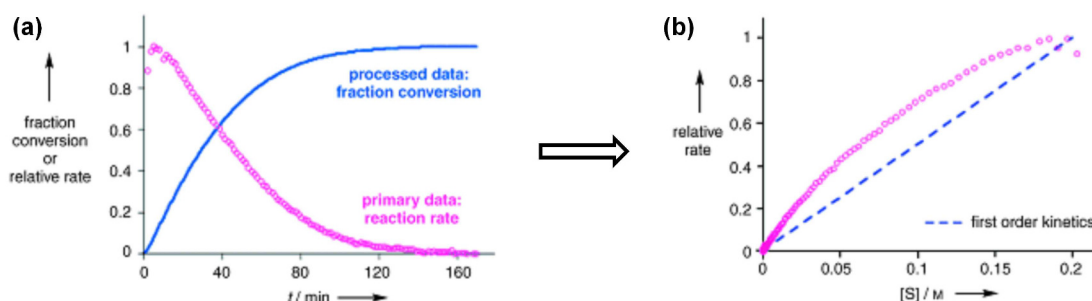


Figure 4.2: (a) Example of reaction rate data obtained over time (pink circles) and the processed fractional conversion over time (blue curve); (b) “Graphical rate equation” produced from the processed data (pink circles) plotted with a theoretical overall first order kinetics line. Plots taken from reference [23].

converted to fractional conversion over time (blue curve, Figure 4.2a). Therefore a graphical rate equation can now be produced where it is immediately clear that the reaction from this example does not follow overall first order kinetics (Figure 4.2b).

A key part to RPKA involves using the reaction stoichiometry. For example in the modified Ullmann amination reaction between piperidine and iodobenzene, for every molecule of piperidine reacted, a molecule of iodobenzene must also have reacted. Using a parameter called the excess ($[e]$), which is defined as the difference in initial substrate concentrations, the concentration of one substrate can be easily related to the other by the following equations:

$$\begin{aligned} [\text{Piperidine}]_0 - [\text{Piperidine}] &= [\text{PhI}]_0 - [\text{PhI}] \\ [e] &= [\text{Piperidine}]_0 - [\text{PhI}]_0 \\ [\text{Piperidine}] &= [e] + [\text{PhI}] \end{aligned}$$

One type of experiment which is used to determine orders in substrate or reagent concentrations is called a “different excess” experiment. This involves performing a reaction with a different $[e]$ to the standard conditions and comparing graphical rate plots. For example, in the Diels-Alder reaction shown in Scheme 4.6, the reaction rate vs $[\text{Diene}]$ graphical rate equations for when $[e] = [\text{Dienophile}]_0 - [\text{Diene}]_0$ equal 0.21 and 0.41 M are shown in Figure 4.3a.^[24] The rate for this reaction can be described by Equation 4.1 where x and y represent the orders in $[\text{Diene}]$ and $[\text{Dienophile}]$ respectively.

$$\text{rate} = k[\text{Diene}]^x[\text{Dienophile}]^y \quad (4.1)$$

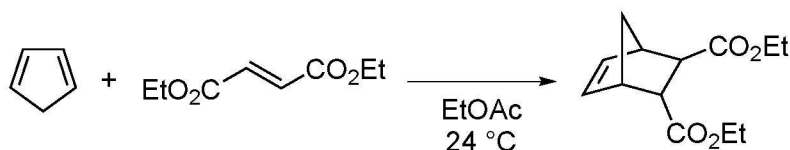
When the reaction rate is normalised by the instantaneous $[\text{Dienophile}]$ at a given time for both experiments, the resultant plots are linear and also overlay (Figure 4.3b). This process is mathematically described in Equation 4.2 where $y = 1$.

$$\frac{\text{rate}}{[\text{Dienophile}]^1} = k[\text{Diene}]^x \quad (4.2)$$

The linearity means that $\text{rate}/[\text{Dienophile}]^1$ is related to the gradient equal to k with first order in $[\text{Diene}]$ ($x = 1$) in the linear equation shown in Equation 4.3.

$$\frac{\text{rate}}{[\text{Dienophile}]^1} = k[\text{Diene}]^1 \quad (4.3)$$

In addition, the plots produced when the rates were divided by $[\text{Dienophile}]$ to the power of one overlay (Figure 4.3b). As the reactions used different $[\text{Dienophile}]_0$, the overlay confirms that



Scheme 4.6: Example Diels-Alder reaction that was monitored and analysed using RPKA.^[24]

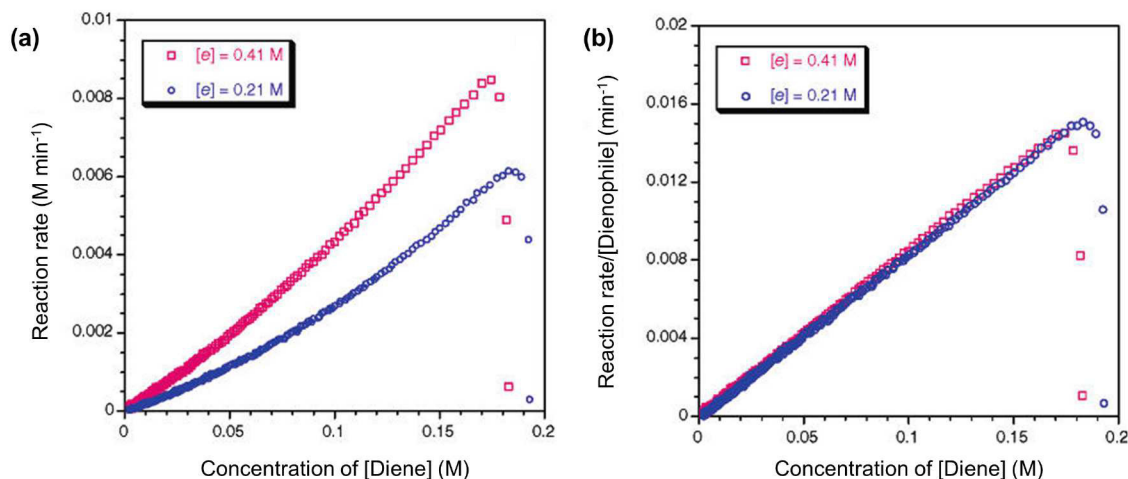
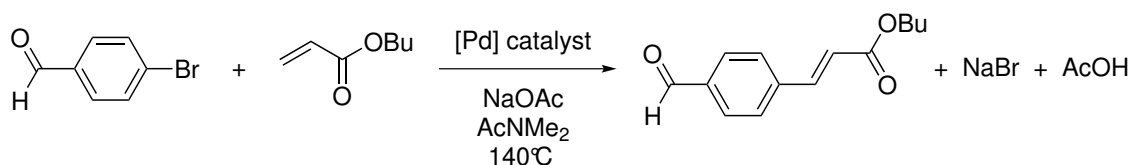


Figure 4.3: (a) Graphical rate equations for the reaction shown in Scheme 4.6 conducted with two different $[e]$ values; (b) Normalised rate by $[\text{Dienophile}]$ plotted against $[\text{Diene}]$. Plots taken from reference [24].

$\text{rate}/[\text{Dienophile}]^1$ is not a function of $[\text{Dienophile}]$, i.e. $[\text{Dienophile}]$ is not present on the right-hand side of Equation 4.3. Therefore the reaction exhibits first-order kinetics in $[\text{Dienophile}]$. This approach demonstrates how the rate law in Equation 4.4 can be determined in a two substrate reaction using only two experiments.

$$\text{rate} = k[\text{Diene}]^1[\text{Dienophile}]^1 \quad (4.4)$$

Another type of experiment that can be used to identify processes such as catalyst deactivation or inhibition is called a “same excess” experiment. This involves performing a reaction with the same $[e]$ to the standard conditions but changing the initial substrate concentrations and then comparing graphical rate plots. For example, when the same excess methodology was applied to the Heck coupling of aryl bromides shown in Scheme 4.7, the graphical rate plots in Figure 4.4 were obtained.^[23,25] Reaction 1 in Figure 4.4, started at higher initial substrate concentrations than reaction 2 (Figure 4.4) but with the same $[e]$. Therefore the catalyst in reaction 1 would have performed more turnovers when the substrate concentrations were the



Scheme 4.7: Example Heck coupling that was monitored and analysed using RPKA.^[23,25]

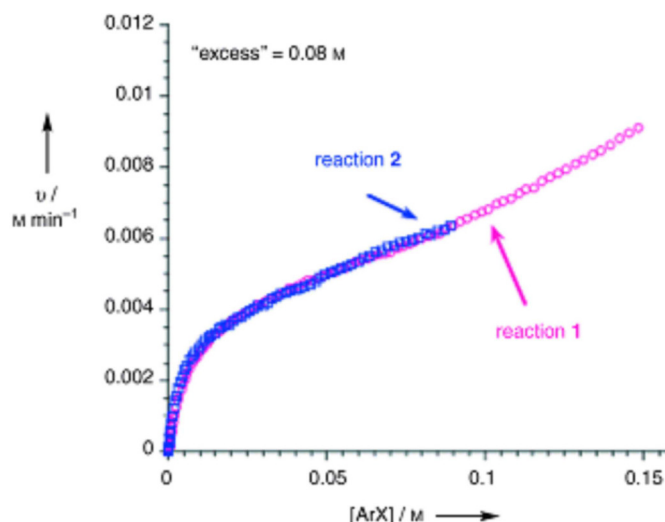


Figure 4.4: Graphical rate equations for the reaction shown in Scheme 4.7 conducted with the same $[e]$ values but different initial substrate concentrations. Reaction 1 (pink curve): $[\text{ArX}]_0 = 0.16 \text{ M}$, $[\text{olefin}]_0 = 0.24 \text{ M}$; Reaction 2 (blue curve): $[\text{ArX}]_0 = 0.12 \text{ M}$, $[\text{olefin}]_0 = 0.20 \text{ M}$. Figure taken from reference [23].

same as the initial concentrations in reaction 2. The overlaying curves in this case mean that the extra turnovers performed did not affect the catalyst stability nor is there any inhibition by the product, sodium bromide or acetic acid by-products. If either of these two factors were present, then the curve at higher initial concentrations would be at lower rate when it reaches the same point as the lower initial concentrations reaction.

In the literature, notable mechanistic investigations of copper-catalysed reactions which have benefitted from the RPKA methodology were the *N*-arylation of pyrrolidinone reported by Buchwald and co-workers^[26,27] and oxidative coupling reaction between *N*-phenyl tetrahydroisoquinoline and silyl enol ethers recently reported by Klussmann and co-workers.^[28] The kinetic analyses performed in both reports allowed the authors to identify the presence or absence of catalyst deactivation and inhibition and the orders with respect to the reactant concentrations in the rate equation. For each reaction, potential solution equilibria and copper intermediates

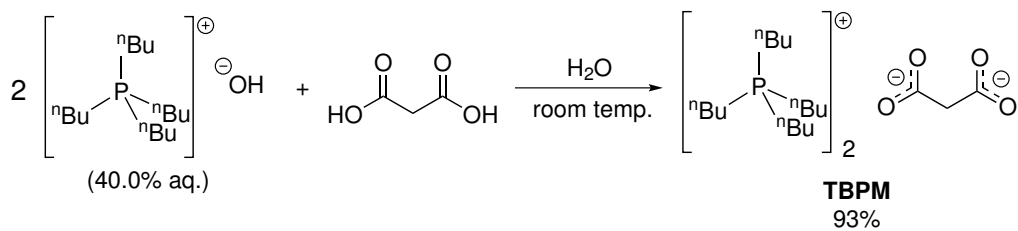
were then proposed and subsequently probed through spectroscopic and reactivity studies. Overall, this method allowed the mechanisms to be further refined compared to previous mechanistic reports. This approach to elucidating reaction mechanisms has not been applied to copper-catalysed cross coupling reactions between alkylamines and aryl iodides in the literature. Therefore an initial RPKA study followed by reactivity and spectroscopic studies were performed in this work to identify possible solution equilibria and intermediate species for this type of reaction.

4.2 Results and Discussion

4.2.1 Synthesis and use of TBPM as a base

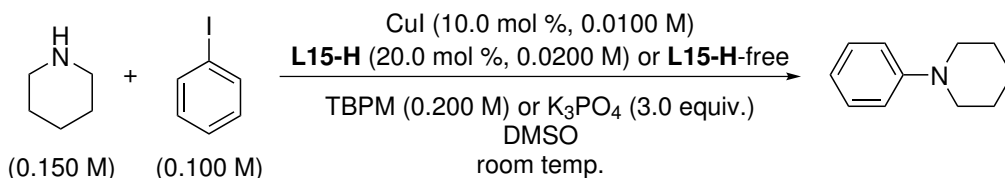
Having established the methodology for the kinetic studies, the first stage of this work will involve identifying a model reaction and ideal conditions to investigate. As mentioned in the Section 4.1.1.2, TBPM is to be used as the base instead of potassium phosphate in the copper-catalysed cross-coupling of piperidine and iodobenzene.

Firstly, TBPM was synthesised according to the method by Liu *et al* by stirring malonic acid and two equivalents of aqueous tetra(*n*-butyl)phosphonium hydroxide for two hours under a nitrogen atmosphere (Scheme 4.8).^[21] However, the workup was modified from the method in the literature in order to produce a purer compound. The original workup method reported by Liu *et al* only involved evaporating the water solvent and then drying the TBPM product under vacuum for 24 hours at 50 °C. In this work, the completed reaction solution was first evaporated to dryness and then the residue was dissolved in acetonitrile to suspend an unknown white solid side-product. After filtration, the clear filtrate was then evaporated again to dryness and the resultant pure hygroscopic solid was stored in a nitrogen-filled glovebox.



Scheme 4.8: Reaction scheme for the synthesis of TBPM.

The conditions for the first reaction carried out utilising TBPM as the base involved catalytic loadings of 10.0 mol % copper(I) iodide, 20.0 mol % 2-acetylcyclohexanone (**L15-H**) and two equivalents of TBPM (0.200 M) in DMSO at room temperature (Scheme 4.9). It should be noted that TBPM was completely soluble under these conditions. These conditions are similar to those employed by Liu and co-workers for the amination of aryl bromides except they used *N,N*-dimethylglycine as an ancillary ligand and 1.5 equivalents of TBPM.^[21] To determine if TBPM is sufficiently basic to deprotonate **L15-H** in the reaction solution, a DMSO-*d*₆ solution containing both compounds was analysed by ¹H NMR spectroscopy. **L15-H** in DMSO-*d*₆ is present predominantly in its enol tautomer form, as there is a significant enol O–H proton



Scheme 4.9: Reaction scheme for the copper-catalysed cross-coupling performed using TBPM or potassium phosphate as the base in the presence or absence of 2-acetylcyclohexanone ligand (**L15-H**).

resonance at $\delta = 15.92$ ppm in the ^1H NMR spectrum. After treating this solution with TBPM, the acidic enol O–H proton resonance was no longer present in the ^1H NMR spectrum and the other diketone proton resonances had also shifted (see Section 4.4.4 for experimental details). This indicated that deprotonation of **L15-H** by TBPM occurs rapidly on mixing and therefore confirms the diketonate anion can be formed in the catalytic reaction above.

Pleasingly, the reaction rate when soluble TBPM was employed was significantly faster than the reaction that utilised poorly soluble potassium phosphate as the base (Figure 4.5, red and green curves). In addition, the substrates reacted cleanly to give 97% yield after only approximately three hours using TBPM base compared to 81% yield after 26 hours using potassium phosphate base. Interestingly, when the reaction was conducted under ligand-free

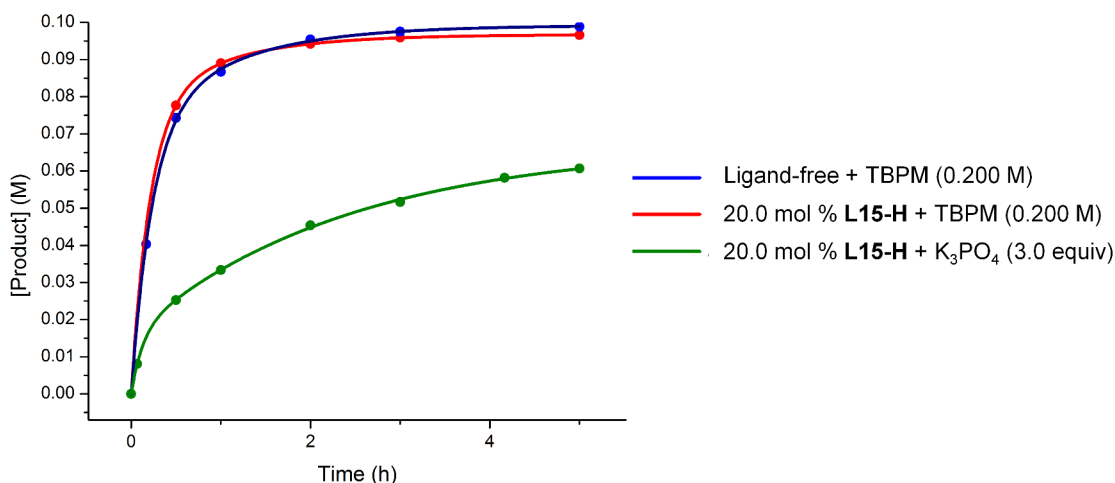
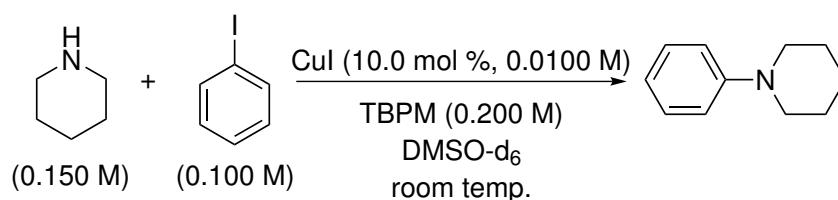


Figure 4.5: Reaction rate comparison when using TBPM or potassium phosphate as the base in the presence or absence of 2-acetylcyclohexanone ligand (**L15-H**) for the reaction shown in Scheme 4.9. Product concentrations were determined by GC using naphthalene as an internal standard.

conditions, a very similar [Product] – time profile was produced compared to when 20.0 mol % diketone was used (Figure 4.5, red and blue curves). Therefore despite being able to coordinate to copper(I),^[29] the presence of the diketonate did not significantly affect the catalytic reactivity when TBPM was used as the base. This suggests that the excess malonate anion of TBPM may be acting as a more strongly coordinating ligand than the diketonate.

¹H NMR analysis of the final reaction mixtures when TBPM was used as the base confirmed that the remaining 3% of iodobenzene had converted to benzene from a hydrodehalogenation process *via* an unknown mechanism. Hydrodehalogenation side reactions of aryl halides have been reported to occur in other copper-mediated reactions in the literature!^[30–39] Hydrodehalogenation in the reactions mentioned in this report will be discussed in greater detail below in Section 4.2.6. Even though there is this side-reaction present, the small quantity of benzene generated is unlikely to affect the RPKA data interpretation.



Scheme 4.10: Reaction scheme for the cross-coupling performed to compare the effect of stirring on the reactivity.

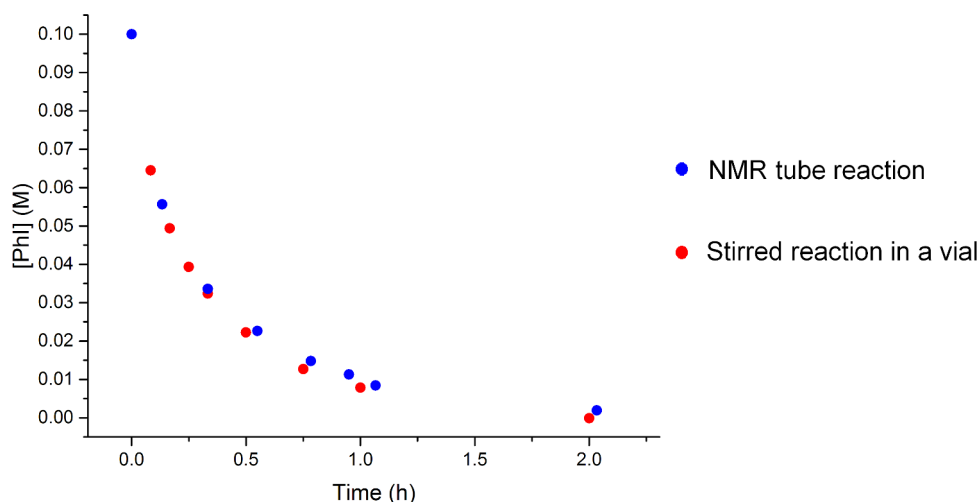


Figure 4.6: Rate comparison for the reaction shown in Scheme 4.10 when it is conducted in an NMR tube without stirring and in a vial with stirring. Product concentrations for stirred reaction were determined by GC using naphthalene as an internal standard.

Mass transfer effects were also confirmed to not be present in the homogeneous reaction mixture using TBPM as similar [PhI] – time profiles were observed for an unstirred reaction performed in a NMR tube and a stirred reaction performed in a vial (Scheme 4.10 and Figure 4.6).

As expected, the use of soluble TBPM as a base produced significantly faster reaction rates over using very poorly soluble potassium phosphate in the copper-catalysed cross-coupling of piperidine and iodobenzene in DMSO solvent at room temperature (Section 4.1.1.2). However, as there was no rate benefit when **L15-H** was utilised as an ancillary ligand, subsequent reactions were performed under ligand-free conditions.

4.2.2 Background of reaction calorimetry

The *in situ* monitoring technique used for collecting RPKA data was reaction calorimetry, which involves detecting the heat flow produced from a reaction. For a reaction that cleanly yields its product, the instantaneous heat flow, q , at a given time is related to the reaction rate by a proportionality constant called the heat of reaction, ΔH_{rxn} , (also known as the enthalpy of reaction) and the reaction volume, V (Equation 4.5).

$$q = \Delta H_{rxn} \cdot V \cdot \text{rate} \quad (4.5)$$

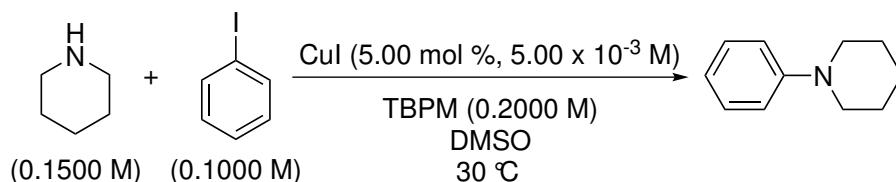
One of the advantages of monitoring by reaction calorimetry is that reaction rate data is obtained directly. Data obtained by other techniques such as infrared spectroscopy and NMR monitoring provide concentrations, which require differentiating against time to obtain rate information. A by-product of this extra processing is inevitably noise.^[24,40] The fractional conversion, f , of the reaction can be calculated from the product of the final conversion, f_{final} , and sum of the heat generated to time, t , divided by the total heat generated from the reaction when $t = t_f$ (Equation 4.6). The fractional conversion can then be related to the concentration of the limiting substrate in the reaction using Equation 4.7.

$$f = f_{\text{final}} \cdot \frac{\int_{t=0}^{t=t} q \cdot dt}{\int_{t=0}^{t=t_f} q \cdot dt} \quad (4.6)$$

$$[\text{Substrate}] = [\text{Substrate}]_0 \cdot (1 - f) \quad (4.7)$$

4.2.3 Kinetic studies of the Ullmann amination reaction using TBPM as the base

The reaction run in the calorimeter is shown in Scheme 4.11 and is the same as shown in Scheme 4.10 except 5 mol % copper(I) iodide was used and the reaction temperature was increased to 30 °C from room temperature to ensure more accurate and reliable thermostating (Scheme 4.11). When the heat being released from the reaction vessel became negligible, indicating the reaction had finished, three corrections were applied to the raw heat flow over time data before it was analysed. The first correction is called a “tau”-correction and accounted for the time it took the instrument to detect the heat from the reaction vessel. The next was a baseline correction and then the final correction was for the heat of mixing associated with the addition of copper(I) iodide solution to initiate the reaction (see Section 4.4.7 for



Scheme 4.11: Reaction scheme for the cross-coupling performed with the standard quantities of substrates, catalyst and base.

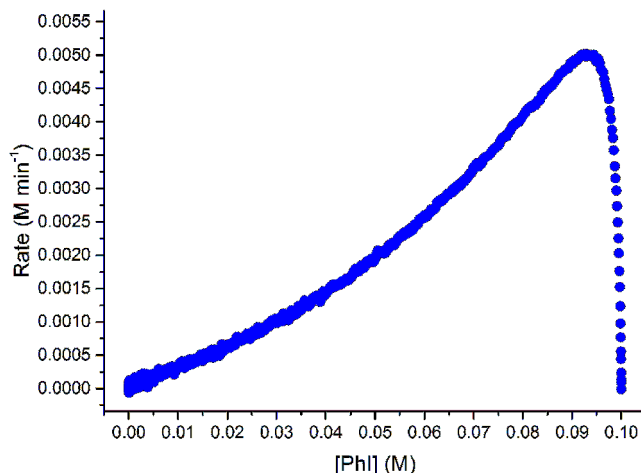


Figure 4.7: Graphical rate equation produced from the data obtained for the reaction shown in Scheme 4.11.

details regarding the corrections). After the corrections and processing to convert the heat flow to reaction rate, the graphical rate plot in Figure 4.7 was produced (enthalpy of reaction, $\Delta H_{rxn} = 172.5 \pm 3.5 \text{ kJ mol}^{-1}$). The non-linear shape of the data in Figure 4.7 revealed that the overall kinetics were not first order at these reaction concentrations.

To confirm that the calorimetry data accurately represents the reaction, it was repeated under the same conditions but was monitored using ^1H NMR spectroscopy instead. The excellent correlation between the conversion calculated from the heat flow and the conversion determined by ^1H NMR analysis at certain reaction times shown in Figure 4.8 validated the use of calorimetry as a monitoring tool for this copper-catalysed cross-coupling reaction.

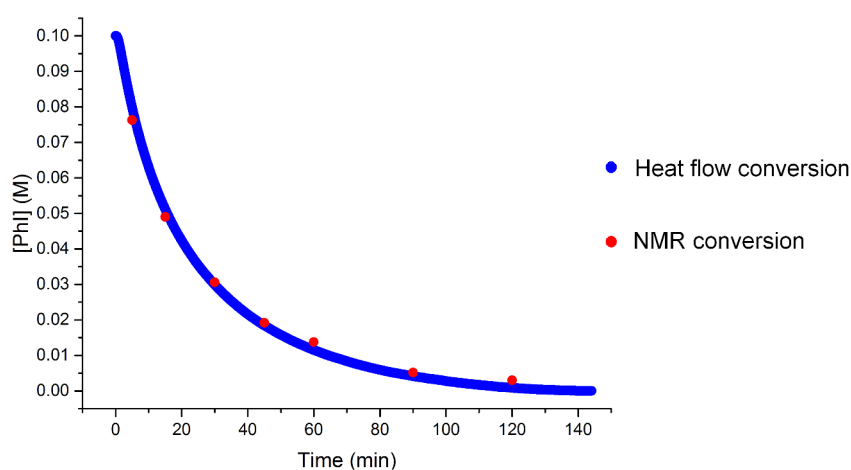


Figure 4.8: Comparison between the conversions calculated from the calorimetry heat flow and from ^1H NMR spectroscopy.

The calculated enthalpy of reaction across reactions with various initial reactant concentrations discussed herein were all within $\pm 2\%$ of the mean value. In addition, the observed degree of hydrodehalogenation side reaction varies with the initial reactant concentrations used (discussed in Section 4.2.6). Therefore the low variance in enthalpy of reaction indicates that the heat produced from this side reaction contributes minimally towards the total detected heat. Overall, these points further support the use of calorimetry as a viable tool for reaction progress monitoring.

In the following subsections, only the data between 20 – 80% conversion is shown in the graphical rate equations in order to exclude any effects on the rate by potential induction periods and also to limit inaccuracies as the limiting substrate concentration approaches zero.^[24]

4.2.3.1 Rate dependence on catalyst concentration

In order to determine the rate dependence on catalyst concentration, two reactions were studied, both using the same substrate and base concentrations but either 2.50 or 5.00 mol % of copper(I) iodide (Figure 4.9a). Assuming the total active catalyst concentration, $[\text{Cu}]_{\text{total}}$, remains unchanged throughout the reactions in both cases, the plots of reaction rate normalised by $[\text{Cu}]_{\text{total}}^{0.9}$ overlay (Figure 4.9b), according to the overlay margins reported in other calorimetric graphical rate plots in the literature.^[24,27,28] This indicates that the reaction is approximately first order in $[\text{Cu}]_{\text{total}}$.

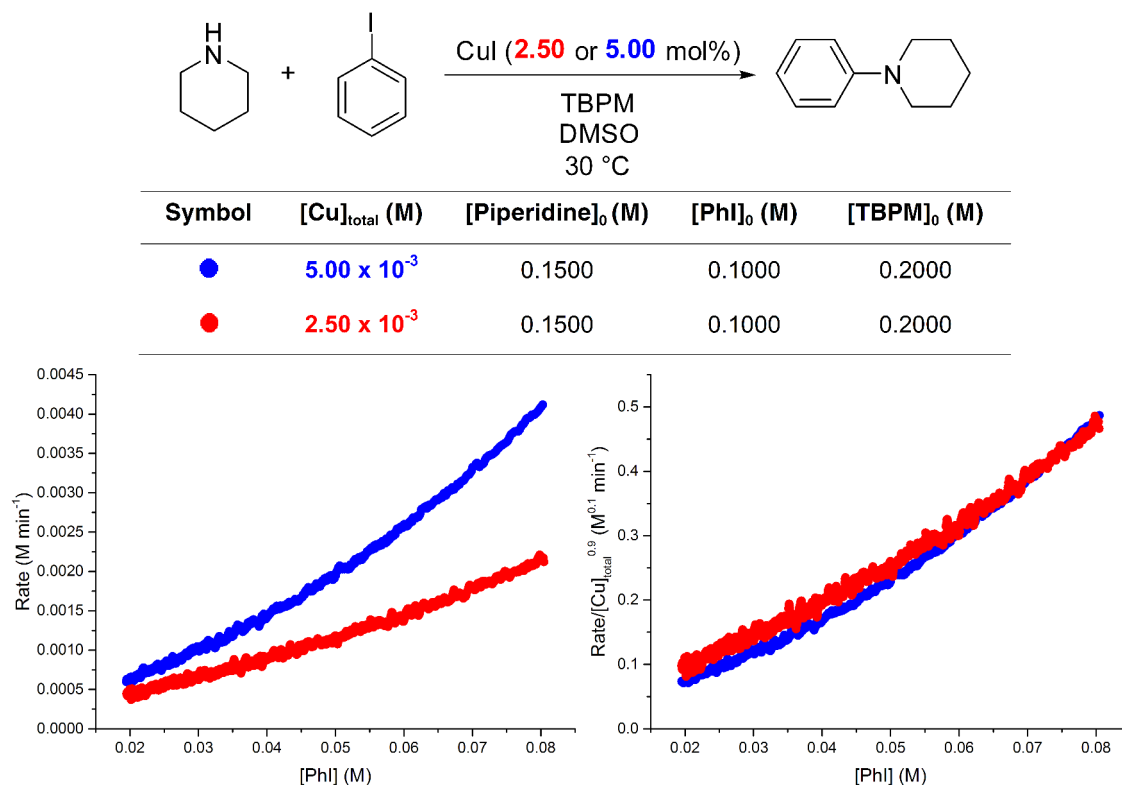


Figure 4.9: (a) Graphical rate equations of experiments using concentrations listed in the table above; (b) normalised rate by $[\text{Cu}]_{\text{total}}^{0.9}$ to identify the rate dependence on $[\text{Cu}]_{\text{total}}$.

4.2.3.2 “Same excess” experiments

The “same excess” protocol mentioned in Section 4.1.2 was then employed to obtain kinetic information about catalyst stability and any potential catalyst inhibition. The first “same excess” experiment performed involved reducing $[\text{TBPM}]_0$, $[\text{Piperidine}]_0$ and $[\text{PhI}]_0$ by 0.0500 M to keep the same $[e] = [\text{Piperidine}]_0 - [\text{PhI}]_0 = 0.0500$ M (Figure 4.10a) as the standard concentra-

tions experiment (Scheme 4.11). The lack of overlay of the graphical rate equations of the standard and “same excess” experiments and faster rate in the “same excess” experiment indicates that another process was present other than the intrinsic kinetics related to [TBPM], [Piperidine] and [PhI]. Furthermore, the curve produced from another “same excess” experiment with added 0.0500 M concentrations of *N*-phenylpiperidine, mono-anion of malonic acid and tetra(*n*-butyl)phosphonium iodide (Figure 4.10b) overlaid well with the previous “same excess” experiment. This suggests that catalyst inhibition by product coordination; potential processes by mono-anionic malonic acid such as protonating the piperidine substrate; or solution conductivity changes from increasing tetra(*n*-butyl)phosphonium iodide concentration were negligible in this cross-coupling reaction. The negligible rate difference with added mono-anionic malonic acid and tetra(*n*-butyl)phosphonium iodide also suggests that the possible malonate ligand

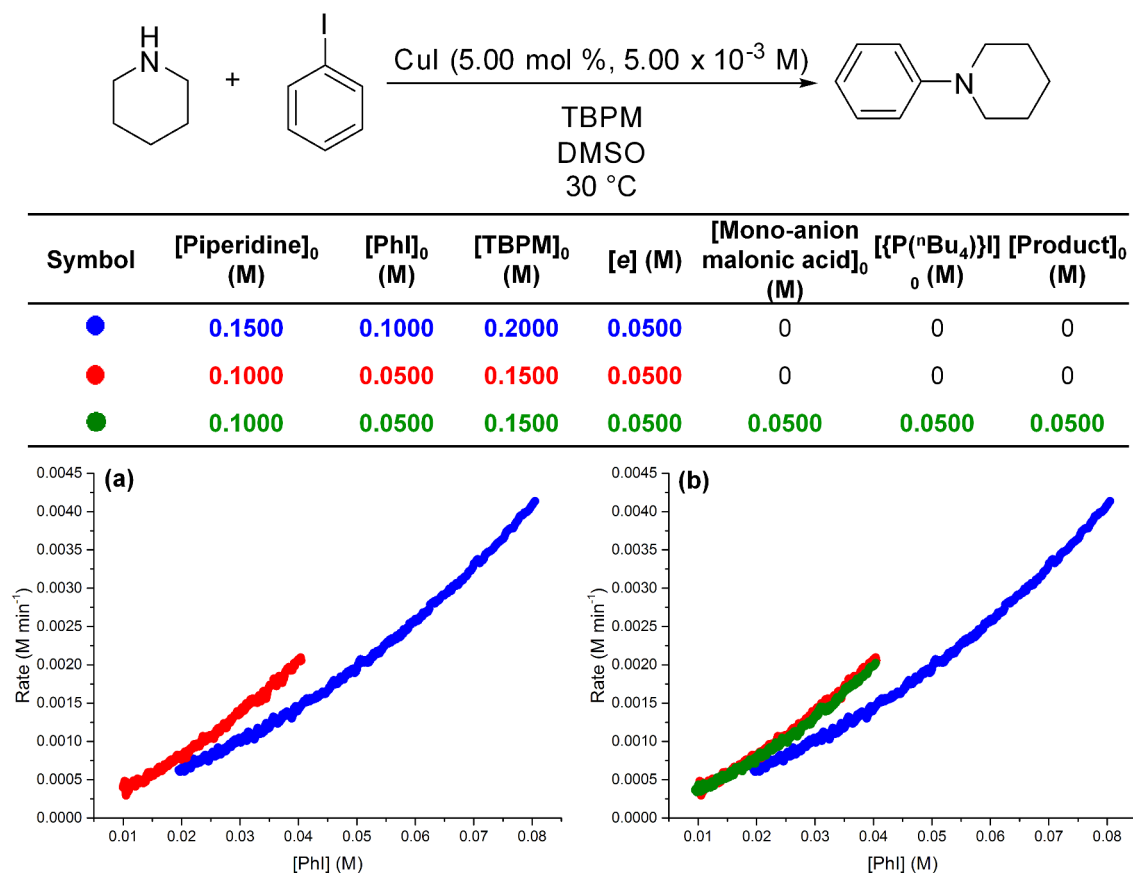
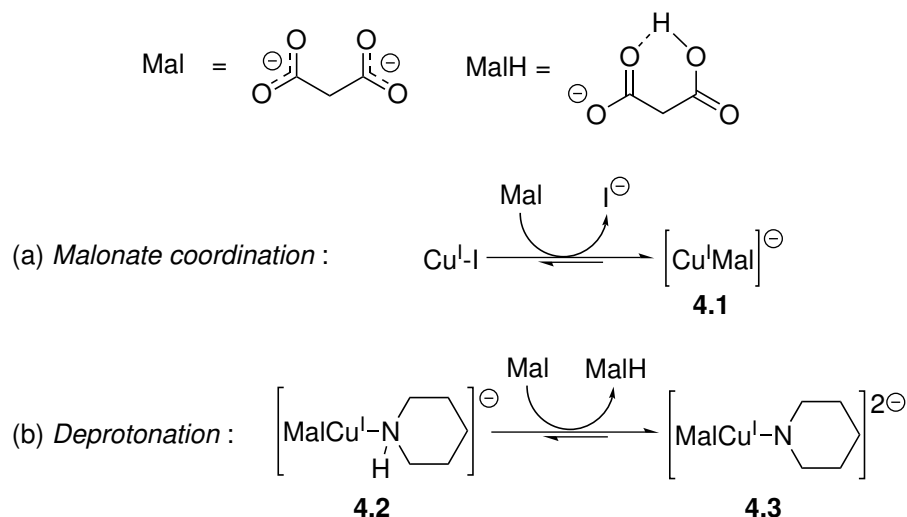


Figure 4.10: Graphical rate equations from experimental using concentrations listed in the table above: (a) Standard and “same excess” experiments; (b). Added the graphical rate equation for the “same excess” experiment with added *N*-phenylpiperidine, mono-anion of malonic acid and tetra(*n*-butyl)phosphonium iodide.



Scheme 4.12: Inferred equilibria from “same excess” experiments for (a) malonate coordination to displace iodide and (b) N–H deprotonation of coordinated piperidine. Tetra-(*n*-butyl)phosphonium counter cations are not shown.

displacement of iodide from copper(I) iodide to malonate-ligated complex **4.1** (Scheme 4.12a) and N–H deprotonation of piperidine from complex **4.2** to **4.3** (Scheme 4.12b) are strongly favoured processes. Overall, these findings suggest catalyst deactivation was the likely cause for the lack of overlap between the standard and same excess experiments.

4.2.3.3 “Different excess” experiments

The “different excess” protocol mentioned in Section 4.1.2 was then used to extract kinetic information regarding the rate dependence on [TBPM], [Piperidine] and [PhI]. Firstly, a reaction with 0.2000 M [Piperidine]₀ was performed and gave the graphical rate equation shown in 4.11a. Poor overlap of the normalised graphical rate equations from dividing rate by [Piperidine] to the power of 0.5 (Figure 4.11b) and 2 (Figure 4.11d) indicates that the order in [Piperidine] is not 0.5 or 2. In contrast, when the reaction rate is normalised by [Piperidine] to the power of 1, the plots overlay and therefore indicates that the reaction is first order in [Piperidine] (Figure 4.11c).

Figure 4.12a shows two graphical rate equations from experiments carried out with different [e], where [PhI]₀ was decreased to 0.0500 M from 0.1000 M in the experiment with standard concentrations. The plots produced when the rates of both experiments are normalised by [PhI] to the power of 0.5 (Figure 4.12b) or 2 (Figure 4.12d) against [Piperidine] do not overlay which indicates order in [PhI] is not 0.5 or 2. In comparison, the plots of rate normalised by [PhI] to

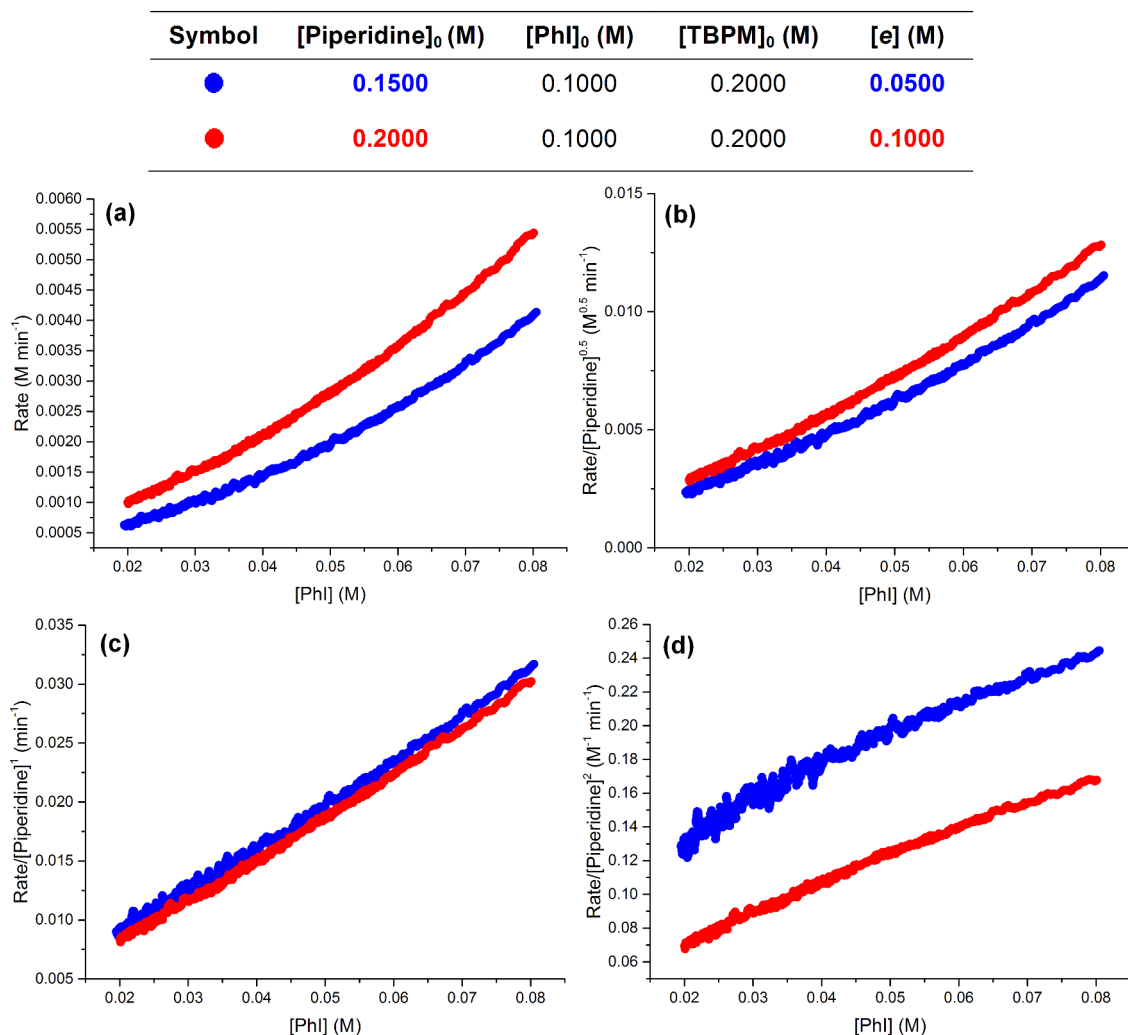


Figure 4.11: Graphical rate equations of experiments carried out using the “different excess” protocol to obtain the rate dependence on [Piperidine]: (a) Graphical rate equations of the standard and “different excess” experiments, and normalised graphical rate equations from dividing rate by [Piperidine] to the power of (b) 0.5, (c) 1 and (d) 2.

the power of 1 do overlay which indicates that there is a first order dependence in [PhI] on the reaction rate (Figure 4.12c).

When the “different excess” protocol was applied to identify the rate dependence on [TBPM], the graphical rate equations shown in Figure 4.13a were produced. Reactions that employed higher [TBPM]₀ concentrations were unexpectedly slower, which indicates there is a negative rate dependence on the [TBPM]. When the reaction rate is multiplied by [TBPM], the normalised curves overlay reasonably well and therefore suggests the order in [TBPM] is approximately negative first order in this concentration regime (Figure 4.13b). The negative dependence on

Symbol	[Piperidine] ₀ (M)	[PhI] ₀ (M)	[TBPM] ₀ (M)	[e] ⁻ (M)
●	0.1500	0.1000	0.2000	0.0500
●	0.1500	0.0500	0.2000	0.1000

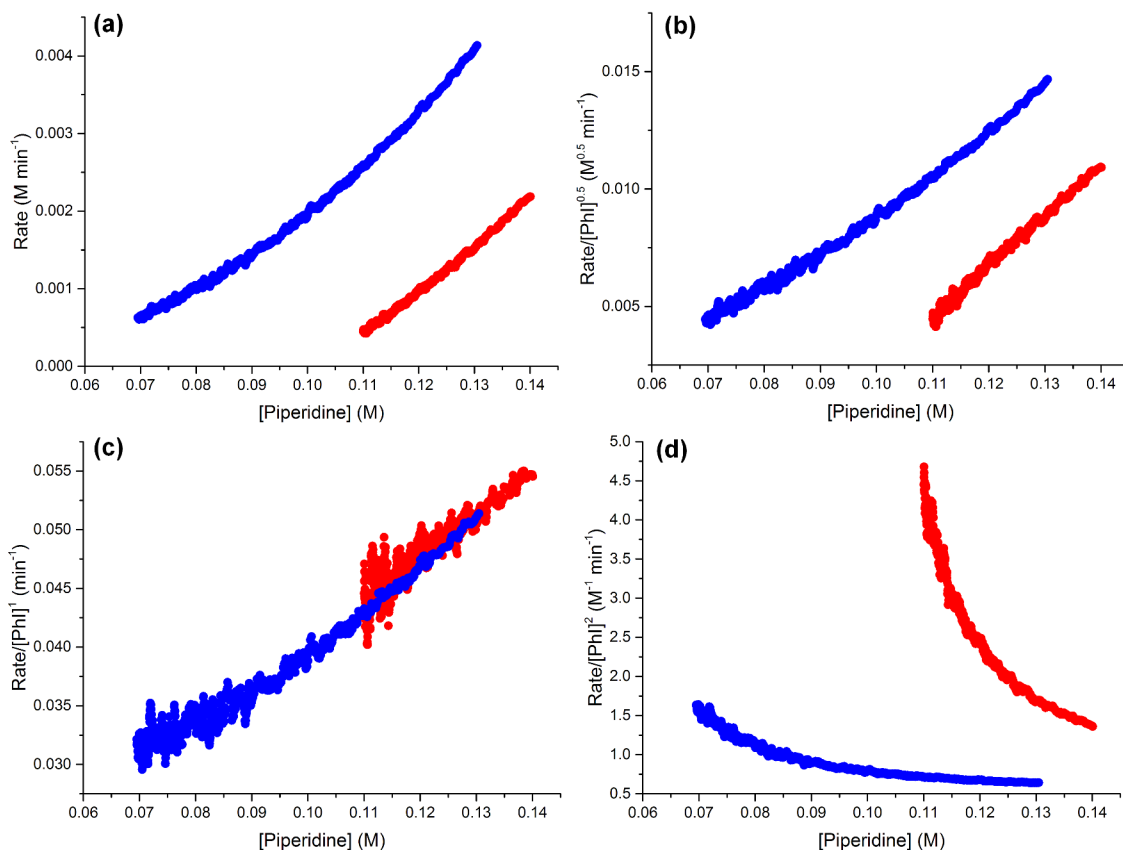


Figure 4.12: Graphical rate equations of experiments carried out using the “different excess” protocol to obtain the rate dependence on [PhI]: (a) Graphical rate equations of the standard and “different excess” experiments, and normalised graphical rate equations from dividing rate by [PhI] to the power of (b) 0.5, (c) 1 and (d) 2.

[TBPM] could be attributed to an additional malonate anion binding to complex **4.1** to give an off-cycle copper(I) di(malonate) complex (**4.4**) (Scheme 4.13). Coordination of carboxylate bases has also been suggested by Fukuyama and co-workers when caesium acetate was used as the base in an Ullmann amination reaction.^[13] However kinetic studies to find the consequences of this on the rate were not performed.

To summarise, for relatively low [Piperidine]₀, [PhI]₀, [TBPM]₀ and [Cu]_{total} (≤0.3 M), all of the reaction components were determined to have an effect on the reaction rate with first order kinetics with respect to [Piperidine], [PhI] and [Cu]_{total} but approximately negative first order

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

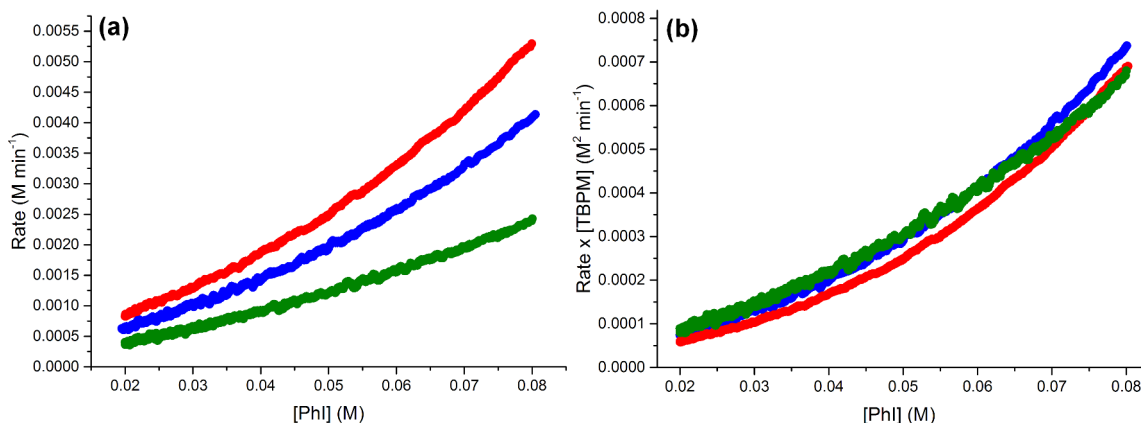
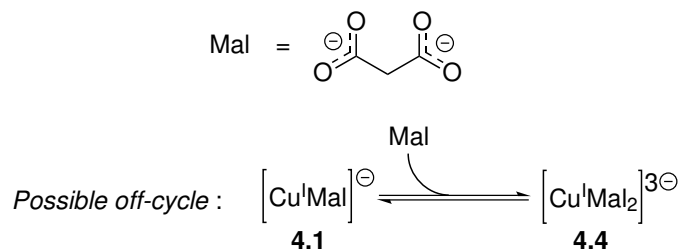


Figure 4.13: Graphical rate equations of experiments carried out using the “different excess” protocol to obtain the rate dependence on [TBPM]: (a) Graphical rate equations of the standard and “different excess” experiments; (b) Normalised graphical rate equations by multiplying rate by [TBPM].

kinetics in [TBPM]. In addition, the “same excess” experiments performed suggested that the catalyst deactivates over the course of the reaction. Given the large number of factors that affect the rate, it is likely by coincidence that the graphical rate equations appear to exhibit overall second order kinetics by observation as demonstrated in Figure 4.11c, where the normalised rate curve appears linear. This suggests the decrease in rate caused by decreasing $[\text{Cu}]_{\text{total}}$ could have been offset by the increase in rate caused by the continually decreasing [TBPM] during the reaction.



Scheme 4.13: Possible off-cycle equilibrium inferred from the negative rate dependence on [TBPM]. Tetra-(*n*-butyl)phosphonium counter cations are not shown.

4.2.3.4 Catalyst deactivation

To confirm catalyst deactivation, an experiment that involved monitoring for decreases in rate between reactions using the same catalyst solution was performed. Firstly, a reaction with initial concentrations as shown in Figure 4.14 was initiated by adding copper(I) iodide (Figure 4.14a and b, blue curve). After the reaction reached completion, when no additional heat was

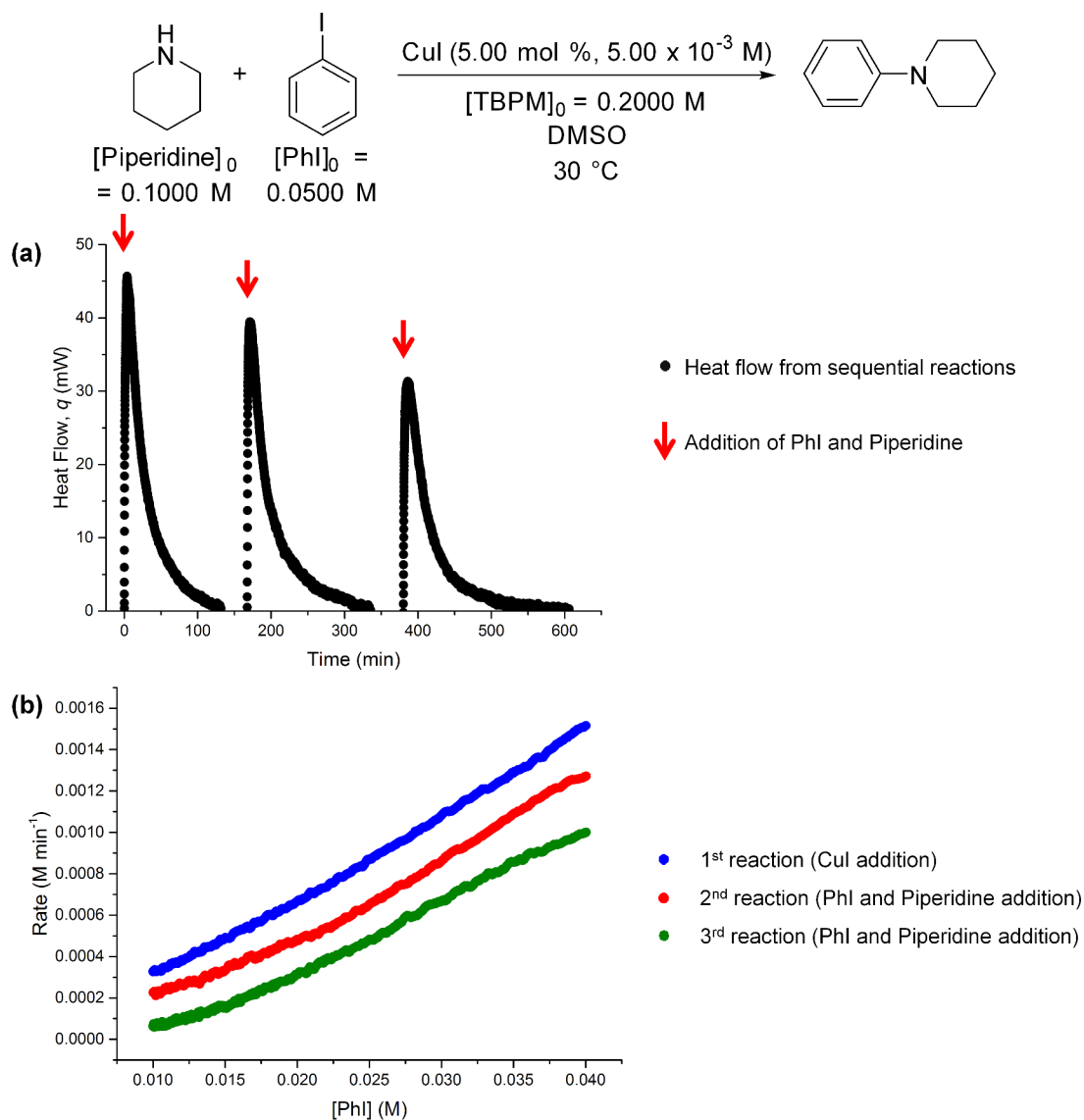


Figure 4.14: (a) Heat flow over time of reactions starting from the conditions in the scheme above and sequential additions of piperidine and iodobenzene (adding approximately 0.0500 M each) to the same reaction solution to restart the reaction; (b) Graphical rate equations for each sequential reaction.

detected by the calorimeter, piperidine and iodobenzene (0.500 mmol each) were added to the completed reaction solution simultaneously to start another reaction using the same catalyst. The amounts of each substrate added approximately reproduced the concentrations of the first reaction but now with a lower 0.1500 M [TBPM]. So if no catalyst deactivation had occurred, the second reaction would be faster than the first reaction due to the lower [TBPM]. However the second reaction produced a lower peak heat flow than the first reaction (Figure 4.14a) and therefore had a slower rate (Figure 4.14b, red curve). Furthermore, the reaction rate after a second addition of piperidine and iodobenzene (overall third reaction) was also slower than the previous reaction and also only reached 85% conversion (Figure 4.14b, green curve). Each addition of piperidine and iodobenzene increased the total solvent volume by only 2% and as a result $[\text{Cu}]_{\text{total}}$ reduced by same percentage. As the decrease in reaction rate between the sequential reactions is greater than 2%, a factor other than the minor reduction in $[\text{Cu}]_{\text{total}}$ is the predominant cause of the rate decrease. Taken together, these findings confirm that catalyst deactivation occurs during this cross-coupling reaction.

To identify a possible cause for catalyst deactivation, a series of experiments were performed where the standard reaction was initiated by a different compound after a 60 minute delay time between the penultimate and final added compounds (Figure 4.15). Compared to when copper(I) iodide was used to start the reaction (blue, Figure 4.15), the reaction rate remained approximately unchanged when copper(I) iodide was stirred in reaction solutions for 60 minutes before initiating by adding TBPM alone (red, Figure 4.15), or TBPM and piperidine together (green, Figure 4.15). These two results indicate that the copper pre-catalyst is stable in the absence of TBPM and presence of iodobenzene with and without piperidine. When the reaction was started by adding only iodobenzene (orange, Figure 4.15), a similar conversion-time profile was observed and therefore indicates that the pre-catalyst has good short-term stability in the presence of TBPM and piperidine together. In contrast, prior to initiating a reaction by adding piperidine (purple, Figure 4.15), the reaction solution containing the copper pre-catalyst had changed from colourless to blue colour within 15 minutes, which suggested the formation of copper(II) species had occurred. This observed blue colour was also similar to the colour of the final reaction solution in the kinetic experiments discussed previously. When piperidine was added to start this reaction, the reaction rate was significantly suppressed with only 14% iodobenzene conversion therefore confirming that the catalyst had significantly decomposed in the absence of piperidine.

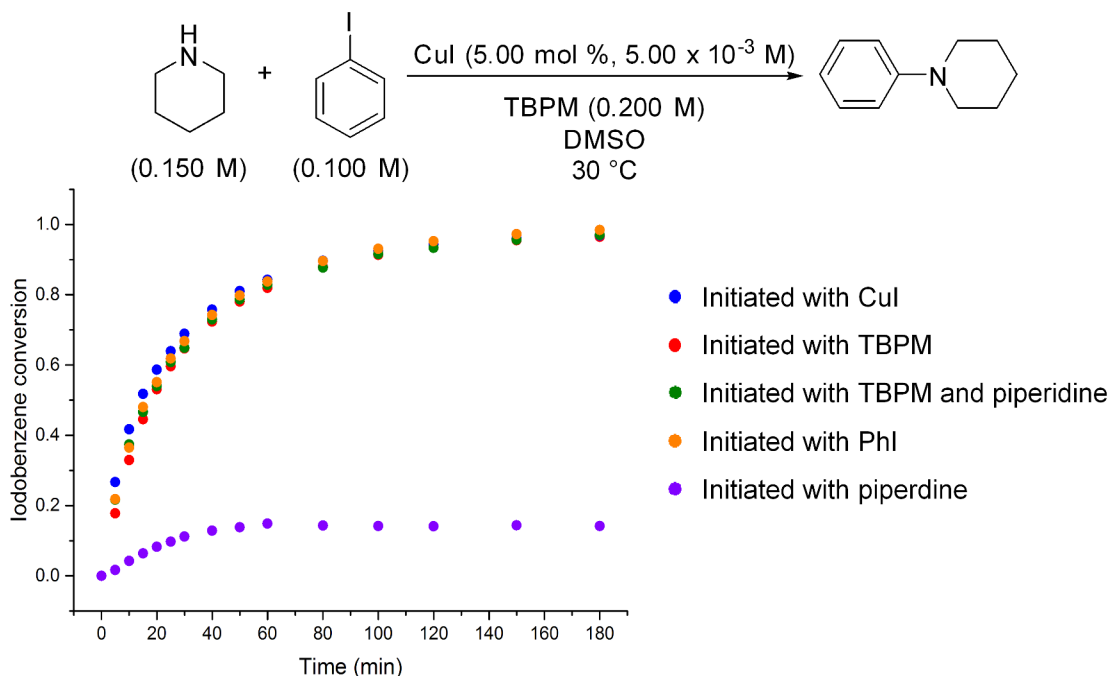
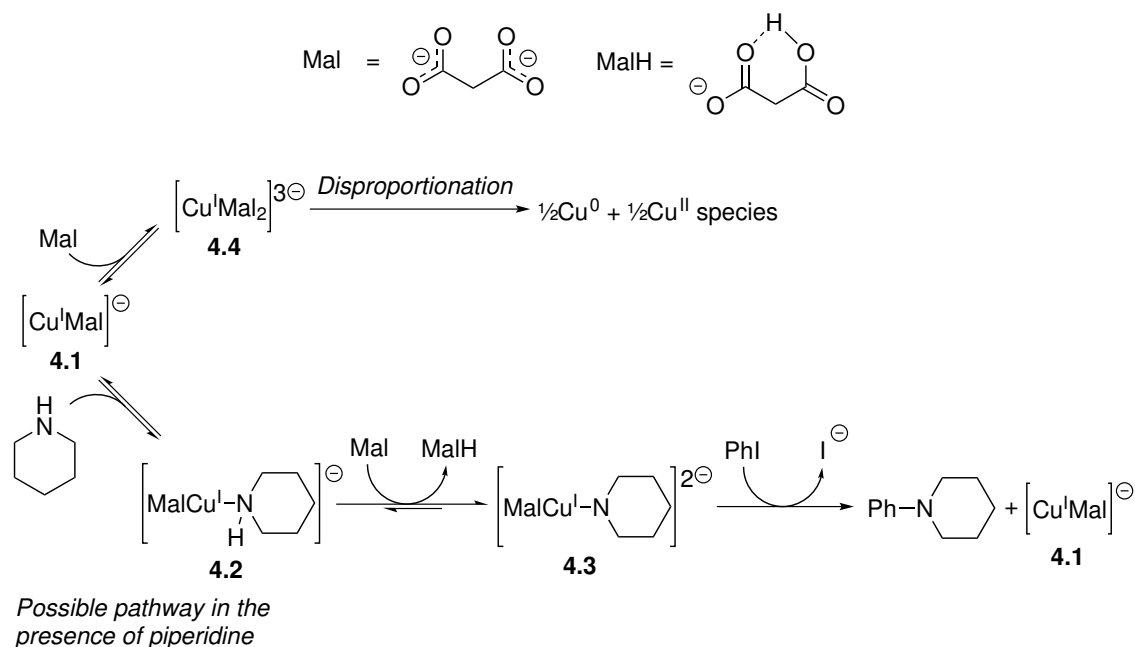


Figure 4.15: Iodobenzene conversion was monitored over time where a different compound was used to initiate the reaction after 60 minutes delay. Iodobenzene conversions were determined by GC using naphthalene as an internal standard.

In addition, mixtures of only copper(I) iodide and TBPM in DMSO were found to disproportionate to give copper(II) and copper(0) species by visual observation of the characteristic blue colouration for copper(II). In the literature, copper(I) carboxylate complexes without stabilising co-ligands, such as phosphines and alkenes, are known to be unstable and prone to disproportionation in solution at room temperature even under inert atmospheres.^[41–57] Only two successfully isolated copper(I) malonate complexes containing triphenylphosphine co-ligands have been reported^[45,50] and no ancillary ligand-free examples. Similar to what was commonly observed in Chapter 3 using 2-acetylcyclohexanone (**L15-H**) as the ligand, the copper concentrations used in the reactions in Section 4.2.3 were sufficiently low such that no visually observable copper(0) nucleation occurred in the reactions.

To summarise, piperidine aids in reducing disproportionation of potential copper(I) malonate intermediates by acting as a co-ligand, analogous to the role of triphenylphosphine co-ligands in copper(I) malonate complexes in the literature.^[45,50] Scheme 4.14 shows piperidine preventing catalyst deactivation by disproportionation through competitively coordinating to intermediate **4.1** to give **4.2** against an additional equivalent of malonate, which would form complex **4.4**.

Although disproportionation is shown to occur from a copper(I) dimalonate species in Scheme 4.14, it is possible it could occur from the initial copper(I) malonate species given that the mechanism for copper(I) carboxylate disproportionation is still not known.



Scheme 4.14: Scheme for the copper(I) catalysed coupling of piperidine and iodobenzene showing the possible pathway in the reaction when piperidine is present in the reaction and how it reduces catalyst deactivation by disproportionation. Tetra-(*n*-butyl)phosphonium counter cations are not shown.

To confirm the stabilising effect of piperidine against catalyst deactivation, an experiment that involved sequential additions of iodobenzene to a reaction solution containing a large excess of piperidine was performed to observe for changes in reactivity between runs. After the first reaction had finished, two sequential portions of iodobenzene were added and the reactions were then monitored (Figure 4.16). The large excess of piperidine would have favoured the formation of piperidine-ligated copper(I) intermediate **4.2** and prevented significant malonate coordination to **4.1** to give off-cycle complex **4.4**, which would remove the negative rate dependence in malonate. In addition, assuming that N–H deprotonation is highly favoured as suggested by the negligible effect of mono-anionic malonic acid on the reaction rate, the high [Piperidine] would result in saturation of the malonate-ligated copper(I) piperidine complex **4.3**. Therefore, from this study the rate equation when high [Piperidine] is used can be estimated as being dependent only on [PhI] and [Cu]_{total} (Equation 4.8).

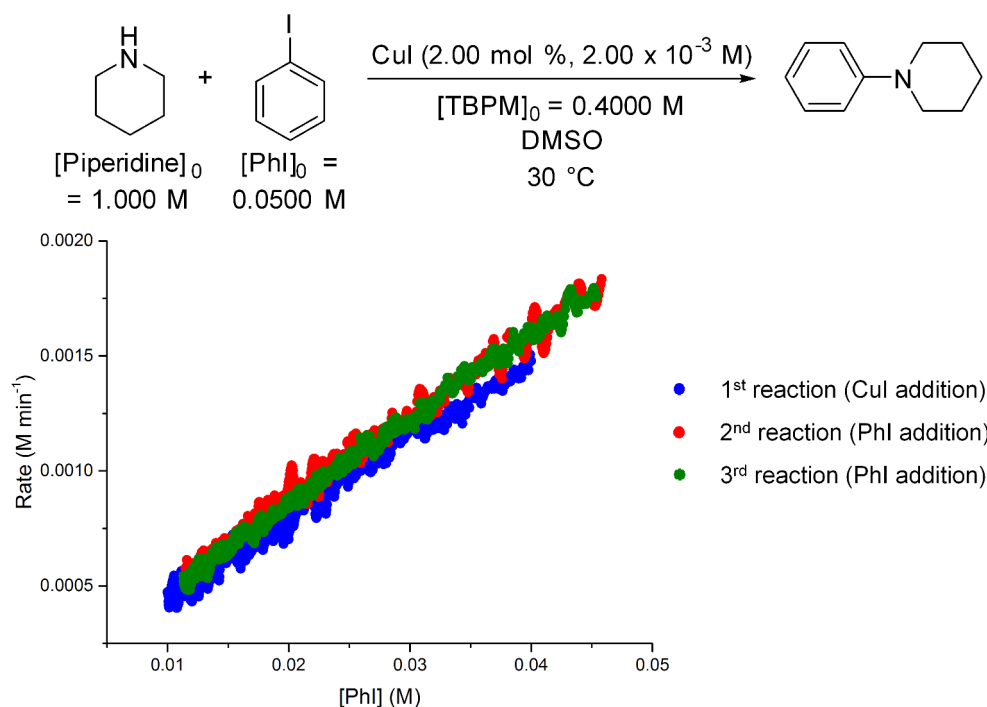


Figure 4.16: Graphical rate equations that involved sequential 0.585 mmol additions of iodobenzene to the same reaction solution after completion.

$$rate = k' [Cu]_{total} [PhI] \quad (4.8)$$

Depending on whether catalyst deactivation was still present or not, the graphical rate equations will either be curved and not overlaying due to decreasing $[Cu]_{total}$, or linear and overlaying due to constant $[Cu]_{total}$. As shown in Figure 4.16, the graphical rate equations overlay well and are approximately linear which indicates that catalyst deactivation was not present and that the reaction rate exhibited first order dependence in $[PhI]$. Overall, this result suggests that piperidine has an important role in minimising catalyst deactivation.

4.2.4 ^1H NMR spectroscopic study

After identifying some potential solution equilibria from the kinetic and catalyst deactivation studies, NMR spectroscopy was then used to further probe the interaction between the reaction components and also proposed potential intermediates. Figure 4.17 shows ^1H NMR spectra of various combinations of the reactive components. Although the N–H resonance is not present at $\delta = 1.84$ ppm in the ^1H NMR spectrum of piperidine and TBPM together (Figure 4.17c), the remaining resonances of piperidine and TBPM remain unchanged compared to the ^1H NMR

spectra of the pure compounds (Figure 4.17a and b respectively). As the amine N–H is not sufficiently acidic to be appreciably deprotonated by TBPM (pK_a in DMSO of the N–H group of the similarly structured pyrrolidine is 44)^[58], the loss of this resonance in Figure 4.17c is

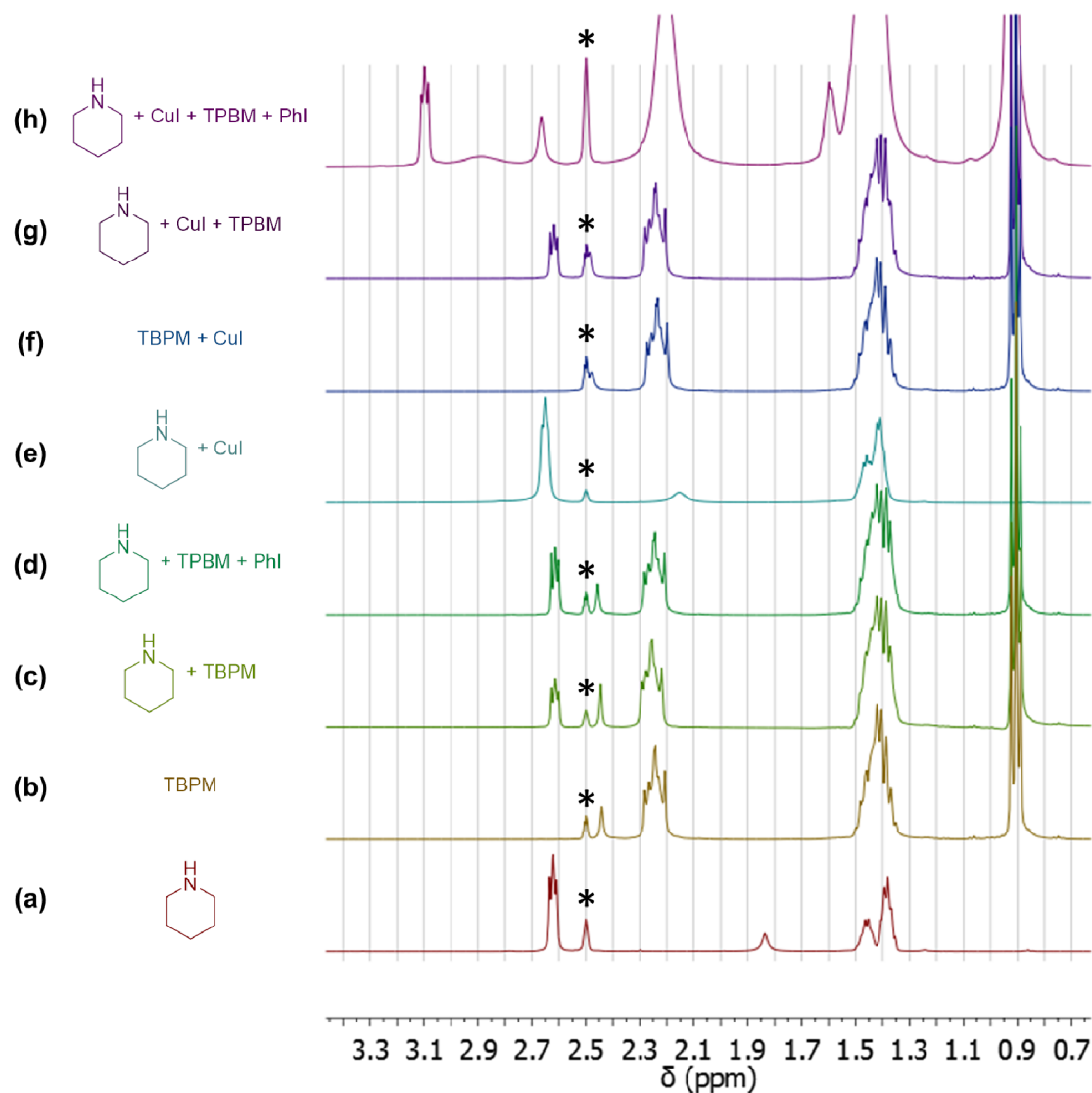


Figure 4.17: ^1H NMR spectra in DMSO-d_6 : (a) piperidine (0.150 M); (b) TBPM (0.200 M); (c) piperidine (0.150 M) and TBPM (0.200 M); (d) piperidine (0.150 M), TBPM (0.200 M) and iodobenzene (0.100 M); (e) piperidine (0.150 mmol) and copper(I) iodide (0.0100 mmol); (f) immediately after mixing TBPM (0.100 M) and copper(I) iodide (0.0100 M); (g) piperidine (0.150 M), TBPM (0.20 M) and copper(I) iodide (0.0100 M); and (h) piperidine (0.150 M), TBPM (0.20 M) and copper(I) iodide (0.0100 M) immediately after addition of iodobenzene (0.100 M). Residual solvent resonance is at 2.50 ppm labelled with asterisk (*).

likely due to severe broadening caused by H-bonding between piperidine and malonate. The downfield shift of the piperidine resonances such as the N–H resonance shifts from $\delta = 1.84$ ppm to 2.15 ppm in the presence of a catalytic amount of copper(I) iodide (Figure 4.17e) confirms that coordination of piperidine to copper(I) is possible in the cross-coupling reaction. Comparison of spectra of TBPM alone and TBPM in the presence of a catalytic quantity of copper(I) iodide also reveals a small downfield shift of the malonate CH₂ resonance from 2.44 to 2.48 ppm in the latter case (Figure 4.17b and f). This observation confirms that malonate is able to coordinate to copper(I) and may represent the formation of copper(I) malonate complex **4.1**. When the same solution of copper(I) iodide and piperidine in Figure 4.17e was treated with TBPM, the ¹H NMR spectrum shows the malonate CH₂ resonance shifted slightly downfield which indicates that malonate has coordinated (Figure 4.17g). The piperidine resonances have also shifted in this ¹H NMR spectrum such that they appear as though minimal interaction between piperidine and copper(I) remained. However, if this was the case disproportionation would have occurred, which was not observed in this experiment or in the catalyst deactivation study when copper(I) iodide was found to be stable in the presence of TBPM and piperidine (Section 4.2.3.4). Therefore the piperidine resonances could be part of malonate and piperidine ligated copper(I) complexes **4.2** or **4.3**. Finally, while there is a lack of change to the piperidine and TBPM resonances after addition of iodobenzene in the absence of copper(I) iodide (Figure 4.17d), significant broadening and slight downfield shift of the piperidine and TBPM resonances does occur when it is added in the presence of copper(I) iodide (Figure 4.17h). Reaction turnover ensues immediately after iodobenzene addition in the presence of copper(I) iodide.

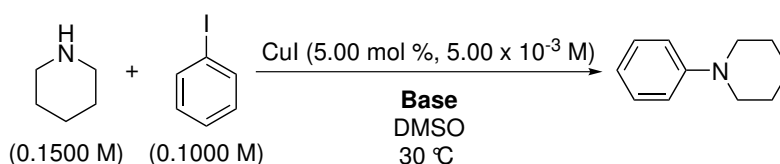
These results aid in determining the nature of some equilibria present and the relative abundance of the intermediates. To summarise, malonate has been shown to coordinate to copper(I) in the absence or presence of piperidine, where a malonate-ligated copper(I) piperidine complex was observed in the latter case. Upon addition of iodobenzene to this system, the significant broadening and changes in chemical shifts of the piperidine and TBPM resonances is indicative of rapidly equilibrating intermediate complexes containing piperidine and malonate ligands.

4.2.5 Malonate coordination and base strength

The ¹H NMR spectroscopy study in Section 4.2.4 revealed that malonate anions are able to coordinate to copper(I) in the cross-coupling reaction. In order to investigate the importance

of malonate coordination and base strength to the reactivity of the system, the use of tetra(*n*-butyl)phosphonium mono-anionic malonic acid as the base in the reaction was attempted (Scheme 4.15).

Firstly, 0.200 M concentration of tetra(*n*-butyl)phosphonium mono-anionic malonic acid was utilised as the base in the cross-coupling reaction between piperidine and iodobenzene. As shown in Figure 4.18, the reaction rate was significantly slower than when TBPM was used, with only 11% yield formed after 150 minutes whereas the reaction using TBPM was almost complete after the same duration. Although some reactivity was observed when mono-anionic malonate was used as the base, the previously performed “same excess” protocol confirmed that its effect on the reactivity during the standard reaction was negligible (Figure 4.10). Similar to the negative rate dependence in [TBPM] identified previously, increasing the mono-anionic malonic acid concentration to 0.400 M to match the number of carboxylate groups that are



Scheme 4.15: Reaction scheme for the copper(I) catalysed reaction between piperidine and iodobenzene using various organic ionic bases.

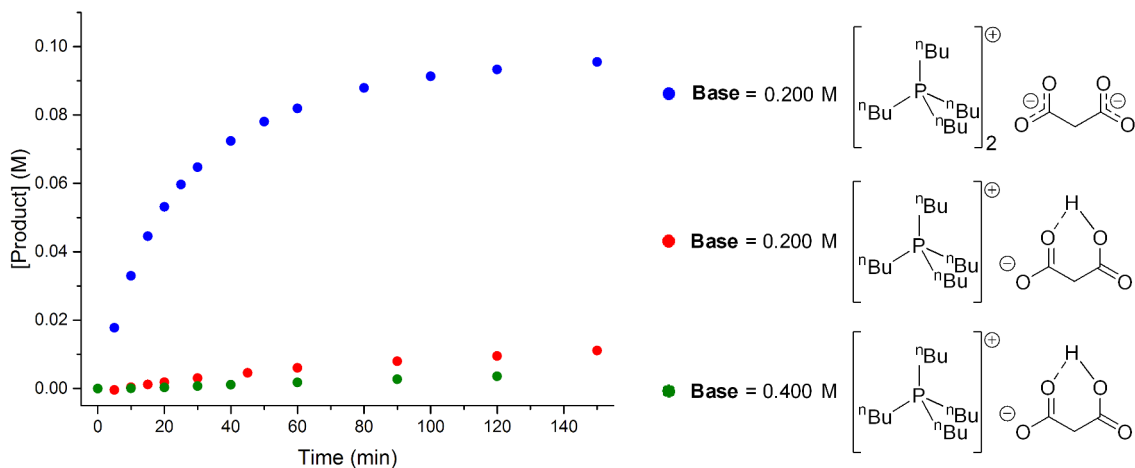


Figure 4.18: Comparison of between using 0.200 M TBPM (blue circles), 0.200 M or 0.400 M tetra(*n*-butyl)phosphonium mono-anionic malonic acid (red or green circles) as the base for the reaction shown in Scheme 4.15. Concentrations were determined by GC using naphthalene as an internal standard.

present in 0.200 M [TBPM] caused an even slower reaction rate (Figure 4.18). The cause of the inverse relationship between concentration and reaction rate using this base is likely the same as for when TBPM is used, which implies that mono-anionic malonic acid also coordinates to copper(I).

The molecular structure of copper(I) (bis(triphenylphosphine)) mono-anionic malonate ($[\text{Cu}(\text{O}_2\text{CCH}_2\text{COOH})(\text{PPh}_3)_2]$) has been determined by X-ray crystallography and shows that the carboxylate coordination to copper(I) in the solid-state is monodentate.^[48] However the analogous complex using the more basic acetate ligand has been shown to coordinate in a bidentate mode by X-ray crystallography.^[59] Hammond and co-workers noted that more basic carboxylate ligands in these types of complexes generally coordinate to give bidentate structures (Figure 4.19).^[41] Therefore, assuming that piperidine and triphenylphosphine coordinate to copper(I) in a similar manner, this trend can be used to explain the difference in reactivity observed in Figure 4.18. As di-anionic malonate is more basic than both mono-anionic malonic acid and acetate ($\text{p}K_a$'s of malonic acid in DMSO at 25 °C: $\text{p}K_{a1} = 7.2$, $\text{p}K_{a2} = 18.6$;^[60] and acetic acid in DMSO at 25 °C, $\text{p}K_a = 12.3$),^[61] it likely coordinates more strongly than mono-anionic malonic acid in a bidentate mode. Therefore the slower rate observed using mono-anionic malonic acid as the base may be due to the lack of chelation to copper(I) and also its lower basicity slowing the deprotonation rate.

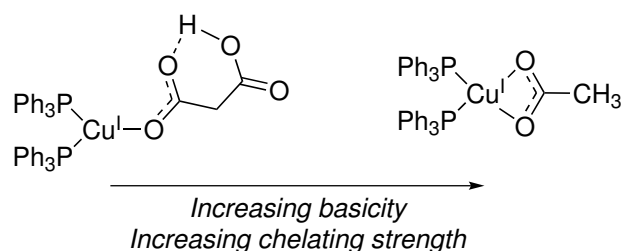
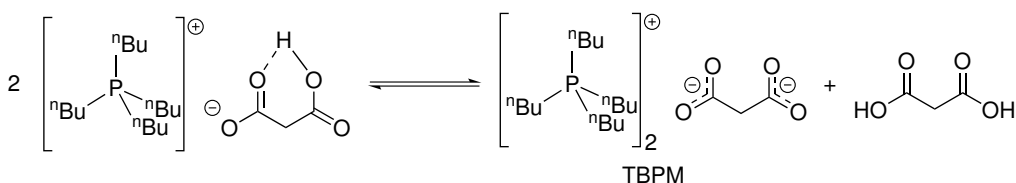


Figure 4.19: Trend observed by Hammond and co-workers between the coordination mode (mono- or bidentate) and the basicity of the carboxylate ligand in copper(I) (bis(triphenylphosphine)) carboxylate complexes.^[41]

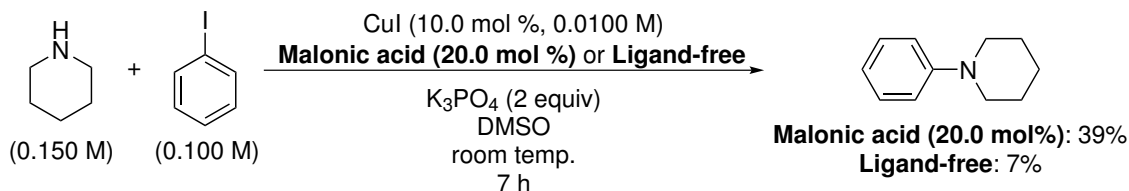
Alternatively, the C–N cross-coupling reactivity exhibited when tetra(*n*-butyl)phosphonium mono-anionic malonic acid was utilised may be exclusively due to low concentrations of *in situ* generated TBPM (Scheme 4.16) acting as both the base and ligand, with the mono-anionic malonic acid present as an unreactive reservoir of malonate. This would be in agreement with the negligible effect of the mono-anionic malonic acid identified in the previously performed “same



Scheme 4.16: Possible equilibrium to form reactive TBPM *in situ* from tetra(*n*-butyl)phosphonium mono-anionic malonic acid.

excess” protocol (Figure 4.10) and also the negative rate dependence with the concentration of mono-anionic malonic acid as increased concentrations would lead to more TBPM.

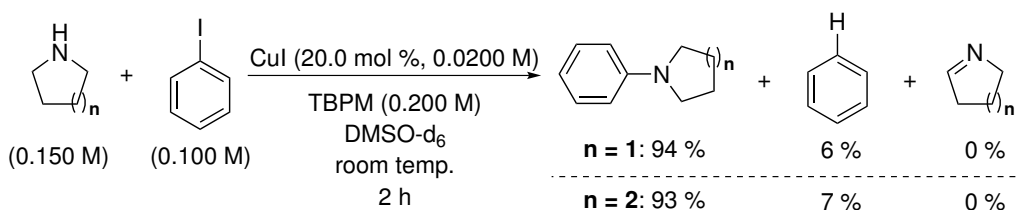
As coordination of the carboxylates has been suggested to be important for good reactivity, a reaction employing malonic acid as the ancillary ligand was performed to see if it would improve the yield. When 20 mol % malonic acid was added to the copper-catalysed reaction between piperidine and iodobenzene shown in Scheme 4.17, the yield increased from 7% to 39% compared to ligand-free conditions. This yield improvement confirms that coordination of malonate to the copper catalyst can occur to promote reactivity by acting as an ancillary ligand.



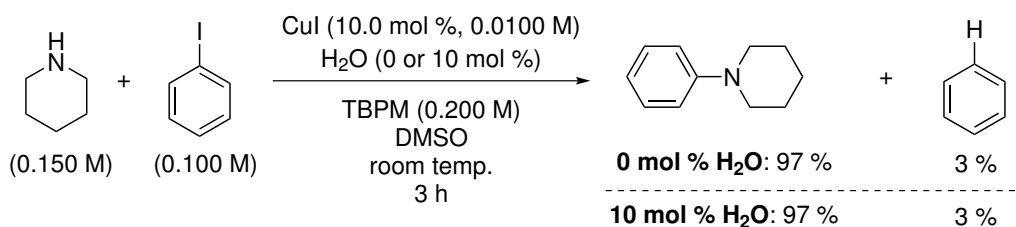
Scheme 4.17: Reaction scheme for the copper(I) catalysed reaction between piperidine and iodobenzene comparing the yields obtained when malonic acid is used as the ancillary ligand to ligand-free conditions. Yields were determined by GC using naphthalene as an internal standard.

4.2.6 Hydrodehalogenation side reaction

As mentioned in Section 4.2.1, a small amount of unwanted benzene is formed over the course of the reaction from a hydrodehalogenation process. To gain more information regarding this process, the origin of the new hydrogen atom in the benzene was investigated. When the copper-catalysed cross-coupling between piperidine and iodobenzene was performed in DMSO- d_6 (Scheme 4.10 in Section 4.2.1), benzene- H_6 still formed which ruled out the solvent as the source of the hydrogen. ^1H NMR analysis of finished reaction solutions using piperidine or pyrrolidine as substrates in cross-couplings with iodobenzene also did not contain any imines



Scheme 4.18: Reaction scheme for the cross-coupling between piperidine or pyrrolidine with iodobenzene to identify if imine is formed by β -H elimination. Yields were determined by ^1H NMR analysis using mesitylene as an internal standard.



Scheme 4.19: Reaction scheme for the cross-coupling between piperidine with iodobenzene to identify if water affects the amount of benzene formed by hydrodehalogenation. Yields were determined by ^1H NMR analysis using naphthalene as an internal standard.

which indicates β -H elimination is not the source of the hydrogen either (Scheme 4.18). Addition of 10 mol % water at the start of the reaction also made no noticeable difference to the amount of benzene formed (3% yield) and therefore ruled out the role of adventitious water as the hydrogen source (Scheme 4.19). Cohen and Hartwig and co-workers found that more acidic protons result in greater hydrodehalogenation.^[34,37] However the amount of benzene produced did not change (2% yield) when the mono-anion of malonic acid was added in the “same excess” reaction shown in Section 4.2.3.2. Lin, MacArthur and co-workers have suggested that the hydrogen source in their reported copper-catalysed hydrodehalogenation of aryl halides was the added diamine compound.^[39] When the experimental findings and literature are considered together, they indicate that the hydrogen atom likely originates from the N–H group of piperidine.

The quantity of benzene formed after complete iodobenzene conversion was found to vary with $[\text{Piperidine}]_0$ and $[\text{Cu}]_{\text{total}}$. As shown in Figure 4.20a, the amount of benzene formed was proportional to $[\text{Cu}]_{\text{total}}$, whereas it was inversely proportional to $[\text{Piperidine}]_0$ (Figure 4.20b). The proportional relationship between the amount of benzene formed and the copper(I) iodide loading was not due to an impurity in the metal salt as no difference in the reaction rate, yield or amount of benzene formed was observed when freshly purified copper(I) iodide was

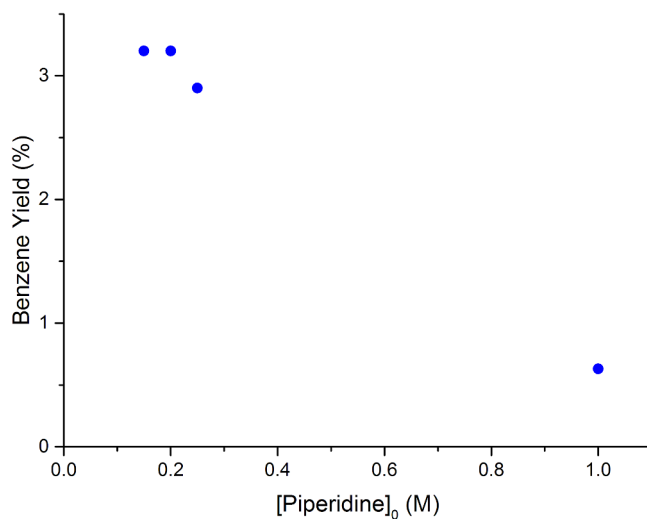
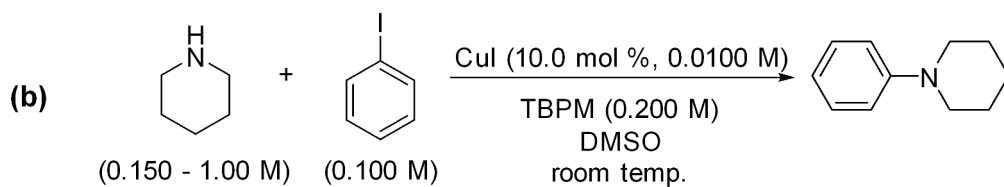
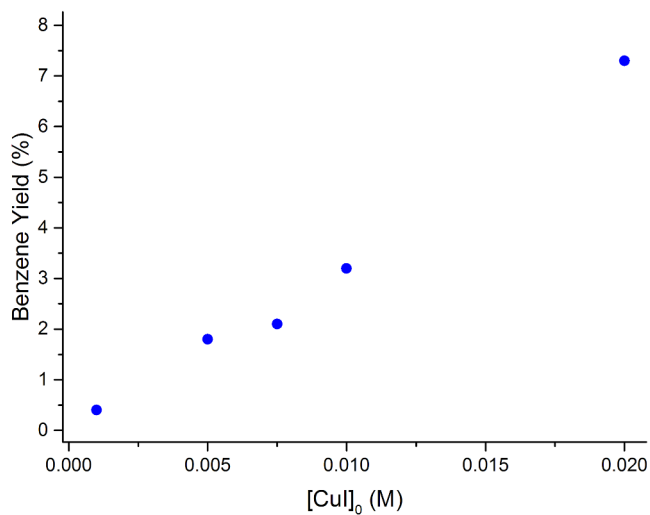
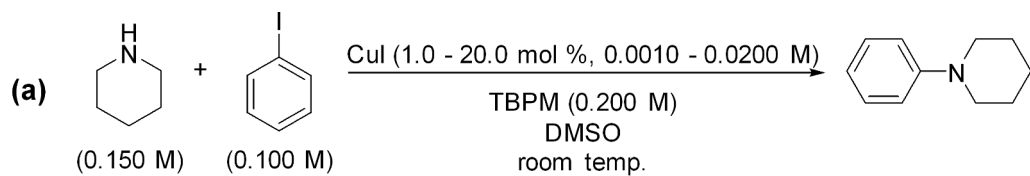


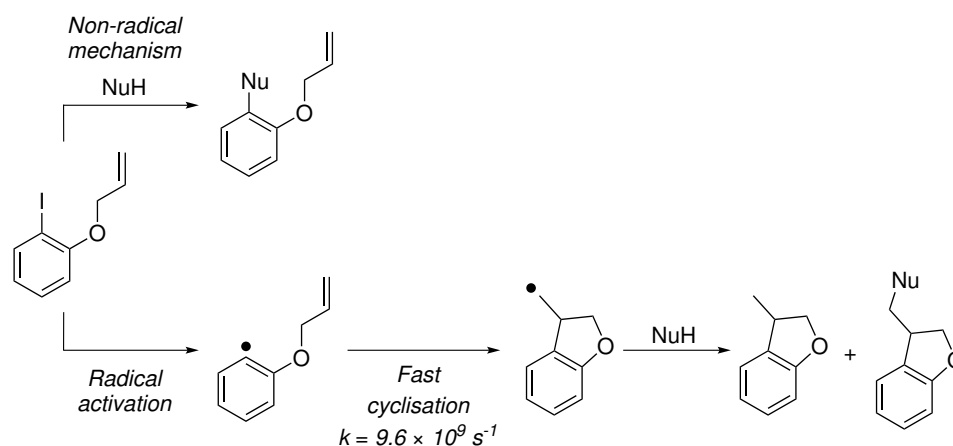
Figure 4.20: Yields of side-product benzene formed after complete iodobenzene conversion when (a) [CuI]₀ and (b) [Piperidine]₀ were varied. Yields were determined by ¹H NMR analysis using naphthalene as an internal standard.

used (copper(I) iodide purified according to the method reported by Dieter *et al*^[62]). This positive relationship indicates that the rate of dehalogenation is more greatly influenced by increasing $[\text{Cu}]_{\text{total}}$ than the aryl amination rate. Therefore the $[\text{Cu}]_{\text{total}}$ order for dehalogenation is higher than first order. Although the lowering benzene yield with increasing $[\text{Piperidine}]_0$ may contradict with the proposal that the hydrogen atom originates from the N–H group of piperidine, it can be explained if the dehalogenation process is mediated by the copper species formed after a bimolecular disproportionation process. Unfortunately, the precise mechanism for the dehalogenation was not determined and detailed mechanistic studies for this process have not been reported in the literature.

4.2.7 Aryl halide activation mechanism

An important aspect of the mechanism that has not yet been explored is how aryl halide activation occurs in the copper-catalysed amination reaction between piperidine and iodobenzene with TBPM as the base. Firstly, when the reaction was performed in the dark, the same product yield was obtained after three hours as when it was performed under ambient light. Although this control experiment indicates that the reaction is not photochemically induced, it does not exclude the potential intermediacy of aryl radicals.

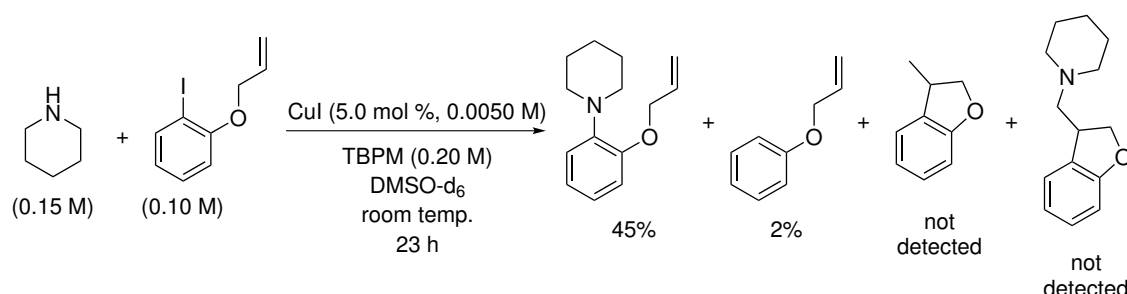
Additional information regarding the aryl halide activation mechanism was obtained by using 2-(allyloxy)iodobenzene as the substrate and radical probe. If a non-radical based mechanism was present for the cross-coupling, C(sp²)-Nu bond formation *via* the top route shown in Scheme



Scheme 4.20: Possible routes for the reaction between 2-(allyloxy)iodobenzene and a nucleophile depending on the nature of the aryl iodide activation.^[63,64]

4.20 will occur. However if radical activation of the aryl iodide occurs in the reaction, the free aryl radical will rapidly ring-close *via* a 5-*exo-trig* process to give the corresponding methyl radical ($k = 9.6 \times 10^9 \text{ s}^{-1}$) (bottom route, Scheme 4.20).^[64] The methyl radical will then react to give either 3-methyl-2,3-dihydrobenzofuran or the compound with the nucleophile bonded to the pendant methyl moiety. Therefore in the case of a radical mechanism cyclisation will occur. Conversely if the desired *N*-arylated product is exclusively formed, either the radical driven piperidine coupling is even faster than the rapid 5-*exo-trig* cyclisation or more likely the aryl halide activation occurs by a non-radical mechanism such as oxidative addition.

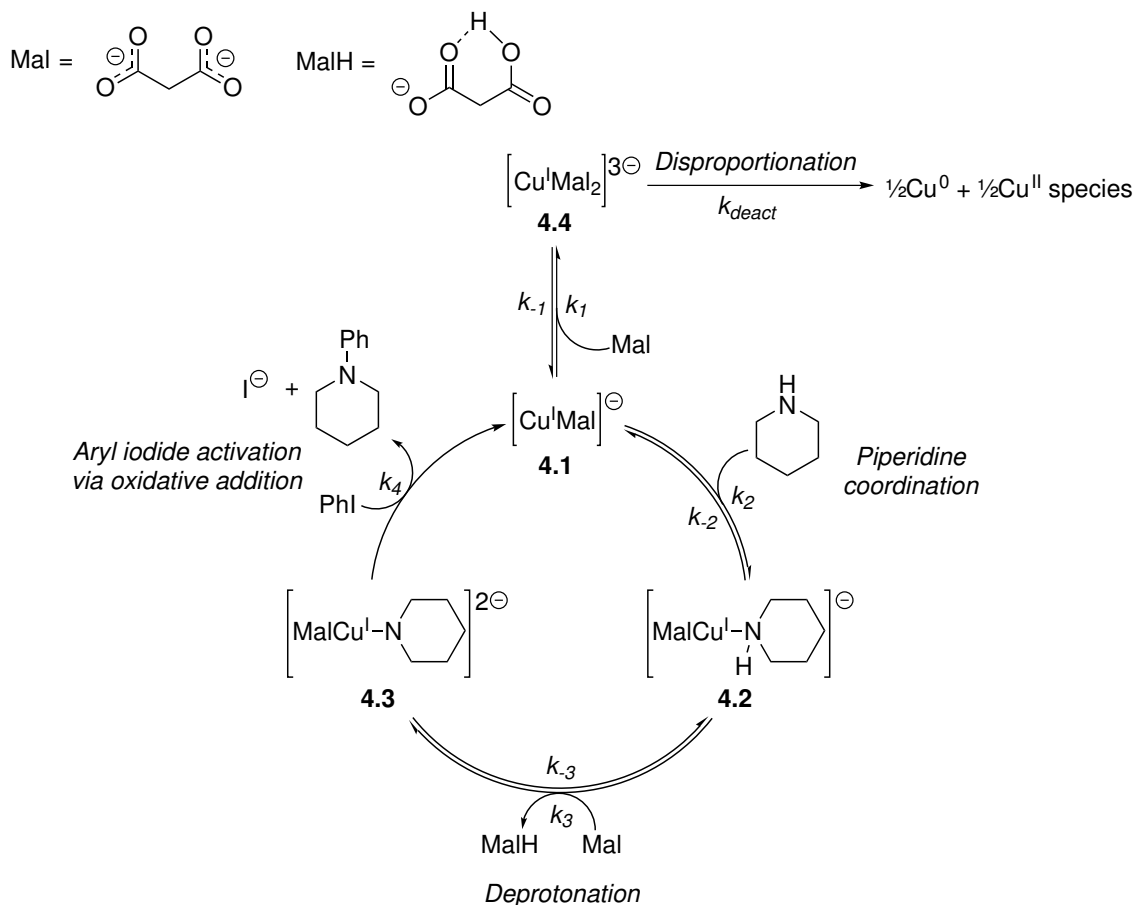
The copper-catalysed reaction between piperidine and 2-(allyloxy)iodobenzene yielded 45% of the *N*-arylated product and 2% yield of allyl phenyl ether after 23 hours (Scheme 4.21). Neither cyclised side-products were detected by either ¹H NMR spectroscopy or GC-MS which suggests that the aryl halide activation mechanism for both the cross-coupling reaction and the hydrodehalogenation reaction do not occur *via* aryl radicals. This result is in agreement with the absence of biphenyl formed from phenyl radicals when iodobenzene was used as the substrate previously in this report.^[33,35] Therefore the copper-catalysed amination and hydrodehalogenation reactions likely involve oxidative addition as the aryl halide activation mechanism.



Scheme 4.21: Reaction scheme for the reaction between piperidine and 2-(allyloxy)-iodobenzene to identify if the aryl halide activation proceeds *via* a radical-based mechanism. Yields were determined by ¹H NMR spectroscopy using naphthalene as an internal standard.

4.2.8 Proposed mechanism and kinetic modelling

A proposed reaction mechanism for the copper-catalysed amination reaction that fits the results obtained from the mechanistic studies is shown in Scheme 4.22. Given the large number of possible coordination modes of dianionic malonate,^[65] malonate coordination to copper(I) is not defined in the proposed mechanism. To account for the negative rate dependence on



Scheme 4.22: Proposed reaction mechanism that includes a potential off-cycle species and a possible deactivation pathway in the copper-catalysed cross-coupling reaction between piperidine and iodobenzene with TBPM as the base. Tetra-(*n*-butyl)phosphonium counter cations are not shown.

[TBPM], an additional equivalent of malonate can coordinate to give the off-cycle copper(I) di(malonate) (**4.4**) from the initially formed copper(I) malonate (**4.1**). Catalyst deactivation by disproportionation is shown in Scheme 4.22 to occur from the off-cycle species **4.4**. Piperidine was found to stabilise the catalyst from deactivation by competitively coordinating against malonate for copper(I). Piperidine coordination is shown in the formation of malonate and piperidine ligated copper(I) intermediate **4.2** from **4.1**. The following step is deprotonation of the N–H group of the coordinated piperidine ligand in **4.2** by an equivalent of malonate to give malonate-ligated copper(I) piperidide complex **4.3**. Complex **4.3** has the same general structure as other commonly proposed catalytic active species with a 1 : 1 : 1 ratio of ligand, copper(I) and deprotonated nucleophile (refer to Section 1.4.2, Chapter 1 for examples), where

malonate acts as the ancillary ligand. This intermediate should have an ancillary ligand because copper(I) piperidide in the absence of an ancillary ligand is insoluble in DMSO solvent (see Chapter 2 for more information regarding copper(I) piperidide). Complex **4.3** can then undergo a rate determining aryl halide activation with iodobenzene, which was determined to proceed *via* oxidative addition in Section 4.2.7, to give the desired *N*-arylated product and regenerate complex **4.1**.

The [PhI] – time data determined by reaction calorimetry was fitted to the mechanism shown in Scheme 4.22 by identifying the equilibrium and rate constants for each individual step. The rate constant estimation is an iterative procedure that was carried out using a reaction simulation and data-fitting program called COPASI (see Section 4.4.18 for details about the fitting procedure).^[66] The hydrodehalogenation side reaction was not taken into account for the kinetic modelling because it does not significantly affect [PhI]. The estimated kinetic parameters for the reaction steps shown in Table 4.1 were optimised with low standard deviation values. In contrast, attempts to fit the kinetic data to other possible mechanisms that involved the opposite order of malonate and piperidine coordination, or disproportionation from copper(I) malonate (**4.1**) instead of copper(I) di(malonate) (**4.4**), or disproportionation from one equivalent of **4.1** and **4.4**, or a possible di(piperidido)cuprate off-cycle species from additional coordination and deprotonation of piperidine to complex **4.3** all either failed or gave estimated rate constants

Reaction step	Rate constant, k ($\text{M}^{-1} \text{min}^{-1}$)		Estimated rate or equilibrium constants, k or K
Complex 4.4 formation	k_1	10.0*	$K_1 = k_1/k_{-1} = 30.9 \text{ M}^{-1}$
	k_{-1}	0.324	
Disproportionation	k_{deact}	9.22	$k_{deact} = 9.22 \text{ M}^{-1} \text{min}^{-1}$
Piperidine coordination	k_2	59.6	$K_1 = k_2/k_{-2} = 5.96 \text{ M}^{-1}$
	k_{-2}	10.0*	
Deprotonation	k_3	2730	$K_3 = k_3/k_{-3} = 273$
	k_{-3}	10.0*	
Iodobenzene activation	k_4	22.2	$k_4 = 22.2 \text{ M}^{-1} \text{min}^{-1}$

Table 4.1: Kinetic parameters for the mechanism in Scheme 4.22 estimated using COPASI. Values reported to three significant figures. Rate constants labelled with an asterisk (*) were kept constant at $10.0 \text{ M}^{-1} \text{min}^{-1}$ during the parameter estimation process.

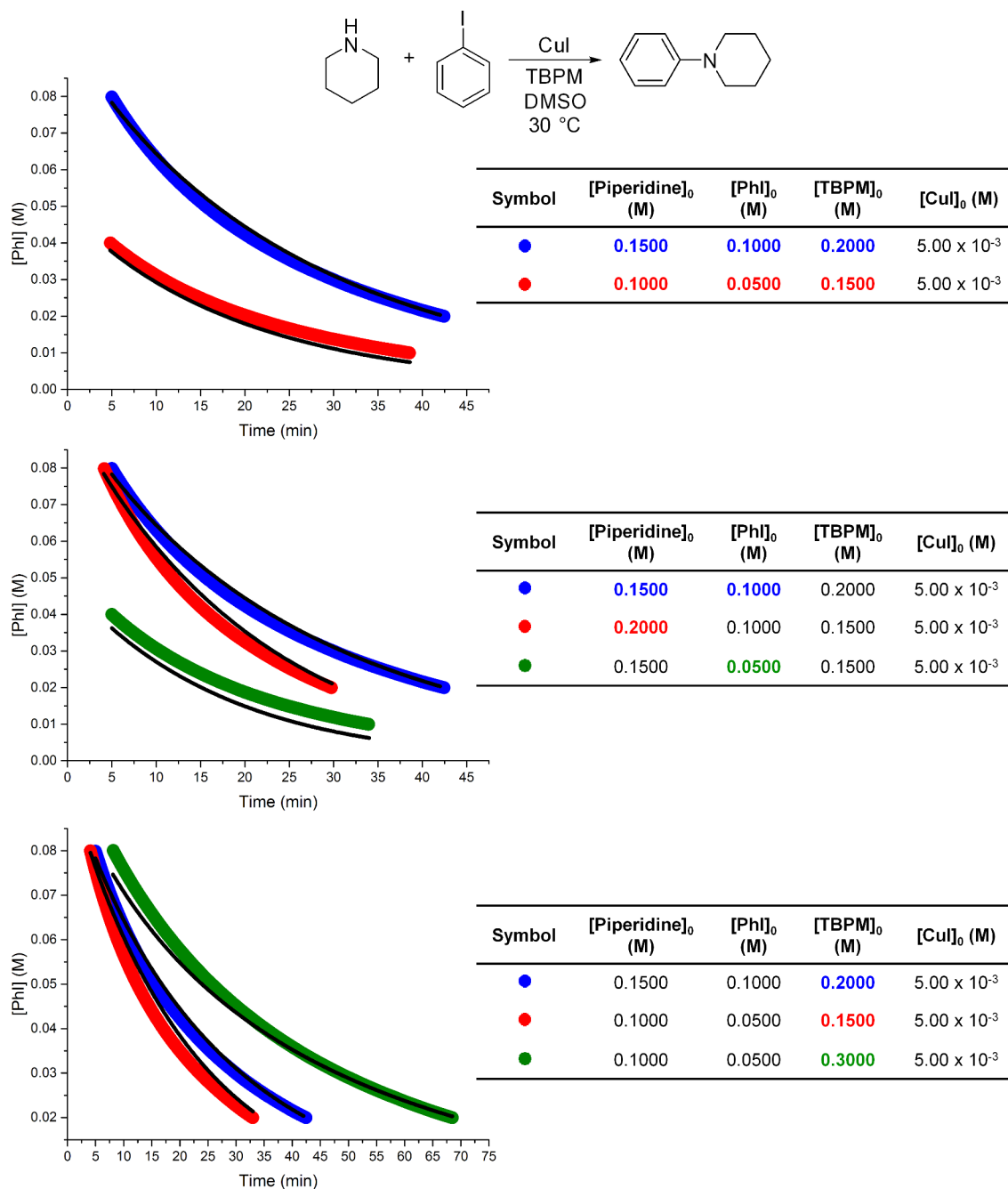


Figure 4.21: Comparison of experimental [PhI] – time profiles (coloured lines) and simulated [PhI] – time profiles (black lines) produced in COPASI using the optimised kinetic parameters shown in Table 4.1.

with high standard deviations (see Section 4.4.18 for the estimated values). The simulated [PhI] – time profiles produced using the optimised parameters in COPASI in Table 4.1 (Figure 4.21) are in agreement with the experimental data and therefore supports Scheme 4.22 as a viable mechanism. This indicates that although dianionic malonate can coordinate to two

copper(I) ions at each carboxylate group as demonstrated by Oldham,^[45] the kinetic modelling supports a mechanism that implicates one copper(I) ion in the reactive intermediates.

The estimated kinetic parameters for the mechanism in Scheme 4.22 indicated that K_1 (30.9 M^{-1}) was greater than K_2 (5.96 M^{-1}) and therefore suggests that malonate coordination to give copper(I) di(malonate) (**4.4**) from copper(I) malonate (**4.1**) is more favoured than piperidine coordination to give piperidine-ligated copper(I) malonate complex **4.2**. This is illustrated in Figure 4.22 which shows that the simulated concentration of **4.4** is high at the start of the reaction but diminishes over time due to disproportionation to give copper(II) and copper(0). Deprotonation of **4.2** ($k_3 = 2730 \text{ M}^{-1} \text{ min}^{-1}$) to give the malonate-ligated copper(I) piperidide complex **4.3** is highly favoured compared to the dissociation of piperidine from **4.2** ($k_2 = 10.0 \text{ M}^{-1} \text{ min}^{-1}$) back to **4.1** therefore **4.2** is deprotonated as soon as it is formed. In addition, the relatively high K_3 value ($K_3 = 273$) implies that the conversion of **4.3** back to **4.2** is highly disfavoured. Finally, the low k_4 value ($k_4 = 22.2 \text{ M}^{-1} \text{ min}^{-1}$) results in a high concentration of the catalyst resting state **4.3**. These points are illustrated in Figure 4.22 by the low and high concentrations of **4.2** and **4.3** respectively over the course of the reaction. The unfavourable equilibria from catalyst resting state **4.3** to unstable off-cycle complex **4.4** in the reverse direction *via* complexes **4.2** and **4.1** prevents immediate complete catalyst deactivation when copper(I) iodide, piperidine and TBPM are reacted together. This is in agreement with observations highlighted in Sections 4.2.3 and 4.2.4 which showed mixtures of copper(I) iodide and TBPM to be stable in the presence of

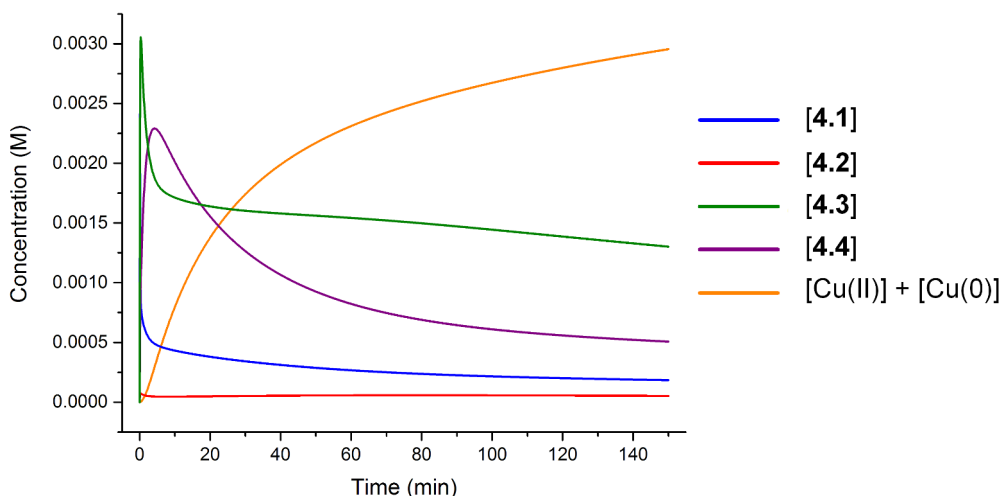
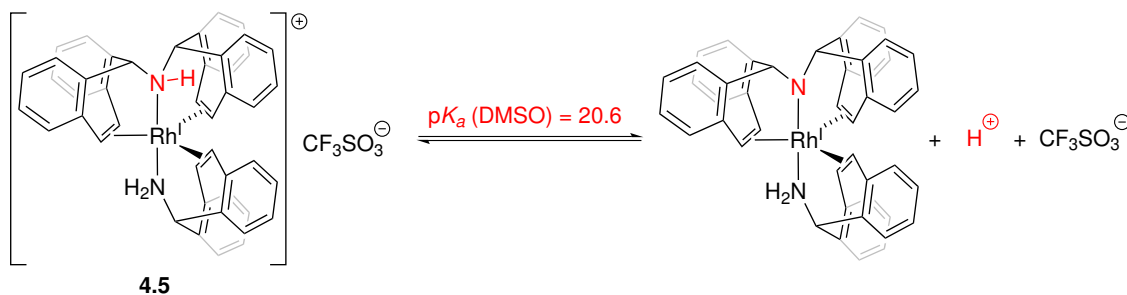


Figure 4.22: Simulated concentrations of complexes **4.1**, **4.2**, **4.3**, **4.4** and $[\text{Cu(II)}] + [\text{Cu(0)}]$ (from disproportionation) over the course of the reaction in Scheme 4.11 produced in COPASI using the optimised kinetic parameters shown in Table 4.1.

piperidine.

Using the estimated K_3 value and the reported pK_a of mono-anionic malonic acid (pK_a in DMSO at 25 °C = 18.6)^[60], the pK_a of the N–H group of the piperidine ligand in intermediate **4.2** was calculated to be approximately 16.2 (See Section 4.4.19 for derivation). This value is a significant decrease of about 28 orders of magnitude from the pK_a of free piperidine (pK_a in DMSO of the N–H group of the similarly structured pyrrolidine is 44)^[58] and demonstrates the expected dramatic increase in acidity as a result of coordination to copper(I).^[67,68] Although the pK_a in DMSO of an alkylamine N–H group coordinated to copper(I) has not been reported in the literature, the calculated value is quite similar to the reported pK_a of 20.6 in DMSO of the N–H group in rhodium(I) complex **4.5** shown in Scheme 4.23.^[69] Therefore, the calculated pK_a of 16.2 for the N–H group in complex **4.2** is realistic.



Scheme 4.23: pK_a in DMSO of the N–H group in the rhodium(I) complex **4.5** reported by Grützmacher and co-workers.^[69]

It is clear that minimising the formation of off-cycle complex **4.4** is essential to ensuring high TON. A possible method for reducing **[4.4]** during the C–N cross-coupling reaction is to use high $[\text{Piperidine}]_0$. Using the kinetic parameters in Table 4.1 for the mechanism in Scheme 4.22, the percentage of copper that has become deactivated, % Cu_{deact} , over the course of the C–N cross-coupling reaction with different $[\text{Piperidine}]_0$ can be simulated using COPASI. As illustrated in Figure 4.23 for initial $[\text{Cu}]_{\text{total}} = 0.005 \text{ M}$, the amount of catalyst deactivation that has occurred by any given time decreases as $[\text{Piperidine}]_0$ increases, where there is a less than 2% total loss in active copper concentration when $[\text{Piperidine}]_0$ is greater than 1.05 M. Whilst high concentrations of amine will ensure excellent catalyst stability, it may be impractical to employ such a large excess of amine for the cross-coupling reaction.

Alternatively, although formation of the off-cycle complex **4.4** from copper(I) malonate (**4.1**) is more favourable compared to forming the piperidine-ligated copper(I) malonate intermediate

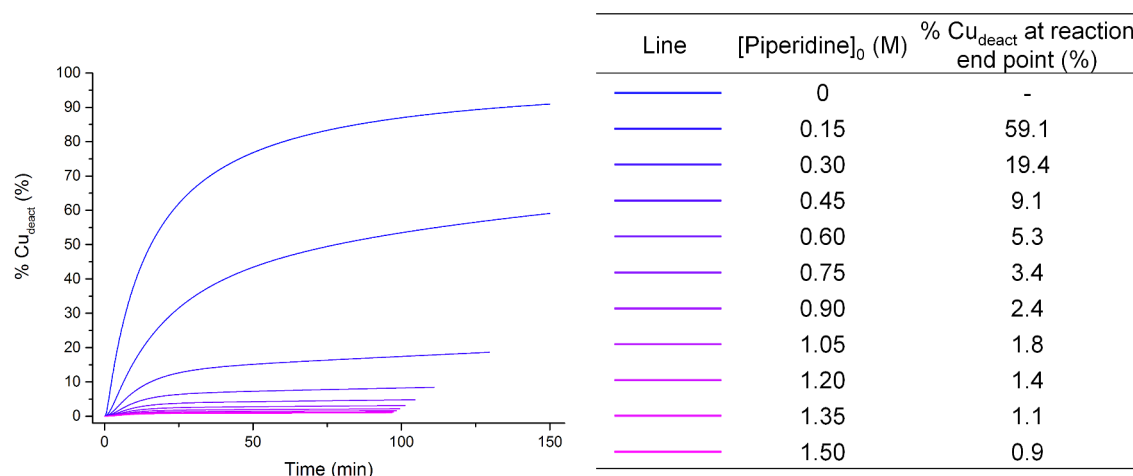


Figure 4.23: Simulated percentage deactivated copper, % Cu_{deact}, over time profiles for the reaction in Scheme 4.11 using different [Piperidine]₀ produced in COPASI using the optimised kinetic parameters shown in Table 4.1.

4.2, a low [TBPM] in the reaction solution could be used to minimise **[4.4]**. Therefore a possible method for prolonging the lifetime of the catalyst could be to add TBPM slowly in to the reaction as this will ensure a low [TBPM] over the course of the C–N cross coupling reaction. In addition, the low [TBPM] present will also be advantageous because of its negative first order dependence on the reaction rate.

A mechanism involving irreversible disproportionation of off-cycle complex **4.4** was fitted in COPASI (Scheme 4.22). However, the on- and off-cycle species and deactivation method in this mechanism are similar to those in the proposed mechanism using 1,3-diketone ligands described in Section 3.2.4, Chapter 3, which was found to have a reversible catalyst deactivation process. Therefore, it may be possible to increase the product yield of the TBPM promoted reaction using similar methods described in Section 3.2.2.5, Chapter 3. For example, by adding additional copper catalyst, such as copper(0) metal, may reverse catalyst deactivation by promoting comproportionation of deactivated copper(II) and copper(0) species.

4.3 Conclusions

A combination of RPKA and spectroscopic studies has facilitated the elucidation of key aspects of the mechanism such as the identification of various solution equilibria. All of the reaction components were found to influence the reaction rate with first order kinetics with respect to [Piperidine], [PhI] and $[\text{Cu}]_{\text{total}}$ successfully identified in the concentration regime studied. Other important mechanistic findings such as the effect of a chelating base on the reaction rate were also determined. This coordination represents the first reported example of unexpected negative first order kinetics in the base concentration for an Ullmann amination reaction. In addition, malonate as the ancillary ligand for this type of reaction is also unreported in the literature. The “same excess” protocol was also successfully utilised for an Ullmann amination reaction for the first time and provided new insights into the catalyst deactivation and negligible inhibition by the *N*-arylated product and by-products. The kinetic studies also highlighted an additional key role of the piperidine substrate in minimising catalyst deactivation by disproportionation. Future work involving the incorporation of ancillary ligands and how they affect the catalyst stability and rate dependences on the reaction components warrants an investigation. Initial experimental results to identify the aryl halide activation mechanism rule out the likelihood it proceeds *via* free aryl radical formation. As a result, oxidative addition was proposed as the most suitable mechanism for the rate determining step.

A reaction mechanism that accounts for the observed experimental results has been proposed with preliminary kinetic modelling data supporting its viability. However, further studies such as investigating the kinetic competency of the intermediates, and the experimental identification of the equilibrium constants or rate constants should ideally be performed to refine the proposed mechanism and further support its validity. Additional work to identify copper(II) and copper(0) species using techniques such as EPR, *in situ* IR and UV-Vis also warrants further study to confirm disproportionation as the catalyst deactivation mechanism. Additional experimental studies to improve the product yield using the methods described previously in Section 4.2.8 could be performed to obtain further information regarding the catalyst deactivation process. Liu and co-workers proposed that the cause of the significant rate acceleration when using TBPM as the base in the copper-catalysed cross-coupling reaction between amines and aryl halides was its excellent ionising ability in solution.^[21] Although this was not confirmed in this work, kinetic studies using malonate bases with different counter cations should reveal

some insight into the effect of the ionising ability on the reaction rate. Finally, the scope of the mechanism using other substrates such as primary amines or aryl bromides should be identified to reveal how general the mechanism is when TBPM is used as the base.

4.4 Experimental

4.4.1 General information

Glassware used for the catalytic reactions were all oven-dried for at least 12 h. Anhydrous DMSO was purchased from Sigma Aldrich and stored over 3 or 4 Å molecular sieves under a nitrogen atmosphere. The DMSO- d_6 used as the solvent in catalytic reactions was stirred over calcium hydride at room temperature under nitrogen overnight and distilled under reduced pressure and stored over 4 Å molecular sieves under a nitrogen atmosphere prior to use. Potassium phosphate base was dried by heating under vacuum for at least 24 h at 180 °C prior to use. Amines were purified by stirring over calcium hydride or sodium at room temperature under a nitrogen atmosphere and distilled under nitrogen for storage over 4 Å molecular sieves. 2-(Allyloxy)iodobenzene was synthesised according to the procedure by Hilmersson and co-workers.^[70] All other chemicals were used as received without further purification. All products and reagents used in the catalytic reactions were stored in a nitrogen-filled glovebox, with liquid reagents other than 2-acetylcyclohexanone also dried using 4 Å molecular sieves.

^1H and ^{13}C NMR analysis was carried out at room temperature using Bruker AV-400 spectrometers. CHN microanalyses were carried out at the London Metropolitan University, UK. Reaction calorimetry was performed using an Omnical SuperCRC reaction calorimeter. GC analyses were performed using a Hewlett-Packard 5890 Series II GC instrument with an FID detector equipped with a 30 m x 0.25 mm I.D. (5%-phenyl)-methylpolysiloxane stationary phase capillary column. The following GC oven temperature program was used when analysing the samples from reactions that did not use 2-acetylcyclohexanone as an ancillary ligand: (i) 70 °C upon injection, (ii) hold at 70 °C for 2 min, (iii) increase the temperature to 250 °C at a rate of 45 °C per minute, (iv) hold at 250 °C for 5 min. Injector temperature: 250 °C; Detector temperature: 250 °C. The oven temperature increase rate was changed from 45 °C per minute to 10 °C per minute for samples from reactions that used 2-acetylcyclohexanone as an ancillary ligand. Quantities of products and aryl halides present in the catalytic reactions were measured by GC using calibrations against a naphthalene internal standard. GC-MS analysis was performed on a Micromass Autospec Premier/Agilent HP6890 GC.

^1H and ^{13}C NMR data were analysed using MESTRELAB MestReNova; GC data were analysed using DataApex Clarity software; and reaction calorimetry data was captured using

WinCRC and processed in Microsoft Excel.

4.4.2 Preparation of bis(tetra(*n*-butyl)phosphonium) malonate (TBPM)

Malonic acid (2.602 g, 25.00 mmol) was treated with a solution of tetra(*n*-butyl)phosphonium hydroxide in water (33.430 mL, 40.0 wt. %, 50.0 mmol) and stirred at room temperature for 2 h in air. Afterwards, most of the water was removed by rotary evaporation until a viscous, colourless liquid remained. The liquid was vigorously dried with stirring at 50 °C under high vacuum for at least 2 days to completely remove any residual water. To ensure the product remains dry, the following steps were performed using standard Schlenk techniques under a nitrogen atmosphere. The evaporated residue was dissolved in acetonitrile (20 mL) to give a colourless solution with some suspended insoluble white solid, which was removed by filtration through Celite. The solvent was removed from the filtrate under vacuum to give a viscous liquid, which was vigorously dried with stirring at 50 °C under high vacuum for 2 days. After drying, within a few hours at room temperature the viscous liquid solidified to a waxy, white solid which was isolated and stored inside a nitrogen-filled glove box (14.506 g, 23.36 mmol, 93%). ¹H NMR (400 MHz, DMSO-*d*₆, 21 °C, TMS): δ=0.91 (t, ³J_{HH}=7.0 Hz, 24H; butyl-CH₃), 1.33 – 1.53 (m, 32H; butyl-CH₂), 2.14 – 2.27 ppm (m, 16H; butyl-CH₂), 2.39 (s (br), 2H; malonate-CH₂); ¹³C NMR (101 MHz, DMSO-*d*₆, 22 °C, TMS): δ=13.1 (s; butyl-CH₃), 17.2 (d, ¹J_{CP}=47.5 Hz; butyl-CH₂), 22.7 (d, ³J_{CP}=3.9 Hz; butyl-CH₂), 23.2 (d, ²J_{CP}=15.8 Hz; butyl-CH₂), 50.1 (s (br); malonate-CH₂), 172.5 ppm (s; malonate-COO⁻); elemental analysis calcd (%) for C₃₅H₇₄O₄P₂: C 67.70, H 12.01; found: C 67.62, H 12.14.

4.4.3 Procedure for the catalytic reactions using potassium phosphate or TBPM as the base in the presence or absence of 2-acetylcyclohexanone ligand

In a nitrogen-filled glovebox, potassium phosphate (128 mg, 0.600 mmol) or TBPM (800 µL of 0.5000 M solution in DMSO, 0.400 mmol), 2-acetylcyclohexanone (400 µL of 0.100 M solution in DMSO, 0.0400 mmol) (if required), piperidine (200 µL of 1.500 M solution in DMSO, 0.300 mmol), iodobenzene (200 µL of 1.000 M solution in DMSO, 0.200 mmol), naphthalene (200 µL of 0.100 M solution in DMSO, 0.0200 mmol) as an internal standard and DMSO (volume required to make up to 2.000 mL total liquid) were added to a screw-cap vial and stirred. At room temperature, copper(I) iodide (200 µL of 0.100 M solution in DMSO, 0.0200 mmol) was added to the stirring mixture and the vial was capped and kept in the glovebox to react. To monitor the

reaction, 100 μL samples of the reaction solution were taken and quenched at certain reaction times outside of the glovebox using a mixture of ethyl acetate (300 μL) and water (100 μL). The mixture was closed and shaken. After the mixture was allowed to settle, the top organic layer was taken and passed through a pasteur pipette containing a pad of silica gel (1.0 – 1.5 cm height of silica gel) into a clean GC vial. More ethyl acetate (3 x 200 μL) was added to wash the silica gel to ensure all of the iodobenzene and *N*-phenylpiperidine had passed through. The GC vial containing the combined organic fractions was capped and analysed by GC.

4.4.4 Procedure for the deprotonation of 2-acetylcyclohexanone by TBPM

A solution of 2-acetylcyclohexanone (6.50 μL , 0.0500 mmol) in DMSO-d_6 (900 μL) in a J. Youngs tap NMR tube was prepared in a nitrogen-filled glovebox and transferred to a NMR spectrometer for analysis. The NMR tube was taken back into the glovebox and TBPM (100 μL of 0.500 M solution in DMSO-d_6 , 0.0500 mmol) was added directly to the solution and shaken to mix well. The NMR tube was transferred to a NMR spectrometer for re-analysis. ^1H NMR analysis

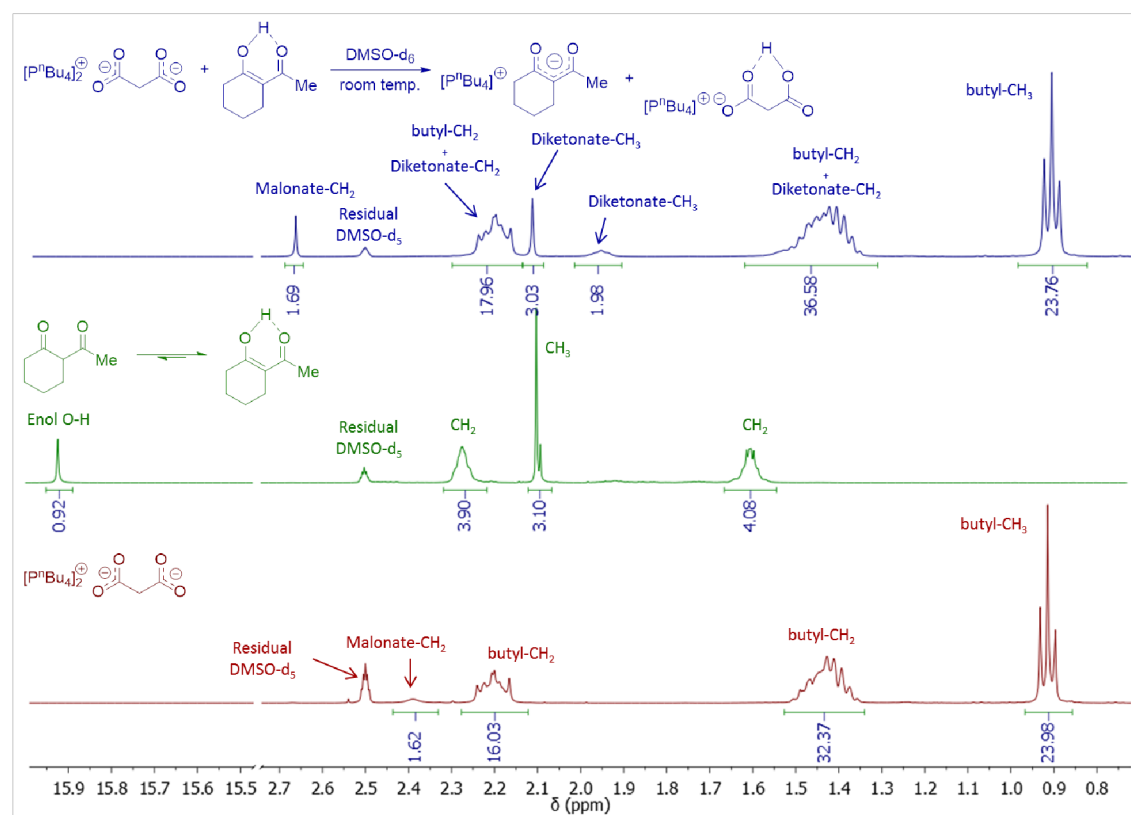


Figure 4.24: Comparison of ^1H NMR spectra of TBPM only (lower, red), 2-acetylcyclohexanone only (middle, green) and TBPM and 2-acetylcyclohexanone together (top, blue).

revealed that complete deprotonation of 2-acetylcyclohexanone had occurred on addition of TBPM (Figure 4.24).

4.4.5 Procedure for the catalytic reaction monitored by NMR using TBPM as the base

In a nitrogen-filled glovebox, TBPM (400 μ L of 0.500 M solution in DMSO- d_6 , 0.200 mmol), DMSO- d_6 (200 μ L), piperidine (100 μ L of 1.500 M solution in DMSO- d_6 , 0.150 mmol), iodobenzene (100 μ L of 1.000 M solution in DMSO- d_6 , 0.100 mmol) and naphthalene (100 μ L of 0.100 M solution in DMSO- d_6 , 0.0100 mmol) as an internal standard were added to a J. Youngs tap NMR tube and to shaken to mix well. Copper(I) iodide (100 μ L of 0.10 M solution in DMSO- d_6 , 0.010 mmol) was added at room temperature and the NMR tube was immediately transferred to an NMR spectrometer for analysis to calculate the product yield and iodobenzene conversion over time.

4.4.6 Procedure for the kinetic studies using reaction calorimetry

The Omnical SuperCRC reaction calorimeter used for the kinetic studies contains an internal magnetic stirrer and a differential scanning calorimeter (DSC) to compare the heat released or absorbed between a sample vial and reference vial. The heat flow was measured from the reaction vessels every three seconds to produce the raw heat flow curves. The reaction vessels consisted of 16 mL borosilicate screw-thread vials which were capped using open-top caps with septa and further sealed with PTFE tape. The reference vial contained only dry DMSO (10 mL). The temperature of the reaction was maintained using a cooling/heating circulator.

For example, the following was the procedure in the calorimetry experiment using standard concentrations of the reactants in Scheme 4.11. The quantities added were changed accordingly to modify the initial reactant concentrations for other calorimetry experiments. In a nitrogen-filled glovebox, TBPM (4.000 mL of 0.5000 M solution in DMSO, 2.000 mmol), DMSO (2.500 mL; volume required to make up to 10.000 mL total liquid), iodobenzene (1.000 mL of 1.000 M solution in DMSO, 1.000 mmol), piperidine (1.000 mL of 1.500 M solution in DMSO, 1.500 mmol) and naphthalene (1.000 mL of 0.100 M solution in DMSO, 0.100 mmol) were added to a reaction vial. For “same excess” experiments with added N phenylpiperidine and tetra(*n*-butyl)phosphonium iodide, these compounds were added as DMSO solutions at this stage. Mono-anionic malonic acid was produced *in situ* in the reaction vessels by the combining the

required amounts of malonic acid and TBPM. The reaction vial was sealed with a septum-lined open-top screw-cap and further sealed with PTFE tape. Copper(I) iodide (0.500 mL of 0.100 M solution in DMSO, 0.0500 mmol) was loaded into a gas-tight syringe in the glovebox with the tip of the needle also sealed using soft PTFE plugs. The sealed reaction vessel and gas-tight syringe were taken out of the glovebox. The reaction vessel was placed in the temperature controlled calorimeter set at 30 °C and stirred to allow the contents of the vessel to reach thermal equilibrium. Simultaneously, the gas-tight syringe containing copper(I) iodide was placed in the sample injection port of the calorimeter on top of the reaction vessel to allow it to also reach thermal equilibrium. Thermal equilibrium was reached when the detected heat flow from the vessel stabilised, which took between one and two hours. When the reaction vessel and syringe had both reached thermal equilibrium, the reaction was initiated by injecting the copper(I) iodide solution, which caused the heat flow to rapidly increase. The empty syringe was immediately removed from the calorimeter. When the heat flow became negligible, detected heat flow was corrected by performing a “tau” correction on the same reaction vessel to account for the time delay between the instantaneous moment heat was emitted from the reaction vessel to the time the sensor of the calorimeter detected the heat (more information for this process can be found below). The reaction vessel was removed from the calorimeter and a 100 µL sample of the reaction solution was taken. The sample was diluted with DMSO- d_6 (500 µL) for ^1H NMR analysis to determine the product and benzene yields and iodobenzene conversion.

4.4.7 “Tau”, baseline and heat of mixing corrections to raw calorimetry data

As noted previously, a “tau”-correction was applied to all calorimetry data to correct for the time delay between the instantaneous moment heat was emitted from the reaction vessel to the time the sensor of the calorimeter detected the heat. The “tau”-correction involved applying a current across a resistor in the Omnical SuperCRC reaction calorimeter to produce a known amount of heat. This heat was detected and transformed into a square wave by correcting for the response time of the calorimeter (using the WinCRC software) (Figure 4.25a). The response time correction was applied to the raw heat flow data to produce the tau-corrected heat flow data (Figure 4.25b). After baseline correction (Figure 4.25c), the heat of mixing associated with the addition of copper(I) iodide solution to initiate the reaction was substrated from the tau-corrected heat flow data (Figure 4.25d). The heat of mixing was obtained by performing the same steps as above in Section 4.4.6 except copper(I) iodide solution was injected into a stirred

solution without iodobenzene present.

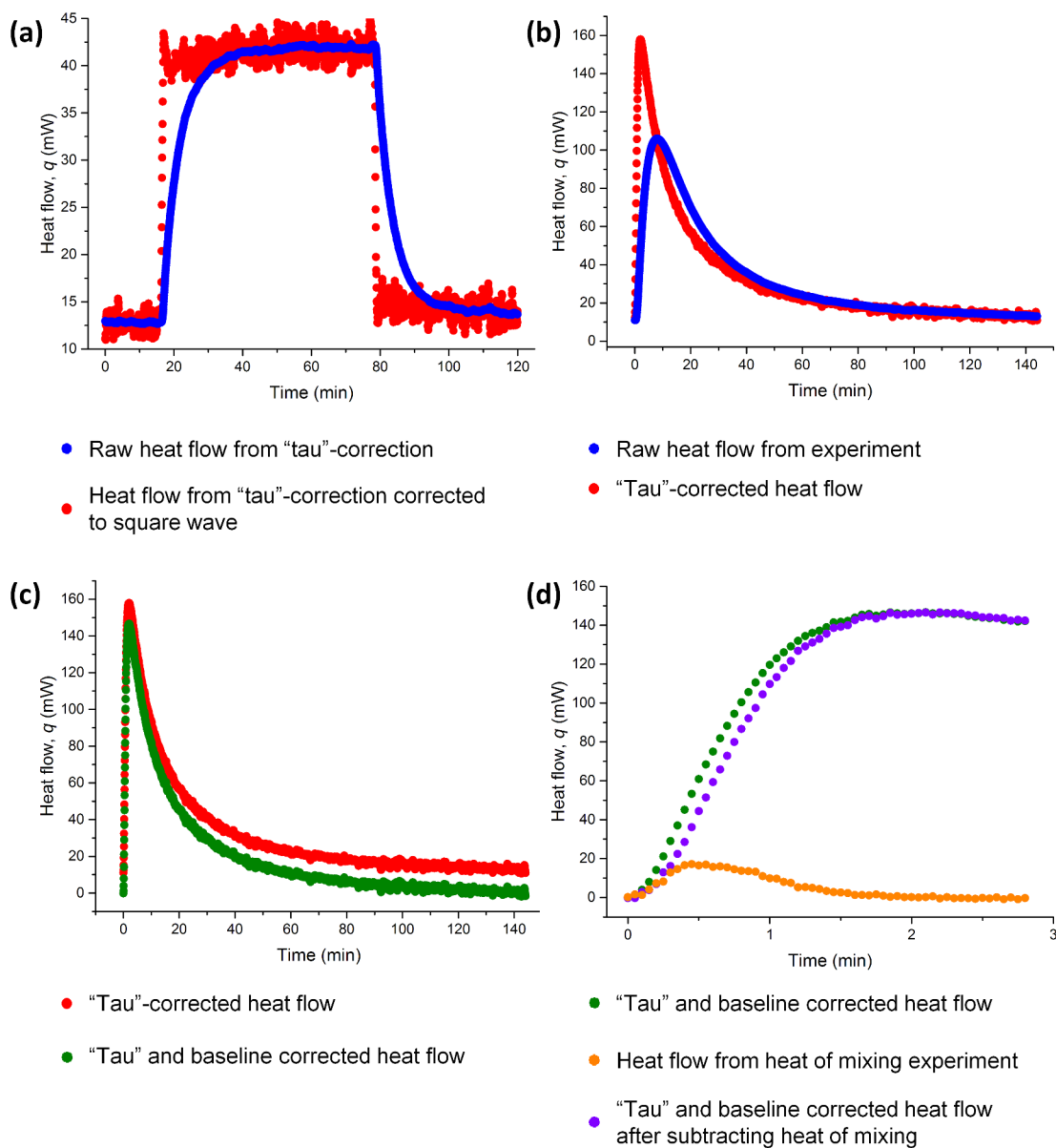


Figure 4.25: Example of applying "tau", baseline and heat of mixing corrections to the calorimetry data from the reaction using standard reactant concentrations (Scheme 4.11).

4.4.8 Procedure for validating the use of calorimetry as a monitoring tool using NMR analysis

The method described in Section 4.4.6 was used to set up the reaction vessel containing TBPM, piperidine, iodobenzene and naphthalene in DMSO and the gas-tight syringe containing copper(I) iodide. The reaction vessel was taken out of the glovebox and allowed to reach

thermal equilibrium at 30 °C using a vial heating block. After one hour, the reaction was initiated by injecting copper(I) iodide from the gas-tight syringe into the stirring solution. The reaction was monitored by taking 100 μL samples of the reaction solution and quenching at certain reaction times using a mixture of CDCl_3 (300 μL) and water (100 μL). The mixture was closed and shaken. After allowing the mixture to settle, the bottom organic layer was taken and passed through a pasteur pipette containing a pad of silica gel (1.0 – 1.5 cm height of silica gel) into a NMR tube. More CDCl_3 (3 x 200 μL) was added to wash the silica gel to ensure all of the iodobenzene and *N*-phenylpiperidine had passed through. The combined organic fractions was analysed by NMR spectroscopy.

4.4.9 Procedure for probing catalyst deactivation using multiple addition experiments and reaction calorimetry

The method described in Section 4.4.6 was used to set up the reaction vessel containing TBPM, piperidine, iodobenzene and naphthalene in DMSO. In addition to a sealed gas-tight syringe containing copper(I) iodide, a syringe containing a DMSO solution of iodobenzene and/or piperidine (100 – 200 μL from 5.00 M solutions in DMSO) was also sealed using a PTFE plug and taken out of the glovebox. After thermal equilibration in the calorimeter, copper(I) iodide was injected to initiate the reaction. The empty gas-tight syringe was removed from the sample injection port and immediately replaced with the syringe containing the DMSO solution of iodobenzene and/or piperidine. When the heat evolved from the initial reaction became negligible, the DMSO solution of iodobenzene and/or piperidine was injected in to the vial to start another reaction using the same catalyst. The empty syringe was removed from the sample injection port and replaced with another syringe containing more substrate if another subsequent reaction was required.

4.4.10 Procedure for probing catalyst deactivation by using iodobenzene, TBPM and/or piperidine to initiate the reaction

In a nitrogen-filled glovebox, a combination of naphthalene (200 μL of 0.100 M solution in DMSO, 0.0200 mmol), TBPM (800 μL of 0.5000 M solution in DMSO, 0.400 mmol), piperidine (200 μL of 1.500 M solution in DMSO, 0.300 mmol) and iodobenzene (200 μL of 1.000 M solution in DMSO, 0.200 mmol) in DMSO (400 μL) were added to a calorimetry reaction vial. The compounds that were used to initiate the reaction were not added at this stage. Instead, the required amounts of

the initiators and copper(I) iodide (200 μ L of 0.100 M solution in DMSO, 0.0200 mmol) were stored separate syringes sealed by a PTFE plugs. The capped reaction vessel and syringes were taken out of the glovebox. After the reaction vial was allowed to reach thermal equilibrium at 30 $^{\circ}$ C, copper(I) iodide was added to the vial and the combined solution was stirred for 60 min at 30 $^{\circ}$ C. After this time period, iodobenzene, TBPM and/or piperidine were added to initiate the reaction. The reactions were monitored using the same method described in Section 4.4.3.

4.4.11 Preparation of solutions used in ^1H NMR spectroscopic study

In a nitrogen-filled glovebox, combinations of TBPM, piperidine, copper(I) iodide and iodobenzene in DMSO- d_6 were added to J. Youngs tap NMR tubes and immediately transferred to a NMR spectrometer after the addition of the final compound.

4.4.12 Procedure for the catalytic reaction using tetra(*n*-butyl)phosphonium mono-anionic malonic acid as the base

To obtain 0.20 M and 0.40 M concentrations of mono-anionic malonic acid, TBPM (200 or 400 μ L of 1.00 M solution in DMSO, 0.200 or 0.400 mmol), DMSO (900 μ L or 500 μ L), malonic acid (200 or 400 μ L of 1.000 M solution in DMSO, 0.200 or 0.400 mmol), piperidine (200 μ L of 1.500 M solution in DMSO, 0.300 mmol), iodobenzene (200 μ L of 1.000 M solution in DMSO, 0.200 mmol) and naphthalene (200 μ L of 0.100 M solution in DMSO, 0.0200 mmol), in DMSO (400 μ L) were added to a calorimetry reaction vial in a nitrogen-filled glovebox. A gas-tight syringe containing copper(I) iodide (200 μ L of 0.100 M solution in DMSO, 0.0200 mmol) was also prepared, with the end of the needle sealed by a PTFE plug. The capped reaction vessel and gas-tight syringe were taken out of the glovebox. The reaction vial was stirred and allowed to thermally equilibrate for 60 min at 30 $^{\circ}$ C. Afterwards, copper(I) iodide was added to the vial and the reaction solution was stirred at 30 $^{\circ}$ C. The reactions were monitored using the same method described in Section 4.4.3.

4.4.13 Procedure for the catalytic reactions using potassium phosphate as the base in the presence or absence of malonic acid as the ligand

In a nitrogen-filled glovebox, potassium phosphate (43 mg, 0.20 mmol), DMSO (580 or 600 μ L; volume required to make up to 1 mL total liquid), malonic acid (20.0 μ L of 1.000 M stock solution, 0.0200 mmol) (if required), piperidine (100 μ L of 1.500 M solution in DMSO, 0.150 mmol),

iodobenzene (100 μ L of 1.000 M solution in DMSO, 0.100 mmol), naphthalene (100 μ L of 0.100 M solution in DMSO, 0.010 mmol) as an internal standard were added to a screw-cap vial and stirred. At room temperature, copper(I) iodide (100 μ L of 0.100 M solution in DMSO, 0.0100 mmol) was added to the stirring mixture. The vial was capped and allowed to react in the glovebox at room temperature. After stirring for 7 h, 100 μ L of the final reaction mixture were taken and quenched at certain reaction times outside of the glovebox using a mixture of ethyl acetate (300 μ L) and water (100 μ L). The mixture was closed and shaken. After allowing the mixture to settle, the top organic layer was taken and passed through a pasteur pipette containing a pad of silica gel (1.0 – 1.5 cm height of silica gel) into a clean GC vial. More ethyl acetate (3 x 200 μ L) was added to wash the silica gel to ensure all of the iodobenzene and *N*-phenylpiperidine had passed through. The GC vial containing the combined organic fractions was capped and analysed by GC.

4.4.14 Procedure for the catalytic reactions between pyrrolidine or piperidine with iodobenzene to determine if imine formation occurs

In a nitrogen-filled glovebox, TBPM (400 μ L of 0.500 M solution in DMSO- d_6 , 0.200 mmol), DMSO- d_6 (100 μ L), pyrrolidine or piperidine (100 μ L of 1.500 M solution in DMSO- d_6 , 0.150 mmol), iodobenzene (100 μ L of 1.000 M solution in DMSO- d_6 , 0.100 mmol) and naphthalene (100 μ L of 0.100 M solution in DMSO- d_6 , 0.0100 mmol) as an internal standard were added to a J. Youngs tap NMR tube and shaken to mix well. Copper(I) iodide (200 μ L of 0.100 M solution in DMSO- d_6 , 0.0200 mmol) was added at room temperature to initiate the reaction. The product, benzene and imine yields were measured by ^1H NMR analysis.

4.4.15 Procedure to test if added water affects the amount of benzene formed in the catalytic reaction

In a nitrogen-filled glovebox, TBPM (800 μ L of 0.5000 M solution in DMSO, 0.40 mmol), DMSO (400 μ L), piperidine (200 μ L of 1.500 M solution in DMSO, 0.300 mmol), iodobenzene (200 μ L of 1.000 M solution in DMSO, 0.200 mmol) and naphthalene (200 μ L of 0.100 M solution in DMSO, 0.0200 mmol) as an internal standard were added to a vial that was sealed with a septum-lined cap. A gas-tight syringe containing copper(I) iodide (200 μ L of 0.100 M solution in DMSO, 0.0200 mmol) was also prepared, with the end of the needle sealed by a PTFE plug. The reaction vial and syringe were taken out of the glovebox. Degassed water (0.36 μ L) was

added through the septum using a microliter syringe, after which copper(I) iodide was injected to initiate the reaction. After stirring at room temperature for 3 h, 100 μL of the reaction solution was taken and diluted with DMSO-d_6 (500 μL). The diluted solution was analysed by ^1H NMR analysis to determine the product and benzene yields.

4.4.16 Procedure for catalytic reactions with different catalyst loadings and $[\text{Piperidine}]_0$ to observe how the amount of benzene formed is affected

In a nitrogen-filled glovebox, TBPM (800 μL of 0.50 M solution in DMSO, 0.40 mmol), DMSO (volume required to make up to 2.000 mL total liquid), piperidine (29.6, 39.6, 49.4 and 197.6 μL , 0.300, 0.401, 0.500 or 2.000 mmol), iodobenzene (200 μL of 1.000 M solution in DMSO, 0.200 mmol) and naphthalene (200 μL of 0.100 M solution in DMSO, 0.0200 mmol) as an internal standard were added to a screw-cap vial and stirred. Copper(I) iodide (40.0, 100, 150, 200 or 400 μL of 0.100 M solution in DMSO, 0.00400, 0.0100, 0.0150, 0.0200 and 0.0400 mmol) was added to the vial at room temperature whilst stirring to initiate the reaction. When complete iodobenzene conversion had occurred, 100 μL of the reaction solution was taken and diluted with DMSO-d_6 (500 μL). The diluted solution was analysed by ^1H NMR analysis to measure the final product and benzene yields.

4.4.17 Procedure for the catalytic reaction between piperidine and radical probe 2-(allyloxy)iodobenzene

In a nitrogen-filled glovebox, TBPM (400 μL of 0.500 M solution in DMSO-d_6 , 0.200 mmol), DMSO-d_6 (250 μL), piperidine (100 μL of 1.500 M solution in DMSO-d_6 , 0.150 mmol), 2-(allyloxy)iodobenzene (100 μL of 1.00 M solution in DMSO-d_6 , 0.100 mmol) and naphthalene (100 μL of 0.100 M solution in DMSO-d_6 , 0.0100 mmol) as an internal standard were added to a J. Youngs tap NMR tube and shaken to mix. Copper(I) iodide (50 μL of 0.100 M solution in DMSO-d_6 , 0.0050 mmol) was added at room temperature and the NMR tube was immediately transferred to an NMR spectrometer for analysis. After 23 hours, ^1H NMR analysis indicated that the reaction had produced 45% yield of the *N*-arylated product, 2% yield of allyl phenyl ether and no cyclised side-products. GC-MS analysis of the final reaction mixture was in agreement with the NMR results.

4.4.18 Kinetic modelling using COPASI

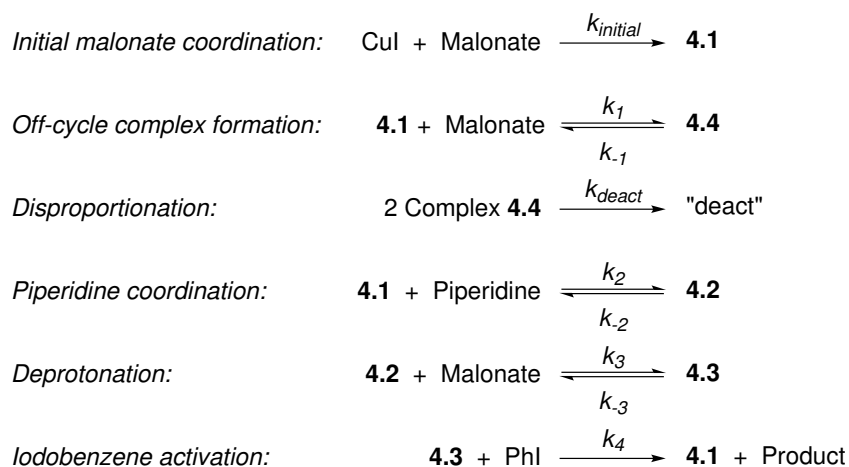
COPASI is a reaction simulation and data-fitting program that can be used to estimate the rate constants for catalytic processes.^[66] This is achieved by the user inputting the series of elementary reactions that make up the catalytic system into the program and also providing datasets containing the experimentally determined concentrations. The parameter estimation function in COPASI will iteratively determine the rate constants for the elementary reaction steps which produce simulated concentration-time plots that best fits the provided datasets.

The [PhI] over time data determined by reaction calorimetry (dependent data in COPASI) and the initial concentrations ([Piperidine]₀, [PhI]₀, [TBPM]₀, [CuI]₀; independent data in COPASI) for the all of the datasets in Table 4.2 were simultaneously fitted to the inputted mechanism in COPASI.

Entry	[Piperidine] ₀ (M)	[PhI] ₀ (M)	[TBPM] ₀ (M)	[CuI] ₀ (M)	Experiment	
1	0.1500	0.1000	0.2000	5.00×10^{-3}	Standard concentration	Scheme 4.11
2	0.1000	0.0500	0.1500	5.00×10^{-3}	“Same excess” experiment	Figure 4.10
3	0.2000	0.1000	0.2000	5.00×10^{-3}	Increased [Piperidine] ₀ to 0.2000 M	Figure 4.11
4	0.1500	0.0500	0.2000	5.00×10^{-3}	Decreased [PhI] ₀ to 0.0500 M	Figure 4.12
5	0.1500	0.1000	0.1500	5.00×10^{-3}	Decreased [TBPM] ₀ to 0.1500 M	Figure 4.13
6	0.1500	0.1000	0.3000	5.00×10^{-3}	Increased [TBPM] ₀ to 0.3000 M	Figure 4.13
7	1.000	0.0500	0.4000	2.00×10^{-3}	Multiple addition experiment	Figure 4.16 (1 st reaction)

Table 4.2: Datasets containing experimental determined concentration data used in the fitting process in COPASI to estimate rate constants for the proposed mechanisms.

The elementary reaction steps for the proposed mechanism in Scheme 4.22 inputted into COPASI are shown below in Scheme 4.24. The concentrations of the tetra(*n*-butyl)phosphonium iodide and mono-anionic malonic acid by-products were not in the elementary reaction steps in the kinetic modelling as they do not have an effect on the reactivity.^[27] The $k_{initial}$ rate constant



Scheme 4.24: Elementary reaction steps for the proposed mechanism in Scheme 4.22 inputted into COPASI to be fitted with the datasets in Table 4.2.

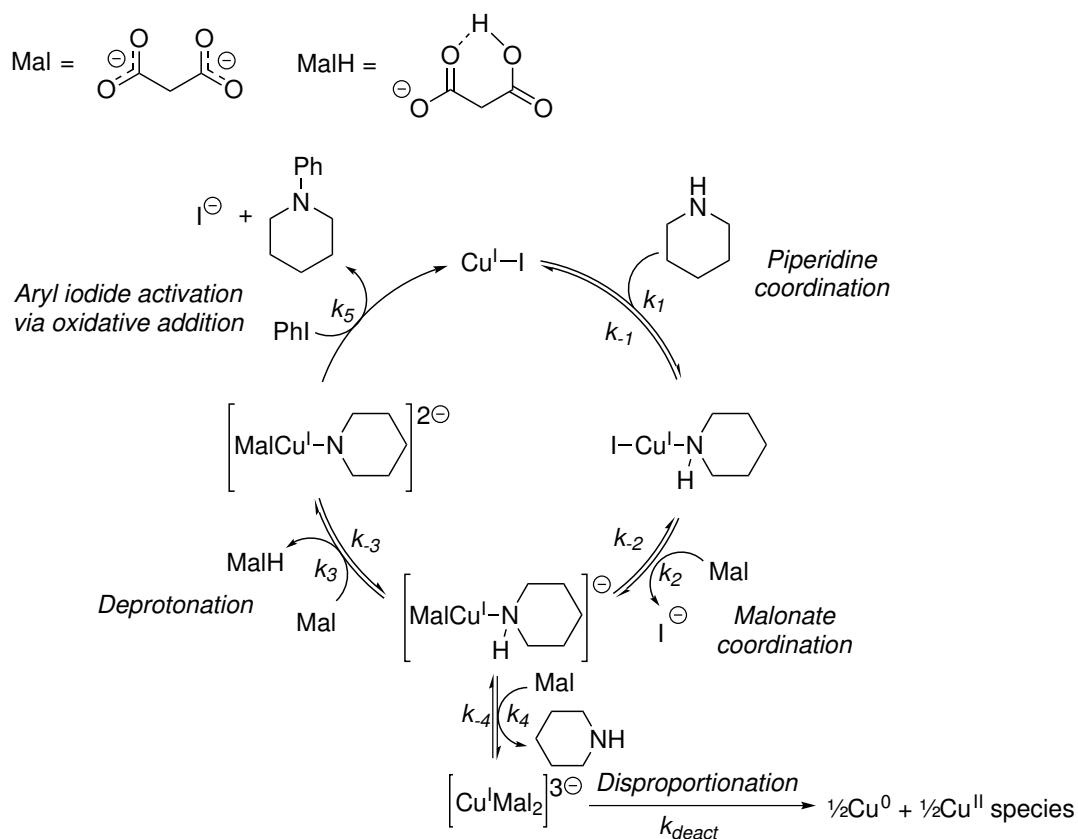
was held constant at a high value ($1.00 \times 10^6 \text{ M}^{-1} \text{ min}^{-1}$) because an induction period was not observed in the kinetic studies and the phosphonium iodide by-product did not have an effect on the reactivity. For the elementary reaction steps in equilibrium, either the forward or backwards directions were held constant during the parameter estimation process ensure low standard deviations for the estimated rate constants. Attempts to optimise all the rate constants for the equilibria in both directions simultaneously led to values with high standard deviations. The backwards rate constant for deprotonation, k_{-3} , was kept constant at a low value of $10 \text{ M}^{-1} \text{ min}^{-1}$ because the mono-anionic malonic acid was shown to have negligible effect on the reaction rate. As the amine was shown to stabilise the catalyst from deactivation, piperidine dissociation from complex **4.2** should be relatively unfavoured therefore the backwards rate constant for piperidine coordination, k_{-2} , was kept constant at a low value of $10 \text{ M}^{-1} \text{ min}^{-1}$. The stability of the copper catalyst in the presence of piperidine and TBPM indicates that malonate coordination to form off-cycle complex **4.4** is likely to be less favoured than piperidine coordination to form complex **4.2** therefore the rate constant for **4.4** formation, k_1 , was kept at a low value of $10 \text{ M}^{-1} \text{ min}^{-1}$. The rate constants produced after performing the parameter estimation function in COPASI are shown in Table 4.3.

As noted in Section 4.2.8, the parameter estimation function in COPASI was also employed to try to fit the kinetic data to other possible mechanisms. A mechanism with the opposite order of malonate and piperidine coordination to copper(I) (Scheme 4.25) failed to fit using COPASI. Similar mechanisms to the one shown in Scheme 4.22 except with disproportionation from **4.1**

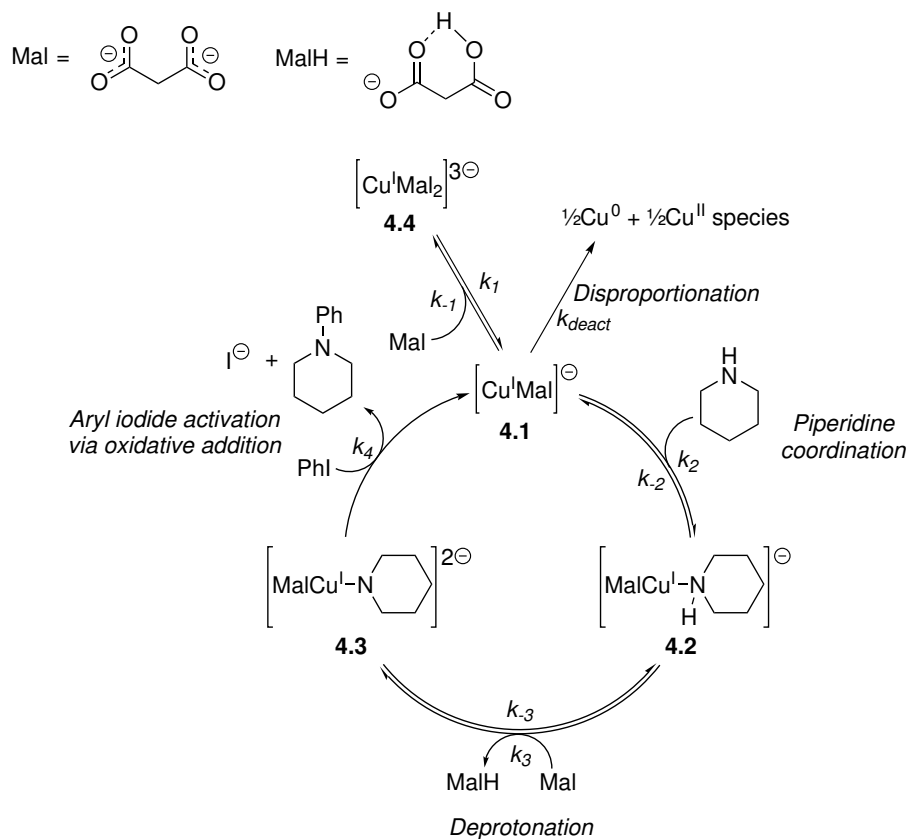
Reaction step	Rate constant, k	Comment	Value ($\text{M}^{-1} \text{min}^{-1}$)	Standard deviation	Estimated rate or equilibrium constants, k or K
Initial malonate coordination	k_{initial}	Held constant	1.00×10^6	-	$k_{\text{initial}} = 1.00 \times 10^6 \text{ M}^{-1} \text{min}^{-1}$
Complex 4.4 formation	k_1 k_{-1}	Held constant Estimated	10.0 0.324	- 0.0374	$K_1 = k_1/k_{-1} = 30.9 \text{ M}^{-1}$
Disproportionation	k_{deact}	Estimated	9.22	1.08	$k_{\text{deact}} = 9.22 \text{ M}^{-1} \text{min}^{-1}$
Piperidine coordination	k_2 k_{-2}	Estimated Held constant	59.6 10.0	3.71 -	$K_1 = k_2/k_{-2} = 5.96 \text{ M}^{-1}$
Deprotonation	k_3 k_{-3}	Estimated Held constant	2730 10.0	182 -	$K_3 = k_3/k_{-3} = 273$
Iodobenzene activation	k_4	Estimated	22.2	0.361	$k_4 = 22.2 \text{ M}^{-1} \text{min}^{-1}$

Table 4.3: Kinetic parameters kept constant or estimated in COPASI for the proposed mechanism in Scheme 4.22. Standard deviation values were calculated by COPASI during parameter estimation process. Values reported to three significant figures.

instead of **4.4** (Scheme 4.26), or disproportionation from one equivalent of **4.1** and **4.4** (Scheme 4.27) were fitted to the kinetic data with the estimated rate constants shown in Table 4.4 and Table 4.5 respectively. However these mechanisms do not fit the experimental data as well as the mechanism shown in Scheme 4.22 as indicated by the very large standard deviations for the estimated disproportionation rate constant, k_{deact} , for Scheme 4.26 and the rate constant k_3 , for Scheme 4.27. A similar mechanism to the one shown in Scheme 4.22 except with a possible di(piperidido)cuprate off-cycle species **4.6** from additional coordination and deprotonation of piperidine to complex **4.3** (Scheme 4.28) was fitted to the kinetic data with the estimated rate constants shown in Table 4.6. However this mechanism does not fit the experimental data as well as the mechanism shown in Scheme 4.22 as the estimated rate constant k_{-5} , has a very large standard deviation.



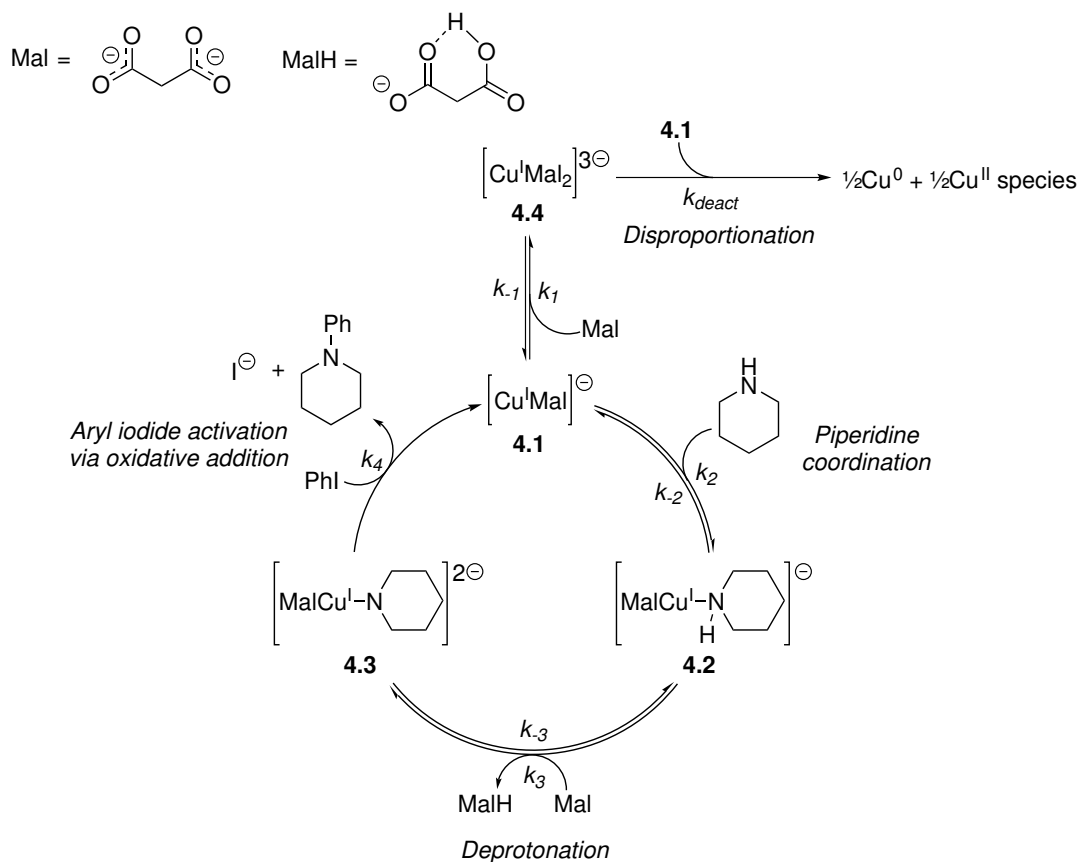
Scheme 4.25: Possible mechanism with the opposite order of malonate and piperidine coordination compared to the one shown in Scheme 4.22 that failed to fit to the kinetic data. Tetra-(*n*-butyl)phosphonium counter cations are not shown.



Scheme 4.26: Possible mechanism that involves disproportionation from **4.1** instead of **4.4** compared to the one shown in Scheme 4.22. Tetra-(*n*-butyl)phosphonium counter cations are not shown.

Reaction step	Rate constant, k	Comment	Value ($\text{M}^{-1} \text{min}^{-1}$)	Standard deviation	Estimated rate or equilibrium constants, k or K
Initial malonate coordination	k_{initial}	Held constant	1.00×10^6	-	$k_{\text{initial}} = 1.00 \times 10^6 \text{ M}^{-1} \text{min}^{-1}$
Complex 4.4 formation	k_1	Held constant	10.0	-	$K_1 = k_1/k_{-1} =$
	k_{-1}	Estimated	0.0500	0.00187	200 M^{-1}
Disproportionation	k_{deact}	Estimated	1.14×10^{-6}	1.66×10^{-5}	$k_{\text{deact}} = 1.14 \text{ M} \times 10^{-6} \text{ M}^{-1} \text{min}^{-1}$
Piperidine coordination	k_2	Estimated	135	3.65	$K_1 = k_2/k_{-2} =$
	k_{-2}	Held constant	10.0	-	13.5 M^{-1}
Deprotonation	k_3	Estimated	4270	589	$K_3 = k_3/k_{-3} =$
	k_{-3}	Held constant	10.0	-	427
Iodobenzene activation	k_4	Estimated	21.0	0.441	$k_4 = 21.0 \text{ M}^{-1} \text{min}^{-1}$

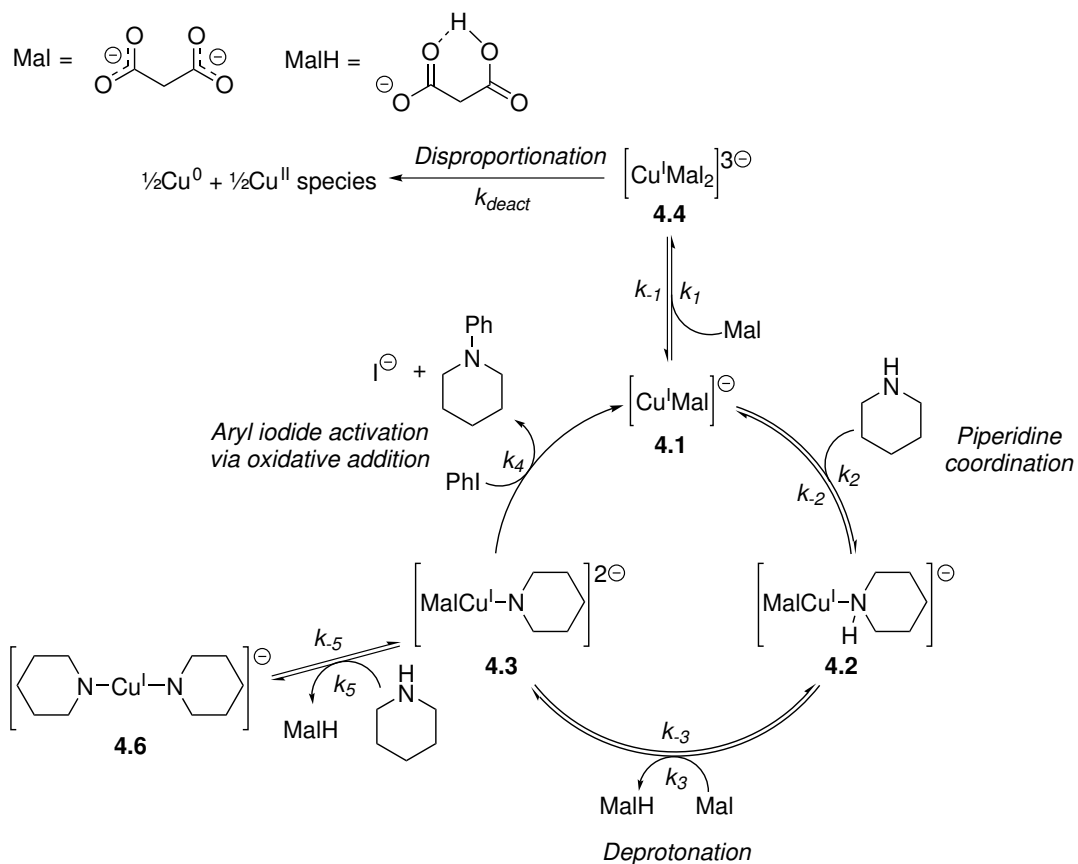
Table 4.4: Kinetic parameters kept constant or estimated in COPASI for the possible mechanism in Scheme 4.26. Standard deviation values were calculated by COPASI during parameter estimation process. Values reported to three significant figures.



Scheme 4.27: Possible mechanism that involves disproportionation from one equivalent of **4.1** and **4.4**. Tetra-(*n*-butyl)phosphonium counter cations are not shown.

Reaction step	Rate constant, k	Comment	Value ($\text{M}^{-1} \text{min}^{-1}$)	Standard deviation	Estimated rate or equilibrium constants, k or K
Initial malonate coordination	k_{initial}	Held constant	1.00×10^6	-	$k_{\text{initial}} = 1.00 \times 10^6 \text{ M}^{-1} \text{min}^{-1}$
Complex 4.4 formation	k_1	Held constant	10.0	-	$K_1 = k_1/k_{-1} =$
	k_{-1}	Estimated	0.226	0.0259	44.2 M^{-1}
Disproportionation	k_{deact}	Estimated	90.5	6.11	$k_{\text{deact}} = 90.5 \text{ min}^{-1}$
Piperidine coordination	k_2	Estimated	77.3	4.66	$K_1 = k_2/k_{-2} =$
	k_{-2}	Held constant	10.0	-	7.73 M^{-1}
Deprotonation	k_3	Estimated	31600	59.1	$K_3 = k_3/k_{-3} =$
	k_{-3}	Held constant	10.0	-	3160
Iodobenzene activation	k_4	Estimated	20.5	0.384	$k_4 = 20.5 \text{ M}^{-1} \text{min}^{-1}$

Table 4.5: Kinetic parameters kept constant or estimated in COPASI for the possible mechanism in Scheme 4.27. Standard deviation values were calculated by COPASI during parameter estimation process. Values reported to three significant figures.



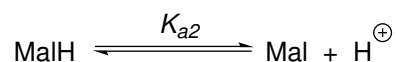
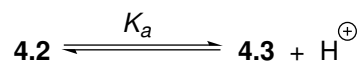
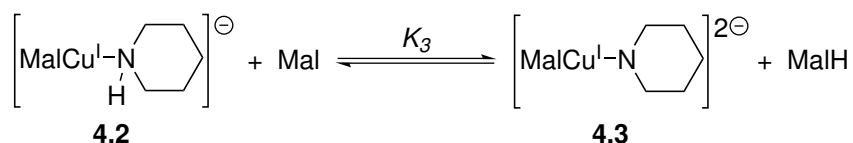
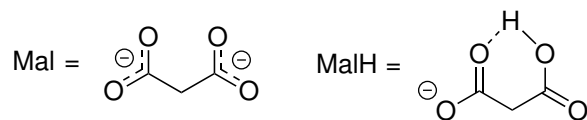
Scheme 4.28: Possible mechanism that involves a possible di(piperidido)cuprate off-cycle species **4.6**. Tetra-(*n*-butyl)phosphonium counter cations are not shown.

Reaction step	Rate constant, k	Comment	Value ($\text{M}^{-1} \text{min}^{-1}$)	Standard deviation	Estimated rate or equilibrium constants, k or K
Initial malonate coordination	k_{initial}	Held constant	1.00×10^6	-	$k_{\text{initial}} = 1.00 \times 10^6 \text{ M}^{-1} \text{min}^{-1}$
Complex 4.4 formation	k_1	Held constant	10.0	-	$K_1 = k_1/k_{-1} =$
	k_{-1}	Estimated	0.361	0.0489	27.7 M^{-1}
Disproportionation	k_{deact}	Estimated	10.2	1.43	$k_{\text{deact}} = 10.2 \text{ min}^{-1}$
Piperidine coordination	k_2	Estimated	56.9	4.02	$K_1 = k_2/k_{-2} =$
	k_{-2}	Held constant	10.0	-	5.69 M^{-1}
Deprotonation	k_3	Estimated	2610	171	$K_3 = k_3/k_{-3} =$
	k_{-3}	Held constant	10.0	-	261
Iodobenzene activation	k_4	Estimated	22.1	0.365	$k_4 = 22.1 \text{ M}^{-1} \text{min}^{-1}$
Complex 4.6 formation	k_5	Held constant	10.0	-	$K_5 = k_5/k_{-5} =$
	k_{-5}	Estimated	1.32×10^5	2.11×10^6	7.58×10^{-5}

Table 4.6: Kinetic parameters kept constant or estimated in COPASI for the possible mechanism in Scheme 4.28. Standard deviation values were calculated by COPASI during parameter estimation process. Values reported to three significant figures.

4.4.19 Derivation for the pK_a of the N–H group in intermediate **4.2**

The pK_a of the N–H group in piperidine-ligated copper(I) malonate intermediate **4.2** can be calculated by firstly considering the deprotonation and acid-base equilibria for **4.2** and mono-anionic malonic acid:



The equilibrium constants and equations for these equilibria are shown below:

$$K_3 = \frac{[\text{4.3}][\text{MalH}]}{[\text{4.2}][\text{Mal}]} \quad K_3 = 273 \text{ (at } 30^\circ\text{C)}$$

$$K_a = \frac{[\text{4.3}][\text{H}^+]}{[\text{4.2}]}$$

$$K_{a2} = \frac{[\text{Mal}][\text{H}^+]}{[\text{MalH}]} \quad pK_{a2} = 18.6 \text{ (at } 25^\circ\text{C)}^{[60]}$$

Assuming that the small 5°C temperature difference for K_3 and pK_{a2} has a negligible effect on the calculated pK_a of the N–H group in intermediate **4.2**, it can be solved using the following derivation:

$$K_3 = \frac{K_a}{K_{a2}}$$

$$K_a = K_3 \times K_{a2}$$

$$pK_a = -\text{Log}_{10}(K_3 \times K_{a2})$$

$$pK_a = -\text{Log}_{10}(273 \times 10^{-18.6})$$

$$pK_a = 16.2$$

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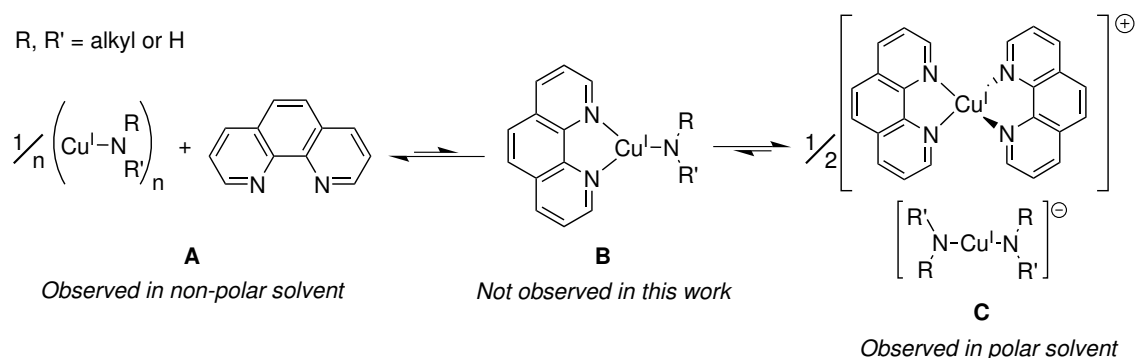
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Chapter 5

Overall Conclusions

5.1 Overall Conclusions

The structural characterisation and reactivity study of copper(I) alkylamide complexes reported in Chapter 2 showed that they are active towards aryl halide activation in the absence or presence of neutral *N,N*-chelating ligand 1,10-phenanthroline (phen) and therefore are potential intermediates in the modified Ullmann amination reaction. The effect of phen on the product yield was shown to be dependent on the polarity of the reaction solvent due to its influence on the equilibria between ligand-free copper(I) amide and free phen (**A**, Scheme 5.1), the neutral active catalyst species [(phen)Cu(NRR')] (**B**, Scheme 5.1) and an inactive ionic pair [Cu(phen)₂]⁺[Cu(NRR')₂]⁻ (**C**, Scheme 5.1). In non-polar benzene solvent, the equilibrium lies almost exclusively on the side of **A** and therefore copper(I) amides react with iodobenzene to give similar yields in absence or presence of phen. In contrast in polar DMSO solvent, inactive ionic pair **C** is the predominant copper species therefore lower product yields in stoichiometric reactions are observed in the presence of phen compared to without phen. The decrease in yield caused by phen in DMSO solvent was also observed in catalytic Ullmann amination reactions and therefore further confirms the intermediacy of phen-ligated and ligand-free copper(I) alkylamide complexes.

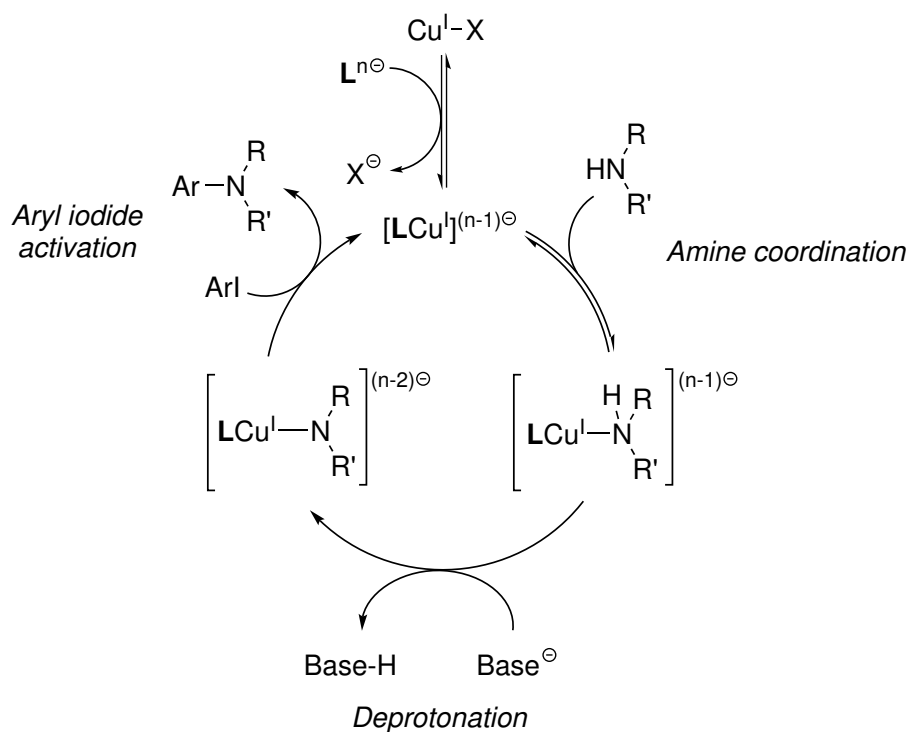


Scheme 5.1: The effect of solvent polarity on the solution equilibria between ligand-free copper(I) amide and free phen (**A**), the active catalyst species (**B**) and an inactive ionic pair (**C**).

The reaction rate of the catalytic Ullmann amination reaction with 2-acetylcyclohexanone as the ancillary ligand studied in Chapter 3 was found to be mass transfer limited due to the heterogeneous nature of the potassium phosphate base in DMSO. This base effect prevented a quantitative kinetic study to identify the numerical orders with respect to the substrate and reagent concentrations in the rate equation. When bis(tetra(*n*-butyl)phosphonium) malonate

(TBPM) was utilised as a soluble base in the studies discussed in Chapter 4, a homogeneous reaction mixture was present. As a result, mass transfer effects were no longer present and the reaction rate was significantly higher than when potassium phosphate was used (Section 4.2.1, Chapter 4). Overall, if the highest possible reaction rate is desired, poorly soluble bases should not be used in order to avoid potential mass transfer effects.

The kinetic studies reported in this thesis reveal the dramatic effects of the ligand on the solution equilibria, reactivity and stability of the catalytic intermediates. The on-cycle species in the catalytic cycles for the 2-acetylcyclohexanone-ligated reaction (see Chapter 3) and the reaction involving TBPM as the base (see Chapter 4) are proposed to be formed from the same steps: ancillary ligand coordination to the copper(I) precursor, amine coordination, N–H deprotonation and then aryl halide activation. The on-cycle intermediates also have the same general structures as each other after each step in the mechanism. Furthermore, the same on-cycle intermediate species in the same order are also proposed in the reported mechanism by Jutand and co-workers.^[1–3] Therefore, it is likely that the on-cycle intermediates do not differ greatly in modified Ullmann amination reactions that utilise different ancillary ligands. Scheme



Scheme 5.2: Proposed general catalytic cycle for the modified Ullmann amination reaction between aryl iodides and alkylamines. **L** = ancillary ligand.

5.2 shows a proposed general catalytic cycle containing the on-cycle intermediates involved in the modified Ullmann amination reaction mechanism starting from a copper(I) halide precursor. However, although the addition of bidentate ligands generally improves cross-coupling product yields, they can also introduce potential pathways to unreactive or unstable off-cycle copper species, which are not shown in Scheme 5.2. The introduction of these pathways consequently has a negative effect on the rate of reaction and catalyst TON.

As mentioned previously, the negative effect of neutral *N,N*-chelating phen on the product yield compared to when no ancillary ligand is used in polar DMSO solvent is attributed to the low concentration of the active catalyst species **B**, caused by it equilibrating to the inactive ionic pair **C** in polar DMSO solvent (Scheme 5.1). In comparison, instead of forming an inactive off-cycle complex, copper(I) species ligated by anionic oxygen-coordinating 2-acetylcyclohexanonate (**3.6**) or malonate (**4.4**) ligands are highly unstable (Figure 5.1) and readily undergo disproportionation to give inactive copper(II) and copper(0) species, which consequently reduces the concentration of active catalyst in the system. Although the amine substrate was shown to reduce the catalyst deactivation rate by acting as a co-ligand in the diketone or malonate-ligated systems, disproportionation still inevitably occurs in the presence of the ancillary ligands using synthetically relevant amine concentrations.

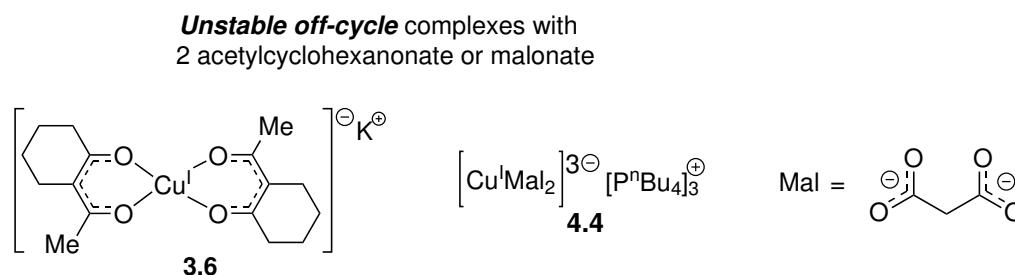


Figure 5.1: Proposed inactive and unstable off-cycle complexes formed using 2-acetylcyclohexanonate (**3.6**) or malonate (**4.4**) as the ancillary ligands reported in this thesis.

Although the formation of inactive off-cycle complexes has a negative effect to the reaction rate, if this process is readily reversible, the off-cycle species can potentially act as a stable reservoir of inactive catalyst. As suggested by Blackmond and co-workers, this could advantageously aid in suppressing catalyst deactivation.^[4] Other possible methods for alleviating catalyst deactivation could include carrying out the reaction in a manner that reduces the formation of the unstable copper intermediates, for example by slowly adding the compound

responsible for catalyst deactivation as suggested in Section 4.2.8, Chapter 4. Alternatively, the ancillary ligand and solvent could be carefully chosen or designed to mitigate the formation of unstable copper(I) intermediates, or to tune for desirable redox properties to minimise the instability of the deactivating copper(I) intermediates.^[5]

To summarise, the effect of the ligand on catalyst deactivation pathways, in addition to its effect on the aryl halide activation rates, and the synergy of the solvent and base with the ligand should be considered to avoid significant formation of inactive off cycle species and ensure high reaction rates. This better understanding could be used to improve existing catalytic systems or aid in the design of new systems such that copper-based reactions could become more viable and attractive than palladium-catalysed reactions in the formation of key bonds in total syntheses.

5.2 References

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