Investigations on the use of amidic ligands in copper-catalysed arylation reactions

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The candidate confirms the work submitted is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

References for the jointly authored publications are the following:

1) Carlo Sambiagio*, Stephen P. Marsden, A. John Blacker and Patrick C. McGowan*, Copper catalysed Ullmann type chemistry: from mechanistic aspects to modern development, *Chem. Soc. Rev*, 2014, **43**, 3525-3550

All the literature research and most of the writing were done by the candidate Carlo Sambiagio; Patrick McGowan modified and reviewed the manuscript throughout the process of writing; Stephen Marsden and John Blacker reviewed the manuscript. Part of this review has been included in Chapter 1, schemes and text were modified and updated when necessary.

2) Carlo Sambiagio, Rachel H. Munday, Stephen P. Marsden, A. John Blacker and Patrick C. McGowan*, Picolinamides as effective ligands for copper-catalysed aryl ether formation: structure–activity relationships, substrate scope and mechanistic investigations, *Chem. Eur. J.* 2014, **20**, 17606-17615.

All the experimental work and most of the writing were done by the candidate Carlo Sambiagio; Patrick McGowan supervised the project, modified and reviewed the manuscript, Rachel Munday, Stephen Marsden and John Blacker co-supervised the project, reviewed and commented the manuscript. Results reported here appear in Chapters 2 and 4, schemes and text were modified where necessary.

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Abstract

This thesis reports investigations on the use of amidic ligands, in particular picolinamide ligands, in copper-catalysed arylation of nucleophiles with aryl halides. An introduction to the field of copper-catalysed arylations of nucleophiles, mostly focusing on the mechanistic aspects of these processes, from the early investigations to the most recent developments, is reported in Chapter 1.

Following this introduction, the results of this research are presented in three chapters, each dealing with a different topic. Chapter 2 reports on the synthesis of a range of differently substituted picolinamide ligands and their use in the copper-catalysed arylation of phenols and amides. The catalytic screenings reported in this chapter are the basis for the mechanistic investigations reported in Chapter 4. A range of phenols, amides and aryl halides were tested under optimised conditions to assess the validity of the method. All the coupling products were isolated and characterised.

Chapter 3 describes the synthesis of copper complexes with picolinamide ligands, to be used for mechanistic investigations. Five different types of complexes, with differently substituted ligands, were obtained, and their structural features in the solid state are summarised in this chapter. Discussion on the mechanism of formation of these complexes, and on the role of the base in the process is also included.

Investigations on the mechanism of the coupling reaction between phenols and aryl halides, facilitated by picolinamide ligands, are reported in Chapter 4. The complexes synthesised in Chapter 3, used as pre-catalysts for the coupling process, and electrochemical measurements on these complexes, are employed to investigate the role of the electronic properties of the ligands in the reaction, and its influence on the metal centre. Other miscellaneous experiments, such as radical clock experiments, are also reported.

The final two chapters of this thesis, Chapters 5 and 6, contain general conclusions and suggestions for further investigation topics (Chapter 5), and detailed experimental procedures and characterisation data for all of the compounds prepared in Chapters 2-4 (Chapter 6).

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Abbreviations

Å	Angstrom, 1 x 10^{-10} m
σ	Hammett values
δ	NMR chemical shift (expressed in ppm)
π	Pi orbital/electron
υ	frequency (expressed in cm^{-1})
°C	degree centigrade
A	Ampere
Ac	acyl
acac	acetylacetonate
Am	amyl/pentyl
Anal.	elemental analysis
APCI	atmospheric pressure chemical ionisation
approx.	approximately
ca.	approximately
cat.	catalytic
Bu	butyl
CI	chemical ionisation
CV	cyclic voltammetry
cm	centimetre
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DCM	dichloromethane
DMSO	dimethylsulfoxide
dt	doublet of triplets
e.g.	*exempli gratia* (for example)
EDG	electron-donating group
EI	electron impact
EPR	electron paramagnetic resonance
eq.	stoichiometric equivalents
ESI	electrospray mass ionisation
Et	ethyl
EWG	electron-withdrawing group
g	gram
h	hours
HAT	halogen atom transfer

HRMS	high resolution mass spectroscopy
Hz	Hertz
i.e.	*id est* (that is)
IAT	iodine atom transfer
in situ	performed in place, in the reaction mixture
IR	infrared
J	coupling constant in NMR (expressed in Hz)
M	molar (concentration)
m	multiplet
m.p.	melting point (expressed in °C)
mg	milligram
MHz	megahertz
mL	millilitre
mV	millivolt
m/z	mass to charge ratio
Me	methyl
MeCN	acetonitrile
MeOH	methanol
Min.	minutes
MS	mass spectrometry
N.B.	*nota bene* (note well)
NMR	Nuclear Magnetic Resonance
OAc	acetate
Ph	phenyl
phen	phenanthroline
ppm	parts per million
Pr	propyl
q	quartet
quint	quintet
r.t.	room temperature (20-25°C)
s	second (for CV experiments)
s	singlet (for NMR experiments)
sept	septet
SET	single electron tranfer
sex	sextet
St. Dev.	standard deviation
T	Temperature (expressed in °C)
t	triplet

UV-*vis*	Ultraviolet-Visible Spectroscopy
V	volts

Chapter 1:

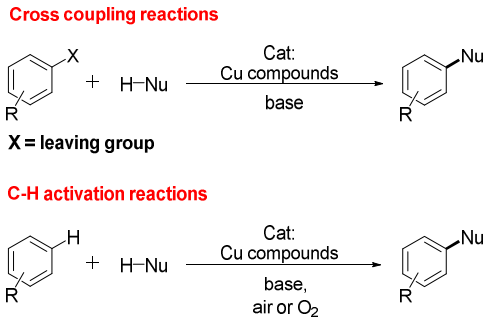
Introduction: copper-catalysed Ullmann reactions

1.1 – Introduction

"The substitution of an aryl, vinyl, or alkyl halide or pseudohalide by a nucleophile that takes place with catalysis by a transition metal complex is generally referred to as a cross-coupling reaction if it follows the mechanistic course of oxidative addition, transmetalation and reductive elimination". This definition of cross-coupling reaction was given in the editorial letter of a 2008 special issue of *Acc. Chem. Res.* by Stephen Buchwald,[1] even before the Nobel Prize for chemistry was assigned to Negishi, Suzuki and Heck for their work on the field.

This definition includes many of the transformations of this type possible with transition metals (especially palladium-catalysed). However, since then the definition of cross-coupling has somewhat changed to include transformations similar from the outside, but different at a more detailed level, that have been developed over the last two decades. In part, these changes refer to a broader range of "pseudohalides" (electrophiles) and nucleophiles that can now be used in cross coupling substrates, and in part to the mechanism of the process. The expansion of the range of electrophiles is evidenced, for example, by the use of C-O electrophiles, such as aryl ethers and derivatives.[2, 3] The range of nucleophiles has broadened from mostly carbon-based to heteroatom-based compounds, such as N-, O-, S-nucleophiles. Moreover, a range of different metals can now be used for cross-coupling catalysis, and, as acknowledged in the above editorial, first-row metals are now commonly employed along with the more popular palladium catalysts, thanks to lower toxicity and cost. This influences the substrate range available and the mechanism of the cross-coupling itself, which can follow an oxidative addition mechanism, often the case with nickel,[2, 4] but also radical pathways, as occurs with cobalt.[5]

Copper has long been known for its ability to form alkynyl complexes, famous applications of which being the bimetallic-catalysed Sonogashira coupling and the cycloaddition reaction with azides (click chemistry). Although these are still among its most common applications in catalysis, together with conjugate addition to unsaturated organic compounds,[6] Cu is also an effective catalysts for cross coupling reactions. The most common aryl donors in these reactions are aryl halides and boronic acids (Chan-Lam coupling), but a range of others have been successfully used, a list of which can be found in a recent review by Thomas.[7] Cu catalysis has also been recently extended to the functionalisation of unsubstituted arenes through oxidative C-H activation, (Scheme 1.1).[8-19]



Scheme 1.1: *Cu-catalysed cross couplings and C-H activations*

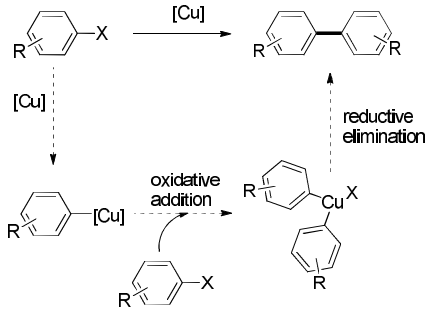
Despite having been known for a long time, Cu-catalysed couplings have not reached yet the high levels of prominence which characterise Pd-based catalysis, either in rate, efficiency or scope. Moreover, Cu-based coupling reactions are still in some sense unpredictable, the mechanism not being yet completely understood. On the other hand, Cu catalysis shows some interesting advantages over Pd and other metals. Firstly, Cu is cheaper than many other metals used in catalysis, and has recently attracted high interest from the industry. The range of nucleophiles suitable for Ullmann arylations has become wider with time, and now N-, O-, S-, Se-, P- and C-aryl bond formation are easily accessible through these processes. Such bonds can be found in many bioactive organic compounds,[20, 21] as well as in materials chemistry.[22, 23] The substrate scope of Cu-catalysed cross coupling reactions is also increasing, and seems to be somewhat complementary to that of Pd-based methodologies.[24-26] This complementarity is shown, for example, in the chemoselectivity between the two methods in multifunctionalised substrates; moreover, while Pd catalysis gives better results in the arylation of N-nucleophiles, Cu is generally preferred for O-arylations. Finally, in many cases, Cu-catalysed reactions work well without any ligand, and when required, the ligands are usually structurally quite simple and inexpensive (ligands for Pd chemistry, for example, are often expensive and air-sensitive phosphines).

This chapter contains a discussion on Cu-catalysed cross-coupling reactions between aryl halides and carbon- or heteroatom-nucleophiles, which have been investigated during this PhD project. These arylation reactions will be from now on referred to as “Ullmann couplings”. The chapter focuses on the mechanistic aspects reported in the literature for these processes, which are of interest for the topic of this thesis.

1.2 – The discovery of Cu-catalysed aromatic C-C and C-heteroatom bond formation

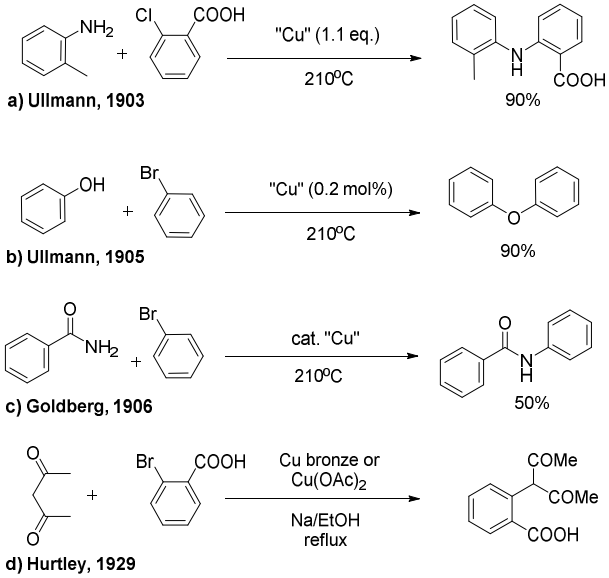
In 1901 Fritz Ullmann observed that Cu compounds were able to catalyse/mediate (stoichiometric amounts) the formation of biaryl moieties *via* the coupling of two molecules of an aryl halide.[27] This reaction became what is now called the “classical Ullmann reaction”. The mechanism now generally accepted for this reaction involves the formation of an organocopper intermediate from a molecule of aryl halide, which then reacts with a second molecule through

oxidative addition, yielding the final product after reductive elimination (Scheme 1.2).[28, 29] Detailed mechanistic investigations on this process are rare in the literature, and nowadays heterogeneous Pd or Au catalysis is more commonly used for this process, rather than Cu catalysis.[30-35]



Scheme 1.2: *Mechanism of the Cu-mediated synthesis of biaryls*

A few years after the discovery of the classical Ullmann reaction, the same methodology was applied by Ullmann to the synthesis of *N*-aryl amines (stoichiometric Cu) and ethers,[36, 37] and in 1906 the first Cu-catalysed synthesis of aryl amines and amides was reported by Irma Goldberg[38] (Scheme 1.3a-c). The arylation of *β*-dicarbonyl compounds mediated by Cu bronze or $Cu(OAc)_2$ was finally reported by William Hurtley in 1929 (Scheme 1.3d).[39]



Scheme 1.3: *Ullmann, Goldberg and Hurtley reactions in early 1900s*

Despite the early discovery, these Cu-mediated reactions generally required harsh conditions (high temperature, strong bases, long reaction time and stoichiometric amounts of copper), and electron-poor aromatic substrates and high-boiling polar solvents were often necessary. Moreover, problems related to the solubility of many Cu compounds were evident, hence excess amounts of Cu source had often to be used.[40] Therefore, these couplings were not

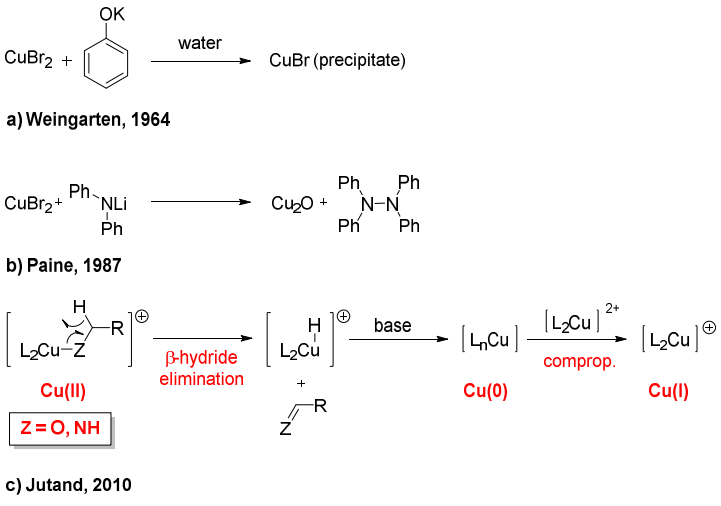
extensively utilised until 50-60 years later, when interest in these processes began to re-emerge, together with the first mechanistic studies.

1.3 – The mechanistic debate

1.3.1 – Oxidation state of the active Cu species

Many different copper sources (Cu(0), Cu(I) and Cu(II)) have been used to catalyse Ullmann-type reactions, and either salts and oxides seemed to work well for the arylation of several nucleophiles since the early investigations.[40] This suggested that a common active species could be formed during the reaction from the different sources. Much work has been carried out since the early 1960s in this direction, investigating the particular electrochemical behaviour of Cu.[41-43] Since Cu(I) led to slightly higher reaction rates, Weingarten suggested in 1964 that Cu(I) species could have been a common intermediate.[41] Thus, the formation of Cu(I) from Cu(II) or Cu(0) became an essential part of the mechanistic study, either before and after the introduction of exogenous ligands in the reactions.

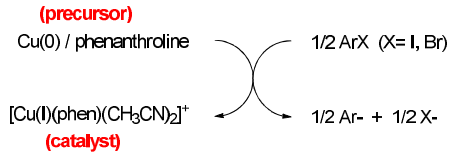
It was soon observed that Cu(II) species used as catalysts could be reduced to Cu(I) in the presence of coordinating solvent/nucleophiles, and that phenoxides and amines used as nucleophiles in the coupling could be oxidised as the redox counterpart (Scheme 1.4, a and b).[41, 42] In 2010 Jutand observed spectroscopically a $[Cu(II)(phen)_2]^{2+}$ → $[Cu(I)(phen)_2]^{+}$ (phen = 1,10-phenanthroline) transition after the addition of nucleophile (benzylalcohol or benzylamine) and base (Cs_2CO_3).[44] This transition was suggested to occur through a two-electron reduction to Cu(0) *via* *β*-hydride elimination from the nucleophile, and following comproportionation of Cu(0) and Cu(II) (Scheme 1.4c).[44]



Scheme 1.4: *Formation of Cu(I) from Cu(II)*

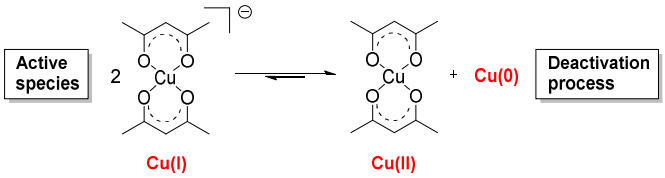
The oxidation of Cu(0) to Cu(I) in a coordinating environment, occurring with the reduction of the aryl halide used, was recently observed by Taillefer *et al.* through *in-situ* cyclic voltammetry studies (Scheme 1.5).[45] In 2011, performing the coupling between aryl halides and

amines in water with metallic Cu powder, Wei and co-workers also proposed the oxidation of the Cu(0) source to Cu(I) by the atmospheric oxygen in the reaction, on the basis of colour change and the different catalytic results under different conditions.[46] The contamination of Cu(0) with Cu(I) species was also blamed for the catalytic activity of metallic copper: in 1987, Paine found, by means of electron microscopy and X-ray powder diffraction, that Cu(0) particles used as catalyst were actually covered in a layer of Cu_2O.[42] This Cu(I) species, leaching into solution during the reaction, was considered responsible for the catalysis.[42]



Scheme 1.5: *Formation of Cu(I) from Cu(0) by reduction of aryl halides*

These and other studies (*vide infra*) seem to demonstrate the active catalyst to be a Cu(I) species, but it is generally agreed that the initial copper source is not very important for the outcome of the reaction, due to oxidation/reduction processes always leading to Cu(I) at some stage during the reaction.[43, 47] The formation of Cu(II) or Cu(0) species during reactions where Cu(I) is used as catalyst is instead a far less explored field, and to date, only Lei and co-workers have reported investigations on this aspect of the mechanism. During the coupling between aryl halides and *β*-diketones, the authors observed a labile Cu(I) species, considered to be the active species, undergoing disproportionation to Cu(II) and Cu(0) (Scheme 1.6).[48] Cu(II) species were detected through *in situ* IR during the catalytic reaction, while *in situ* X-ray absorption techniques showed the formation of metallic copper during the process. The disproportionation of the initial Cu(I) species resulted in only small amounts of active catalyst left in solution, with the consequence of slowing down the coupling process.



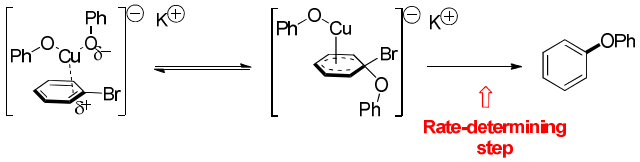
Scheme 1.6: *Deactivation of Cu(I) active species*

1.3.2 – Different types of mechanism

Between the 1960s and the 1990s different types of mechanism, starting from a Cu(I) active species, were proposed for the coupling processes. The most important difference in these mechanisms is the activation of the aryl halide.[41, 43, 49-52] The mechanisms proposed until the 1990s can be conveniently divided into four main classes:

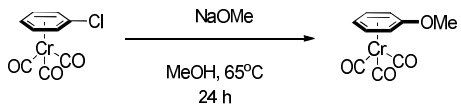
- Aromatic nucleophilic substitution, with Cu(I) π-coordinating to the aromatic ring of the aryl halide to render the aromatic position more electrophilic and susceptible to substitution (Scheme 1.7);
- Mechanisms *via* Single Electron Transfer (SET) or Halogen Atom Transfer (HAT), involving the redox couple Cu(I)/Cu(II) and radical intermediates (Schemes 1.10 and 1.11);
- Metathesis mechanisms, leading to the formation of four-membered cyclic transition states, through coordination of Cu to the halogen atom of the aryl halide, making it a better leaving group (Figure 1.1);
- Mechanisms involving an oxidative addition/reductive elimination cycle with Cu(III) intermediates, either *via* direct oxidation Cu(I)/Cu(III) or stepwise oxidation Cu(I)/Cu(II)/Cu(III) (Scheme 1.12).

In 1964 Weingarten suggested that the rate determining step of the Cu-catalysed arylation was the cleavage of the aryl-halogen bond.[41] On the basis of kinetic studies upon the coupling between potassium phenoxide and bromobenzene, the existence of a cuprate species $[Cu(OPh)_2]^-$ was hypothesised which would coordinate to the aryl halide during the reaction. The suggested interaction was a π-coordination to the aromatic ring, the metal acting essentially as an activating group, making the aryl halide more susceptible to nucleophilic substitution (Scheme 1.7).[41]



Scheme 1.7: *Aromatic nucleophilic substitution mechanism*

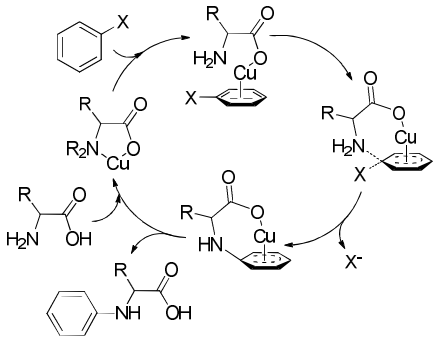
This mechanism was judged attractive for two reasons: i) η^2-Cu(I)-benzene complexes had been synthesised the year before,[53] and ii) η^6-haloarene tricarbonylchromium(0) complexes had been demonstrated to be very effective substrates for nucleophilic substitution (Scheme 1.8).[54]



Scheme 1.8: *Aromatic nucleophilic substitution on tricarbonylchromium complexes*

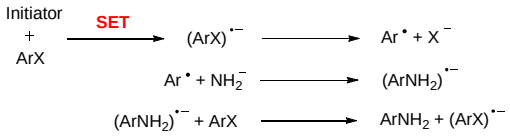
However, as Paine pointed out later,[42] this mechanism did not explain the accelerating effect of an *ortho* carboxylate group on the aryl halide, whereas the same group in *para* had no such effect. Also the analogy with the chromium π-complexes was not valid, because the order

of halide reactivity in the latter was Cl>Br>I, opposite of that observed for copper catalysed reactions.[55] Weingarten's mechanism was reconsidered by Ma in 1998 to explain the coupling between amino-acids and aryl halides (Scheme 1.9). However, no explanation for the two problems above was supplied.[56]



Scheme 1.9: *Aromatic nucleophilic substitution mechanism with amino-acid ligands*

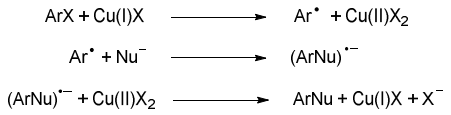
Some years after Weingarten's proposal, a radical type of aromatic nucleophilic substitution, called $S_{RN}1$, was postulated by Bunnett when studying the reaction of iodoarenes with potassium amide.[49] The authors proposed a radical chain mechanism for this reaction, involving single electron transfer (SET) as initiation step (Scheme 1.10). This type of electron transfer is called "outer sphere" electron transfer, where the initiator does not coordinate to the aryl halide, and only the electron is transferred to it, leading to the formation of a radical anion.



Scheme 1.10: *Single electron transfer (SET) mechanism*

Although Bunnett's studies were not based on metal-catalysed reactions, a metal that can undergo single electron transfer would be suitable for this process, easily furnishing the initial aromatic radical anion. Both Cu(I) and Cu(II) species are known to act as single electron oxidants in many reactions, thus leading to radical cations,[57-59] whereas Cu(I) species acting as single electron reductants are found in Atom Transfer Radical Polymerisation (ATRP) processes.[60]

Another radical mechanism was proposed for the Ullmann coupling, based on Kochi's studies on radical reactions (Scheme 1.11).[50, 61] In this mechanism, the aromatic radical moiety is formed by transfer of a neutral halogen atom from the aryl halide to the Cu species (*i.e.* the electron transfer occurs simultaneously to the C-X bond cleavage, leading directly to the formation of an aromatic radical). This mechanism is called "halogen atom transfer" (HAT) or "inner sphere" electron transfer.



Scheme 1.11: *Halogen atom transfer (HAT) mechanism*

A combination of a radical mechanism and a substitution reaction was proposed by Litvak in 1974,[51] with the Cu involved in both SET and coordination to the nucleophile. A similar mechanism, in which the Cu species remains in its Cu(I) oxidation state, had already been proposed by Bacon in the mid 1960s for various nucleophiles,[52] and was also suggested for amides in the 1970s.[62] These mechanisms are often referred to in the literature as metathesis, and their transition states are depicted as four-centred structures (Figure 1.1).

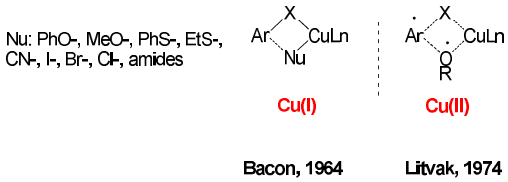
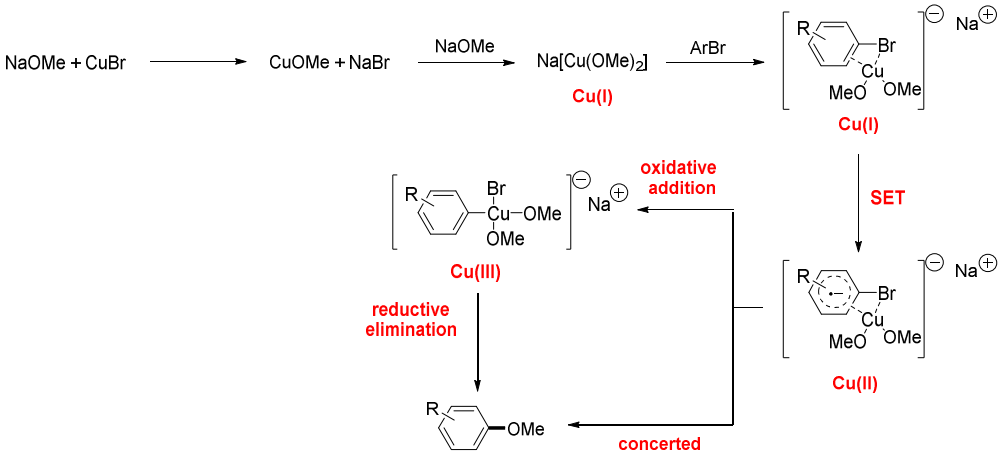


Figure 1.1: *Metathesis type mechanisms by Bacon and Litvak*

A few researchers during this period started to suggest different types of oxidative addition mechanisms, similar to those established today for Pd-catalysed reactions. [63, 64] An interesting version was suggested by van Koten and co-workers, in which the oxidative addition occurred stepwise, *via* a Cu(II) intermediate, derived from an SET process (Scheme 1.12).[43]



Scheme 1.12: *Stepwise oxidative addition mechanism by Van Koten*

The initial formation of a radical anion on the aryl donor *via* a SET process would in theory facilitate the oxidative addition process, thus making the formation of Cu(III) intermediates more favoured. However, despite the existence of Cu(III) organocopper intermediates having been previously suggested,[63] the authors thought a Cu(III) intermediate would still be improbable, especially in an environment where even Cu(II) was reduced to Cu(I)

(Scheme 1.4). Therefore, they suggested a concerted mechanism for the coupling.[43]

Recently, a halogen-bond activated oxidative addition mechanism has been proposed by Jutand and Ciofini, on the basis of calculations upon the coupling between aryl halides and amines, using diketones as ligands.[65] The theory of halogen-bonding (XB) is based upon the fact that halogens can, in certain cases, behave as Lewis acids, and this makes halogen atoms potential acceptors for negative charges.[66, 67] In the coupling, this interaction is in theory possible between the halogen atom of the aryl donor and the Cu/ligand/nucleophile anionic complex, in which the negative charge is mostly localised on the nucleophilic nitrogen atom (Figure 1.2a, **A**).[65] The authors also calculated that the positive charge on the halogen atom decreases from iodine to chlorine, which would explain the decreasing reactivity along this series. They hypothesised that for aryl chlorides, which cannot be involved in such an XB interaction, the reaction would proceed differently, with a normal oxidative addition lacking any favourable activation, and therefore much more energy-expensive (Figure 1.2b). Calculations on the Cu-catalysed hydroxylation of aryl halides performed by the same authors led to the suggestion of a similar mechanism.[68]

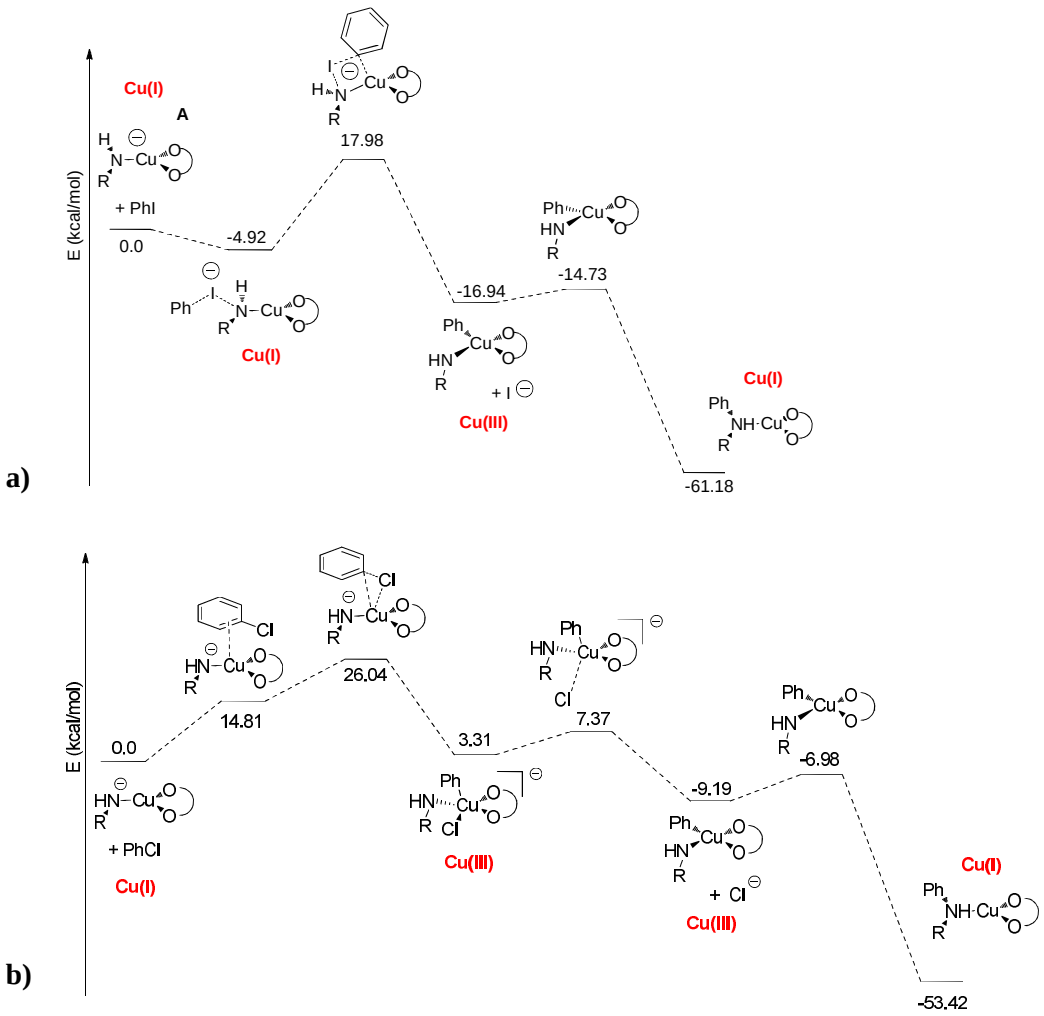
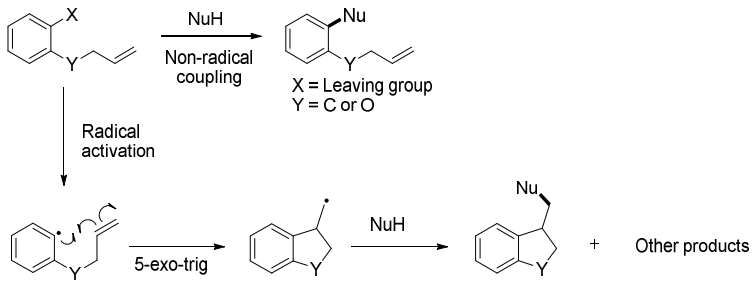


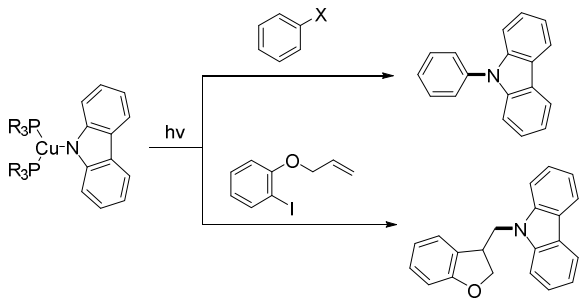
Figure 1.2: *Energy diagram for the coupling between amines and aryl halides; a) aryl iodide: halogen bond activation; b) aryl chloride: non-activated oxidative addition mechanism*

The nucleophilic substitution and the metathesis mechanisms are not considered realistic theories anymore, and oxidative addition mechanisms and radical mechanisms are the only two classes of mechanism still under debate. The only direct evidence of a Cu(III) intermediate in Ullmann-type couplings derives from a particularly stable macrocyclic system (see Section 1.6), thus not applicable to typical reaction systems. Experimental evidence and theoretical discussion was provided both for and against the existence of radical intermediates. For example, van Koten argued that a radical mechanism would easily explain the formation of de-halogenated products, which are often observed as side-products during the reaction,[43] and radical processes may account for the inhibition of the reaction from atmospheric oxygen. Studying the reaction between haloanthraquinones and aminoethanol in the 1970s, Hida and co-workers observed, through EPR experiments, the formation of an organic radical species and Cu(II) species.[69, 70] The radical species was suggested to be derived from the haloquinone through an SET process. A radical mechanism was also demonstrated, through radical clock and EPR experiments, when performing the reaction under photochemical conditions, by Fu, Peters and co-workers in 2012.[71] Radical clock experiments are based upon the fact that, in radical conditions, the formation of a methylcyclopentane moiety through a 5-*exo*-*trig* closure (Scheme 1.13) is the most kinetically favoured transformation.[72, 73] The efficacy of this test is based on the high rate of the closure reaction: in the case of radical mechanism in the Ullmann reaction, the coupling with the nucleophile should be incredibly fast to avoid the formation of the cyclic moiety.



Scheme 1.13: *Typical radical clock experiment*

Ullmann couplings under photochemical conditions gave positive results in these experiments, leading to the expected 5-exo-trig-derived product in good yields, indicating a radical process (Scheme 1.14).



Scheme 1.14: *Ullmann-type couplings in photochemical conditions*

It must be noted, however, that radical processes are very common under photochemical conditions and using quinonic substrates. This fact, added to the normal tendency of Cu itself to undergo one-electron reductions or oxidations, make the results from Arai and Fu/Peters not at all comparable to the typical systems used for Ullmann couplings (thermal conditions, using normal aryl halides).

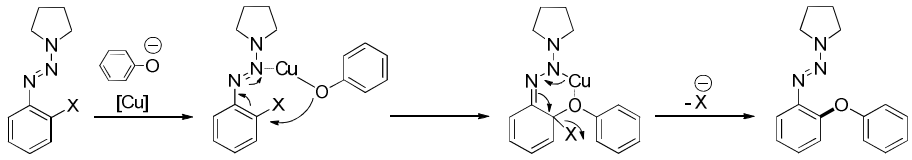
Evidence was also reported against the formation of radicals during the reaction. In a comparative study between different $S_{RN}1$ procedures available for the synthesis of heterocycles, Bowman found the Cu-catalysed coupling the most efficient, but at the same time, this strategy appeared to be particularly different from other radical processes.[74, 75] For example, the lack of inhibition by radical scavengers or oxygen in the reaction mixture, made the authors think that this coupling did not occur through radical aromatic substitution.[74, 75] Radical clock experiments have been performed many times under thermal conditions,[75-82] and negative results have always been obtained. A small amount of radical-derived product was detected only once from these experiments, showing that radical mechanisms can actually occur in the reaction, although to a minimal extent.[82]

Another series of experiments were reported in 2008 by Hartwig and co-workers using aryl chlorides and bromides with higher reduction potentials than the corresponding aryl iodide.[78] If a radical mechanism was involved, the reaction rate should increase with increasing reduction potentials, although bromides and chlorides are known to be less effective in the reaction. Again, the results for these experiments were negative, and higher reaction rates were observed for the less reducible aryl iodides, making the authors exclude a radical mechanism.[78]

In 2010 Buchwald contested these series of experiments by suggesting that the intermediate aryl radical could exist not in the form of a free radical, available to reaction with the alkene moiety in radical-clock experiments, but in the form of caged radical pairs, which would prevent this reaction, thus invalidating the results of these tests.[83] The negative results obtained from experiments with highly reducible aryl halides were instead explained in terms of less effective coordination properties of these substrates with the Cu atom.[83]

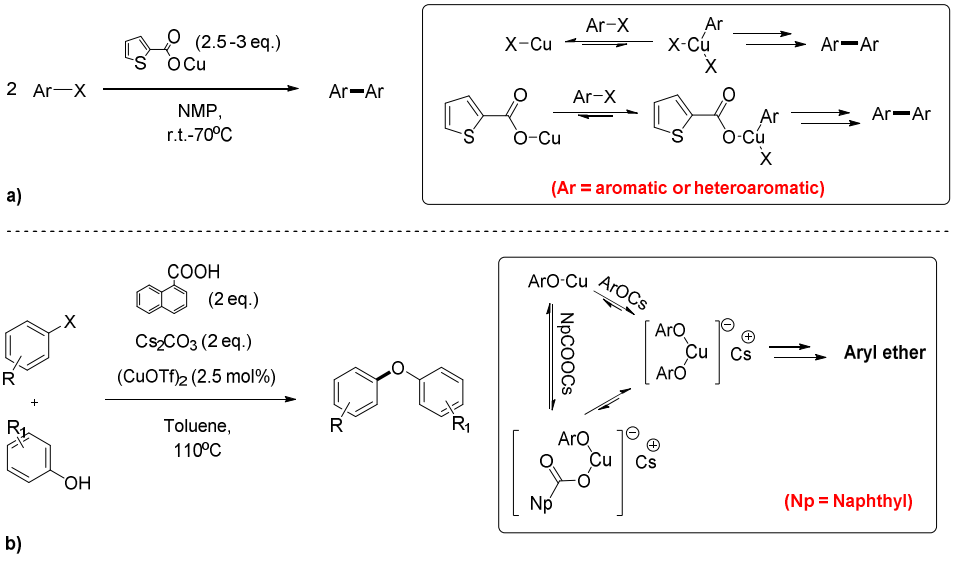
1.4 – The role of the ligand

In 1964 Weingarten noted that some esters or ketones could accelerate the coupling reaction between aryl halides and phenols/phenoxides,[41] but their role was mostly linked to the increased solubility of the Cu catalyst, rather than to other effects. In 1997, the coupling of phenols with *o*-triazene-substituted haloarenes was reported by Nicolaou and co-workers.[84] The triazene unit was proposed to act as a coordinating agent (a directing group) for the copper atom, thus facilitating the aromatic substitution (Scheme 1.15).



Scheme 1.15: *Triazene group-directed C-O coupling*

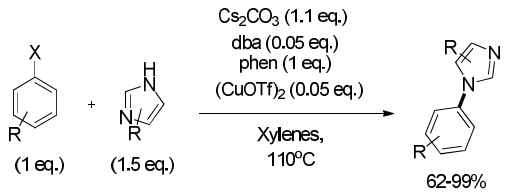
In the same year Liebeskind and Buchwald reported the use of exogenous (overstoichiometric) additives to facilitate the coupling, respectively, for the Cu-catalysed synthesis of biaryls[85] and aryl ethers.[86] Two different roles were at the time attributed to the additives. While Liebeskind suggested that copper thiophenecarboxylate would facilitate the oxidative addition of the aryl halide to the Cu catalyst, thus accelerating the coupling (Scheme 1.16a), Buchwald proposed that the combined effect of naphthoic acid and caesium carbonate would enhance the solubility of an intermediate cuprate species (Scheme 1.16b), similar to those reported by Weingarten[41] and van Koten[43] (Schemes 1.7 and 1.12).



Scheme 1.16: ***a)*** *Liebeskind's mechanism for homocoupling;* ***b)*** *Buchwald's mechanism for C-O coupling*

Later, investigating the coupling of aryl halides with imidazoles, Buchwald used a stoichiometric amount of phenanthroline (phen) as ligand and dibenzylideneacetone (dba) as a

catalytic additive (Scheme 1.17).[87] The role of the ligand and the additive were not clear, and were suggested to be involved in the stabilisation of the Cu(I) active species, the increase of solubility, or avoidance of aggregation or multiple ligation of imidazole to the Cu species.[87]



Scheme 1.17: *Phenanthroline as exogenous ligand in the C-N coupling*

In the following years, the first studies on different types of bidentate ligands, which appeared to be much more efficient than monodentate ones,[88] were published. The ligands used in Ullmann-type reactions were generally *N*-donors or mixed *N*- and *O*-donors, while *P*-based ligands were generally found to be scarcely effective.[89] Some of the first successful ligands are reported in Figure 1.3.[87, 88, 90-99]

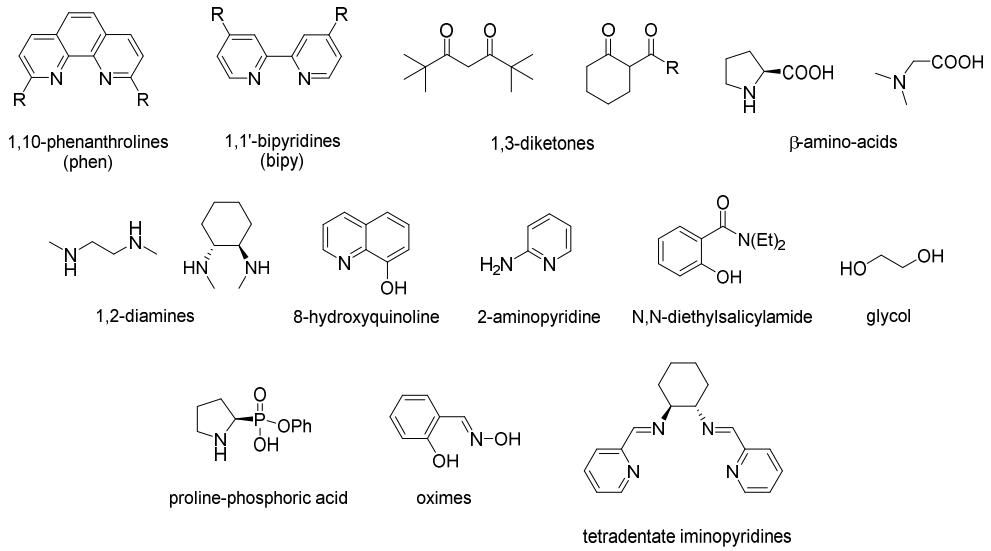
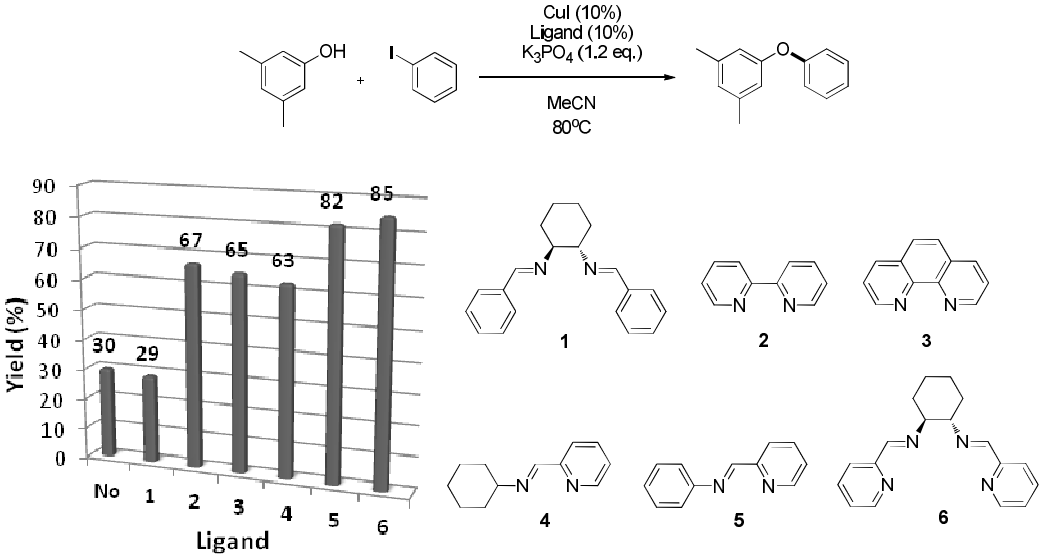


Figure 1.3: *Examples of ligands used for Cu-catalysed couplings*

The introduction of ligands in Ullmann type reactions made the use of much milder reaction conditions possible, and temperatures <100°C (usually 80-100°C) could be used achieving good results. An amount of Cu source and ligand in the range 5-20% relative to the substrate were normally used.

Since 2004 much effort has been put into the discovery of the role of the ligand in these couplings. Among major contributions is the work performed in Taillefer's and Buchwald's groups, which focused on different aspects of the problem. Work in Taillefer's group was mostly focused on the development and modification of new classes of imine-based ligands and their Cu complexes for Ullmann *N*- and *O*-arylations.[98, 100-104] Moreover, interesting mechanistic investigations were performed through cyclic voltammetry experiments.[45, 68, 104, 105] In 2007

Taillefer *et al*. reported one of the first structure-activity relationship studies in the literature of Ullmann couplings: this study allowed them to make the first hypothesis on the effect of the ligand structure in the catalytic reactions (Scheme 1.18).[103]



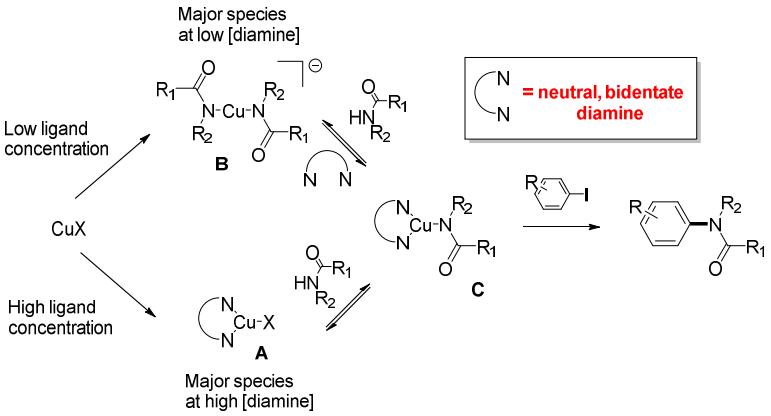
Scheme 1.18: *Structure-activity relationships for iminopyridine ligands*

Imine ligands alone were found to be ineffective in enhancing the reaction yield (ligand **1** in Scheme 1.18). However, when an aromatic imine group was bound to a pyridine group (ligand **5**), the reaction yield was enhanced even more than with bipyridines or phenanthrolines. A tetradentate version of this ligand (ligand **6**), resulted in slightly higher yields.[103] It is important to note here that not many tetradentate ligands have been proved effective in Ullmann-type couplings, and the efficacy of this particular ligand may be due to the fact that it actually coordinates to two metal centres in a bidentate N,N fashion to each of them.[104]

The authors also observed that an electron-withdrawing substituent on the imine moiety and an electron-donating substituent on the pyridine nucleus of the bidentate precursor (ligand **5** in Scheme 18) led to higher yields. Based on these data, they proposed that the two different ligand moieties could intervene in two different steps of the catalytic cycle. The electron-rich pyridine, transferring electrons to the Cu atom, would increase its tendency to oxidative addition, while the electron-poor imine would make the Cu centre more electrophilic, hence more susceptible to reductive elimination.[103]

A different effect was proposed by Buchwald and co-workers.[106, 107] On the basis of kinetic investigations, they proposed that a series of equilibria between different Cu species was involved in the arylation process.[106] Since the concentration of CuI used was only 0.02 M, and the reaction reached the maximum rate at a ligand concentration of *ca*. 0.2 M, the exclusively solubilising effect initially supposed for the ligand was ruled out. The authors suggested that the ligand could have the role of preventing the association of two amide molecules to the Cu atom,

making the formation of Cu monoamidate complex more favourable, which in turn would allow a faster reaction (Scheme 1.19).[106]



Scheme 1.19: *Effect of relative concentration of ligand and nucleophile*

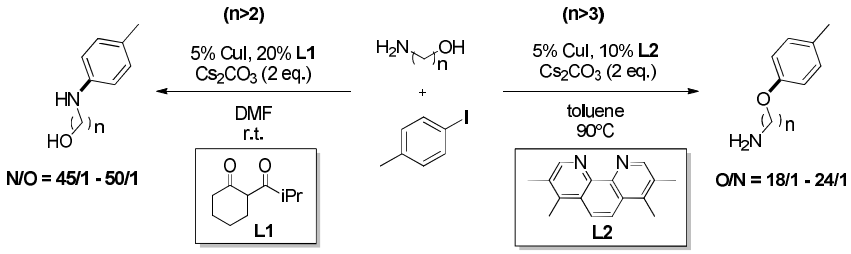
Their hypothesis was that, at high ligand concentration, the Cu source is initially coordinated by the diamine ligand (**A**, Scheme 1.19) and then the halogen atom undergoes substitution with the amide anion, furnishing the intermediate amidate complex **C**. Finally, complex **C** reacts with the aryl donor to give the coupling product. Alternatively, at low ligand concentration, the Cu atom is coordinated to two molecules of amide (**B**, a bis-amidate complex, inactive), which can still undergo substitution and formation of the intermediate **C**, but much less effectively, because of its stability. The authors found that Cu bis-amidate species exist, in the absence of the diamine ligand, as aggregated oligomers, and that the addition of the ligand gives monomeric compounds, which reacted with the aryl halide in a quantitative, fast and mild coupling (0°C, $t_{1/2}$ = 3.1 min).[106] Also, the reaction rate was suppressed with increasing amide concentration (at low ligand concentrations), thus demonstrating the inactivity of the species **B**, and the role of the ligand in preventing its formation.[106]

1.4.1 – Ligand effect on the chemoselectivity of N/O arylation

Because of the importance of the functionalised amino-alcohol motif in medicinal chemistry, the advances in Cu-catalysed arylation methods prompted the research toward the application of this catalysis on these substrates. The arylation of amino-alcohols faces the problem of selectivity between *O*- and *N*-arylation, which strongly depends on the reaction conditions and the coordinating ability of the amino-alcohol itself.

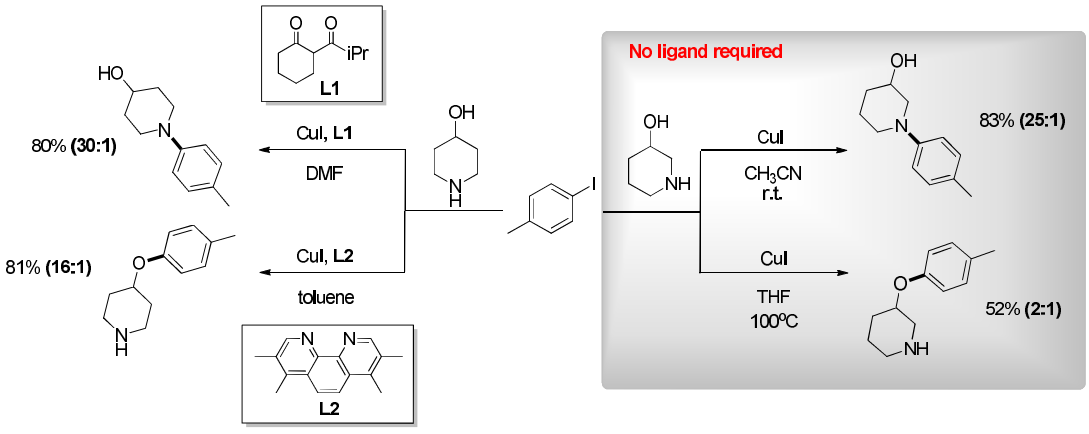
Although some reports had already been published before 2000,[56, 70] it was only later that some better understanding of the selectivity of the reaction was achieved. In 2002, Buchwald *et al.* performed the arylation of *β*-amino-alcohols of the ephedrine family without additional ligands.[108] The authors observed that changing the reaction conditions had dramatic effects on the selectivity of the arylation. Using NaOH as a base and DMSO/H_2O (or isopropanol) as solvent, the *N*-arylation was highly favoured, whereas the *O*-arylation was favoured using

Cs_2CO_3 in butyronitrile.[108] The use of non-branched amino-alcohols required the presence of an additional ligand for the reaction to be effective. In particular, performing the reaction with neocuproine (**L2**, Scheme 1.20) as a ligand in toluene, *O*-arylation was favoured, while the use of **L1** in DMF favoured the *N*-arylation (Scheme 1.20).[109] In general, acceptable selectivities were observed for longer chain amino-alcohols, while C_2 and C_3 compounds led to poorer results, supposedly due to their stronger coordinating ability. The coordination of both groups to the Cu atom make them both susceptible to arylation, thus explaining the poor selectivity.[109] It is noteworthy that similar results were obtained by Chan and co-workers in 2008 using a ligandless system: the use of DMF and CuI for the arylation of linear amino-alcohols favoured the formation of the *N*-arylated product, while toluene led only to *O*-arylated and *O,N*-diarylated products.[110]



Scheme 1.20: *Chemoselectivity in aliphatic amino-alcohols*

To investigate the selectivity in short chain substrates, researchers in Buchwald's group studied the reaction with cyclic substrates: the non chelating 4-piperidinol reacted according to the previous results (see Scheme 1.20 for conditions), whereas 3-piperidinol performed better without any additional ligand using different solvents/conditions (Scheme 1.21).[109]



Scheme 1.21: *Chemoselectivity in 3- and 4-piperidinols*

To explain the role of the ligand in the selectivity, it was proposed that the anionic ligand **L1** renders the Cu(I)-ligated species less electrophilic, so that alcohol coordination through the hydroxyl group is disfavoured, and the amine is bound, being more nucleophilic. On the other

hand, the neutral ligand **L2** could make the species more electrophilic, and able, to some extent, to coordinate to the hydroxy group, thus leading to the observed selectivity (Figure 1.4).[109]

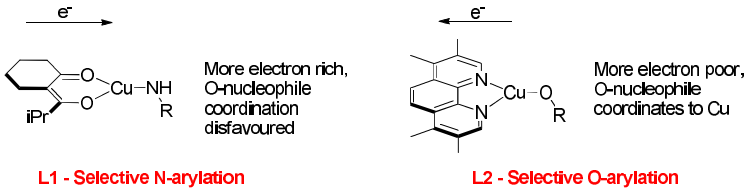
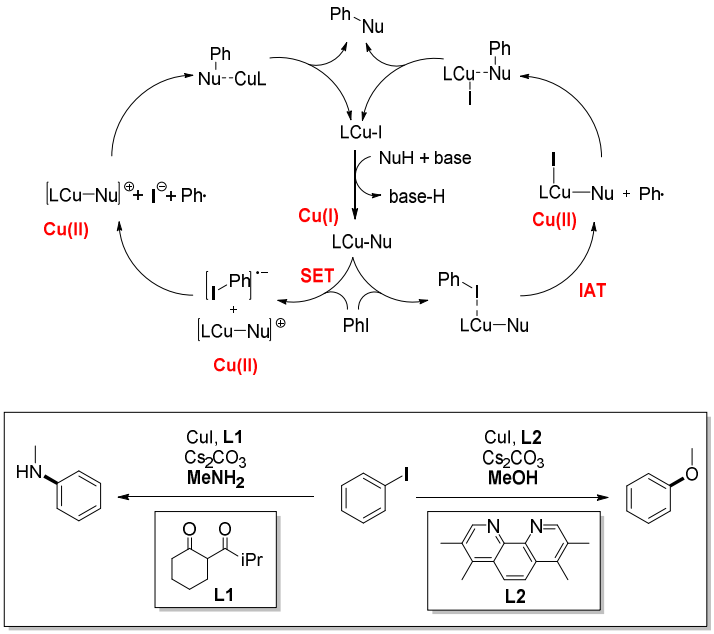


Figure 1.4: *Rationale for the observed selectivity with **L1** and **L2***

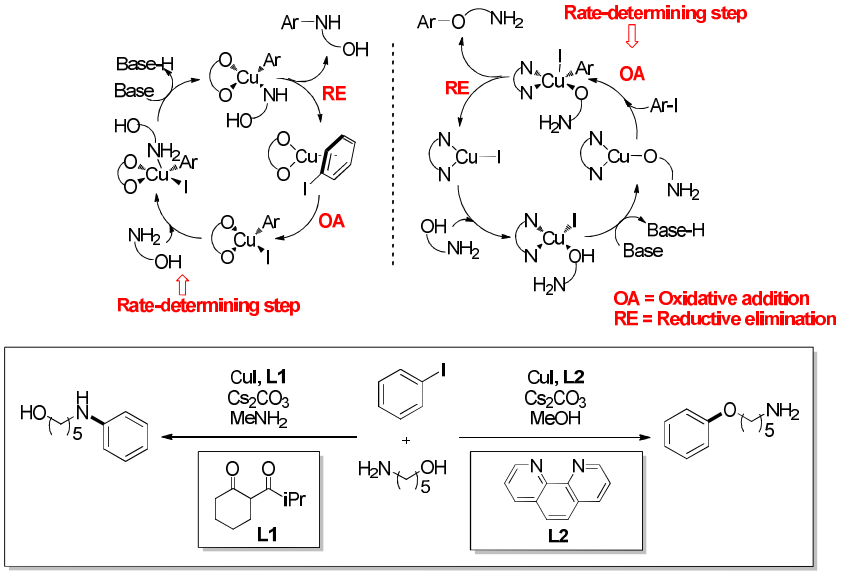
A few years later, Buchwald and co-workers reported a computational study to explain the selectivity they observed with the two ligands (see Scheme 1.20). They calculated that such selectivity could not arise during the coordination of the nucleophile to the Cu atom, because *O*-coordination was always energetically preferred over *N*-coordination.[83] Instead, it could be explained in terms of aryl halide activation. The authors calculated that the activation energies for radical mechanisms would be much lower than those required for an oxidative addition/reductive elimination cycle.[83] Using the diketone ligand **L1**, the *N*-arylation was always favoured over *O*-arylation, and the lower energy pathway resulted an outer sphere SET mechanism. Using neocuproine (**L2**) as a ligand instead, the *O*-arylation activation energy *via* inner sphere IAT was lower than for the *N*-arylation (Scheme 1.22).[83]



Scheme 1.22: *Chemoselectivity explanation through calculations – radical mechanism*

Another computational investigation was reported by Fu to explain the selectivity observed in amino-alcohols. In this case, the calculations were undertaken using an amino-alcohol as model, which was considered a more realistic system (Scheme 1.23, notice however that the neocuproine was substituted with the less electron rich phenanthroline).[111] From their

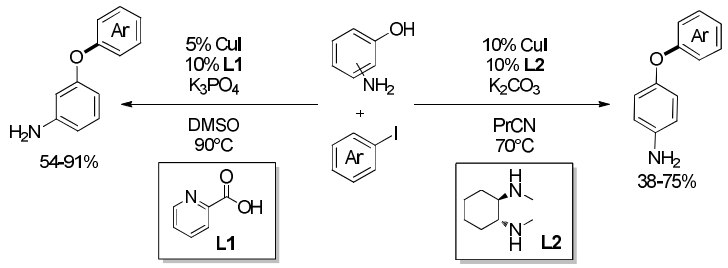
calculations, an oxidative addition/reductive elimination cycle (OA/RE) was suggested as the most favourable mechanism, and the selectivity observed experimentally was explained in terms of a different order of nucleophile coordination and oxidative addition.[111]



Scheme 1.23: *Chemoselectivity explanation through calculations – oxidative addition mechanism*

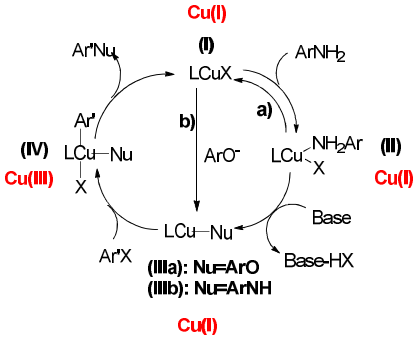
Because **L1** (Scheme 1.23) is an anionic ligand, its Cu(I) ligated species is neutral, and therefore more prone to oxidative addition with the aryl halide than the **L2**-ligated complex, which would need to bind to the nucleophile first (note that the deprotonation occurs after coordination in both cases, due to the weakness of the base used).[111] For this reason, in the **L1**-ligated species the oxidative addition appears to be relatively easy, and the slowest step is the coordination of the nucleophile to the Cu(III) complex, while in the **L2**-ligated species the oxidative addition is the rate determining step. Because of the energy-requiring coordination of the nucleophile to the Cu atom in the **L1**-ligated species, the amino group (more nucleophilic) coordinates selectively, and *N*-arylation is obtained. The **L2**-species coordinates preferentially to the hydroxy group due to its higher acidity, which results in higher selectivity for the *O*-arylation (Scheme 1.23).[111]

In 2009 Buchwald's group investigated the selectivity on aminophenols, developing conditions which led to an almost complete selectivity for the *O*-arylated product in 3-aminophenols.[112] The reaction with analogous 4-aminophenols, however, appeared to be more problematic, leading to lower selectivities and yields, and being more sensitive to steric hindrance in the substrates (Scheme 1.24).[112]



Scheme 1.24: *O-selectivity on aminophenols*

The authors were unable to obtain any *O*-arylated product when using 2-aminophenols as substrates, either in ligand free conditions and with added ligands, and only *N*-arylated or *N,N*-diarylated products were observed.[112] For these compounds, with both groups bound at the same time to the Cu atom, the arylation would take place preferentially to the more nucleophilic amino group.[112] Despite the preference for *N*-arylation in these coordinating substrates, in a competition study using one equivalent of aniline and one of phenol together, only the coupled product for the latter was observed in most cases, and only electron-poor anilines predominated over phenols.[112] On the basis of these results they discussed the possibility of a catalytic cycle where the deprotonation step plays a very important role (Scheme 1.25).



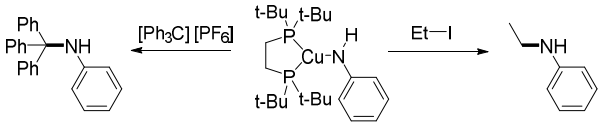
Scheme 1.25: *Deprotonation as selectivity-inducing step*

The amino group, being more nucleophilic, binds to the Cu before deprotonation (path **a**), while the more acidic phenolic group would be deprotonated at the beginning of the reaction, and would bind to the Cu in its anionic form, faster than the amine (path **b**). Depending on the nucleophilicity of the neutral amine and the deprotonation rate, a competition between the two complexes **IIIa** and **IIIb** exists, and the observed selectivity depends on their relative rates of formation and those for the following oxidative addition. When electron-poor amines are involved, though, being more acidic, these can be deprotonated before coordination and proceed through path **b**, thus being more competitive in the reaction.[112]

1.5 – Cu(I) complexes in Ullmann couplings

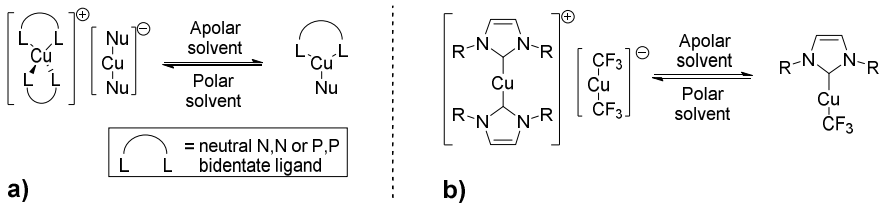
The idea of using well defined complexes as catalysts for Ullmann-type reactions was not new,[88-90, 98, 100, 104, 113-115] but complexes Cu(I)/ligand/nucleophile in a 1/1/1 ratio such as those

proposed by Buchwald (Scheme 19),[106] had not been investigated in Ullmann-type couplings. A notable early report had been published in 2003 by Gunnoe *et al.* about the synthesis of a highly air sensitive trigonal planar diphosphine-anilido Cu(I) complex and its use as coupling partner in a fast reaction with a stable carbocationic moiety or with alkyl halides, leading to the corresponding C-N coupling product (Scheme 1.26).[116]



Scheme 1.26: *Amination of Csp^3 electrophiles with a Cu(I)-amido complex*

In 2008, using a series of different neutral ligands and amides/imides as nucleophiles, Hartwig and co-workers isolated two different classes of compounds, one ionic and one neutral.[78] Through NMR and conductivity studies the authors observed that for each ligand-nucleophile system, these two forms were in equilibrium with each other, and the predominant one in solution strongly depended on the solvent polarity (Scheme 1.27a).[78] The same behaviour was observed for phenoxide complexes.[79] Analogously, Vicic and co-workers reported a similar equilibrium using carbene ligands for the Cu-catalysed trifluoromethylation of aryl halides (Scheme 1.27b),[117, 118] that in the meantime had started to be investigated in Ullmann reactions.[119-121] Some of the complexes isolated by Hartwig and Vicic are reported in Figure 1.5.



Scheme 1.27: *Equilibrium between neutral and ionic Cu(I) species*

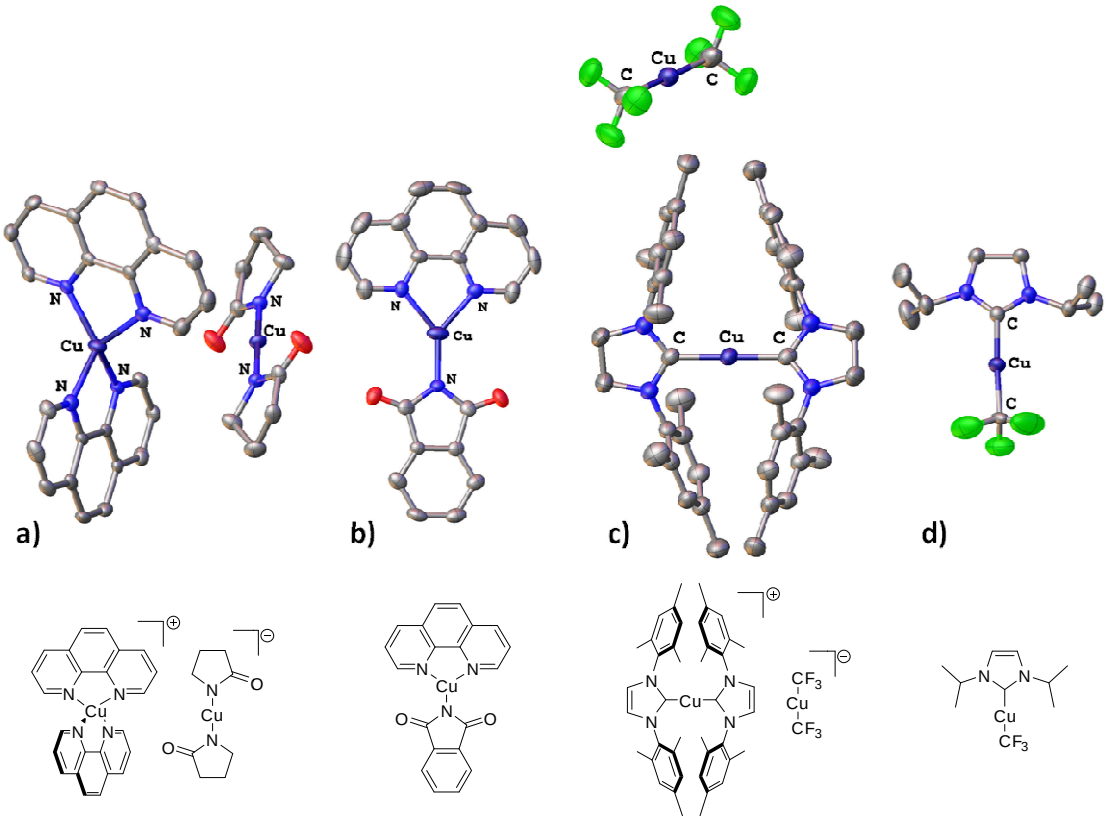


Figure 1.5: *Ionic and neutral Cu(I) complexes with bidentate N,N ligands (Hartwig, a and b)*[78] *and with carbenes (Vicic, c and d)*[117, 118]

When diphenylamines were used as nucleophiles, the same influence of the solvent in stabilising different forms of the complex was not observed, and the complex obtained remained in the ionic form both in very polar and less polar solvents.[77] When, instead of amines, their potassium or lithium salts were used in the formation of complexes, a completely different species was obtained, an ionic complex composed of a bis-amide Cu(I) anion, and a ligated K or Li cation (Figure 1.6). Whereas these complexes were active in catalytic arylation reactions, similar complexes without added ligands were reported to be much less effective.[77] The same complex with a ligated sodium cation was obtained in Shyu's group in 2011.[122]

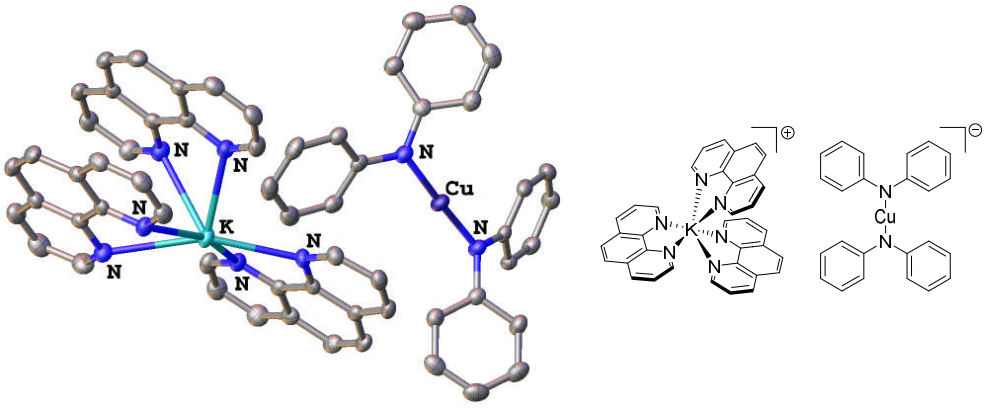


Figure 1.6: *Cu(I)-amido ionic complex from* $KNPh_2$[77]

Neutral complexes were obtained using sulphur nucleophiles, in both a dimeric[80] and a monomeric[123] form (Figure 1.7). Interestingly, conductivity studies on the dimeric thiolate complex in Figure 1.7a did not reveal any solvent dependent equilibria between neutral and ionic species,[80] contrarily to what observed for phenoxide and amide ligands (Scheme 1.27). studies on the Again, these complexes were very reactive in the coupling with aryl donors.

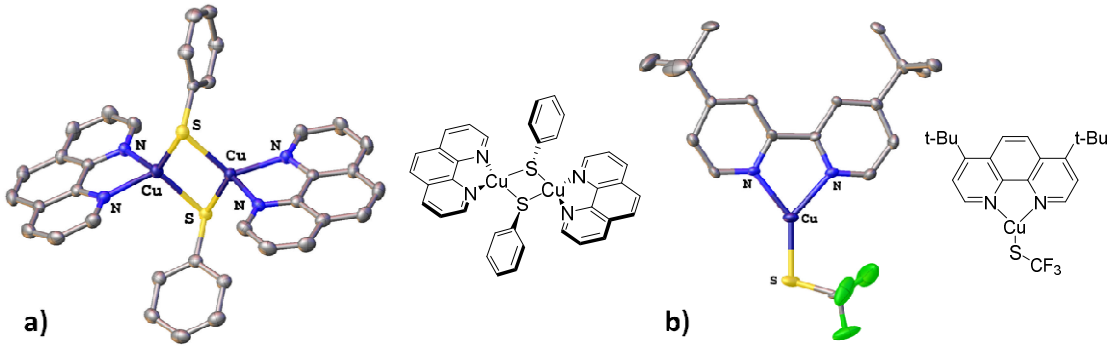
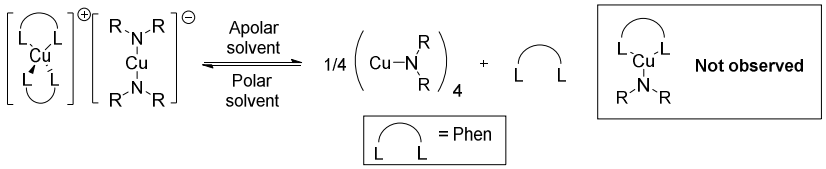


Figure 1.7: *Dimeric and monomeric complexes with sulphur nucleophiles*[80, 123]

Similar monomeric and dimeric complexes were obtained for Cu(I)-trifluoromethylselenates,[124] while similar synthetic procedures using trifluoroethoxides led to a $[Cu(ligand)_2](OCH_2CF_3)$ complex, where the nucleophile is a simple counterion, non-coordinated to the metal centre.[125]

The existence of an ionic complex for thiophenols, analogous to the complex reported in Figure 1.5*a*, has been suggested, on the basis of *in-situ* ESI-MS studies, by Shyu in 2011.[126] Through ESI-MS, Shyu's group also confirmed the existence in solution of potassium/sodium-phenanthroline complexes analogous to that reported in Figure 1.5, which were observed during the arylation of thiols and anilines.[122, 126] Based on the species observed during the reaction, Shyu proposed that cuprate species such as $[Cu(SAr)_2]^-$ or $[Cu(NHAr)_2]^-$ play a central role in the catalytic reaction, and the counter cation notably influences the yield. It is interesting to note this is similar to the theory proposed by Buchwald in 1997 to explain the importance of Cs^+ as counter cation in the stabilisation of Cu(I) intermediates (Scheme 1.16b).[86] On the other hand, this is in contrast with what is showed in Scheme 1.19, where the diamidate complex is actually considered an inactive species.[106]

A different equilibrium than the one in Scheme 1.27 was recently observed by Davies and co-workers, during an investigation on the use of polynuclear Cu(I)-amide complexes in the coupling with aryl halides.[127] Upon addition of phenanthroline to the Cu(I)-amide complexes in an apolar solvent, the neutral 1/1/1 ligand/Cu/nucleophile complex was not observed, while in a polar solvent an ionic complex analogous to Hartwig's and Vicic's could be identified (Scheme 1.28). The lack of reactivity of these polynuclear species upon addition of ligand in apolar solvents again somewhat disagree with the oligomer-breaking role of the ligand postulated by Buchwald (Scheme 1.19).

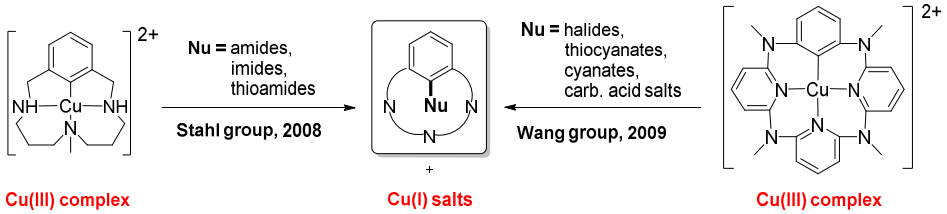


Scheme 1.28: *Equilibrium observed with tetrameric Cu(I)-amide species*

All these equilibria demonstrate at least two interesting points: i) the possibility of different active/resting species in different solvents, and thus different overall mechanisms for the same reaction, and; ii) the possible role of the inorganic base in furnishing coordinated counter ions which is too often not accounted for.

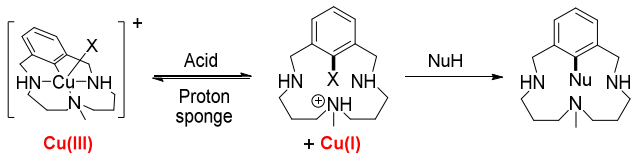
1.6 – Cu(III) complexes in Ullmann couplings

In 2008 Stahl and co-workers reported for the first time the use of Cu(III) organo-macrocyclic complexes for Ullmann type couplings in particular to the arylation of amides.[128] This report was soon followed by another from Wang's group, about the use of a different Cu(III) species for the coupling of different nucleophiles (Scheme 1.29).[129]



Scheme 1.29: *Use of Cu(III) complexes in cross-couplings*

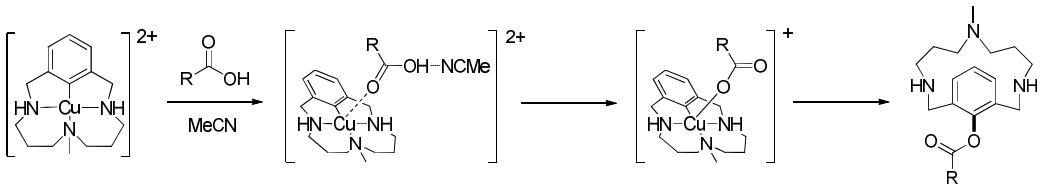
Stahl and Ribas later reported the feasibility (under acidic conditions) of a reductive elimination reaction from penta-coordinated Cu(III) complexes to furnish the coupling product (Nu = halogen) and Cu(I) salts. This reaction could be reversed with the addition of a base to the solution, reforming the initial Cu(III) species. (Scheme 1.30).[130, 131] After the reductive elimination step, the addition of a nucleophile furnished the substituted macrocyclic ligand (Scheme 1.30).



Scheme 1.30: *Oxidative addition-reductive elimination processes in macrocyclic Cu(III) organometallic systems*

The isolation of the analogous penta-coordinate Cu(III) complexes with *N*- and *O*-nucleophiles proved difficult, but their existence was suggested by *in-situ* UV-Vis analyses.[132]

On this basis, Stahl and Ribas proposed, for the Ullmann-type coupling of several O-nucleophiles (carboxylic acids, alcohols and phenols), a mechanism analogous to that observed for halides, suggesting that the acetonitrile (used as solvent) acted as a base to deprotonate the nucleophiles (Scheme 1.31).[132]



Scheme 1.31: *Mechanism of the C-O coupling using carboxylates as nucleophiles*

To explain the different reactivity/acidity relationship observed for different classes of nucleophiles (more acidic amides and phenols reacted faster, while the trend was opposite for carboxylic acids), the authors suggested a difference in the rate determining step of the process: whereas for amides and phenols the deprotonation is a slow step (no base was added in these reactions), carboxylic acids are deprotonated more easily, and the reductive elimination is supposed to be the slowest step instead (notice however that the reductive elimination step in halogenated complexes was actually favoured in acidic conditions, Scheme 28).[132]

Stahl-Ribas system was successively applied to the coupling with different species, including S, Se and P nucleophiles,[133] and to halide exchange reactions.[134] Wang's Cu(III) system also proved affective in the coupling with many different nucleophiles, including azide,[135] alcohols,[136] alkyllithium reagents,[137, 138] and halogens.[139, 140]

1.7 – Summary

From the analysis of the literature it is clear that the mechanism of Ullmann-type reactions is still uncertain. It is probable that the mechanism actually varies depending on the substrates (some substrates tend more than others to undergo radical transformations), the ligands (neutral or anionic ligands can influence in many ways the initial Cu species in solution) and conditions, since Cu compounds are able to promote both radical and non-radical transformations. The (now) generally accepted mechanism involves an oxidative addition/reductive elimination cycle after coordination of the nucleophile to the copper centre. This is because Cu(III) intermediates are not very stable, and an increased electron density on the Cu atom would increase its tendency to undergo the troublesome oxidative addition step. The opposite reaction order has also been proposed, and the deprotonation of the nucleophile can occur before or after coordination to the Cu, depending on the nucleophilicity and acidity of the nucleophile. It is noteworthy that the tri-coordinated Cu(I) species reported in Section 1.5 were only obtained with neutral ligands. Similar complexes with anionic ligands would have to be anionic, and the role of the counter-cation (and thus the inorganic base used) might be very important. These complexes are supposed to have a central role in the reaction mechanism.

It is also evident that the outcome of the reaction depends on many different variables, and their relationship has not yet been identified. Below are listed the variables mostly influencing the reaction.

- Copper amount: copper amounts are usually in the range of 5-10 mol% relative to the substrate, but as a general rule higher amounts of copper lead to higher reaction yields/rates; lower amounts are generally used in heterogeneous reactions;
- Ligand structure: bidentate ligands are the most commonly used, and the pyridine nucleus, secondary or tertiary amines, carbonyl groups and imino-groups are generally good-working ligand moieties; phosphines and sulphur-based ligands are generally not very effective;
- Ligand amount: bidentate ligands are used on average in a ratio 1/1 or 2/1 to copper, but in many cases a higher ratio leads to better results;
- Base: organic bases such as amines do not work well with Ullmann couplings, whereas inorganic bases such as potassium phosphate and carbonate and caesium carbonate are the most effective; 2 equivalents of base are generally used;
- Solvent: depending on the reaction, polar or non-polar solvents produce the best results; DMF, DMSO, dioxane and toluene are among the most used; NMP is commonly used for microwave reactions;
- Temperature: it is now usually in the range 80-120°C, but there are also examples of r.t. reactions (20-25°C);
- Aryl halide: the reactivity of the aryl halide follows the sequence: I>Br>Cl; the reactivity of aryl chlorides can be increased through strong electron withdrawing substituents, *ortho* coordinating substituents or adding a source of I^- in the reaction (halide-exchange reactions are catalysed by Cu); aryl chlorides are also more susceptible of reaction when heterogeneous catalytic systems are used (generally nanoparticles[141]);
- Nucleophile: better nucleophiles (*e.g.* with electron-donating substituents) generally give better results; C-, N-, O-, S-, or P-nucleophiles can all be coupled through Cu-catalysed arylations;
- Steric hindrance: a noticeable sensitivity is usually observed, both on the aryl halide and the nucleophile (sometimes even a methyl group *ortho* to the nucleophilic site or on the halide can dramatically reduce the yield); good tolerance to steric hindrance can sometimes be obtained on phenol nucleophiles (see Chapter 2);
- Group tolerance: potentially chelating substrates are rarely coupled under Cu catalysis conditions, or react without chemoselectivity; heterocycles where the heteroatom is close to the reactive site are also generally problematic; common electron-withdrawing or electron-donating substituents on the coupling partners are generally tolerated;

- Atmosphere: usually a nitrogen or argon atmosphere leads to better results in Cu-catalysed couplings.

Although some generalisations can be made to predict the general outcome of Ullmann-type reactions, there is still much uncertainty about the actual intermediates involved and the oxidation state of the metal during the reaction. This is the major limitation of Cu-catalysed couplings; an understanding of the effect of neutral and anionic ligands, of oxygen and moisture on the reaction is therefore needed to increase the potentially great applications of these strategies on a large industrial scale.

1.8 – References

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Chapter 2:

Applications of picolinamide ligands in Cu-catalysed C-O and C-N bond formation

2.1 – Introduction

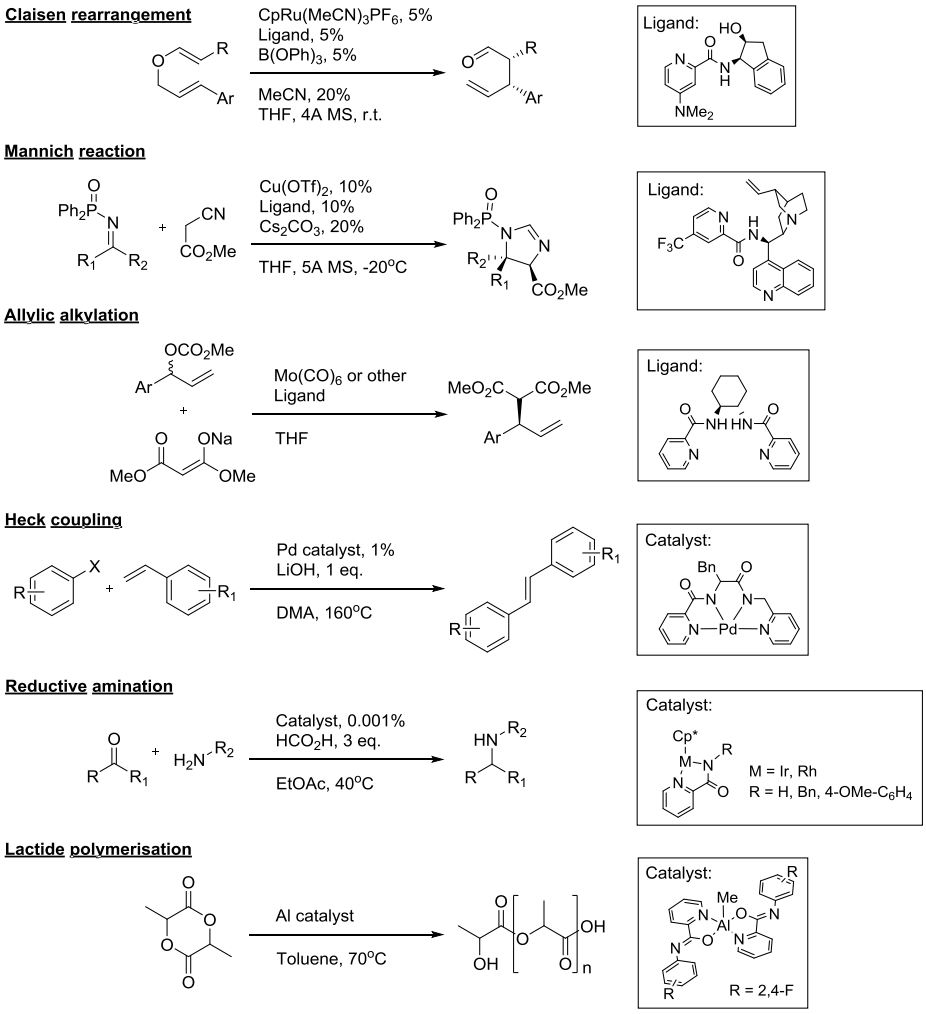
Much investigation has been performed on Cu-catalysed Ullmann type couplings, and many ligands have been used and proved effective. However, despite the fact that some families of ligands can now be considered as privileged for these types of couplings (such as *β*-diamines, *β*-diketones and phenanthroline derivatives), some trial and error screening still needs to be performed before finding the right ligand for a specific transformation. This is due to the fact that the role of the ligand in the catalysis is not totally understood in most of the cases, as discussed in the previous chapter. Structure-activity relationship studies have been undertaken only occasionally in the past 10-15 years, with Taillefer's example in 2007 being so far almost the only comparison of a range of different ligands of the same family (iminopyridine), which allowed proposing a role for the different parts of the ligand in the catalytic mechanism (see Chapter 1).[1] Symmetric ligands are most commonly employed in Ullmann-type couplings, but with asymmetric ligands more complicated effects may arise, as demonstrated by Taillefer's ligands. Asymmetric ligands are therefore interesting from a mechanistic perspective.

The design of new ligands is based on investigations of the effect of structural variations of the ligand backbone, and is a common strategy to improve the performance of transition metal catalysts,[2-4] but little effort has been put into this field for Ullmann-type couplings. For instance, more investigation in this direction is required, aiming to transfer this knowledge to different classes of ligands.

2.2 – Picolinamide ligands in transition metal catalysis

Amides of 2-picolinic acid (referred to as "picolinamides" from now on) have been known and used for a long time as ligands in different transition metal-catalysed reactions. This may be attributed to several reasons: i) the easy synthesis and handling; ii) the low cost and commercial availability of the necessary starting materials; iii) the possibility for wide structural modification; iv) the presence of different coordinating atoms, which allows different coordination modes; and v) the ubiquity of nitrogen donor ligands in transition metal catalysis. These compounds, in either bidentate, tridentate or tetradentate variants, chiral or achiral, have been used as ligands for the catalysis of various types of organic reactions. In Scheme 2.1 are reported examples of Claisen rearrangements,[5] Mannich reactions,[6, 7] allylic alkylations,[8-10] cross couplings,[11, 12] reductive amination[13] and lactide polymerisation,[14] the latter reported from our group. Among those not depicted, worth noting are Ni-catalysed Kumada-type couplings,[15] Co-

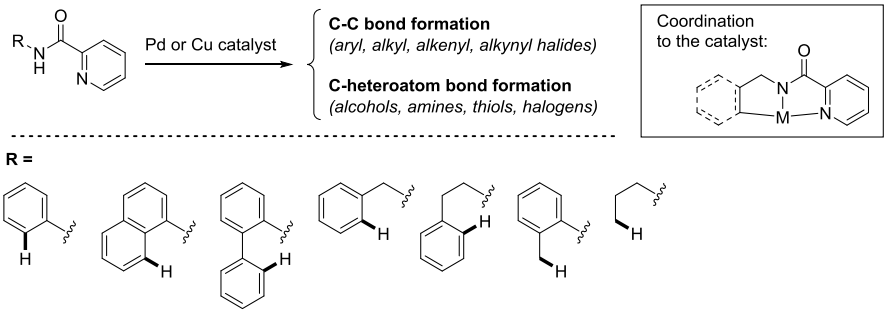
catalysed oxidation reactions,[16] and Co-Zn-catalysed Beckmann rearrangements,[17] employing bidentate or tridentate picolinamide ligands. More recently, while the research reported in this thesis was undertaken, picolinamide ligands were also utilised for the Cu-catalysed synthesis of biphenyls.[18]



Scheme 2.1: *Examples of metal-catalysed processes using picolinamide ligands*[5-14]

Being an excellent coordinating moiety, picolinamide derivatives are also commonly used as substrates in C-H activation processes, where the picolinamide moiety acts as a directing group, allowing selective functionalisation of carbon atoms spatially close to it.[19] Using this strategy, functionalisation of an aliphatic or aromatic carbon up to the δ position (to the amidic NH group) can be achieved, generally with Pd or Cu catalysts. An important advantage of these substrates in this process is the easy cleavage of the amidic bond when the directing group is not required anymore, leaving a widely functionalisable amino group. This cleavage is not possible with other, non-removable directing groups, such as 2-pyridyl groups,[20, 21] which contributed to the diffusion of amidic groups in C-H activation processes. Different types of functionalisation can be performed using this technique: C-C bond formation can be achieved through coupling with organic halides,[22-26] while C-heteroatom bond formation occurs with the addition of

phenols, amines or other nucleophiles to the reaction.[27-31] Halogenation is also possible, using different halogen-containing salts.[32] A survey of functionalisable sites available in picolinamide-directed C-H activation are summarised in Scheme 2.2.



Scheme 2.2: *C-H bonds available to functionalisation using the picolinamide directing group*

The parent picolinic acid has been reported as an effective ligand in Cu-catalysed couplings,[33, 34] thus its derivatives, largely functionalisable, can be an effective and tunable alternative. The structural variation possible and the possibility for different coordination modes[35] (Figure 2.1) make these ligands very suitable for structure activity relationship studies.

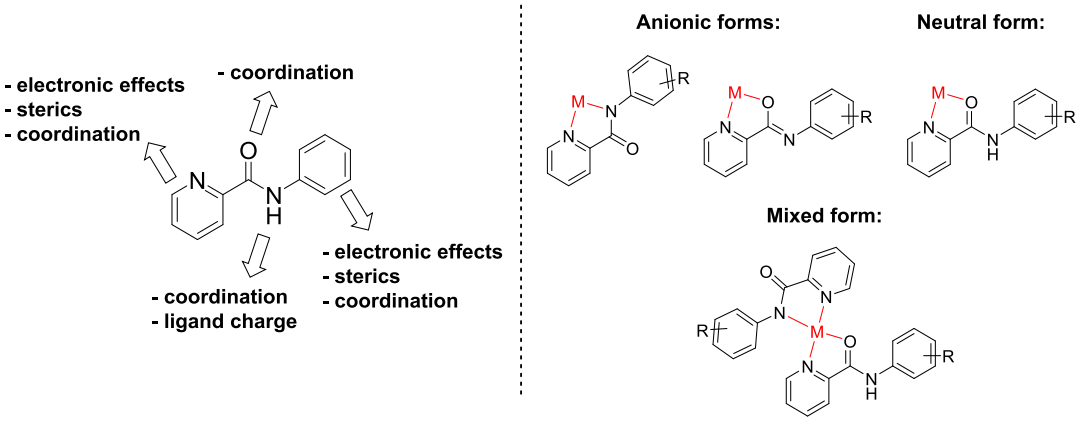


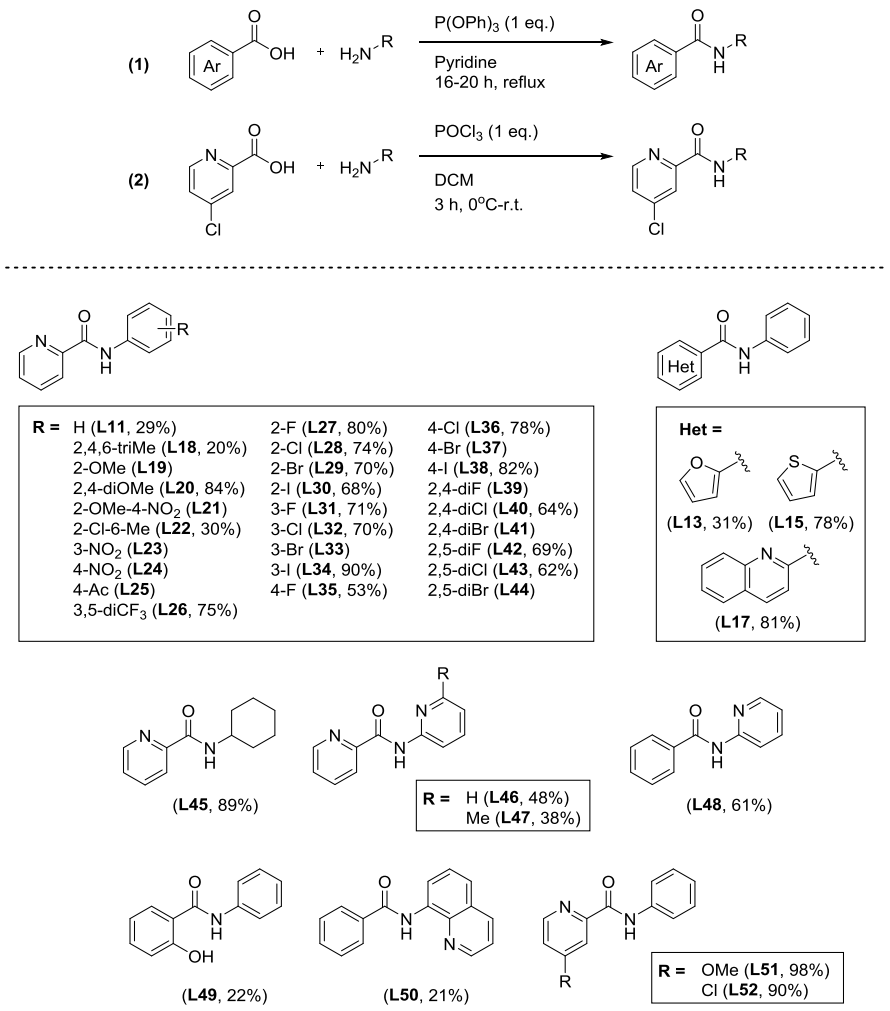
Figure 2.1: *Possible ligand modifications and coordination modes*

Furthermore, their anionic nature (upon addition of a base) is another interesting aspect of the investigation. In fact, different anionic ligands have been used in Ullmann-type couplings (mostly diketones and amino-acids), but most of the mechanistic investigations so far have been carried out using neutral ligands,[1, 36-45] which can lead to completely different intermediates and transition states in the catalytic process. The rare investigations on anionic ligands were reported by Taillefer and Jutand, who investigated the process computationally and electrochemically,[46-48] and by Lei and co-workers, using *operando* spectroscopic techniques.[49, 50] The results of these investigations suggest notable differences from the use of neutral ligands, in particular, changes in oxidation state of the copper centre are generally involved, as will be discussed more in detail in Chapter 4. The anionic nature of the picolinamide ligands is, therefore, an additional point of interest for this research. In the rest of this chapter, the synthesis of picolinamide ligands,

comparison with other ligand classes in a model reaction, and their use in copper catalysed synthesis of aryl ethers will be reported.

2.3 – Synthesis of bidentate amidic ligands

Different picolinamide ligands were synthesised to be screened in catalysis; in particular, different substituents on the *N*-phenyl ring and variation of the heterocyclic group were investigated. Related amidic ligands were also synthesised to investigate the importance of the picolinamide coordinating moiety in the catalysis; examples are *N*-phenylsalicylamide (*N*,*N*-diethylsalicylamide was reported as a successful ligand for C-N bond formation[51]) and *N*-(8-quinoline)benzamide (used in C-H functionalisation reactions[52, 53]). The synthesis of the ligands was performed *via* a modified literature procedure,[54] starting from the corresponding carboxylic acids and amines, and using triphenyl phosphite as coupling agent and pyridine as base (Scheme 2.3, eq. 1). This method proved to be easy and useful for syntheses on a multi-gram scale with good yields (the reaction was performed on a scale of 10 g of starting material in most cases), often without the requirement of chromatographic purification. The use of $POCl_3$ in DCM (Scheme 2.3, eq. 2)[55] was used as an alternative for ligand **L52**. No attempts were made to optimise the synthesis of the amidic ligands. The bidentate ligands utilised for catalytic screenings are shown in Scheme 2.3. The ligands in the scheme reported without yield were previously prepared in the group, and were only recrystallised before use. Ligands **L11-L50** were used in experiments reported in this chapter, while ligands **L51-L52**, substituted on the pyridine ring, were prepared subsequently and used for the synthesis of complexes and for mechanistic investigations, reported in Chapters 3 and 4. Ligands **L1-L10** are commercially available compounds, and are introduced in Figure 2.2.

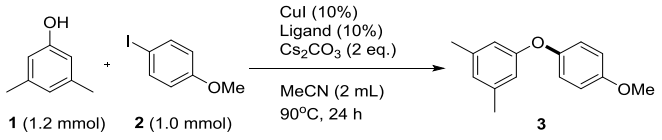


Scheme 2.3: *Bidentate amidic ligands referred to in this thesis*

2.4 – Picolinamide ligands in Cu-catalysed aryl ether synthesis

2.4.1 – Comparison with common ligands / effect of reaction conditions

The model reaction chosen to investigate the use of picolinamide ligands was the coupling between 3,5-dimethylphenol (**1**) and 4-iodoanisole (**2**), leading to aryl ether **3**. CuI, Cs_2CO_3 and acetonitrile were chosen as copper source, base and solvent on the basis of previous literature reports (Scheme 2.4). This reaction would be relatively challenging, due to the electron-donating nature of the substituent on the aryl halide involved, making it less reactive. The use of this substrate was mainly chosen to better observe the differences in efficacy of the different ligands, which would have gone unnoticed using a more reactive substrate.



Scheme 2.4: *Model reaction for the synthesis of aryl ethers*

To test the effectiveness of the parent picolinamide ligand **L11** in the catalytic reaction, this was first compared with other common bidentate ligands, including phenanthroline, bipyridine, *β*-diketones, *β*-diamines and *β*-amino-acids. Picolinic acid and 8-hydroxyquinoline were also tested in the reaction. For each of the ligands in the initial screening, different reaction conditions were studied. On the basis of previous literature reports, the effect of the reaction conditions seems to be dependent on many different factors, and reactions performed under air, under nitrogen/argon, under dry conditions or in water can all be found in the literature for Cu-catalysed couplings. Although in many cases Ullmann-type couplings are performed under air-free conditions, the reaction often proceeds well even under aerobic conditions,[56, 57] depending on the system under investigation. The importance of moisture in these reactions, considering the hygroscopicity of some of the chemicals involved, can also be suggested on the basis of previous literature reports. In particular, studies on the effect of added water to caesium bases utilised in transition metal cross-couplings showed that reaction yields were strongly dependent on this parameter.[58, 59] Thus, three different reaction conditions, Methods A, B, and C, designed to investigate the general effect of moisture and atmospheric oxygen on the catalytic performance, were employed. The three methods are described below:

- Method A: reactions in air, using shelf chemicals and non-treated solvent (aerobic, non-anhydrous);
- Method B: reactions in air using dry reaction components (aerobic, anhydrous);
- Method C: reactions under a nitrogen atmosphere, using anhydrous solvent and dry chemicals (anaerobic, anhydrous).

The results of the preliminary screening are reported in Figure 2.2.

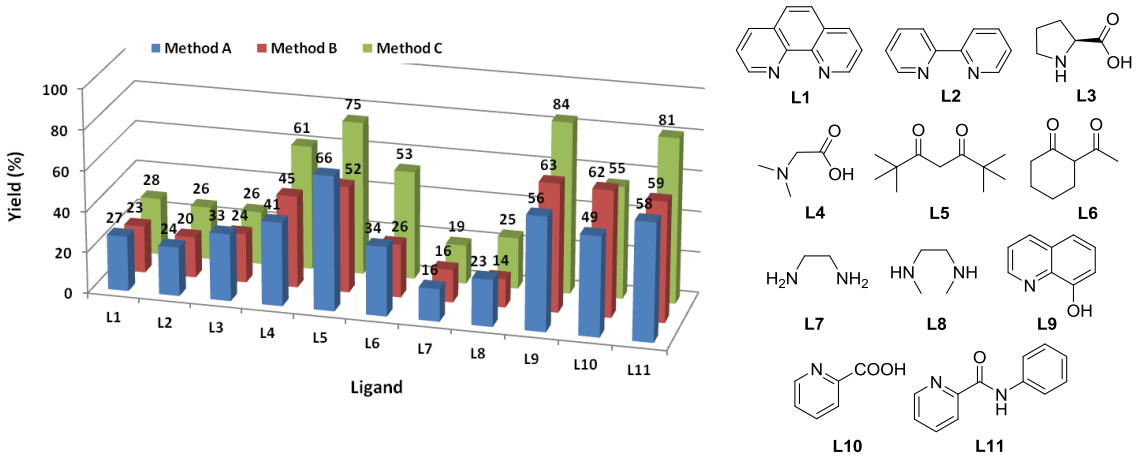


Figure 2.2: *Comparison of picolinamide ligand **L11** with other common bidentate ligands (GC yields)*

As can be seen from Figure 2.2, the reaction outcome is strongly dependent on the ligand used, underlining the importance of structural factors in the ligand. Moreover, the effect of the

experimental conditions is also dependent on the ligand employed, with some of the ligands not being affected by the different conditions, and others showing considerable differences. Notably, the use of anaerobic conditions (Method C) in combination with ligands **L4-L6**, **L9** and **L11** resulted in significantly better yields of aryl ether **3** (> 10% increase), while the influence on the other ligands is insignificant. The use of dry chemicals in an aerobic environment, (Method B) did not influence considerably the reaction outcome, with a decrease or increase in yields only for **L5** and **L10** respectively. It is worth noting that a somewhat higher average amount of the side product anisole, obtained from dehalogenation of iodoanisole **2**, was obtained under anaerobic conditions, although still remaining a minor side product (a maximum of 13% yield of anisole was observed by GC with ligand **L6** with Method A). The reduction of the aryl halide to the dehalogenated product is known to be a side-reaction in Cu-catalysed arylation processes,[60] and the reduced product is observed in small amounts.

2.4.2 – Structure-activity relationships – bidentate picolinamide ligands

The parent picolinamide **L11** appears as a competitive ligand for the synthesis of aryl ether **3**, its activity in the reaction being comparable only to ligands **L5** and **L9** under the different conditions. The screening of different amidic and substituted picolinamide ligands was therefore undertaken, trying to improve the catalytic performance. To start with, the effect of different heterocyclic groups was studied. For this, *N*-phenyl-substituted 2-thiophenecarboxamide, 2-furancarboxamide and 2-quinolinecarboxamide (ligands **L13, L15** and **L17**) were tested in the reaction, together with the corresponding carboxylic acids (**L12, L14** and **L16**). The interest in the carboxylic acid ligands derives from their previous employment in Cu-catalysed couplings, for example 2-picolinic acid was reported as an effective ligand for C-O couplings by Buchwald and co-workers,[33, 34] while Cu-thiophencarboxylate for C-C couplings by Liebeskind.[61] These reactions were performed using Method A; the results are reported in Figure 2.3.

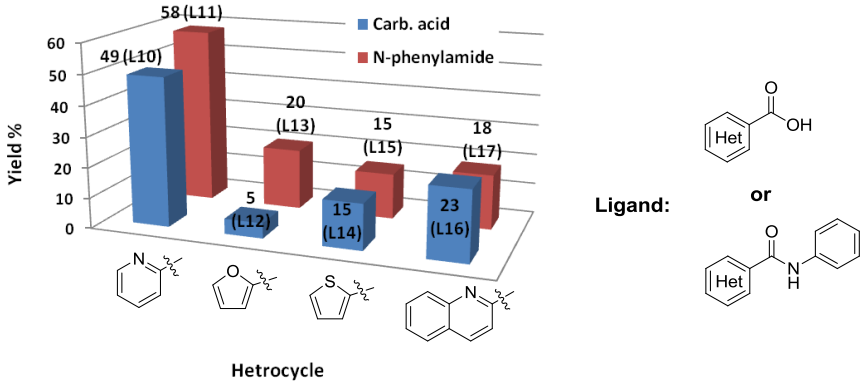


Figure 2.3: *Comparison of different heterocyclic rings in amidic ligands (GC yields)*

The poor results obtained with either the carboxylic acid or the corresponding amide for the three heterocyclic donors denotes a strong influence of the pyridyl ring in the ligand. Even the quinolinic ligands, structurally similar to the picolinic relatives, did not show any considerable improvement from their thiophene or furan analogues.

The study of the effect of the substituent on the phenyl ring of the picolinamide was then undertaken. Differently substituted ligands with electron-donating groups (EDG) and electron-withdrawing groups (EWG) were tested in the catalysis (Method A). The graph in Figure 2.4 shows how electron-donating substituents on the phenyl ring led to poorer yields than the parent ligand **L11**, while EWG-substituted ligands generally resulted in higher yields. The effect of electron-withdrawing substituents is obvious from the results of ligands **L20** and **L21**: the substitution of one of the two methoxy groups of **L20** with a nitro group in **L21** gave a 15% higher yield of **3**.

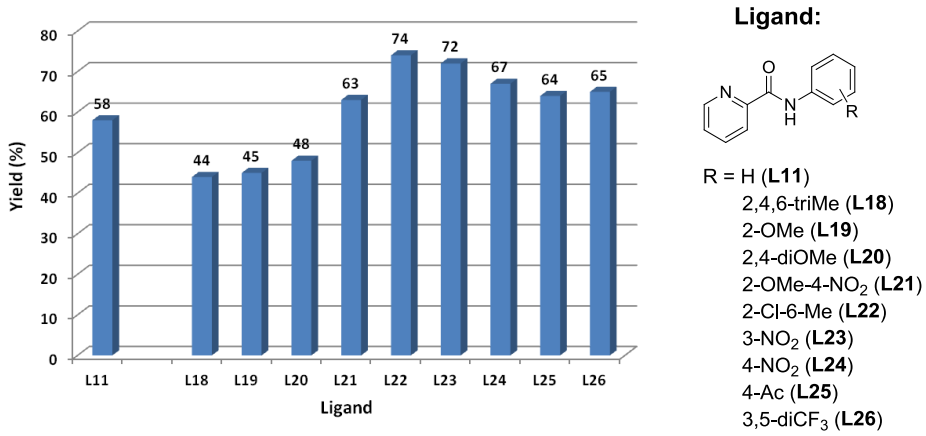


Figure 2.4: *EDG- and EWG- substituted picolinamide ligands (GC yields)*

Ligand **L22**, substituted with a methyl and a chlorine in the two *ortho* positions of the phenyl ring, led to slightly better results than the other ligands in the series. Despite the minimum difference, which can be attributed to experimental error, the presence of a methyl group, supposed to reduce the ligand efficacy, seems to be counter-balanced in this ligand by the presence of the chlorine substituent, leading to a higher yield than the unsubstituted ligand **L11**. This reasoning suggested that halogens could be effective substituents in the picolinamide ligands. This hypothesis resulted in the investigation of a range of different halogen-substituted ligands to be tested in the catalysis. The results of the catalytic screening using these ligands, ordered by substitution position, are shown in Figure 2.5.

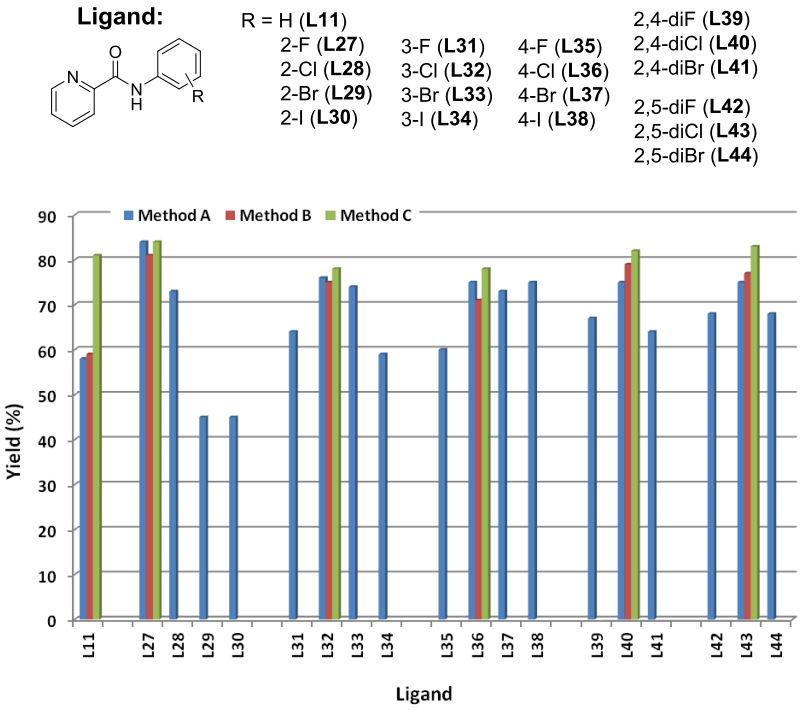
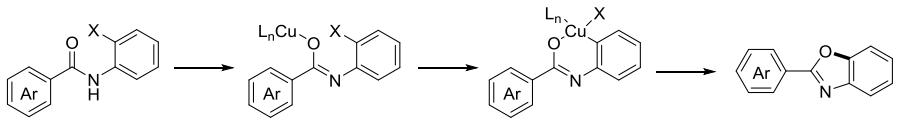


Figure 2.5: *Screening of halogenated ligands in catalysis (GC yields)*

The use of these ligands proved interesting for their efficacy in the catalytic process, and for the understanding of possible roles of the ligand in the reaction. Several of the halogenated ligands proved more effective than other EWG-substituted ligands in Figure 2.4, in particular *N*-(2-fluorophenyl)picolinamide **L27** furnished an excellent 84% yield of **3** in air. The best ligand in each series **(L27, L32, L36, L40** and **L43)** was further tested with Methods B and C for comparison. As in Figure 2.2, Method B did not considerably influence the reaction outcome, and even under anaerobic conditions (Method C) similar yields were obtained, showing a much lower sensitivity to atmospheric oxygen than the parent **L11**.

The efficacy of halogenated ligands in the catalysis strongly depends on the halogen and the substitution position, as is partially to be expected on the basis of the different electronic effects involved. However, electronic effects are not the only factors affecting their behaviour in catalysis, these ligands being themselves potential substrates for a coupling reaction. *Ortho*-substituted ligands, for example, resulted in a gradual decrease in yield of aryl ether **3** when going from fluorine to bromine and iodine substituents. This order also represents the reactivity of the halides in coupling reaction. It has been reported that similar substrates [*N*-(*o*-halophenyl)benzamides] under Cu-catalysis can undergo intramolecular coupling, leading to the formation of benzoxazoles (Scheme 2.5).[62-65] This transformation would make the picolinamide ligand unavailable for the catalytic process. However, despite this process being known and exploited since long time on different substrates, Glorius reported that this specific reaction did not take place on picolinamide substrates,[63] which is probably due to the stable bidentate coordination in which the Cu centre would be found using these compounds, and the

benzoxazole product was not noted during our experiments. Nonetheless, Cu-catalysed couplings of a different type were indeed observed at this position using these ligands in similar conditions, which may have some role in determining their scarce efficacy in the catalytic process. Discussion on these reactions is reported in Chapter 3.



Scheme 2.5: *Formation of benzoxazoles from halogenated amidic ligands*

Interestingly, the yield decreased from *ortho*- to *para*-substituted ligands with fluorine, but increases again when a second fluorine atom is inserted in the *ortho* position (**L39** and **L42**), which confirms the importance of the *ortho* fluorine atom.

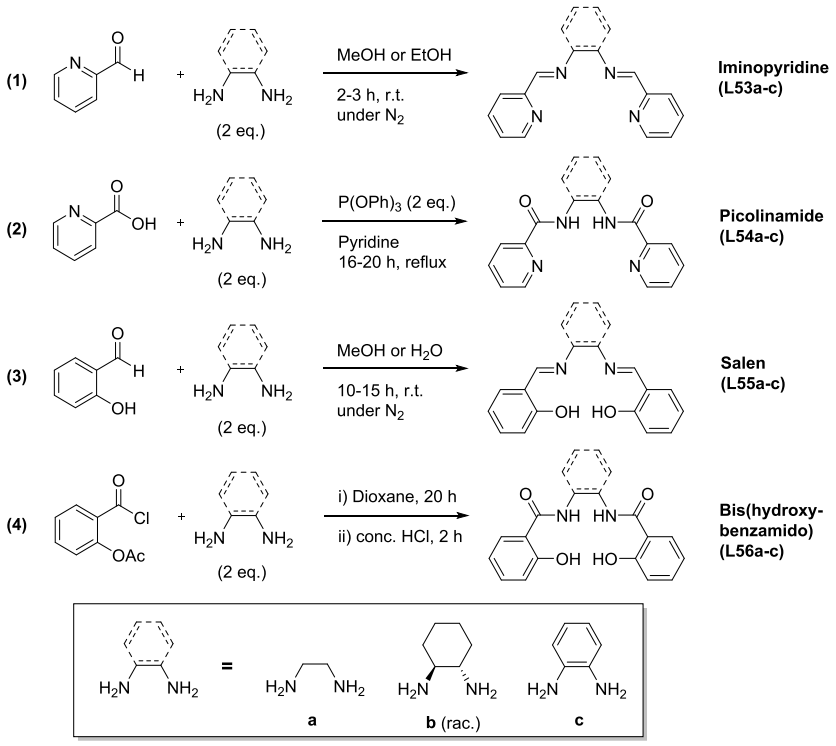
None of the other amidic ligands, structurally related to the picolinamide backbone (**L45-L50**) resulted in yields comparable to picolinamide ligands. Yields between 7% and 41% were obtained in all cases with Method A, except for **L47**, which resulted in a 66% yield of aryl ether **3** (Table 2.1).

Table 2.1: *Performance of other amidic ligands in the synthesis of aryl ether **3** (GC yields)*

Ligand	Yield of 3
L45	11%
L46	41%
L47	66%
L48	40%
L49	7%
L50	14%

2.4.3 – Structure-activity relationships – tetradentate ligands

Although bidentate ligands are the most commonly used in Ullmann-type couplings, sporadic reports on the use of tetradentate ligands are found in the literature of the past decade.[1, 66-72] In particular, the already mentioned Taillefer's iminopyridine ligands[1, 70-72] and salen type ligands[67-69] have been used successfully in several coupling reactions. Due to the good results obtained in the screening of bidentate ligands, several tetradentate ligands were also screened in the model reaction. More specifically, a comparison between tetradentate iminopyridine (**L53**), picolinamide (**L54**), salen (**L55**), and bis(hydroxyl-benzamido) (**L56**) ligands was envisaged. The first three types were synthesised by the author, while bis(hydroxy-benzamido) ligands were synthesised by Miss Jessica Lamb during a summer project in the McGowan group. These ligands were synthesised according to the procedures reported in Scheme 2.6.[54, 73-75]



Scheme 2.6: *Synthesis of tetradentate ligands*

The relative similarity of these families of ligands makes them interesting to investigate the effect of the different moieties in the reaction. In particular, the charge of the ligands can be varied from neutral to di-anionic to tetra-anionic, thus potentially stabilising completely different oxidation states of the metal centre. Both picolinamide and salen ligands are di-anionic, but differ in the position of the acidic sites in the ligand, thus potentially influencing ligand exchange properties of the corresponding Cu complexes. Bis(hydroxy-benzamido) ligands are a combination of picolinamide and salen ligands, and were studied to test the effect of the extra two negative charges on the behaviour of the catalyst. For each class of ligands, three different amines were used, from the flexible ethylenediamine to the rigid *ortho*-phenilenediamine; these changes would also influence the ligand exchange properties, as well as the stabilisation of mononuclear or dinuclear Cu species, which have been reported, for example, with neutral ligands.[44, 66]

All of the tetradentate ligands synthesised were tested in the synthesis of aryl ether **3**, under the conditions used for the bidentate ligands (*i.e.* Method A described above). The results are shown in Figure 2.6.

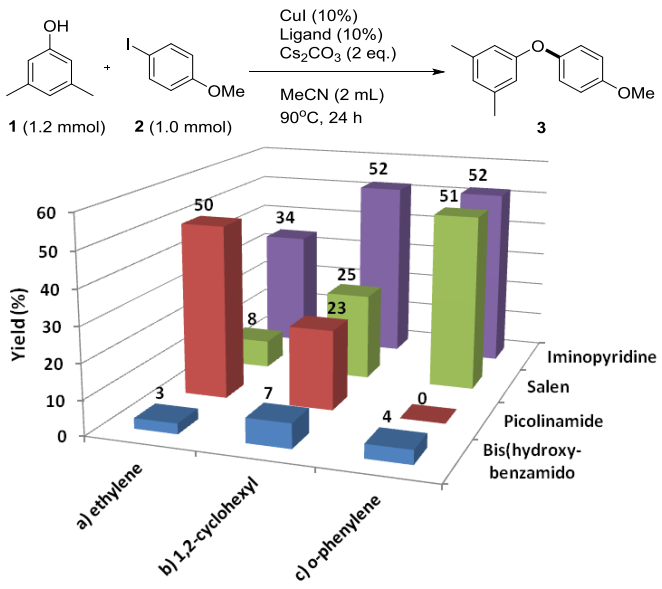


Figure 2.6: *Catalytic results with tetradentate ligands (GC yields)*

In general the tetradentate ligands tested did not lead to very high yields of aryl ether **3**, but interesting trends in the efficacy of the ligands were observed. Iminopyridine ligands **L53a-c** resulted in average yields (30-50%) with the three different amines used, and did not appear very dependent on the amine used. The di-anionic picolinamide and salen-type ligands, however, showed to be strongly dependent on it, but opposite trends were observed for the two ligand families: while the activity decreased from **L54a** to **L54c** for picolinamide ligands, for salen ligands it increases from **L55a** to **L55c**. This denotes that completely different parameters influence the ligand behaviour in the two types of ligands. For picolinamide ligands there are indications that the lability of the ligand might be crucial in determining the catalytic performance, for example the rigid **L54c** forms a very stable Cu(II) complex, which can be detected through LC-MS, contrarily to the others in the series, which undergo ligand dissociation. Moreover, the catalytic reaction performed with this ligand resulted in a light brown solution (same colour as the corresponding Cu(II) complex) that remains stable for all the reaction time, while generally colour changes are observed during the reaction (see Chapter 4). This suggests that ligand exchange might be particularly hindered in this case, while ligands **L54a** and **L54b**, more flexible, gave better yields. The same effect is probably not valid for Salen ligands **L55**. The tetra-anionic bis(hydroxy-benzamido) ligands **L56a-c** only gave very low yields, possibly because of the stability of the complexes formed with the Cu, due to the four anionic sites.

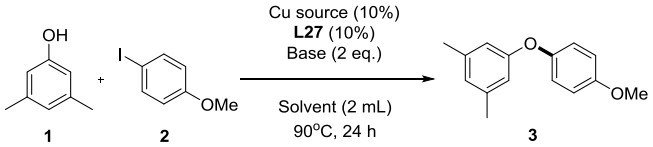
Due to the lower yields obtained with these ligands, studies about this effect were not undertaken, and bidentate ligands were prioritised for the rest of the work reported in this thesis. Initial investigations on the behaviour of these ligands in complexation with Cu sources were undertaken by the author and by Miss Jessica Lamb,[76] but were not concluded, and will not be

reported, but these data suggest that important information for further structure-activity relationship studies might be obtained from the study of these systems.

2.4.4 – Optimisation and substrate scope with ligand L27

Having identified *N*-(2-fluorophenyl)picolinamide **L27** as the best ligand among those tested for the synthesis of aryl ether **3**, a screening of solvents, bases, and copper sources was performed to optimise the process using Method A (Table 2.2).

Table 2.2: *Screening of solvents, bases and Cu sources*[a]



Entry	Solvent	Base	Cu source	Yield % [b]
1	MeCN	Cs_2CO_3	CuI	84
2	DMSO	Cs_2CO_3	CuI	43
3	DMF	Cs_2CO_3	CuI	61
4	NMP	Cs_2CO_3	CuI	48
5	Dioxane	Cs_2CO_3	CuI	59
6	Toluene	Cs_2CO_3	CuI	17
7	MeCN	K_2CO_3	CuI	32
8	MeCN	Na_2CO_3	CuI	8
9	MeCN	*t*-BuOK	CuI	22
10	MeCN	K_3PO_4	CuI	70
11	MeCN	Cs_2CO_3	Cu(0) powder	76
12	MeCN	Cs_2CO_3	CuBr	78
13	MeCN	Cs_2CO_3	CuCl	72 (70) [c]
14	MeCN	Cs_2CO_3	$CuCl_2$ [d]	81

[a] Conditions: 3,5-dimethylphenol (1.2 mmol), 4-iodoanisole (1.0 mmol), base (2.0 mmol), Cu source, (0.1 mmol), ligand **L27** (0.1 mmol), solvent (2 mL); 90°C, 24 h, under air. [b] GC yields using *p*-cymene as internal standard. [c] 4 mL of solvent were used. [d] Anhydrous.

Other polar solvents used as reaction media did not result in any improvement in the reaction outcome (Table 2.2, entries 2-5, yield 43-61%), while the use of toluene resulted in a very poor yield (entry 6, 17%). Since DMSO is a common solvent for Cu-catalysed cross couplings, ligands **L1-L11** were also tested in this solvent, looking for specific ligand-solvent interplays. Similar trends, however, were observed in acetonitrile and DMSO, and none of the ligands showed improved results in the latter solvent (Figure 2.7). The use of other bases commonly employed in cross couplings also resulted in poorer yields (entries 7-9), with only

K_3PO_4 affording a good 70% yield (entry 10). Notably, the use of other carbonates, such as K_2CO_3 and Na_2CO_3, resulted, as expected, in much poorer yields (32% and 8% respectively, entries 7-8). On the contrary, no great differences with different Cu sources were observed, and Cu(I), Cu(II) and Cu(0) all resulted in similar yields (entries 11-14). This effect is widely reported in the literature (see Chapter 1). Further optimisation experiments focused on different amounts of base and catalysts, reaction time and temperature (Table 2.3).

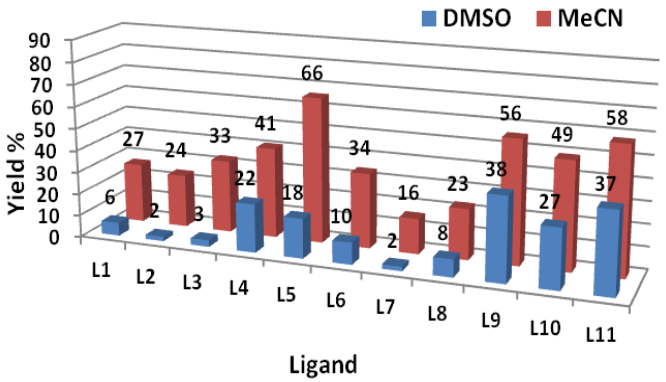
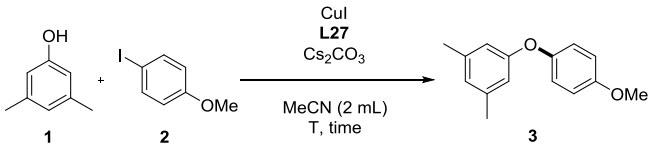


Figure 2.7: *Comparison MeCN/DMSO for ligands **L1-L11** (GC yields)*

Table 2.3: *Optimisation of the reaction for ligand **L27**[a]*



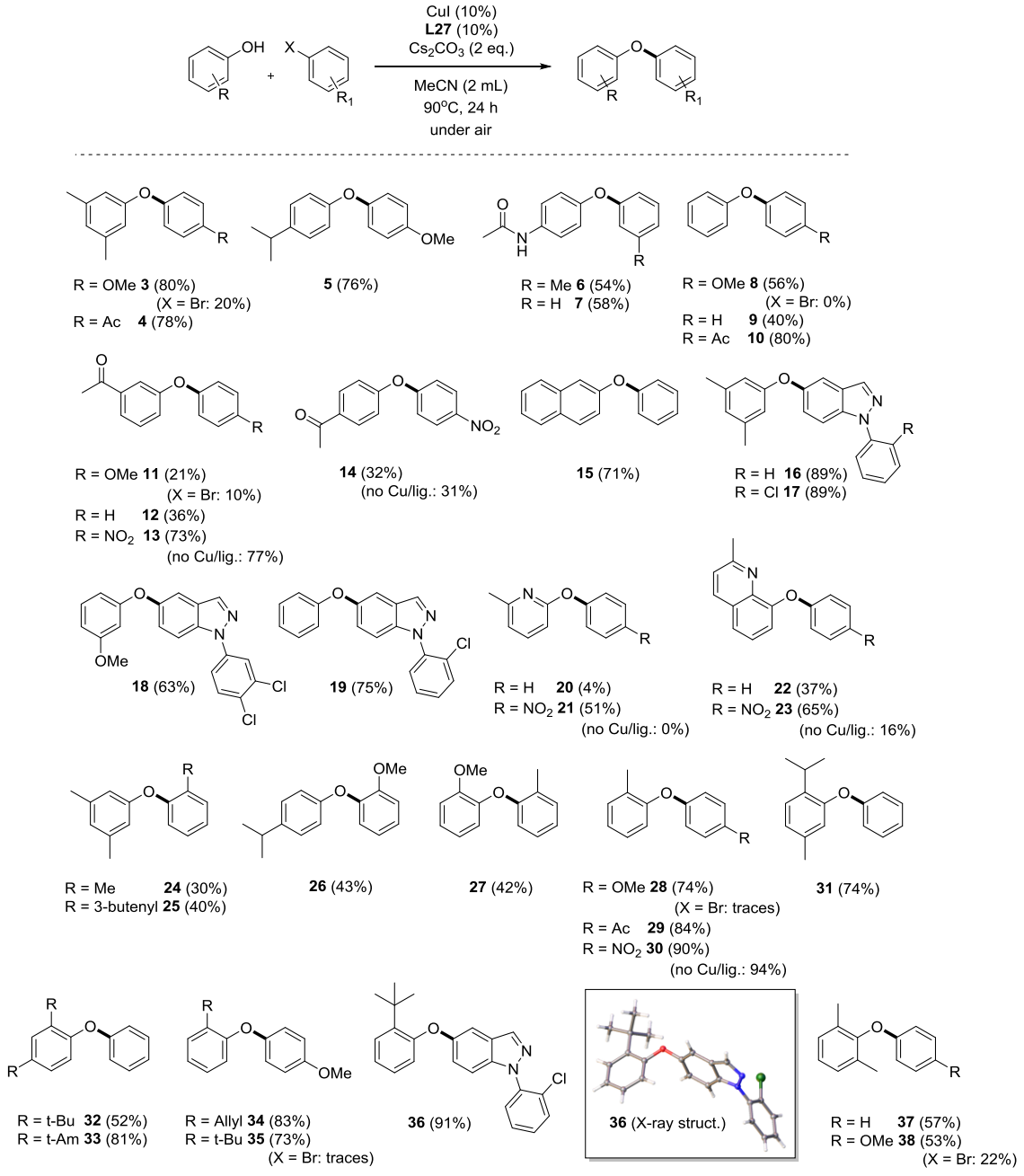
Entry	Equiv. Cs_2CO_3	CuI/L27 (mol %)	Time (h)	T (°C)	Yield % [b]
1	3.0	10/10	24	90	77
2	1.5	10/10	24	90	73
3	1.0	10/10	24	90	52
4	2.0	5/5	24	90	66
5	2.0	5/10	24	90	71
6	2.0	10/20	24	90	78
7	2.0	10/10	18	90	77
8	2.0	10/10	12	90	62
9	2.0	10/10	24	80	68

[a] Conditions: 3,5-dimethylphenol (1.2 mmol), 4-iodoanisole (1.0 mmol), Cs_2CO_3, CuI, ligand **L27**, MeCN (2 mL), under air. [b] GC yields using *p*-cymene as internal standard.

While at least two equivalents (to the aryl halide) of base were necessary for the reaction to occur with good yields, further increases did not furnish any better yields (Table 2.3, entries 1-3). Amounts of copper catalysts lower that 10% resulted in poorer yields, and the increase of the ratio CuI/ligand did not appear beneficial to the reaction (entries 4-6; for a deeper

investigation on this aspect see Chapter 4). Finally, a decrease in temperature or time also afforded lower yields (entries 7-9).

The initial conditions were therefore used to assess the substrate scope available to the C-O coupling with ligand **L27** using phenols as nucleophiles. A range of substrates proved active under these conditions (Scheme 2.7). Among standard substituted substrates, good yields were generally obtained with either EDG-substituted and EWG-substituted aryl iodides when electron-rich phenols were used (compounds **3-7**). Reducing the electron-richness of the phenol, the sensitivity on the electronic properties of the aryl iodide increased, and considerably better yields were obtained with electron-poor iodides (for example, comparison of compounds **8-10** and **11-13**).



Scheme 2.7: *Substrate scope for the synthesis of aryl ethers in MeCN (isolated yields)*

The use of heterocyclic substrates, in particular nitrogen heterocycles, is of high importance due to the recurrence of these rings in natural and biologically active compounds, and much effort has been put into the use of Cu catalysts for coupling reactions involving these substrates.[77] The coupling with novel indazolic substrates to give compounds **16**-**19** occurred with good yields, and no cross-coupling with the chlorine atoms were observed. The indazolic precursors used were tested due to their importance as pharmaceutical ingredients in glucocorticoid receptor modulators[78-81] (for the synthesis of the indazolic precursors see the experimental section, Chapter 6). In other cases the coupling with heterocyclic compounds occurs with poor results or with poor selectivity for the desired product. 2-Hydroxypyridine, for example, is a challenging substrate from this point of view, and the C-N coupling product is obtained most often in preference to the C-O product.[71, 82-84] Under our conditions, this substrate remained unreacted when the coupling with 4-iodoanisole **2** was tried, and reacted at the N site with EWG-substituted aryl halides (see Section 2.5). The use of the 6-methyl substituted analogue resulted in the formation of the C-O product, although in very small yield (**20**, 4%), unless a EWG-substituted aryl halide was used (**21**, 51%). The use of 6-substituted-2-hydroxypyridines has been previously reported to furnish the C-O coupling selectively, due to the steric hindrance close to the nitrogen site, which inhibits couplings at this position.[82, 84] In the case of 8-hydroxyquinoline, which also remained unaffected under our conditions, a few reports can be found in the literature about successful couplings at generally higher temperatures or using microwave techniques.[82, 85, 86] Since this compound is a good bidentate ligand for copper, contemporaneous coordination to the hydroxyl group and the pyridyl nucleus seems to inhibit the coupling by reducing the amount of catalyst available.[82] Again, the methyl substituent in 8-quinaldine (2-methyl-8-hydroxyquinoline) somewhat reduced this effect, allowing the coupling in milder conditions (**22**-**23**, 37% and 65% respectively).

Other generally difficult substrates are those bearing sterically hindered groups in the position *ortho* to the coupling site. In particular, intermolecular versions of these couplings are relatively rare in the literature.[34, 72, 87-92] Good results were obtained under our conditions using hindered substrates. In particular, the phenol substrates seem not to be affected at all by the steric hindrance, and groups from methyl to *tert*-amyl are well tolerated in the reaction, producing yields up to 91% for ether **36**. Only a couple of examples from Hsieh and Beller were found in the literature about the successful use of such hindered (*ortho tert*-butyl substituted) phenols.[89, 92] Even the coupling with the electron-donating 4-iodoanisole **2** led to yields of 73% to 83% (**28**, **34**-**35**). The doubly substituted 2,6-dimethylphenol is considerably less reactive, but similar yields were obtained for the coupling with iodobenzene and 4-iodoanisole (**37**-**38**, 57 and 53% respectively). Similar or even lower yields for couplings with this substrate were reported by Buchwald, Yu, Qian, and Beller,[87, 88, 90, 92] while better results were successively reported by Buchwald using 2-picolinic acid (**L10**) as ligand.[34] Considerably lower tolerance for steric hindrance on the aryl halide was observed: *ortho*-methyl or *ortho*-methoxy substituted

aryl iodides as substrates resulted in 30-43% yield of the corresponding ether (**24, 26-27**), but the use of larger groups does not seem to affect the yield further, as suggested by the use of 2-(3-butenyl)iodobenzene (**25**, 40% yield). Interestingly, sensitivity to steric hindrance on the aryl halide, but not on the phenol was also noticed by Ma and Hsieh using different catalytic systems.[89, 91] Considering the completely different results generally obtained depending on the conditions in Cu-catalysed couplings, this fact is noteworthy, in that it demonstrates similarities between different catalytic methods, and general reproducibility of the results.

Although aryl iodides are generally unreactive in catalyst-free aromatic nucleophilic substitution (S_NAr), EWG-substituted compounds can undergo substitution reaction in the absence of any catalyst, only using Cs_2CO_3 as a base, as recently reported by Taillefer.[93] This proved to be the case for some of the nitro-substituted substrates: the synthesis of ethers **13**, **14**, and **30** without the addition of CuI and ligand, afforded yields comparable to those obtained with the addition of the Cu catalysts (Scheme 2.7). In contrast, compound **21** was not obtained under Cu-free conditions, and **23** was isolated in only 16% yield, *versus* 65% with the addition of CuI/ligand, confirming the different general reactivity of these heteroaromatic substrates.

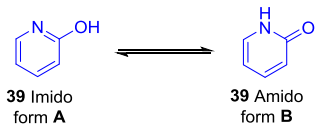
The use of aryl bromides rather than aryl iodides resulted in much lower yields for compounds **3**, **8**, **11**, **28**, **35**, and **38** in these conditions, but the fact that some product was formed even with sterically hindered phenols is encouraging.

2.5 – Coupling between 2-hydroxypyridine and 4-iodoacetophenone

As reported in the previous section, the *O*-arylation of substrates such as 2-hydroxypyridine **39** did not occur under our catalytic conditions. Due to the importance of these substrates and the difficulty in their synthesis, further attempts were made to try to shed some light on the process. The results will be briefly reported in this section.

Arylation of 2-hydroxypyridine **39** can occur either at the nitrogen or at the oxygen site. This compound can act as a bidentate ligand for copper (although the coordination depends on the presence of other ligands and substituents on the ring),[94-96] and this fact alone poses an intrinsic selectivity problem for the reaction, being both sites simultaneously available for functionalisation. Moreover, despite the two tautomers that describe this compound (Scheme 2.8), the prevalent structure in the solid state is the amido form **B**, as demonstrated by crystallographic and IR data,[97, 98] while in solution the prevalent structure depends on the solvent, the imido form **A** being prevalent in non-polar solvents, and the amido form **B** in polar ones.[98, 99] The sensitivity to the solvent used may add to selectivity issues, especially when a range of solvents can be effective for the general catalytic process.

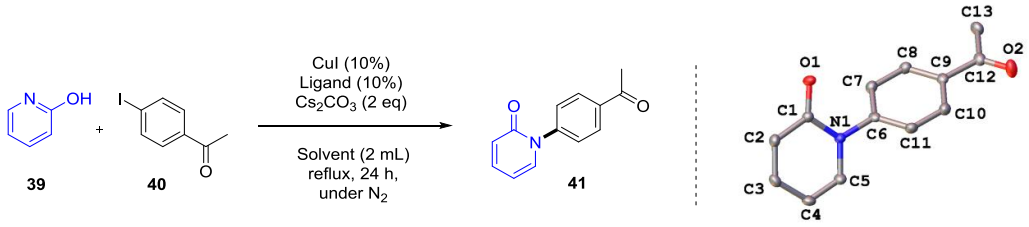
The electronic properties of the ligand may also influence the selectivity of the reaction, favouring the attack of the more nucleophilic *N*- site or the less nucleophilic *O*- site, as suggested to explain the selectivity in amino-alcohols (see Chapter 1, Figure 1.4).[100]



Scheme 2.8: *Tautomers of 2-hydroxypyridine **39***

With the effects of solvent and ligand in mind, the possibility of a specific combination ligand/solvent allowing the desired *O*-arylation could be envisaged, and a screening of solvents of different polarity and differently substituted amidic ligands was performed. Solvents of boiling points >100°C were used, to allow the use of reaction temperatures somewhat higher than in our previous experiments, possibly favouring the arylation process. Moreover, the reactions were performed under nitrogen, which was also supposed to give better results. Six solvents were chosen for the screening; in order of increasing dielectric constant: 1,4-dioxane (2.2), toluene (2.4), butyronitrile (PrCN, for its similarity to acetonitrile, 20.3), *N*-methylpyrrolidinone (NMP, 32.0), DMF (38.3) and DMSO (47.0).[101, 102] Picolinamide ligands substituted with electron-donationg to electron-withdrawing groups were selected (**L45, L20, L11, L27, L26**), together with *N*-(8-quinoline)benzamide **L50** and *N*-phenylsalicylamide **L49**.

The screening with these solvents and ligands invariably resulted in the formation of the *N*-arylated product **41**, identified by NMR and crystal structure analysis (Scheme 2.9). In Figure 2.8 are reported the results for the screening in the different solvents.



Scheme 2.9: *Synthesis and crystal structure of 1-(4-acetylphenyl)pyridin-2-one **41***

It is clear from Figures 2.8a that in solvents such as PrCN, NMP and DMF, which have an intermediate dielectric constant (between 20 and 38),[101, 102] similar yields were obtained using the different ligands, while in other solvents, with a higher or lower dielectric constant, the reaction outcome was more strongly dependent on the ligand, although no definite trends appear.

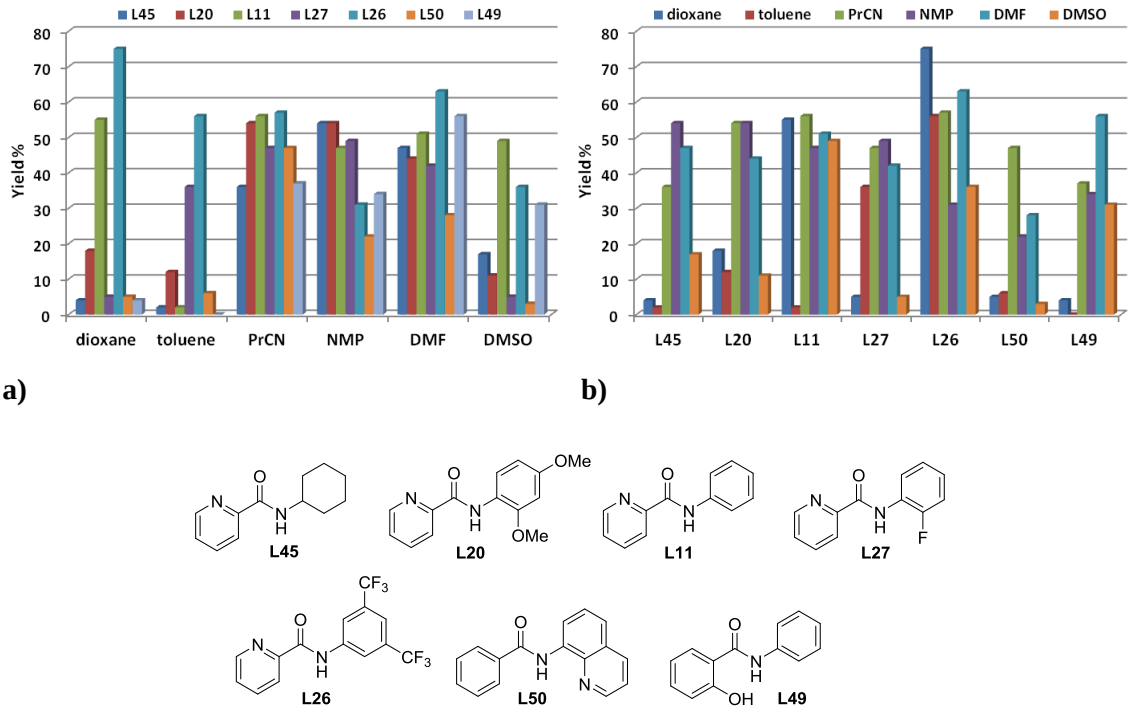


Figure 2.8: *Results for the synthesis of compound **41** according to: a) the ligand, and b) the solvent employed (GC yields; values for dielectric constants are reported in parentheses)*

2.6 – Synthesis of aryl ethers in green organic solvents

The typical reaction media employed for Cu-catalysed couplings are traditionally represented by solvents like toluene, 1,4-dioxane, MeCN, DMF, DMSO or NMP. In the last decade, investigations on the use of greener solvents has been published in many research articles, and reviews on the topic are now also available.[103, 104] For Ullmann-type couplings, however, the term "greener solvents" used above almost exclusively refers to aqueous solvents, while very few reports are available on other green media, such as alcohols[105] or ionic liquids.[106-108] Although the investigation of aqueous solvents is undoubtedly important and fashionable, other green solvents exist, sometimes even more practically important than water, which are not much investigated.

Several pharmaceutical companies have published tables of solvent data and listed them according to their chemical physical, health and safety, and energy/life-cycle assessment (LCA) properties, leading to banned, dangerous, or recommended classes of solvents for industrial processes.[109-112] The ACS Green Chemistry Institute-Pharmaceutical Roundtable (GCI-PR) has also compiled a more general list, developed collaboratively by the members of different companies.[113] Moreover, a comparison between the different solvent guides has also been published, which is helpful for research purposes.[114] Water is the top green solvent in all of the lists published, for obvious reasons, including the easier separation of products and recycling of catalysts, but this does not imply that water is necessarily the best solvent from a practical point of view. From a process point of view, the physical chemical properties of water may not be the

best,[111] and the disposal of large quantities of aqueous waste also poses problems.[115] Another problem is the low solubility of organic compounds in water, which is compensated through the use of additives in the reaction. In Cu-catalysed couplings, the use of water is often found as mixtures with other solvents, such as DMSO, and in the cases in which it is the only solvent, the use of polymers,[116] surfactants[117] or phase transfer catalysts (PTCs)[118] is often required. Finally, water is known to react with aryl halides under catalytic conditions, leading to the formation of phenols as side products.[119, 120]

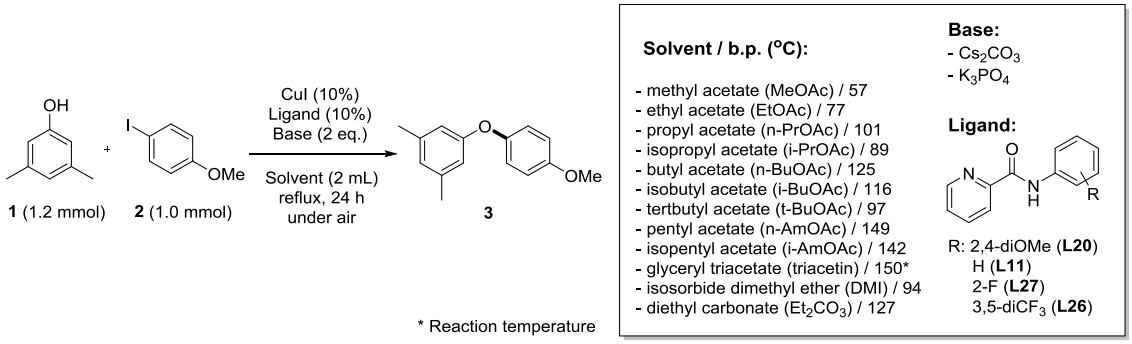
As a consequence, the use of organic solvents is still preferred for these reactions, but greener replacements of the traditional non-green solvents need to be investigated. In all of the green solvents lists, water is followed by organic solvents such as alcohols and esters, particularly acetates, both cheap and easy to obtain from natural products. The range of polarities and boiling points also make these compounds good alternatives to traditional solvents, and preferred from a process point of view. Alcohols present obvious problems in applications such as C-O cross couplings, being able to act as nucleophiles in the reaction,[121] although Buchwald reported the use of isopropanol for the coupling of aryl bromides with aliphatic amines using ethylene glycol as excess ligand.[105] Arylation of isopropanol was not mentioned, but some arylated glycol was observed, depending on the base used.[105] On the other hand, esters, although potentially able to undergo trans-esterification reactions with the phenolic nucleophile, may be valid alternatives to be tested in the catalytic process. Other solvents of interest (which are not usually mentioned in green solvent tables because less established), are those derived from other renewable sources. For example, glycerol and its derivatives (esters/ethers) have been found as good alternatives to other organic solvents in several processes,[122-126] and used in agrochemical formulations;[127] derivatives of isosorbide, another naturally-derived compound, have been used as co-solvents or carriers in many pharmaceutical and cosmetic formulations,[128, 129] thanks to their non-toxicity and favourable chemical properties; organic carbonates have also attracted much attention, due to their low cost and complete biodegradability, together with their remarkable properties as polar aprotic solvents;[130] finally, ethyl lactate is also an increasingly common solvent in several type of processes.[131]

2.6.1 – Screening of green organic solvents in the synthesis of aryl ethers

To investigate the possible use of green organic solvent in the cross-coupling process, a series of acetate solvents were selected to be tested in the catalytic synthesis or aryl ethers, as well as glycerol triacetate (triacetin), isosorbide dimethyl ether (DMI), diethyl carbonate and ethyl lactate. As for the arylation of 2-hydroxypyridine **39**, a selection of four ligands (this time only picolinamides) was used for the screening in each solvent. Furthermore, two bases were selected to expand the screening, namely Cs_2CO_3 and K_3PO_4, which resulted in the best yields for the catalysis in MeCN (see Table 2.2). The same model reaction used for the investigation in

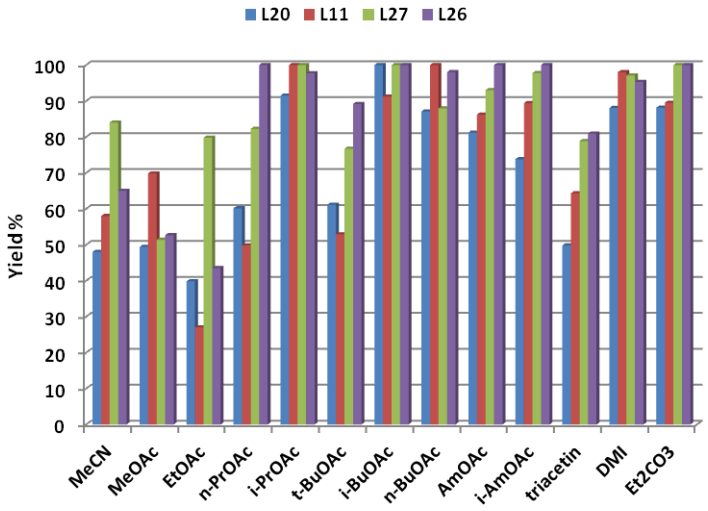
MeCN was also used for these experiments, to allow a better comparison of the results (Scheme 2.10).

All of the reactions were run under reflux conditions, apart from those in triacetin, because the boiling point (259°C) was deemed too high compared to the typical temperature range used for these reactions. Reactions in this solvent were carried out at 150°C. Although reactions in ethyl lactate were also performed, these resulted in all cases in a sticky gel-like solid (unidentified products), insoluble in different solvents, leading to difficult workup and non-reliable results. The results of the screening with the other solvents are reported in Figure 2.9. The catalytic results obtained in MeCN with Cs_2CO_3 as base are also reported in Figure 2.9a for comparison.

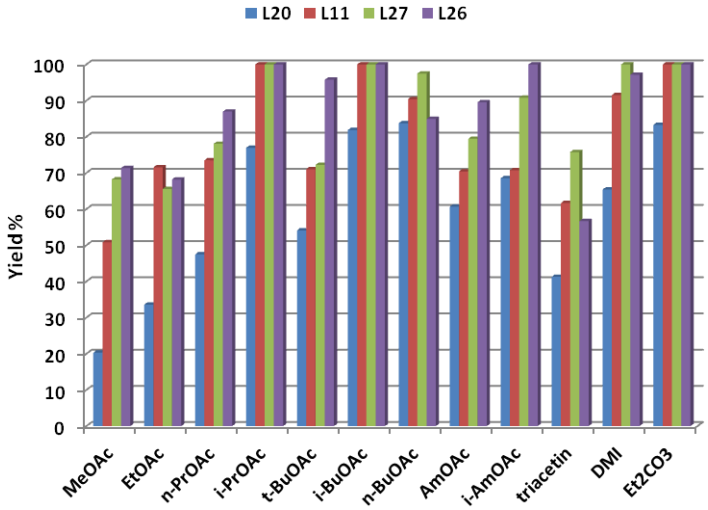


Scheme 2.10: *Screening of green organic solvents for the synthesis of aryl ether **3***

As expected, the use of Cs_2CO_3 resulted in generally better yields than K_3PO_4. As in acetonitrile, the catalytic activity increased using ligands bearing electron-withdrawing substituents on the phenyl ring. The use of ligands **L26** or **L27**, substituted with electron-withdrawing groups were generally more effective than the unsubstituted **L11**, which was in turn generally slightly better than the electron-donating **L20**. This was true using either base, but the difference between the ligands was considerably accentuated using K_3PO_4 (Figure 2.9b). In this case, ligand **L20** was always considerably less effective than the others, while with Cs_2CO_3 its efficacy was sometimes only a little inferior (Figure 2.9a). The better activity of the 2-fluoropicolinamide ligand **L27** in comparison to **L26**, observed in MeCN, is not generally observed in these solvents, and results with these two ligands are similar, or slightly better with **L26**.



a) Base: Cs_2CO_3

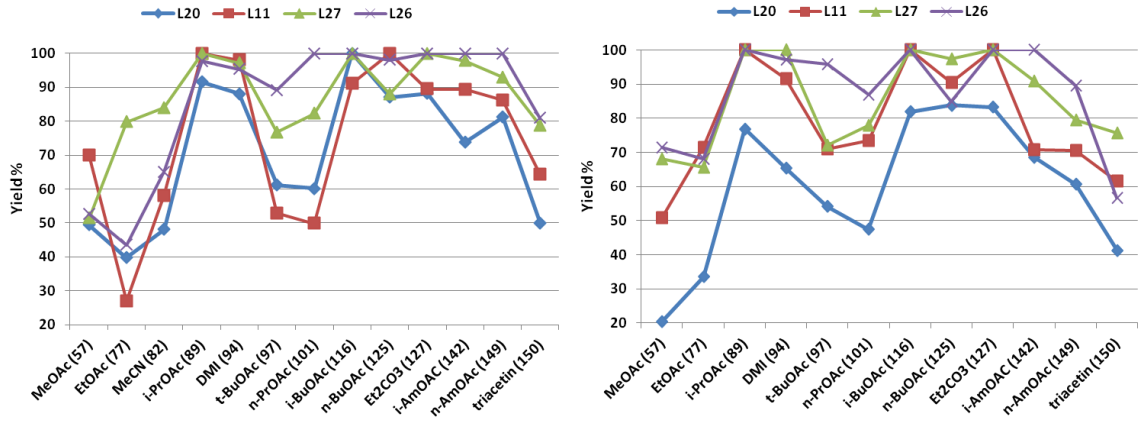


b) Base: K_3PO_4

Figure 2.9: *Catalytic results for the screenings of green solvents in the synthesis of **3** (GC yields)*

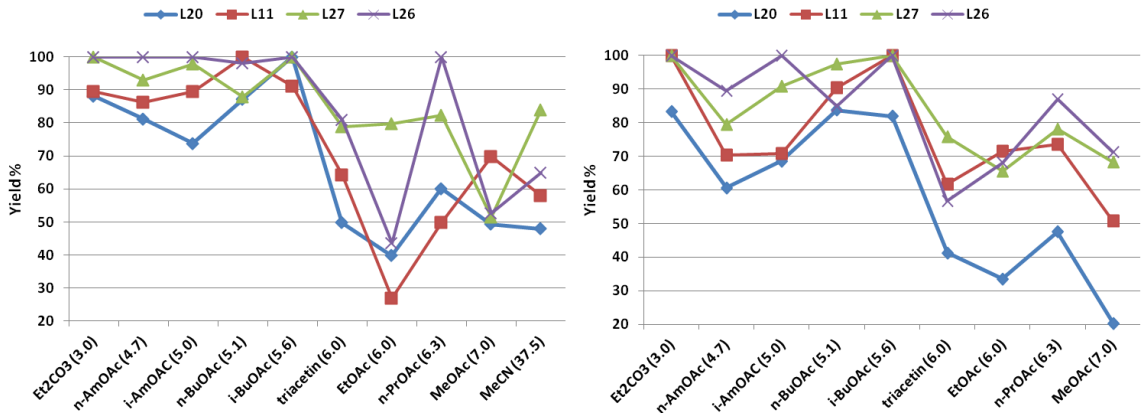
A number of the solvents tested resulted in much better results than MeCN with all the ligands. *i*-PrOAc and *i*-BuOAc proved the best in the acetate series, followed by BuOAc, AmOAc and *i*-AmOAc, although these showed a somewhat higher ligand dependence. Among the other solvents, DMI and Et_2CO_3 resulted in excellent yields, showing them to be interesting alternatives to acetates. The use of PrOAc and *t*-BuOAc, EtOAc and MeOAc, as well as triacetin, resulted instead in lower yields (Figure 2.9a).

Correlation of the product yields with parameters such as reflux temperature and dielectric constants[101, 102] for the solvents were checked as a preliminary explanation of these results (dielectric constant values could not be found in the literature for *i*-PrOAc, DMI and *t*-BuOAc). While no obvious correlation was observed with the reflux temperature of the solvents (Figure 2.10), a general decrease in yields is noted with the increase of the dielectric constant of the reaction solvent (Figure 2.11).



a) Base used: Cs_2CO_3 **b)** Base used: K_3PO_4

Figure 2.10: *Correlation of the catalytic yield of* ***3*** *with the solvent's boiling points (the value for triacetin is the reaction temperature)*

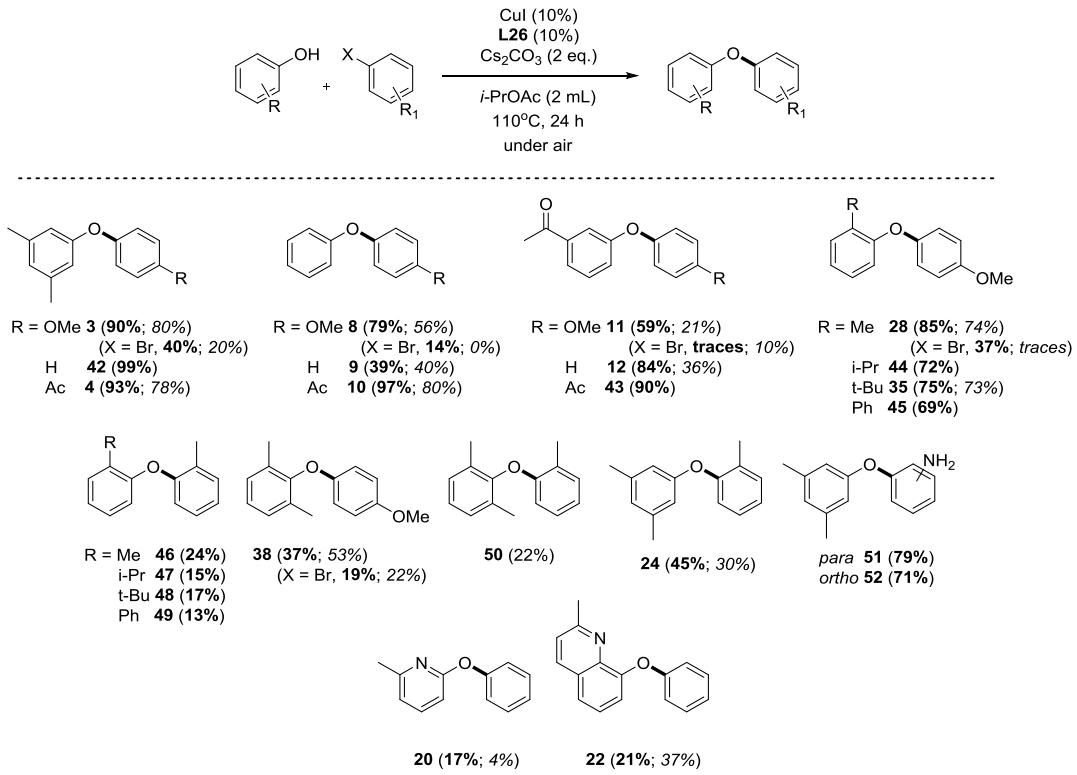


a) Base used: Cs_2CO_3 **b)** Base used: K_3PO_4

Figure 2.11: *Correlation of the catalytic yield of* ***3*** *with the solvent's dielectric constants*

2.6.2 – Substrate scope in *i*-PrOAc

A substrate screening was performed to compare the results with those obtained in MeCN. The reactions were performed using ligand **L26** and Cs_2CO_3 in *i*-PrOAc. This solvent was chosen over the other good solvents due to its lower boiling point and consequently milder conditions. The results are reported in Scheme 2.11.



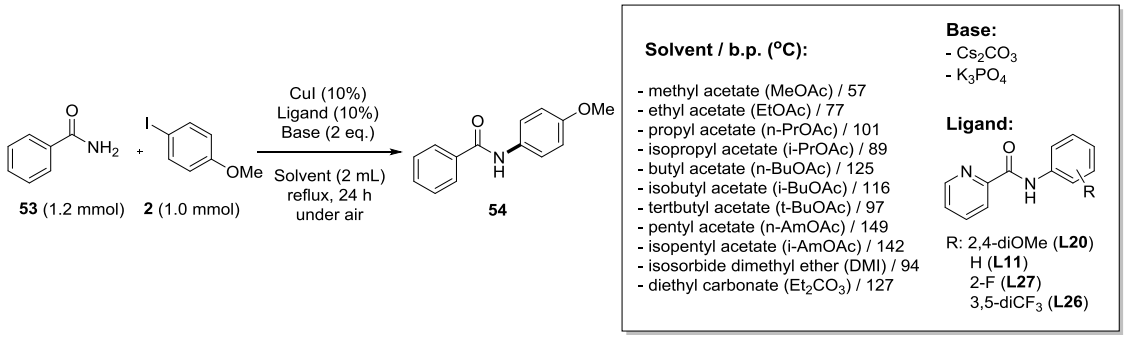
Scheme 2.11: *Substrate scope in i-PrOAc (isolated yields, values reported in italics are yields obtained in MeCN, see Scheme 2.7)*

Isolated yields obtained under these conditions with general electron-donating and electron-withdrawing groups are considerably higher than those obtained in MeCN. Compounds **3-4, 8-12, 42-43**, with EDG and EWG substituents on the phenol, were obtained in very good yields, even when electron-rich aryl halides were used. These yields are approx. 20% higher than in MeCN. Compound **9** was obtained in 39% yield, much lower than expected from the general trend. This anomalous behaviour was also observed in MeCN (Scheme 2.7). Reactions with hindered substrates were also performed. As expected from our previous study, good results were obtained using increasingly bulky substituents on the phenol moiety in the coupling with 4-iodoanisole (compounds **28, 35, 44-45**), comparable with those in MeCN. Steric hindrance on both coupling partners, however, resulted in yields of approx. 20% (compounds **46-49**). As observed before, the use of 2,6-dimethylphenol, hindered at both sides, considerably reduces the reactivity, and coupling products with 4-iodoanisole and 2-iodotoluene were obtained in 37% and 22% yield respectively (**38, 50**, the yield for **38** is lower than in MeCN). The coupling of 3,5-dimethylphenol with 2-iodotoluene furnished **24** in 45% yield, but the reaction with 4-iodoaniline or 2-iodoaniline afforded 79% and 71% yield respectively (**51-52**). No competing arylation of the amino group was observed in these cases. Unfortunately, no coupling product was detected using unsubstituted 2-, 3-, or 4-hydroxypyridines, but 17% of the 6-methyl substituted compound **20** was obtained, while arylation of 8-hydroxyquinaldine (**22**) occurred in 21% yield (in MeCN: 4% and 37% respectively). Reactions with 4-bromoanisole

resulted in max. 40% yield, considerably lower than the corresponding iodide (compounds **3, 8, 11, 28, 38**). No side products derived from the solvent were observed for these couplings.

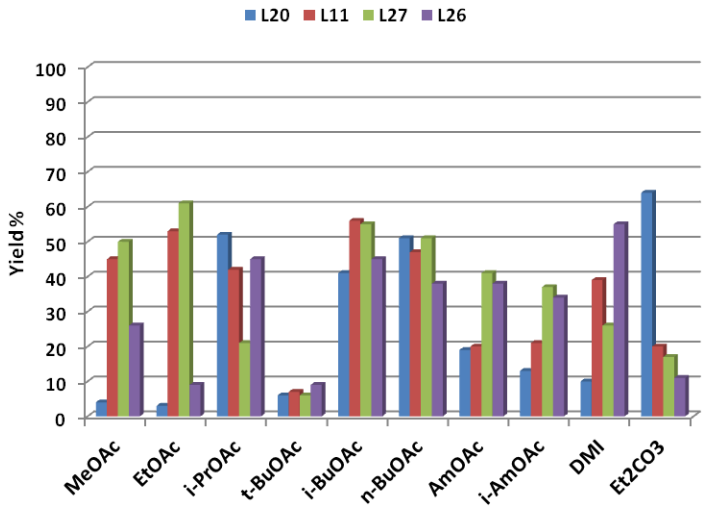
2.7 – Arylation of amides in green organic solvents

The good results obtained with these solvents in the arylation of phenols suggested their possible utilisation in the arylation of other nucleophiles through copper catalysis. Thus, the model reaction between benzamide and 4-iodoanisole was subjected to screening of the same solvents with picolinamide ligands (Scheme 2.12). Also in this case, the reactions were performed under reflux temperature.

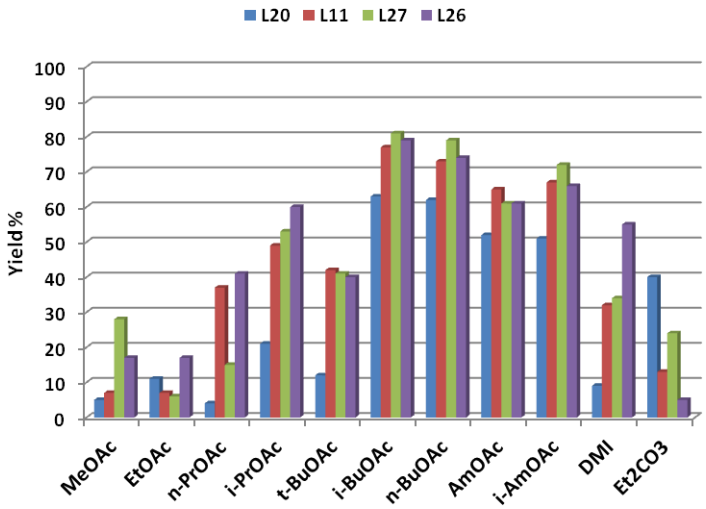


Scheme 2.12: *Screening of green organic solvents for the synthesis of amide **54***

In this case, the use of Cs_2CO_3 as base resulted in generally poor results, and no definite ligand effect could be clearly distinguished (Figure 2.12a). K_3PO_4 resulted instead in much better performances, generally cleaner reactions and more sensible ligand effect. Again, EWG-substituted ligands resulted in better yields, with **L27** slightly better than **L26** (Figure 2.12b). *n*- and *i*-Butyl and pentyl acetates resulted the best solvents among those tested, while DMI and diethyl carbonate did not prove effective solvent for this reaction. The use of triacetin resulted in the formation a dark, dense, semi-solid slurry during the reaction, leading to unreliable stirring. A similar effect was observed using *n*-PrOAc with Cs_2CO_3. Interestingly, no correlation was observed between the catalytic results and boiling point or dielectric constant[101, 102] of the solvent used (Figure 2.13).

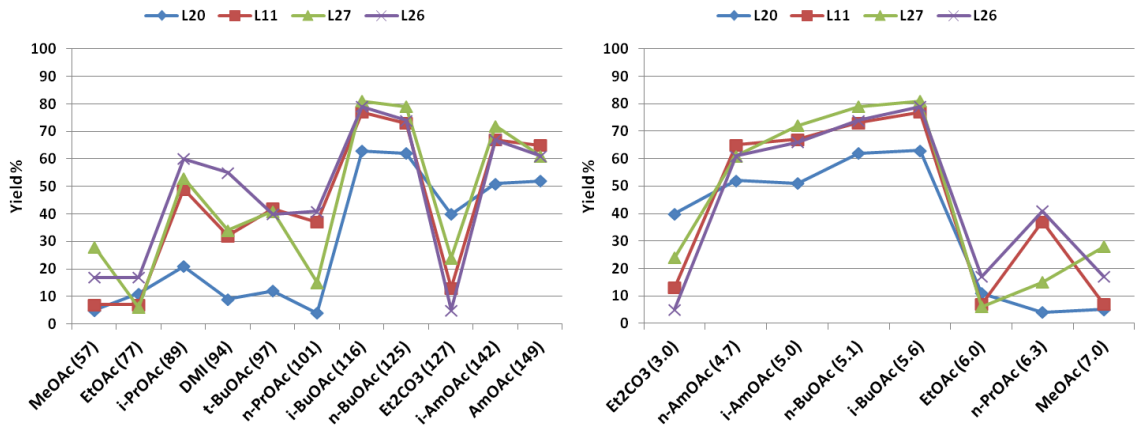


a) Base: Cs_2CO_3



b) Base: K_3PO_4

Figure 2.12: *Catalytic results for the screenings of green solvents in the synthesis of* ***54*** *(^{1}H-NMR yields)*

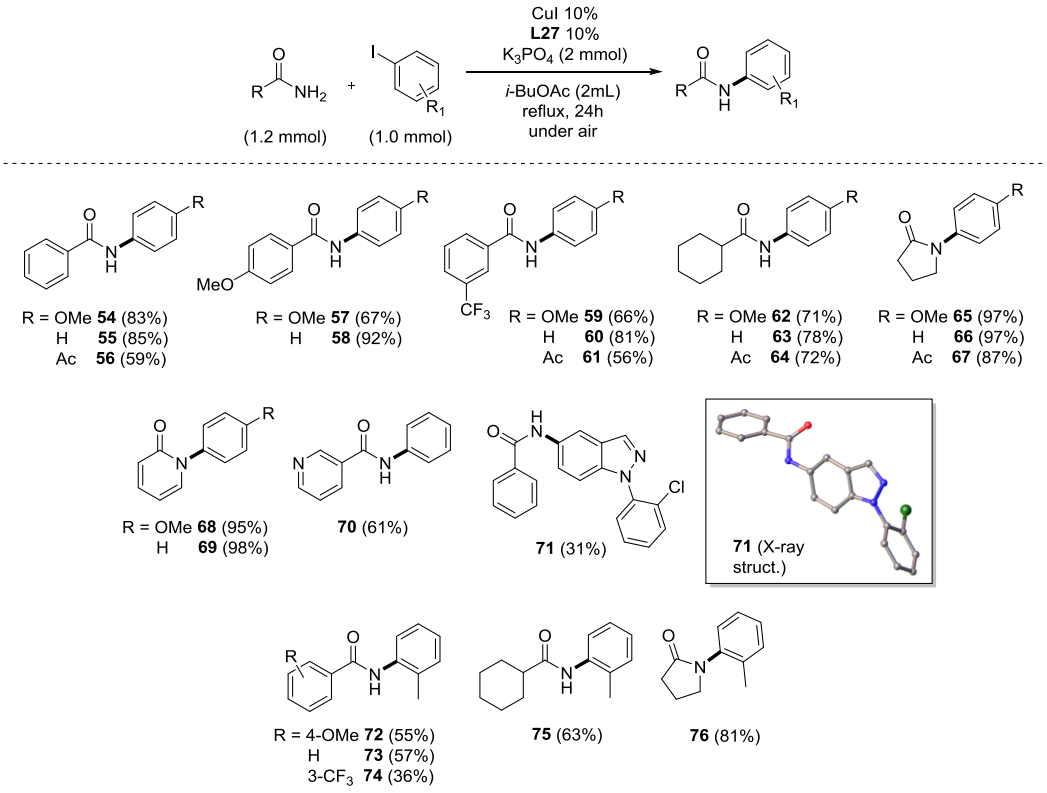


a) Correlation with boiling point

b) Correlation with dielectric constant

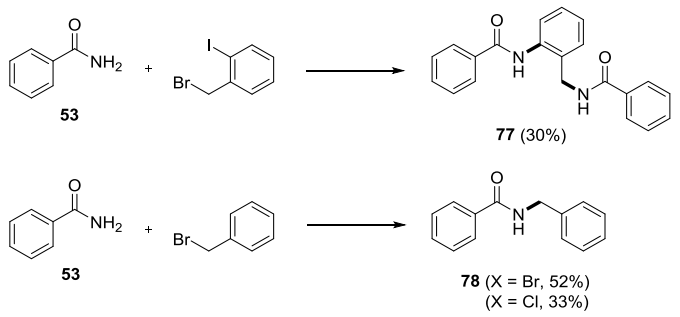
Figure 2.13: *Correlation of the catalytic yield of* ***54*** *(base = K_3PO_4) with: a) the solvent's boiling point, and b) the solvent's dielectric constant*

Iso-butyl acetate and **L27**, which furnished the best results in the screening, were chosen to investigate the substrate scope of this methodology (Scheme 2.13). A range of amides, including aromatic, aliphatic and cyclic amides were explored, resulting in good to excellent yields of the arylated products. The reaction of benzamide, 4-methoxy benzamide and 3-(trifluoromethyl)benzamide with electron-donating to electron-withdrawing aryl iodides occurred with good yields (**54-61**, 56% to 91% yields). These yields compare well with previous reports in the literature.[71, 132-134] Arylation of cyclohexanecarboxamide gave products **62-64** with yields between 71% and 78%, while cyclic amides such as 2-pyrrolidinone and 2-hydroxypyridine gave excellent results, with yields of 87-98% (**65-69**). Arylation of nicotinamide with iodobenzene afforded 61% yield of amide **70**, while compound **71** was obtained in modest yield (31%). The addition of a methyl group in ortho on the halide resulted in lower yields, especially for aromatic amides (products **72-74**, 36-57% yields). The coupling with cyclohexylcarboxamide and 2-pyrrolidinone resulted in 63% and 81% yields respectively for **75** and **76**, only about 10% lower than the corresponding unsubstituted products **63** and **66**.



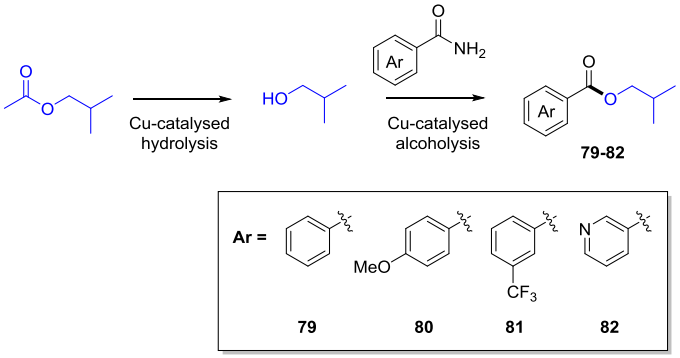
Scheme 2.13: *Substrate scope for the arylation of amides in i-BuOAc (isolated yields)*

The reaction between benzamide **53** and 2-iodobenzylbromide resulted in the formation of compound **77**, substituted at both halogenated sites, suggesting a good reactivity of bromides in these conditions (Scheme 2.14). In fact, the coupling with benzyl bromide occurred with 52% yield, and even benzyl chloride reacted with 33% yield (**78**). However, other aliphatic bromides tested in the reaction did not appear reactive.



Scheme 2.14: *Benzylation of benzamide (isolated yields)*

Contrarily to the arylation of phenols, where no side reactions were observed, the arylation of aromatic amides was accompanied by the formation of a side-product derived by the reaction of the starting amide with the solvent to form the corresponding isobutyl ester. The likely mechanism for the formation of this product involves the hydrolysis of the ester solvent first, followed by the alcoholysis of the benzamides (Scheme 2.15). This side-product was obtained from all the reactions with aromatic amides, and was isolated in few cases; the yields are reported in Table 2.4. It is noteworthy that this process did not occur with cyclohexanecarboxamide.



Scheme 2.15: *Cu-catalysed alcoholysis of benzamides*

Table 2.4: *Isolated yields for side-products* ***79-82***

Entry	Amide	Side-product (yield)
1	**54**	**79** (22%)
2	**55**	**79** (15%)
3	**56**	**79** (9%)
4	**59**	**81** (18%)
5	**60**	**81** (19%)
6	**70**	**82** (6%)
7	**72**	**80** (44%)
8	**73**	**79** (22%)

The involvement of copper catalysis in the hydrolysis of the acetate was demonstrated by the absence of any isobutanol in the commercial solvent used (^{1}H-NMR). Copper sources have been previously used to catalyse the hydrolysis of carboxylic esters.[135-138] On the other hand, the alcoholysis of amides is a thermodynamically difficult process, and is generally performed with metal catalysis. Examples of this process have been reported using Zn,[139] Sc,[140, 141] or Hf[142] triflates, or with CeO_2,[143] but no reports were found in the literature on Cu-catalysed amide alcoholysis.

2.8 – Summary

A series of picolinamides have been synthesised and tested as new ligands in the copper-catalysed synthesis of aryl ethers, and some structure activity relationships have been observed. In particular, the electronic effect of the substituents on the phenyl ring of the ligand proved crucial in determining the efficacy in catalysis. Electron-withdrawing substituents on the ligand result in higher catalytic activity, while the presence of electron-donating groups inhibits the reaction. The results reported in this chapter demonstrate that EWG-substituted picolinamides are effective ligands for the synthesis of aryl ethers, even under aerobic conditions. In particular, sterically encumbered phenols, relatively rarely tolerated substrates in these reactions, could be utilised as coupling partners with aryl iodides without any reduction in yield. Limitations on specific substrates were observed, notably sterically hindered aryl halides and heterocyclic substrates showing chelating properties. Furthermore, the use of aryl bromides as starting materials resulted in considerably poorer yields of aryl ether products. Investigations on green organic solvents as good alternatives to commonly used reaction media proved that alkyl acetate may be safely employed for the synthesis of aryl ethers and the arylation of amides. These solvents had not been investigated before in copper-catalysed processes.

2.9 – References

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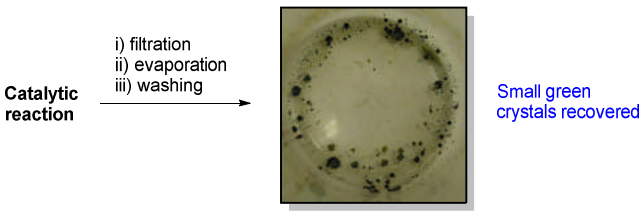
Chapter 3:

Synthesis of Cu-picolinamide complexes

3.1 – Introduction – recovery of Cu(II) species after the catalytic reaction

The catalytic synthesis of aryl ethers often proceeds, under optimised conditions, with the formation of some blue-green solid during the process (even for reactions performed under N_2), and in some cases the resultant solution, after filtration through celite, appears of a green colour. Although the colours of the solid or the solution at the end of the reaction vary considerably with the substrates and solvents used (this was observed, for example, during the screening of green solvents reported in the previous chapter), Cu(II) compounds are likely to be formed under aerobic conditions, and at least part of the colour observed is likely due to these compounds.

For the synthesis of aryl ether **3** (see Chapter 2), the solid and the solution obtained after the reaction are generally of a dark colour, particularly in acetonitrile, but the recovery of Cu(II) complexes from these reactions was actually achieved with several of the ligands tested. After filtration of the crude reaction mixture, if the filtrate is left to slowly evaporate in air, and the solid is successively washed with water and diethyl ether to wash away the residual base and the organic products, in several cases, a green powder or small green crystals can be collected from the bottom of the flask (Scheme 3.1).



Scheme 3.1: *Recovery of Cu(II) species at the end of the catalytic reaction*

Cu(II) species were recovered from reactions with some of the anionic ligands tested in the catalysis, namely **L5**, **L9**, **L24**, **L26** and **L32**. Only a few crystals could be obtained directly from the crude reaction mixture with **L5** and **L9**, and a somewhat higher amount was recovered for picolinamide ligands **L24**, **L26** and **L32** (*ca*. 10-15 mg). Recrystallisation of these compounds (only necessary for the picolinamide complexes) resulted in the collection of single crystals suitable for X-ray analysis, from which all of the complexes were identified as Cu(ligand)$_2$ complexes (with **L26** the complex Cu(**L26**)$_2$(H_2O) was formed, Figure 3.1).

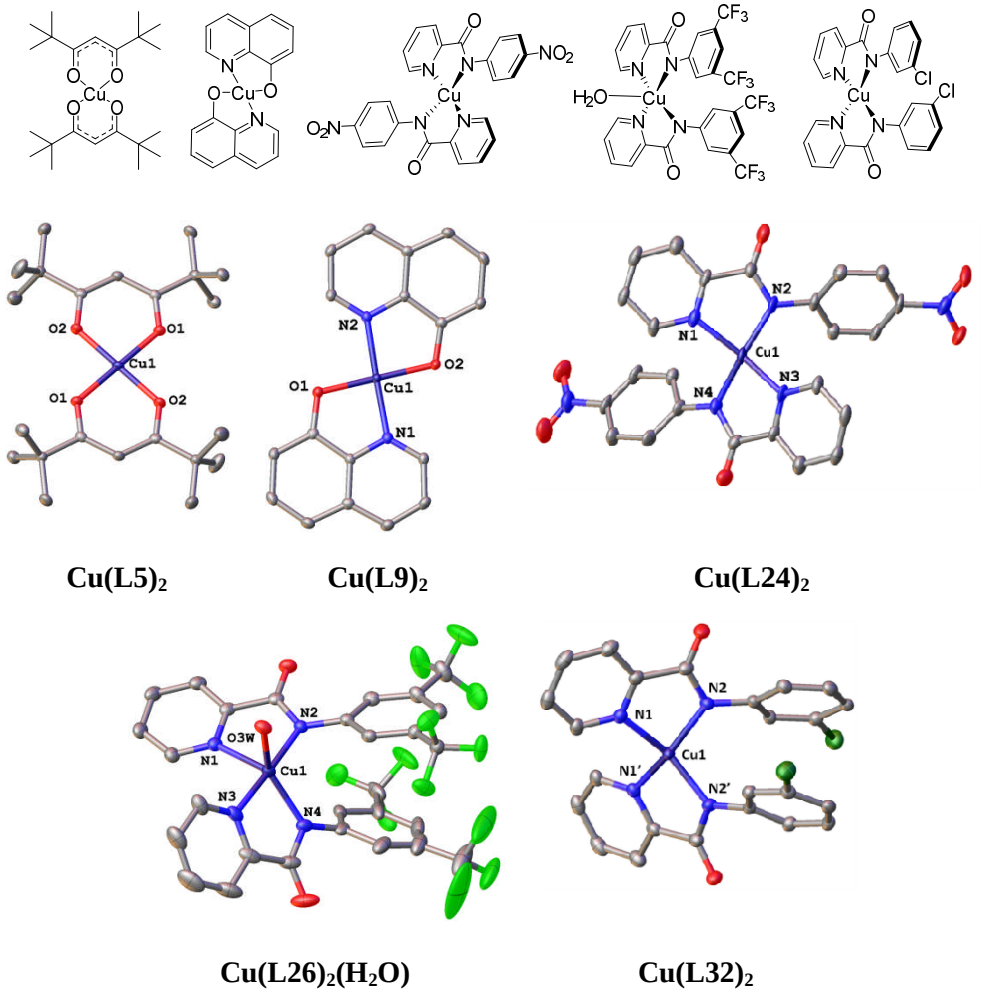


Figure 3.1: *Crystal structures of complexes recovered at the end of the catalysis*

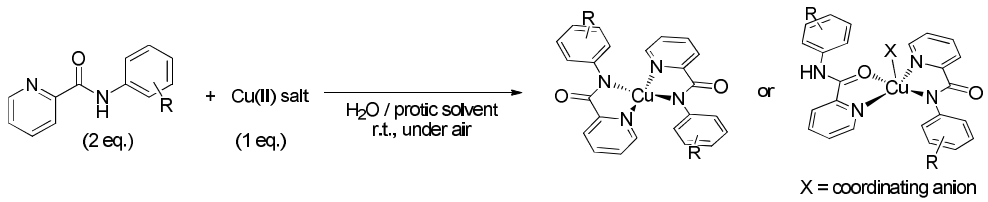
The recovery of Cu species at the end of the reaction is important, in that it gives useful information for the investigation of the mechanism of the catalytic process, and it raises the question of what their role is in the catalytic process. In fact, these Cu(II) complexes may potentially be either catalytically inactive decomposition products, or possible resting states or pre catalysts in the reaction. Investigation on the use of these complexes in the catalysis was therefore pursued as part of the mechanistic investigations on the catalytic reaction, described in Chapter 4. Because of the small amounts recovered from the catalysis, investigations using these species necessarily required the synthesis of these compounds on a larger scale. Moreover, attempts to isolate ligated Cu(I) species were also performed.

The rest of this chapter will describe the synthesis of Cu complexes with picolinamide ligands, and the diversity of the complexes obtained, summarising their structural features in the solid state.

3.2 – Synthesis of Cu(picolinamide)$_2$ complexes

Despite much research being carried out on tridentate[1-11] and tetradentate[12-17] *N*-phenylpicolinamide ligands with copper sources, relatively few reports have been published regarding complexes with simple bidentate picolinamide ligands.[18-21]

In all of the complexes reported in the literature obtained with bidentate picolinamide ligands, the copper centre is in the +2 oxidation state, and the complexes are prepared through the reaction of a Cu(II) salt, such as $Cu(OAc)_2$ or $CuSO_4$, with the ligand in water or other protic solvents.[18-21] Using these procedures, the typical compounds obtained are Cu(picolinamide)$_2$ complexes, with the two ligands coordinating through the pyridinic and amidic nitrogens in a *trans* geometry, which is to be expected on the basis of the steric hindrance of the two phenyl rings.[18] The basic counterions makes the addition of a base to deprotonate the ligand unnecessary, but coordination of these counterions to the metal centre can sometimes be observed, leading to different types of complexes, where one picolinamide acts as a neutral ligand with an *N,O* coordination mode,[20] rather than an anionic ligand (Scheme 3.2).

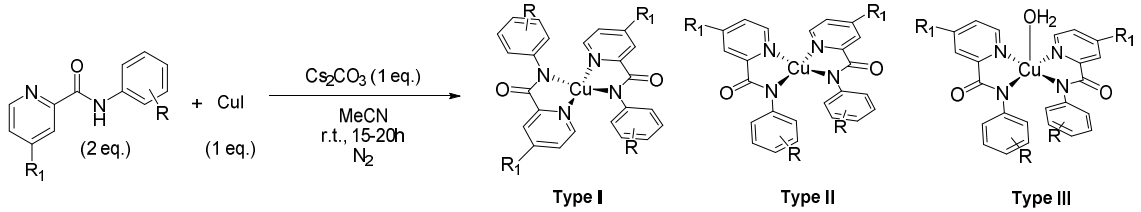


Scheme 3.2: *General literature procedure for the synthesis of Cu(II)-picolinamide complexes*

The isolation of Cu(II) complexes from a Cu(I) source after the catalytic process prompted us to perform the synthesis of complexes under similar conditions to those used in catalysis, and in particular the use of the same base, solvent and copper source. The reactions were, however, performed under nitrogen, to try to avoid the formation of Cu(II) species. This procedure was chosen to investigate potential interplays between the reagents involved in the catalysis, and the formation of complexes likely to be formed under the catalytic conditions. Thus, the formation of the complexes was studied through reactions between the picolinamide ligands and CuI, using Cs_2CO_3 as base.

Reactions without base did not result in any isolable complex, while, with a base, even under anhydrous and anaerobic conditions, Cu(II) complexes were obtained in all cases. Reactions under nitrogen, however, were somewhat cleaner than the reactions under air, furnishing considerably smaller amounts of an unidentified side product, which was obtained as a blue powder from reactions performed in air. A nitrogen atmosphere was thus used for the successive syntheses. The use of only one equivalent of ligand, as in the catalysis, also resulted in the Cu(picolinamide)$_2$ species, therefore two equivalents were used to maximise the yield. Control reactions showed that the same complexes could be obtained using triethylamine as a base, but the possibility of the co-crystallisation of triethylammonium salts encouraged the use

of Cs_2CO_3 for all the successive syntheses. The optimised procedure is reported in Scheme 3.3. The detailed procedure for the synthesis of complexes is reported in Chapter 6.



Scheme 3.3: *Synthesis of Cu(II)-picolinamide complexes, type **I-III***

Using the same procedure, different types of complexes were obtained, depending on the ligand used. In complexes of type **I-III**, the copper centre is coordinated to two molecules of the ligand, through the pyridinic and amidic nitrogens, positioned either in a *trans* or *cis* fashion. The *trans* coordination in these complexes (type **I**) is generally expected on the basis of the steric hindrance due to the substituted phenyl rings,[18] and is almost the only coordination mode reported in the literature for these complexes (*vide infra*). The *cis* coordination in complexes of types **II** and **III** seems to be somewhat stabilised over the *trans* by an intramolecular π-π stacking interaction between the two substituted phenyl rings, and was observed in some of the complexes with electron-withdrawing substituents. A list of complexes of type **I-III** is reported in Table 3.1. The numbering of the complexes follows the one for the ligands reported in Chapter 2, Scheme 2.3 (*e.g.* **C11** is the complex obtained with **L11**).

Table 3.1: *List of synthesised complexes of type **I-III** (isolated yields)*

Complex	R	R_1	Type	Yield	Complex	R	R_1	Type	Yield
C11	H	H	**I**	75%	**C35**	4-F	H	**I**	55%
C20	2,4-OMe	H	**I**	36%	**C36**	4-Cl	H	**I**	60%
C22	2-Cl-6-Me	H	**II**	67%	**C38**	4-I	H	**I**	71%
C23	3-NO_2	H	**I**	48%	**C39**	2,4-F	H	**I**	80%
C25	4-Ac	H	**I**	81%	**C42**	2,5-F	H	**II**	87%
C26	3,5-CF_3	H	**III**	79%	**C43**	2,5-Cl	H	**I**	51%
C27	2-F	H	**I**	83%	**C44**	2,5-Br	H	**II**	81%
C31	3-F	H	**I**	44%	**C51**	H	OMe	**I**	67%
C32	3-Cl	H	**II**	60%	**C52**	H	Cl	**I**	26%
C34	3-I	H	**I**	33%					

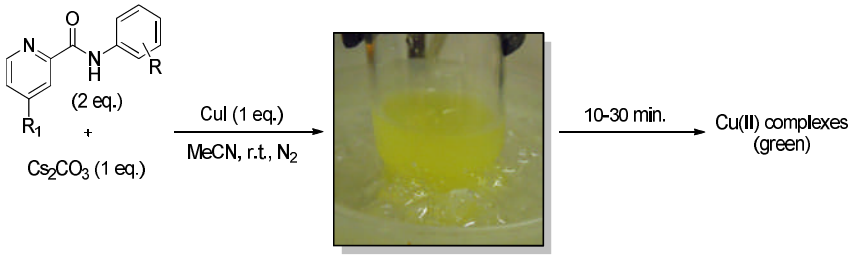
Type **I-III** complexes are generally light or dark green coloured in the solid state, air stable, with good solubility in DCM, methanol, and DMF, whereas a lower solubility is observed in acetone and acetonitrile. The complexes are insoluble in water, hexane and related solvents, and in diethyl ether. They were purified by recrystallisation through vapour diffusion

of diethyl ether into a solution of the complex in DCM or methanol, while the same process for a solution in acetonitrile often resulted in sticky semi-solid products, and in the co-crystallisation of unreacted ligand. In several cases, the use of acetonitrile solution is adequate for cold (-25°C) recrystallisation, but this method does not allow the crystallisation of the entire product. Typical crystal shapes for these complexes obtained from the above crystallisation methods are needles or plates, although, in some cases, large, regularly shaped crystals can be obtained (**C26**). These complexes crystallise generally in the monoclinic or orthorhombic systems (see Appendix for further information on the crystal features). Several of these complexes show solvatochromic properties, with a shift in colour from green to brown when moving from methanol to DCM. The structure of these complexes in solution has not been studied in detail.

3.2.1 – Cu(I)-Cu(II) oxidation in acetonitrile

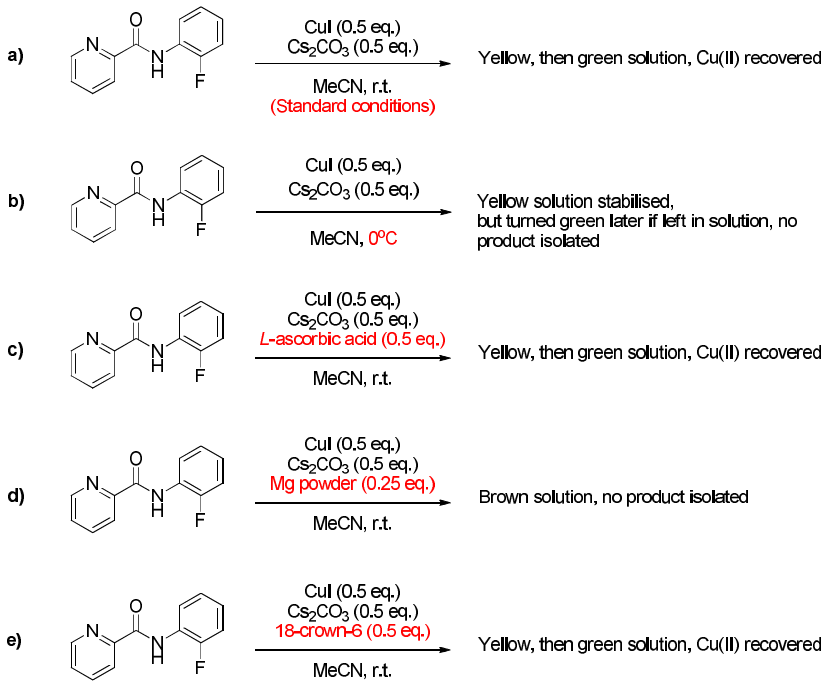
The oxidation of Cu(I) to Cu(II) was always observed during the synthesis of the complexes, even performing the reaction under anhydrous and anaerobic conditions (*i.e.* using dry solvents and chemicals, performing the reaction under a nitrogen flow). This process has been reported before in the literature, although no studies on the mechanism have been reported.[22]

As a general feature of the reaction, the addition of the copper iodide to the ligand/base solution, generally results in the immediate change in colour from colourless to bright yellow, which gradually turns to green, through an orange-brown colour, during a period of 10 to 30 minutes from the addition (Scheme 3.4).



Scheme 3.4: *Yellow intermediate in the synthesis of Cu(II) complexes*

The colour change suggested the formation of a Cu(I) intermediate in the reaction, which is then slowly oxidised to Cu(II). This presumed Cu(I) species would demonstrate that such a species might be formed during the catalytic reaction, therefore a series of experiments to try to isolate and characterise this species was undertaken (Scheme 3.5).

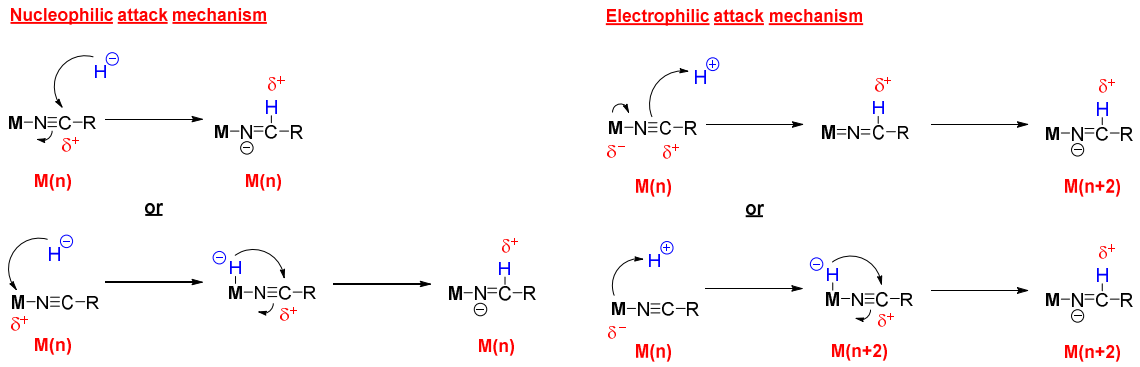


Scheme 3.5: *Attempts to stabilise the Cu(I) intermediate*

Performing the reaction at 0°C rather than at room temperature, the formation of the green solution was delayed considerably, and the bright yellow solution remained stable for more than 30 minutes, with no sign of darkening after that time. Filtering the mixture and storing it at -25°C to recrystallise, however, did not result in any precipitation of the product, and a green colour eventually developed. Another attempt was made through the addition of a reducing agent in the reaction. Reaction with *L*-ascorbic acid, commonly used for the reduction of Cu(II) to Cu(0)[23, 24] or Cu(I),[25-28] also resulted in the formation of the Cu(II) species. Reactions with Mg, intended as a sacrificial anode, resulted in the formation of a brown solution, rather than green, but the product could not be isolated. Speculating about a possible anionic Cu(I) complex, arising from the Cu(I) being coordinated by two anionic ligands, another experiment was performed adding the crown ether 18-crown-6 to the reaction mixture, to stabilise the ionic structure through stabilisation of the necessary Cs^+ counter-cation. However, even in this case, the Cu(II) complex was eventually obtained.

Performing the reaction in DMF with several picolinamide ligands, the Cu(II) complex was also observed, but in this case the formation of a copper mirror at the bottom of the Schlenk tube demonstrated a disproportionation mechanism. This suggested that the solvent could be involved in the oxidation process. Searching the literature for such a phenomenon gave a number of cases in which acetonitrile or other organic nitriles could be reduced to the corresponding imine or amine, when coordinated to a metal centre.[29-41] This process is known for a variety of transition metals across the periodic table (although not for copper specifically), and occurs with two different mechanisms: i) nucleophilic attack of a hydride to a coordinated molecule of nitrile;[38-40] and ii) electrophilic attack of a proton to the coordinated nitrile.[29-32, 34-37]

In a few cases, both a source of electrophilic proton and nucleophilic hydride were added to the process, leading to contributions from the two mechanisms.[33, 41] In the case of nucleophilic attack, the hydride is to be considered the reducing agent responsible for the reduction of the nitrile, and oxidation of the metal does not occur, unless other processes are involved. In the case of electrophilic attack, a proton is added to the nitrile molecule, leading to its formal reduction, and to the consequent oxidation of the metal centre (Scheme 3.6).

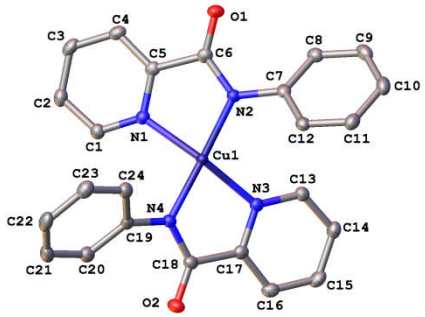


Scheme 3.6: *Reduction of transition metal-coordinated nitriles (oxidation states and charges are only indicative)*

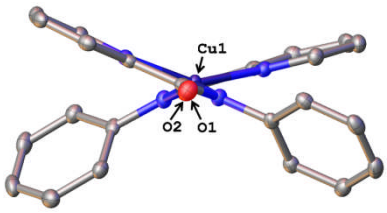
In the case of Cu(picolinamide)$_2$ complexes, although no definitive proof has been obtained so far that demonstrates the reduction of the acetonitrile solvent, an electrophilic attack of a proton from the ligand to a molecule of a coordinated acetonitrile may be suggested to explain the formation of Cu(II) compounds. This would also explain why the Cu(II) species are obtained in DMF through disproportionation, rather than oxidation.

3.3 – Type I complexes

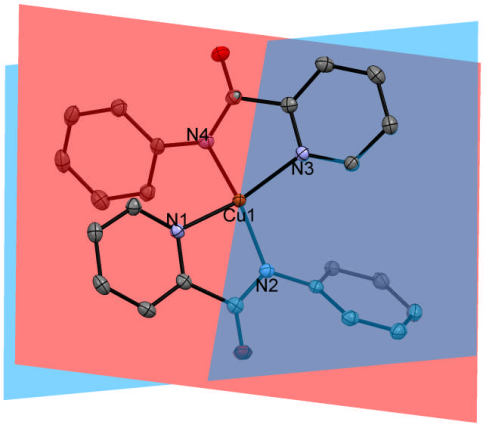
As expected, the coordination type **I** is the most common among the complexes synthesised, due to steric hindrance. Complexes of type **I** show the two picolinamide ligands coordinated in a *trans* fashion, in a distorted square planar geometry. The distortion is evident from the angle between the two ligand planes (in Figure 3.2 these are the N1-Cu1-N2 and N3-Cu1-N4 planes), which is always less than 45°. The Cu-N distances are about 2 Å, with the pyridine nitrogen generally about 0.04-0.05 Å closer than the amide nitrogen, and the angles between the two nitrogens *trans* to each other are in the range 145-168°. Selected bond lengths and angles for all of the type **I** complexes are reported in Table 3.2 at the end of this section (atom numbering scheme is given in Figure 3.2a).



a) Front view



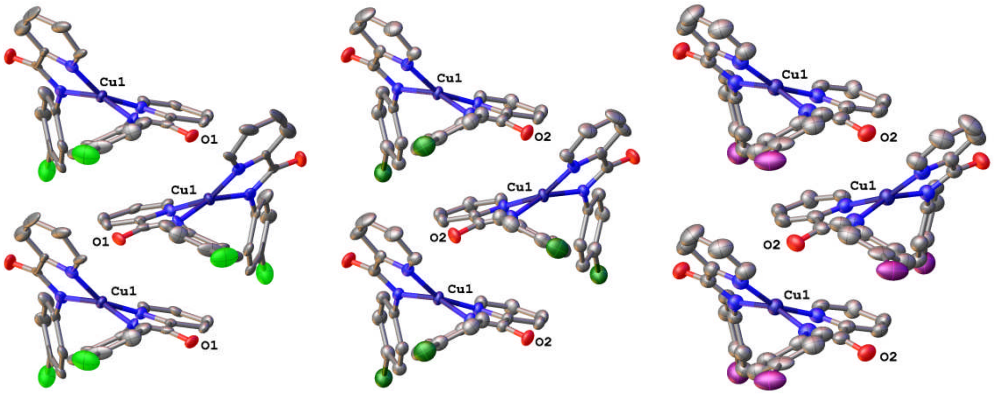
b) Side view along the O1-Cu1-O2 axis



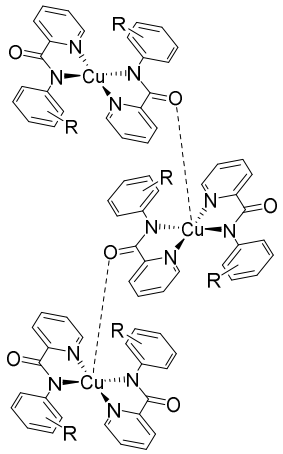
c) Planes N1-Cu1-N2 (red) and N3-Cu1-N4 (blue)

Figure 3.2: *Distortion around the copper atom in type **I** complexes*

In some of the complexes of this type the metal centre shows the tendency to fill a fifth coordination position, through weak coordination to an oxygen donor, either from a carbonyl oxygen of another Cu(picolinamide)$_2$ unit or a water molecule. Complexes with ligands **L35**, **L36** and **L38**, substituted in *para* with a halogen atom, all show a similar packing arrangement in the solid state. Weakly coordinated chains of individual Cu(picolinamide)$_2$ units are observed that run parallel to the *c* axis of the unit cell. (Figure 3.3). The distances between the copper centre in one unit and the closest carbonyl oxygen in the unit immediately above are about 2.5 Å, which is considerably longer than the typical distance observed in *O*-coordinated Cu(II) complexes (around 1.9 Å),[42] thus indicating a weak interaction.



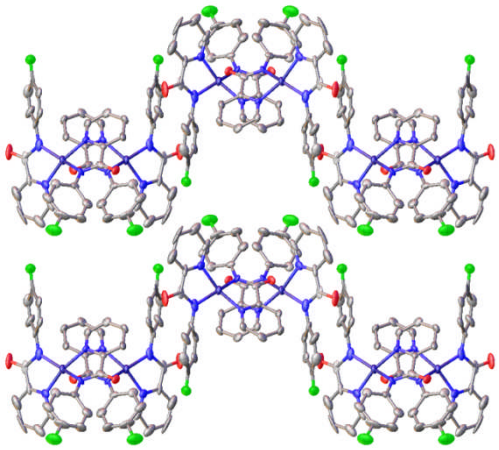
a) C35 (R = 4-F) **b) C36** (R = 4-Cl) **c) C38** (R = 4-I)



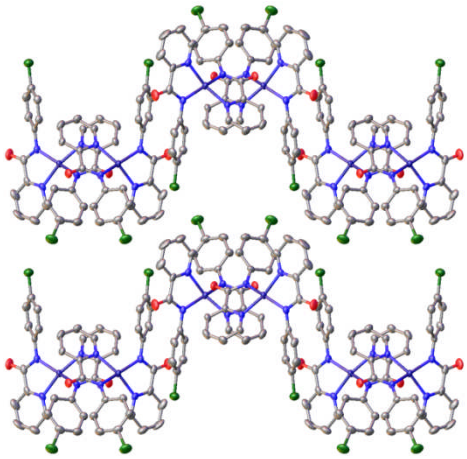
Complex (R)	**Cu-O bond length**
C35 (4-F)	2.55 Å
C36 (4-Cl)	2.55 Å
C38 (4-I)	2.48 Å

Figure 3.3: *Weak intermolecular Cu-O interaction in complexes with para-halogenated ligands*

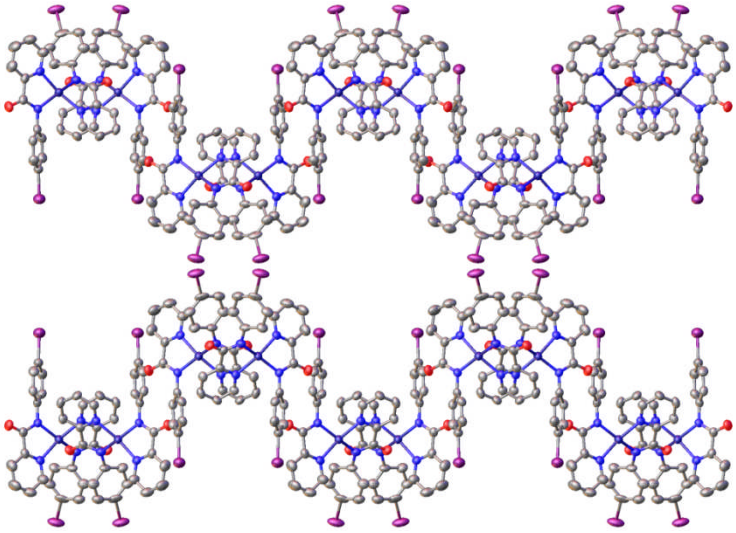
These polymeric "chains" are spatially close to each other, and observed along the *c* axis they appear organised in layers, in which every chain has an opposite orientation to the next. This is similar for all the three complexes described, however, the relative orientation of the layers is the same for complexes **C35** and **C36**, but different in complex **C38**, where the packing results in much larger solvent voids. The packing diagrams for these complexes are depicted in Figure 3.4.



a) C35 (R = 4-F)



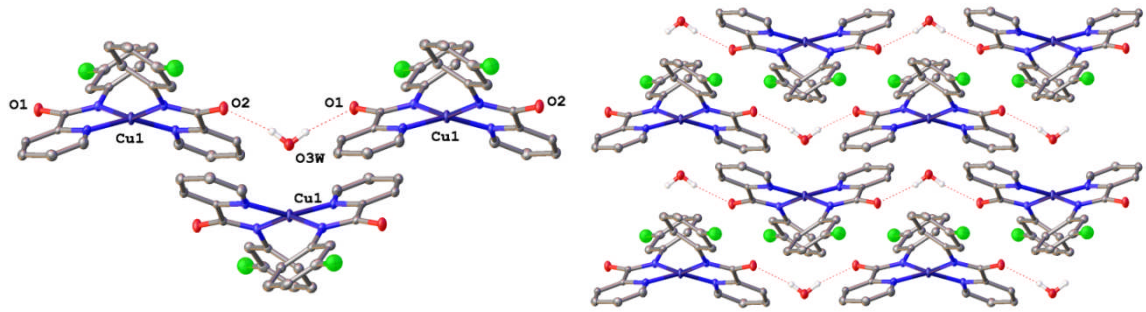
b) C36 (R = 4-Cl)



c) C38 (R = 4-I)

Figure 3.4: *Packing diagrams for complexes **C35**, **C36** and **C38** – view along the c axis*

In complex **C31** (R = 3-F), a weak Cu-O interaction between the Cu centre and a water molecule is observed, with a Cu-O distance of 2.70 Å (Cu1-O3W, Figure 3.5a). The water molecule is involved in hydrogen-bonding with the carbonyl oxygens of other two Cu(picolinamide)$_2$ units, leading to a layered packing diagram (Figure 3.5b).



a) **b)**

Figure 3.5: *a) Detail of the hydrogen-bonding water molecule in* ***C31*** *(R = 3-F); b) structure of the layers parallel to the ac face of the unit cell*

A weak coordination to an oxygen donor in an axial position is a common feature for Cu(II) complexes, and Cu-O bond distances up to 2.8 Å are commonly observed.[21, 43-46] This may, in some cases, result in some difficulties in attributing a geometry to the copper centre, often found in very distorted environments.[43] Strong distortion from typical tetra-coordinated geometries are generally observed for Cu-O distances of 1.9-2.2 Å, with the geometry effectively changing to trigonal bipyramidal or square pyramidal; these bond distances are associated to a real Cu-O coordination.[19, 43-45] In the cases reported above the distortion around the copper centre in not enough to suggest an actual coordination of the axial oxygen donor, and is similar to the other type **I** complexes, as shown by the similar bond distances and angles (Table 3.2).

Table 3.2: *Selected bond lengths and angles for type **I** complexes*[a]

	Complex (R)								
	C11 (H)	**C20** (2,4-OMe)	**C23** (3-NO_2)	**C24** (4-NO_2)[b]	**C25** (4-Ac)	**C27** (2-F)	**C28$_{Na}$** (2-Cl)[c,d,e]	**C31** (3-F)	**C34** (3-I)
Cu1-N1	1.9952(16)	2.020(3)	1.994(3)	1.998(5)	1.987(5)	2.002(4)	2.003(6)	2.0002(19)	2.003(3)
Cu1-N2	1.9403(16)	1.941(3)	1.951(3)	1.950(6)	1.968(6)	1.944(4)	1.936(6)	1.9825(18)	1.935(3)
Cu1-N3	2.0155(16)	2.024(3)	1.994(3)	1.995(5)	1.971(6)	2.018(4)	2.018(6)	1.9991(19)	1.988(3)
Cu1-N4	1.9316(16)	1.936(3)	1.951(3)	1.951(6)	1.947(6)	1.935(4)	1.941(6)	1.9779(18)	1.944(3)
N1-Cu1-N2	83.10(7)	82.62(12)	83.59(11)	83.3(2)	83.2(2)	83.12(16)	83.6(2)	83.31(7)	82.59(12)
N3-Cu1-N4	82.88(7)	82.44(12)	83.59(11)	82.9(2)	83.4(2)	82.80(16)	83.5(2)	83.29(7)	84.05(12)
N1-Cu1-N3	151.67(6)	144.88(11)	147.88(16)	151.7(2)	153.7(2)	150.60(15)	149.0(2)	153.63(8)	144.48(12)
N2-Cu1-N4	158.16(7)	168.64(12)	157.36(16)	158.8(2)	151.6(2)	160.05(16)	159.2(3)	151.43(8)	159.66(12)
N1-Cu1-N4	99.17(7)	102.85(12)	102.73(11)	102.2(2)	104.5(2)	99.08(16)	100.5(2)	103.16(8)	102.04(12)
N2-Cu1-N3	105.45(6)	98.89(12)	102.73(11)	102.0(2)	101.9(2)	105.06(16)	103.5(2)	103.34(8)	103.81(12)

[a] N3 = $N1^1$ and N4 = $N2^1$ for complexes **C23** and **C51** (half molecule in the asymmetric unit)

[b] Complex recovered from the catalytic reaction (see section 3.1)

[c] Synthesised using Na_2CO_3 as base (see section 3.7)

[d] One and a half Cu(ligand)$_2$ molecules in the asymmetric unit, only data for the full molecule are reported

[e] Crystallised with NaI_3: data for the NaI_3 salt are not reported (see section 3.7)

Table 3.2: *Selected bond lengths and angles for type **I** complexes[a] (continued)*

	Complex (R)					**Complex (R_1)**	
	C35 (4-F)	**C36** (4-Cl)	**C38** (4-I)	**C39** (2,4-F)	**C43** (2,5-Cl)	**C51** (R_1=OMe)	**C52** (R_1=Cl)
Cu1-N1	2.001(10)	2.016(6)	2.007(8)	1.999(3)	2.001(4)	1.987(2)	2.021(2)
Cu1-N2	1.951(9)	1.969(6)	1.961(7)	1.948(3)	1.948(4)	1.938(2)	1.939(2)
Cu1-N3	1.990(11)	2.036(5)	2.018(8)	2.010(3)	2.031(3)	1.986(2)	2.024(2)
Cu1-N4	1.944(11)	1.974(5)	1.961(8)	1.932(3)	1.951(4)	1.938(2)	1.933(2)
N1-Cu1-N2	82.7(4)	82.4(2)	82.4(3)	82.85(13)	82.58(15)	83.53(10)	83.28(8)
N3-Cu1-N4	82.7(5)	82.4(2)	82.1(3)	82.69(13)	82.39(15)	83.53(10)	82.50(9)
N1-Cu1-N3	156.7(4)	158.1(2)	160.7(3)	151.63(13)	155.29(17)	143.99(14)	146.24(9)
N2-Cu1-N4	157.1(4)	157.8(2)	156.7(3)	159.11(14)	163.20(18)	156.12(16)	162.02(10)
N1-Cu1-N4	103.3(5)	101.1(2)	102.9(3)	98.64(13)	99.55(15)	103.92(9)	100.15(9)
N2-Cu1-N3	100.6(4)	102.5(2)	100.4(3)	105.91(13)	102.69(14)	103.93(9)	104.54(9)

[a] N3 = $N1^1$ and N4 = $N2^1$ for complexes **C23** and **C51** (half molecule in the asymmetric unit)

[b] Complex recovered from the catalytic reaction (see section 3.1)

[c] Synthesised using Na_2CO_3 as base (see section 3.7)

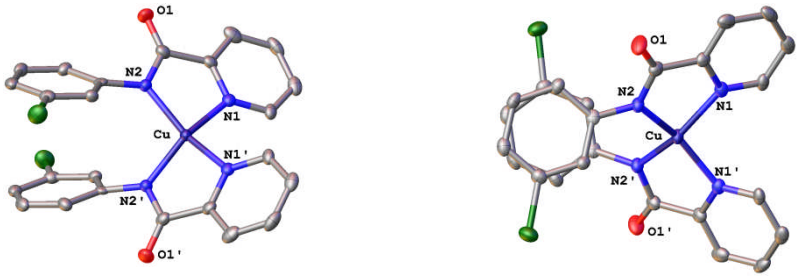
[d] One and a half Cu(ligand)$_2$ molecules in the asymmetric unit, only data for the full molecule are reported

[e] Crystallised with NaI_3; data for the NaI_3 molecule are not reported (see section 3.7)

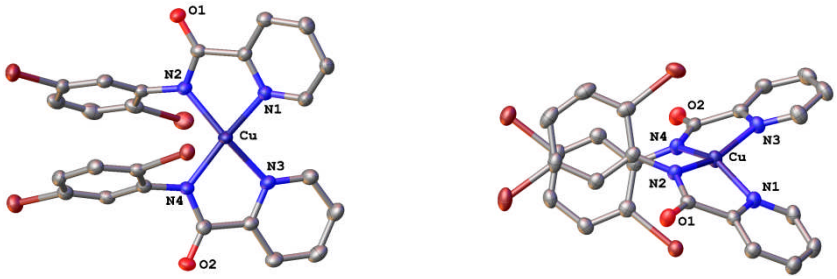
3.4 – Type II complexes

Complexes with **L22**, **L32**, **L42** and **L44** all show coordination of type **II**, with the two ligands in a *cis* arrangement. This type of complex has not been reported before with bidentate picolinamide ligands. The overall geometry around the copper centre is not strongly affected by the *cis* stereochemistry, and the structures are only slightly more distorted from the ideal square planar than in type **I** complexes. The *cis* arrangement of the ligands around the metal is stabilised in these complexes by an intramolecular π-stacking interaction between the two EWG-substituted phenyl rings.

Different types of π-stacking are observed in these complexes, either a sandwich-type or a parallel displaced stacking.[47, 48] For example, complex **C32** (R = 3-Cl) gives rise to a sandwich-type π-stacking, with a centroid distance between the phenyl rings of 3.494 Å, while **C44** (R = 2,5-diBr) shows a parallel displaced π-stacking with one carbon atom of one ring directly above the centre of the other ring. The C-centroid distance in this case is 3.256 Å. The two complexes are depicted in Figure 3.6. Centroid-centroid and C-centroid distances for all of the type **II** complexes are reported in Table 3.3 (these include complexes $\mathbf{C40_{Na}}$ and $\mathbf{C41_{Na}}$, see section 3.7). The atom numbering scheme for type **II** complexes follows the one used for type **I** complexes, reported in Figure 3.2a.



C32 (R = 3-Cl, sandwich type π-stacking)



C44 (R = 2,5-Br, parallel-displaced π-stacking)

Figure 3.6: *Examples of type **II** complexes with different π-stacking interactions: side (left) and top (right) views*

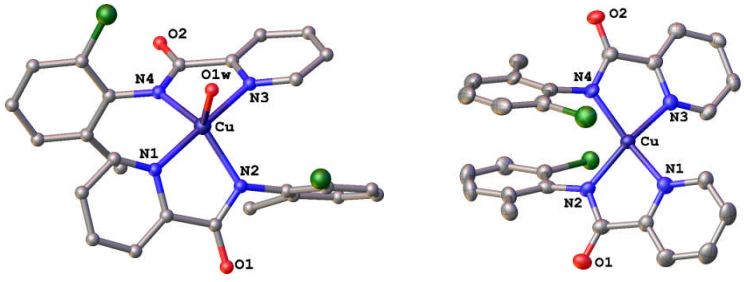
Table 3.3: *π-Stacking interactions in type **II** complexes*

Complex	R	Centroid-centroid distance (Å)	Shortest C-centroid distance (Å)	π-Stacking type
C22	2-Cl-6-Me	3.640	3.385 [C20-(C7-C12)]	Parallel-displaced
C32	3-Cl	3.494	3.578 [C7-($C7^1$-$C12^1$)]	Sandwich
$C40_{Na}$ [a]	2,4-Cl	3.555	3.648 [C19-(C7-C12)]	Sandwich
$C41_{Na}$ [a,b]	2,4-Br	3.433	3.347 [C8-(C19-C24)]	Parallel-displaced
C42	2,5-F	3.616	3.507 [C8-($C7^1$-$C12^1$)]	Parallel-displaced
C44	2,5-Br	3.541	3.256 [C8-(C19-C24)]	Parallel-displaced

[a] Synthesised using Na_2CO_3 as base (see section 3.7)

[b] Two molecules in the asymmetric unit, only data for one molecule are reported; the other molecule is comparable

The Cu(II) complex **C22** (R = 2-Cl-6-Me), here obtained as a type **II** complex (Figure 3.7b), has been reported in the literature with the ligands in the *trans* configuration, and a molecule of water coordinated at the axial position (Cu-O bond length = 2.27Å, Figure 3.7a), giving a (mostly) trigonal bipyramidal coordination environment to the Cu centre.[19] This structure is the *trans* equivalent to the type **III** *cis* complex **C26** (see section 3.5), a coordination that was not observed for any complex reported in this thesis. The two structures are shown in Figure 3.7. It is important to point out that no mixtures of isomers in the solid state were observed for the complexes synthesised, as demonstrated by the homogenous aspect of the crystalline samples, and by the identity of crystal structures / unit cells for different crystals of the same complex, from the same batch or from different batches (for example, complexes **C32** and **C26**, synthesised and recovered from the catalytic reaction). Thus, the different geometry may be due to the different synthetic procedures or different crystallisation conditions.



a) *Trans* geometry (Mukherjee, 1999)[19] **b)** *Cis* geometry

Figure 3.7: *Different structures for complex **C22***

Selected bond distances and angles for type **II** complexes are reported in Table 3.4.

Table 3.4: *Selected bond lengths and angles for type **II** complexes*[a]

	Complex (R)					
	C22 (2-Cl-6-Me)	**C32** (3-Cl)[b]	**C40$_{Na}$** (2,4-Cl)[c]	**C41$_{Na}$** (2,4-Br)[c,d]	**C42** (2,5-F)	**C44** (2,5-Br)
Cu1-N1	1.998(6)	1.986(2)	1.981(10)	2.003(11)	1.983(3)	1.993(3)
Cu1-N2	1.944(6)	1.947(2)	1.936(9)	1.953(11)	1.939(3)	1.951(3)
Cu1-N3	1.989(6)	1.986(2)	1.975(11)	1.993(10)	1.983(3)	1.991(3)
Cu1-N4	1.951(6)	1.947(2)	1.958(10)	1.930(11)	1.939(3)	1.941(3)
N1-Cu1-N2	82.7(2)	83.70(9)	83.0(4)	84.8(4)	84.00(11)	82.95(12)
N3-Cu1-N4	83.5(2)	83.70(9)	82.9(4)	83.9(5)	84.00(11)	82.79(13)
N1-Cu1-N3	102.0(2)	100.84(14)	98.1(4)	99.9(5)	103.29(15)	102.10(13)
N2-Cu1-N4	104.2(3)	104.48(13)	108.0(4)	103.7(4)	101.73(16)	103.39(13)
N1-Cu1-N4	153.5(3)	152.88(9)	153.6(4)	155.6(5)	152.60(11)	150.21(13)
N2-Cu1-N3	152.8(2)	152.88(9)	152.8(4)	150.6(5)	152.60(11)	158.35(14)

[a] N3 = N1^1 and N4 = N2^1 for complexes **C32** and **C42** (half molecule in the asymmetric unit)

[b] Bond lengths and angles for complex **C32** recovered from the catalytic reaction are comparable, and are not reported

[c] Synthesised using Na_2CO_3 as base (see section 3.7)

[d] Two Cu(ligand)$_2$ molecules in the asymmetric unit, only data for one molecule are reported

3.5 – Type III complexes

A type **III** complex was only formed with ligand **L26** (R = 3,5-CF_3). In complex **C26** a water molecule occupies a fifth coordination position around the copper centre, with a Cu-O bond distance of 2.131 Å, much shorter than the Cu-O bond length observed in type **I** complexes (*ca*. 2.5 Å, see section 3.3). The coordination is also evident by the strongly distorted geometry around the metal centre, which is between trigonal bipyramidal and square pyramidal. The distortion is caused by the constrained *N,N* coordination of the ligands and the stabilisation due to the π-stacking interaction. The structures of the synthesised complex and that recovered from the catalysis (see section 3.1) are similar, but because of the different crystallisation solvents (acetone for the recovered complex, DCM for the synthesised complex), which are present in the solid state structure, slight differences are observed in the two cases. In the recovered complex a sandwich-type π-stacking is observed, with a distance between the centroids of 3.636Å, while in the synthesised complex the same interaction is of 3.855 Å, considerably longer, denoting an offset-type π-stacking (shortest C-centroid distance = 3.496 Å, Figure 3.8a,b). The differences in the structure are also visible from the comparison of bond angles for the two complexes (Table 3.5). In particular, the angles N2-Cu1-N3 and N2-Cu1-N4 (numbering scheme in Figure 3.8a and 3.8b) differ in the two structures by *ca.* 5°, and the same is valid for the angles N2-Cu1-O3w and N4-Cu1-O3w, showing a considerable difference in the geometry around the metal centre.

The distinction between the square pyramidal and trigonal bipyramidal geometry in penta-coordinated structures, where the distortion makes it difficult to assign a proper geometry to the metal centre, is the structural index τ, defined in 1984 by Addison *et al.* as: $\tau = (\beta - \alpha)/60$, where β is the largest of the angles between the ligands, and α is the second largest.[44] In a perfect square pyramidal complex, the largest angles are the basal angles, and $\alpha = \beta = 180°$, therefore $(\beta - \alpha) = 0$, and $\tau = 0$. In contrast, in a perfect trigonal bipyramidal complex, β and α are 180° and 120°, corresponding respectively to the angles between the two axial ligands, and between two of the equatorial ligands. In such case, $(\beta - \alpha) = 60$, and $\tau = 1$. Using this parameter it is possible to easily discern if a distorted structure should be described as mostly square pyramidal or trigonal bipyramidal. In the case of the two forms of complex **C26**, the different distortion results in values of τ of 0.717 and 0.656 respectively for the recovered and the synthesised complex. Both of them are therefore mostly trigonal bipyramidal in character (with the N2-Cu1-N3 as the principal axis), but more strongly so for the recovered complex, due to the sandwich-type π-stacking interaction, which results in a more compact structure and a smaller N2-Cu1-N4 angle than in the second form (101.35° and 105.52° respectively, Table 3.5).

The difference between the two structures extends to the crystal packing; while in the recovered complex the Cu(II) units are packed in a hexagonal arrangement, with the pyridyl rings of the ligand ordered around narrow solvent-filled voids (Figure 3.8c, solvent molecules

not shown), in the synthesised complex the Cu(II) units are arranged in layers, kept together by hydrogen bonding between the coordinated water molecule and the carbonyl oxygens of other units (Figure 3.8d,e). This interaction is similar to the one described for complex **C31** (Figure 3.5).

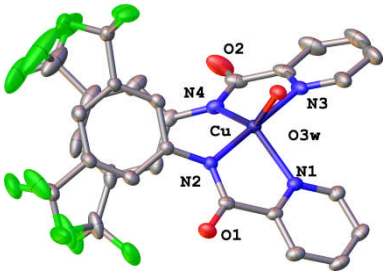
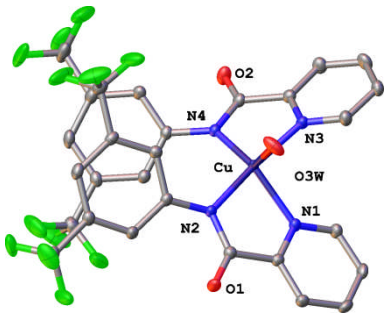
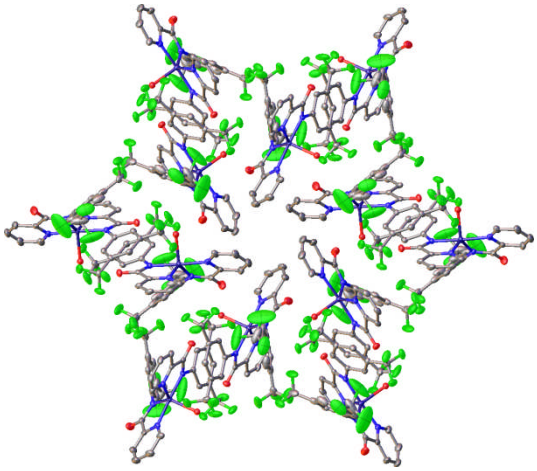
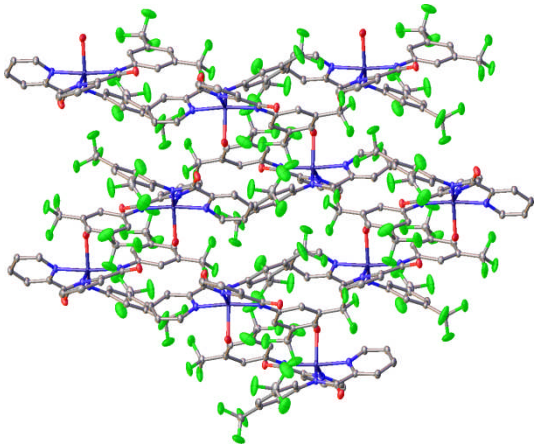
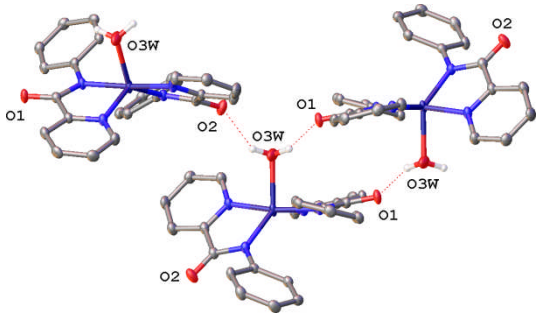
Recovered complex	**Synthesised complex**
	
a) Sandwich-type π-stacking	**b)** Offset π-stacking
	
c) Packing along the *c* axis	**d)** Packing along the *c* axis
	
	e) H-bonding detail (CF_3 groups omitted)

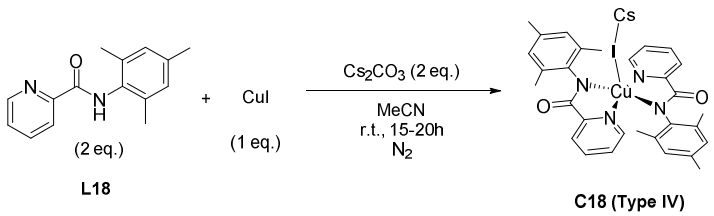
Figure 3.8: *Comparison of the recovered and synthesised forms of complex* ***C26***

Table 3.5: *Selected bond lengths and angles for type **III** complex **C26** (two forms)*

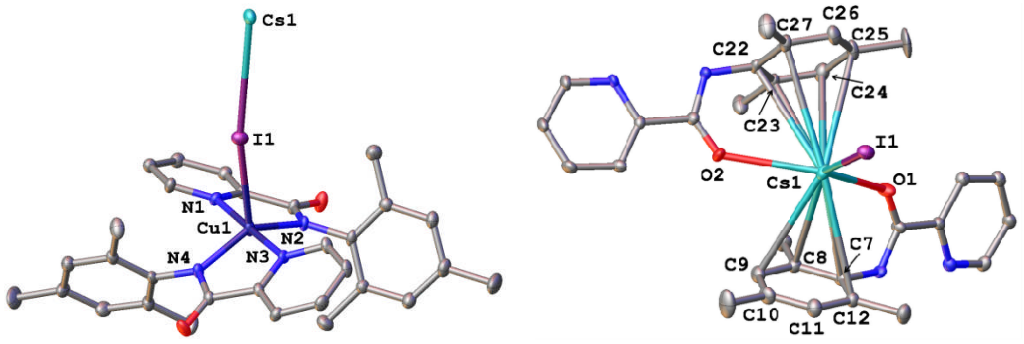
	Complex	
	C26 (Recovered)	**C26** (Synthesised)
Cu1-N1	2.081(2)	2.071(3)
Cu1-N2	1.975(2)	1.992(3)
Cu1-N3	2.005(3)	1.986(3)
Cu1-N4	2.010(3)	2.020(3)
Cu1-O3w	2.156(2)	2.131(3)
N1-Cu1-N2	82.30(10)	82.06(13)
N3-Cu1-N4	81.32(11)	81.51(13)
N1-Cu1-N3	97.28(11)	94.37(13)
N2-Cu1-N4	101.35(10)	106.52(13)
N1-Cu1-N4	131.10(10)	132.24(13)
N2-Cu1-N3	176.83(11)	171.61(13)
N1-Cu-O3w	94.25(9)	98.11(14)
N2-Cu-O3w	91.76(9)	85.97(12)
N3-Cu-O3w	85.13(10)	87.01(13)
N4-Cu-O3w	133.82(9)	128.85(14)

3.6 – Type IV complexes

Apart from type **I-III** complexes, other types were obtained when using different picolinamide ligands; these will be discussed in this and the next section. The reaction of *N*-mesitylpicolinamide **L18** with CuI and Cs_2CO_3 resulted in a type **IV** complex, the only one in the series of complexes reported in this thesis (Scheme 3.7). This unusual type of complex can be seen as an adduct including a Cu(picolinamide)$_2$ unit, in which the two ligands are arranged in a *trans* fashion, and a CsI molecule, obtained as a side product from the complexation reaction. The asymmetric unit of this complex is shown in Figure 3.9a.



Scheme 3.7: *Synthesis of type **IV** complex **C18***

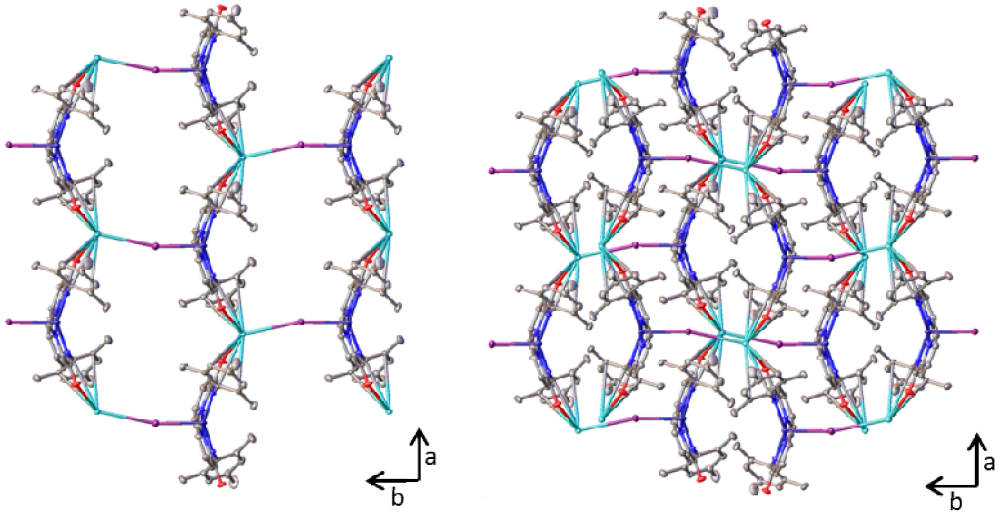


a) **b)**

Figure 3.9: a) *Asymmetric unit of complex **C18**; b) coordination around the Cs ion*

The environment around the Cu centre in complex **C18** can be described as intermediate between a square pyramidal and a trigonal bipyramidal geometry, with $\tau = 0.583$, only slightly shifted toward a trigonal bipyramidal environment with N1-Cu1-N3 as the principal axis (the N1-Cu1-N3 angle is 178.91°). Bond distances and angles for complex **C18** are reported in Table 3.6.

The iodide ligand is coordinated to the Cu centre with a Cu-I bond length of 2.6565 Å, a value considerably shorter than the theoretical sum of the Van der Waals radii of Cu and I, reported to be of 3.38 Å.[42] An interesting feature of the complex is the bridging role of the iodide between the Cu unit and the Cs ion, to which it is coordinated with a Cs-I bond length of 3.711 Å. The almost linear angle of this bridging interaction (the Cu1-I1-Cs1 angle is 167.34°) has not been reported before in the literature, and is of interest in view of the (relatively) long Cu-I distance (*i.e.* whether the iodide is more part of the Cu unit or of a CsI molecule, *vide infra*). Apart from the iodide, the coordination around the Cs ion consists of two picolinamide ligands (from two separate Cu(picolinamide)$_2$ units), each of which coordinates to the cation through the mesityl ring and the carbonyl oxygen, giving the Cs ion a geometry describable as distorted square pyramidal ($\tau = 0.18$, the mesityl ring is considered as occupying a single coordination position, Figure 3.9b). The almost linear Cu-I-Cs linkage in this complex results in a very ordered bi-dimensional structure in the solid state, which develops to form layers parallel to the *ab* plane of the cell, where the Cu-I-Cs connection is responsible for the propagation along the *b* direction, while the Cs-π interactions with the mesityl rings develop along *a* (Figure 3.10a). The relatively low coordination number of the Cs ion allows for moderately open space within each layer (5.26 Å). However, adjacent layers are oriented in opposite directions, not allowing for the formation of channels or other tri-dimensional empty spaces (Figure 3.10b).



a) Single layer **b)** Layers packing

Figure 3.10: *Bi-dimensional arrangement of complex **C18***

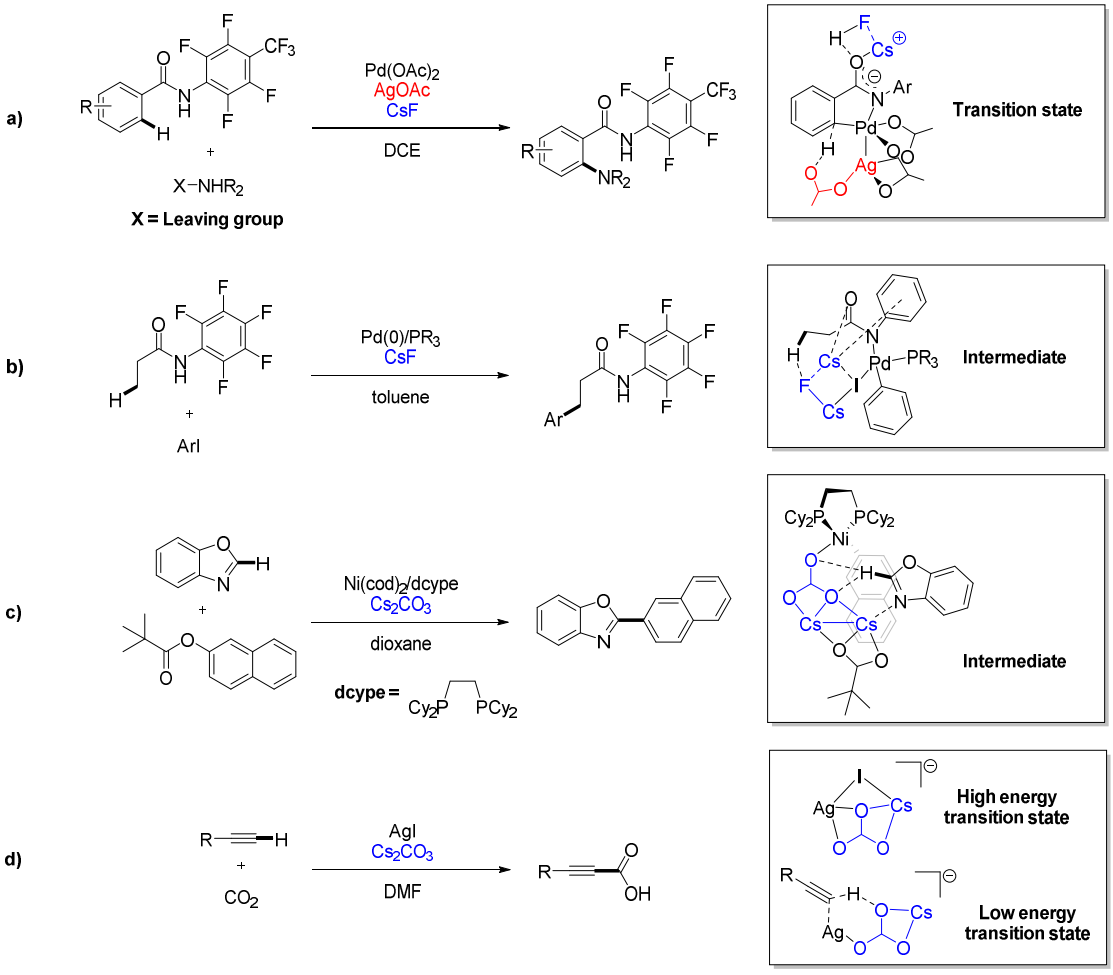
Table 3.6: *Selected bond lengths and angles for type **IV** complex **C18***

Cu1-N1	2.004(4)	**Cu1-I1**	2.9565(8)
Cu1-N2	2.012(4)	**Cs1-I1**	3.7107(5)
Cu1-N3	2.010(4)	**Cs1-O1**	2.973(4)
Cu1-N4	1.997(4)	**Cs1-O2**	2.940(4)
N1-Cu1-N2	81.29(17)	**N2-Cu1-I1**	109.12(13)
N3-Cu1-N4	81.59(17)	**N3-Cu1-I1**	90.30(12)
N1-Cu1-N3	178.91(18)	**N4-Cu1-I1**	106.95(13)
N2-Cu1-N4	143.92(18)	**Cu1-I1-Cs1**	167.344(17)
N1-Cu1-N4	98.93(17)	**I1-Cs1-O1**	125.50(8)
N2-Cu1-N3	98.85(17)	**I1-Cs1-O2**	107.07(8)
N1-Cu1-I1	88.63(13)	**O1-Cs1-O2**	127.12(9)

The incorporation of the CsI molecule in the complex is a unique feature in the series of complexes reported, and may be due to a particular stabilisation effect that the mesityl ring has on the Cs ion. A search of the literature revealed that in the majority of the organocaesium compounds where Cs-arene interactions are involved, these are represented by sterically hindered phenyl rings, generally mesityl or diisopropylphenyl groups, or other 2,6-alkyl/aryl-substituted rings. This is observed for example in caesium phenoxides, which form bi-dimensional or tri-dimensional arrangements kept together by Cs coordination to the oxygen atoms and the phenyl rings;[49-51] the same is valid for caesium phosphanes.[52, 53] Therefore, the mesityl substituent in complex **C18** may be the reason why this interaction has not been observed in other complexes (including complexes with other EDG-substituted ligands, such as **C20**). Without the aid of electron-rich phenyl rings, the other way to stabilise the large Cs ion in

the solid state is the introduction of macrocycles, often crown ethers,[54-59] but also thia-crown ethers,[60, 61] arsoxane,[62] and tetrasilazane rings.[63]

Caesium bases are commonly used in a range of organic reactions, such as nucleophilic substitutions,[64-66] esterifications,[67-70] cross-couplings[71-74] and C-H activation processes,[75-77] and are generally known to furnish much better results than other similar inorganic bases. This effect is known as "caesium effect", and can be related to a number of properties of the caesium bases, such as higher solubility and basicity in organic solvents.[65, 67, 78, 79] Ultimately, these effects are thought to be due to the larger size and polarizability of the Cs ion compared to the other alkali metals, which make its anionic counterpart more nucleophilic, and therefore more reactive. These effects, together with, possibly, a template effect for the synthesis of macrocyclic compounds,[67-69] are likely to be the only effects involved in organic reactions not involving transition metals. For transition metal-catalysed reactions, however, other effects may be involved when using Cs bases. This was evidenced only recently from computational studies on C-H activation and CO_2 activation reactions (Scheme 3.8).[80-83] A brief description of these results is reported here.



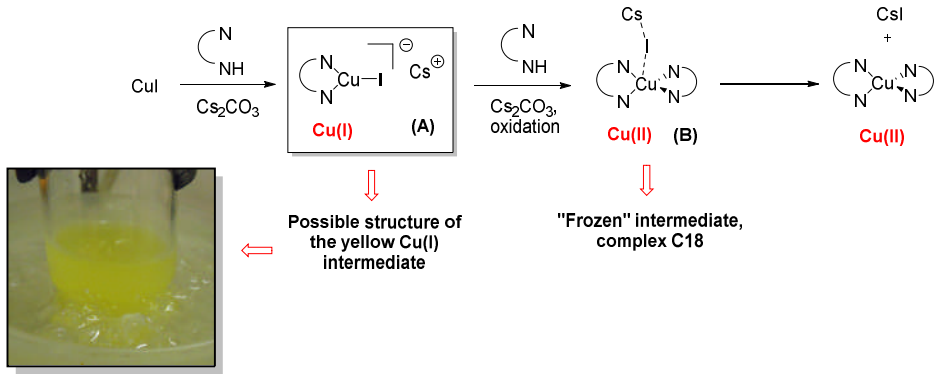
Scheme 3.8: *Interactions of caesium bases with transition metal catalysts*[80-83]

Shaefer III and Sunoj reported that, in amide-directed $Pd(OAc)_2$-catalysed Csp^2-H activation processes, the inclusion of CsF and AgOAc (used in an investigation by Yu[84]) in models of transition states, resulted in lower energies for the activation process.[80] CsF acted primarily as a base, but also facilitated the overall process, leading to lower energy transition states (Scheme 3.8a).[80]

Other insight was given by Musaev and Yu for a similar amide-directed Csp^3-H activation process (Scheme 3.8b).[75, 81] They found that two possible mechanistic pathways could be envisaged. In the first one, the CsF had an important role: i) as a base to deprotonate the amidic directing group, and ii) in facilitating the exchange of the iodide ligand on the Pd with a fluoride ligand, after the oxidative addition of the aryl iodide; this exchange was thermodynamically favoured for the coupling with the Csp^3 atom. CsF again acted as a base in the second mechanism (energetically less expensive that the first), but no iodide-to-fluoride exchange was involved: this was substituted by the concerted Csp^3-H activation and the removal of the iodide ligand from the Pd centre (Scheme 3.8b). In both cases, a Cs-I-Pd interaction was crucial in the removal of the iodide ligand from the metal centre.[81] From calculations on a Ni-catalysed Csp^2-H activation reaction (Scheme 3.8c), a similar process emerged in a subsequent study from Musaev and Itami.[82] Here the Cs base (Cs_2CO_3) proved important in removing the pivaloyl anion from the metal centre after oxidative addition of the naphthyl pivaloate, and in the activation of the C-H bond, acting in this step as a base.[82] Thus, in these two processes, the CsF has the double role of a base and a Lewis acid to remove a soft counter-anion from the metal centre (iodide and pivaloyl).

In a study of the AgI-catalysed carboxylation of alkynes with CO_2, the removal of the iodide from the catalyst resulted in a high energy process, and the Cs ion, despite being involved in a stabilising interaction with the Ag catalyst, mostly appeared to be acting as a base and as a counter-cation for ionic species (Scheme 3.8d), and no other particular role was attributed to it.[83]

The Cs-I-Pd interactions calculated by Musaev and Yu are similar to the Cs-I-Cu interaction in complex **C18**, and the role of Cs in facilitating ligand exchange processes suggests that the Cs base may have a similar effect on the formation of the Cu(picolinamide)$_2$ complexes. Thus, it is possible that complex **C18** represents a "frozen" intermediate for the formation of the complexes (intermediate **B** in Scheme 3.9), its stability only due to the coordination to the mesityl rings. The ionic iodide-coordinated intermediate **A** (or a similar ionic structure) may then represent the yellow Cu(I) intermediate observed during the synthesis of the complexes (Scheme 3.4).



Scheme 3.9: *Possible mechanism for the formation of Cu(II)-picolinamide complexes*

^{133}Cs-NMR spectra of the complex were recorded to investigate the possible dissociation of CsI in solution (MeCN). The spectra were recorded by Mr Grant Sherborne and Mr Simon Barrett. Interestingly, comparison of the ^{133}Cs-NMR of complex **C18** in acetonitrile with pure CsI shows that no dissociation of CsI is obtained in solution, and a single peak is observed, falling at considerably different chemical shift from the CsI (39.82 ppm and 48.69 ppm respectively, Figure 3.11). Although this does not prove that the structure remains as in the solid state, it suggests that an interaction between the Cu(picolinamide)$_2$ complex and the CsI molecule is conserved in solution, either in an ionic form or in a neutral form. This may have importance in determining the role of the base in the synthesis of the Cu(II) complexes, and for the use of complex **C18** as a catalyst for the arylation of aryl ethers (see Chapter 4).

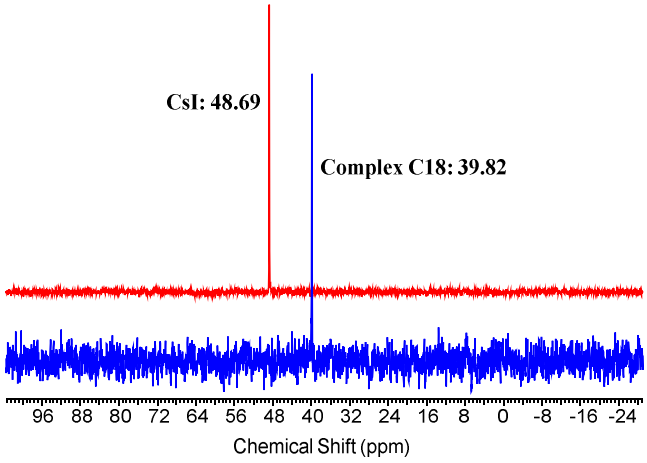


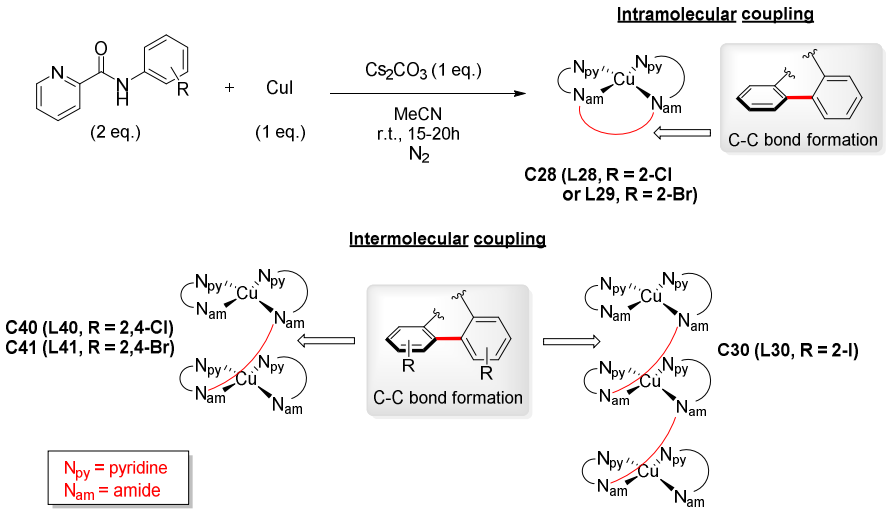
Figure 3.11: *^{133}Cs-NMR of pure CsI (red) and complex **C18** (blue)*

3.7 – Type V complexes

Ligands substituted on the phenyl ring with halogens can in theory be involved in Cu-catalysed couplings, and in particular ligands substituted in the position 2 of the phenyl ring, due to the closeness to the metal centre, which is at the base of group-directed C-H activation processes (see Scheme 2.2 in Chapter 2). Fluorinated ligands should not present reactivity of

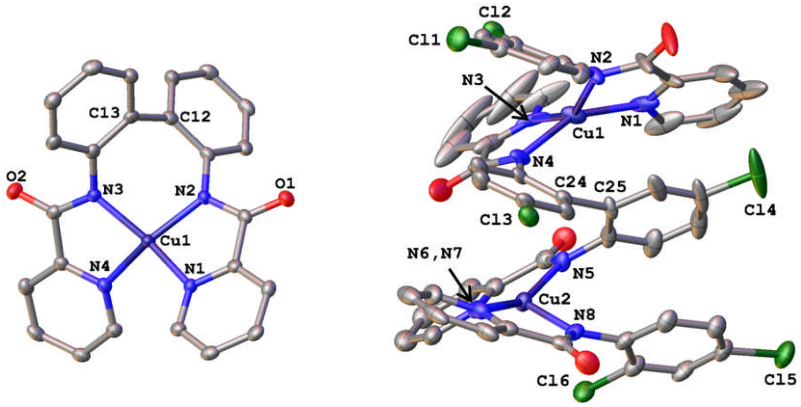
this kind, as they are not commonly involved in cross-coupling reactions, but chlorinated, brominated and iodinated ligands can potentially show a C-halogen bond activation.

As reported above, the complexation reaction of picolinamide ligands mono-substituted with halogens in positions 3 or 4 of the phenyl ring, and di-substituted in the 2,5 positions, resulted in the formation of complexes of type **I** or **II**. For fluorine-substituted ligands, type **I** complexes are also obtained for *N*-(2-fluorophenyl) and *N*-(2,4-difluorophenyl) substituted ligands **L27** and **L39**. However, when other *N*-(2-halophenyl) and *N*-(2,4-dihalophenyl) ligands were used (halogen = Cl, Br, I), a new type of complex was obtained. In type **V** complexes, two ligand molecules are coupled together through a new C-C bond, formed from the homocoupling of the 2-halogenated position of the phenyl rings. Interestingly, either an intramolecular version of this coupling, leading to the formation of a Cu mononuclear complex (**C28**), or an intermolecular version occurred, furnishing dinuclear (**C40** and **C41**) or trinuclear (**C30**) complexes, depending on the ligand used. Here "intramolecular" is used to indicate the coupling between two ligands around the same copper centre, while "intermolecular" refers to the coupling of two ligands attached to two different copper centres in the complex (Scheme 3.10).

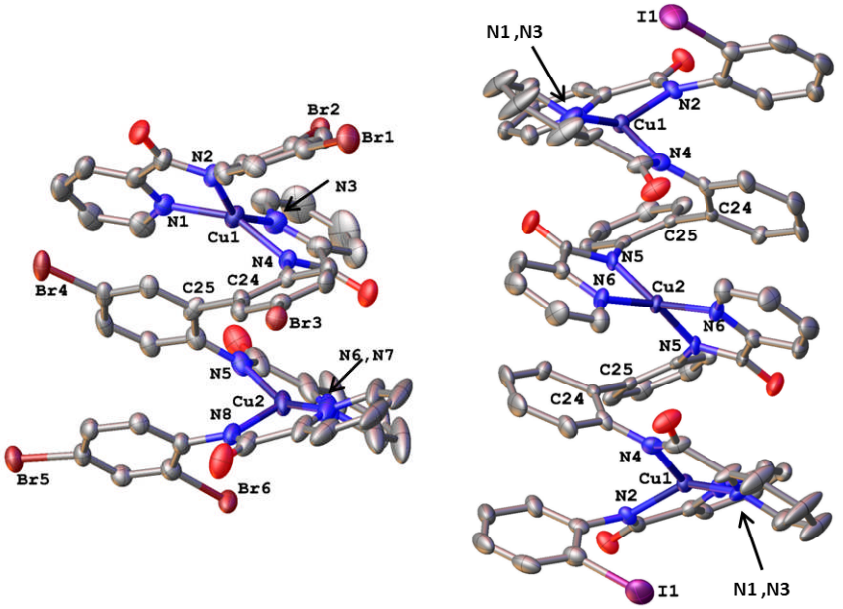


Scheme 3.10: *Synthesis of type* **V** *complexes*

The crystal structures of type **V** complexes are reported in Figure 3.12. The geometry around the metal centre in these complexes is not strongly influenced by the coupling between the two ligands, and the similarity to type **I** or **II** is reflected in the bond lengths and angles (Tables 3.7 and 3.8), comparable to those reported in Tables 3.2 and 3.4. The structure of dinuclear and trinuclear complexes is stabilised by internal π-π stacking interactions between the various aromatic rings of the ligands. An example is given in Figure 3.13, where at least two series of π-π stacking interactions can be observed in the spacefill model for complex **C41** (R = 2,4-Br).



a) Complex **C28** (R = 2-Cl / 2-Br) **b)** Complex **C40** (R = 2,4-Cl)



b) Complex **C41** (R = 2,4-Br) **a)** Complex **C30** (R = 2-I)

Figure 3.12: *Crystal structures of type **V** complexes*

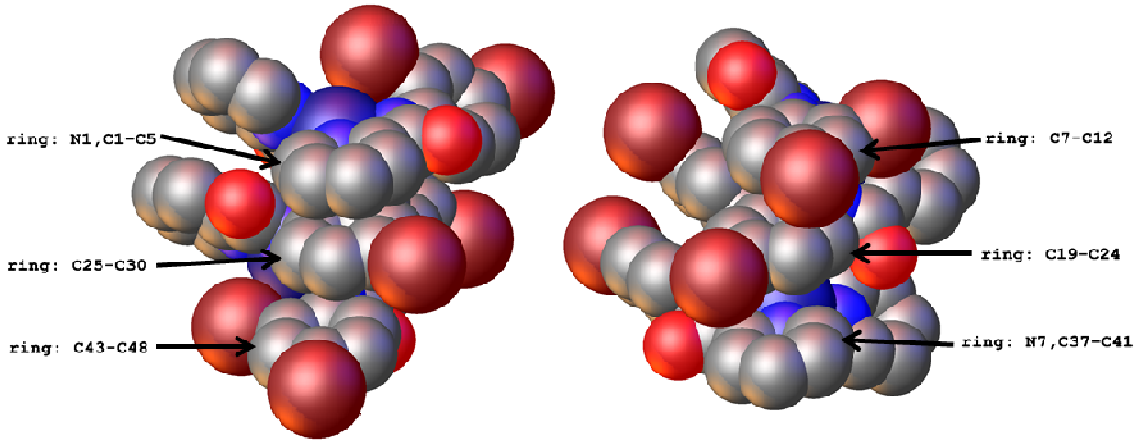


Figure 3.13: *π-Stacking interactions in complex **C41** (spacefill models)*

Table 3.7: *Selected bond lengths for type **V** complexes*[a]

	Complex (R)				
	C28 (2-Cl / 2-Br)		**C40** (2,4-Cl)	**C41** (2,4-Br)	**C30** (2-I)[c]
	Solvated (DCM)[b]	Hydrated			
Cu1-N1	1.999(4)	1.988(3)	1.984(8)	1.977(5)	1.983(11)
Cu1-N2	1.922(4)	1.938(3)	1.950(6)	1.951(5)	1.976(10)
Cu1-N3	1.940(4)	1.931(3)	1.981(8)	1.982(6)	1.984(11)
Cu1-N4	1.982(4)	1.987(3)	1.922(6)	1.922(5)	1.944(11)
Cu2-N5	/	/	1.942(6)	1.944(6)	1.940(10)
Cu2-N6	/	/	1.988(7)	1.987(6)	1.982(10)
Cu2-N7	/	/	1.983(6)	1.991(6)	1.982(10)
Cu2-N8	/	/	1.935(6)	1.957(6)	1.940(10)

[a] Cu2 refers to the second Cu centre in di- or trinuclear complexes, not a second molecule in the asymmetric unit

[b] Two Cu(ligand) units in the asymmetric unit, only data for one molecule are reported

[c] N7 = $N6^1$and N8 = $N5^1$ for complex **C30** (half molecule in the asymmetric unit)

Table 3.8: *Selected bond angles for type **V** complexes*[a]

	Complex (R)				
	C28 (2-Cl / 2-Br)		**C40** (2,4-Cl)	**C41** (2,4-Br)	**C30** (2-I)[c]
	Solvated (DCM)[b]	Hydrated			
N1-Cu1-N2	83.48(16)	83.80(14)	84.1(3)	84.2(2)	84.1(4)
N3-Cu1-N4	83.84(16)	83.78(14)	83.2(3)	83.2(2)	83.8(5)
N1-Cu1-N3	152.32(16)	151.99(14)	104.0(4)	103.0(2)	104.0(5)
N2-Cu1-N4	153.27(16)	151.43(14)	103.6(3)	104.6(2)	104.2(5)
N1-Cu1-N4	105.11(16)	103.92(13)	152.0(3)	152.2(2)	152.5(4)
N2-Cu1-N3	100.32(16)	102.38(14)	149.4(3)	149.1(2)	146.4(4)
N5-Cu2-N6	/	/	82.8(3)	83.5(3)	84.2(4)
N7-Cu2-N8	/	/	83.0(3)	82.6(3)	84.2(4)
N5-Cu2-N7	/	/	153.0(3)	152.7(3)	149.3(4)
N6-Cu2-N8	/	/	148.3(3)	148.8(3)	149.3(4)
N5-Cu2-N8	/	/	103.4(3)	103.0(2)	106.5(6)
N6-Cu2-N7	/	/	105.6(3)	105.6(3)	101.4(6)

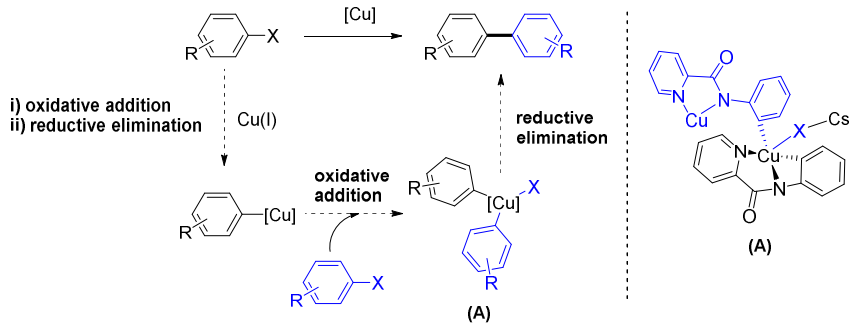
[a] Cu2 refers to the second Cu centre in di- or trinuclear complexes, not a second molecule in the asymmetric unit

[b] Two Cu(ligand) units in the asymmetric unit, only data for one molecule are reported

[c] N7 = $N6^1$and N8 = $N5^1$ for complex **C30** (half molecule in the asymmetric unit)

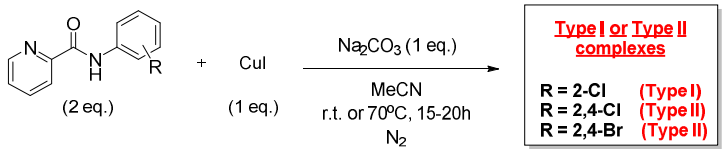
Despite the potential theoretical reactivity of the 2-halogenated picolinamide ligands discussed above, the formation of these complexes was completely unexpected for several reasons: i) 2,5-dihalogenated ligands did not form these type of complexes, although, from a steric hindrance point of view, no obvious limitations can be observed (from the analysis of the crystal structure) to the formation of the same type of complexes; ii) the complexation reactions were performed at room temperature, at which a coupling process mediated by Cu is generally ineffective. The reasons for the formation of these compounds are being investigated through computational studies, but this unusual reactivity prompted some control experiments aimed to identify a possible mechanistic pathway.

The formation of biaryls mediated or catalysed by Cu sources has been a known process for more than a century, as described in Chapter 1 of this thesis, but historically it required temperatures as high as 200°C, and generally strong electron-withdrawing substituents on the phenyl rings to be coupled.[85-87] Room temperature reactions have been reported in the last decades,[88] but these are still relatively rare exceptions. The mechanism for this coupling is generally thought to involve at least one oxidative addition process from Cu(I) to Cu(III).[87, 89] In the case of type **V** complexes, the coordination of the copper to at least one molecule of ligand has to be assumed before the formation of the C-C bond, to explain the directing-group effect on the *ortho* halogen. Therefore, the Cu(III) intermediate derived from an oxidative addition would be a negatively charged species, and would require a suitable counter-cation, such as the large Cs ion from the base, possibly coordinating through a Cu-X-Cs bridge as in type **IV** complex (Scheme 3.11).

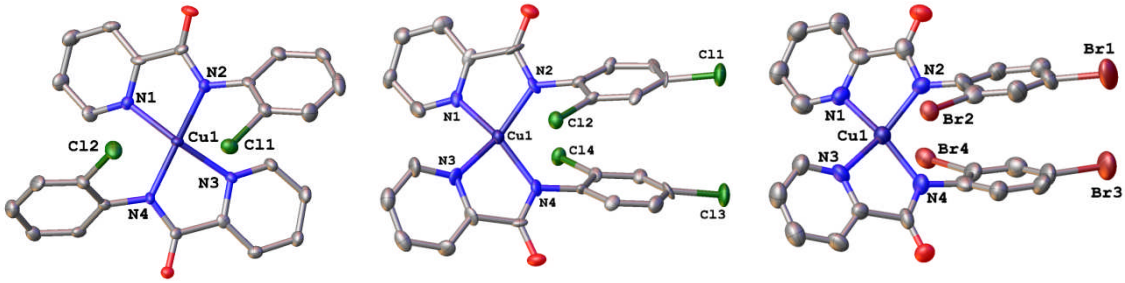


Scheme 3.11: *Hypothesised mechanism and Cu(III) intermediate for the formation of type* ***V*** *complexes*

This reasoning suggested the modification of the synthetic procedure for these complexes into that reported in Scheme 3.12, utilising Na_2CO_3 (with a considerably smaller cation) as base. Interestingly, the use of this base resulted in the formation of type **I** or type **II** complexes (Scheme 3.12), as identified by X-ray crystallography (complexes **C28$_{Na}$**, **C40$_{Na}$** and **C41$_{Na}$**, Figure 3.14). Crystal structures for the corresponding complexes with 2-Br and 2-I ligands (**L29** and **L30**) could not be obtained. Bond distances and angles for these complexes are reported in Tables 3.2 and 3.4, together with the other type **I** and type **II** complexes.



Scheme 3.12: *Inhibition of the C-halogen bond activation by the use of Na_2CO_3*



a) Complex **$C28_{Na}$** (R = 2-Cl)

b) Complex **$C40_{Na}$** (R = 2,4-Cl)

b) Complex **$C41_{Na}$** (R = 2,4-Br)

Figure 3.14: *Structures of type **I** and **II** complexes with ortho-halogenated ligands*

Interestingly, complex **$C28_{Na}$** crystallises with NaI_3 (ratio Cu(picolinamide)$_2$ / NaI_3 = 3/1), evidently formed during the reaction. The coordination of the Na ion to six Cu(picolinamide)$_2$ units (Figure 3.15) results in and extended tridimensional structure at the solid state. The formation of the I_3^- ion is not clear in these conditions, and it was not observed in other cases.

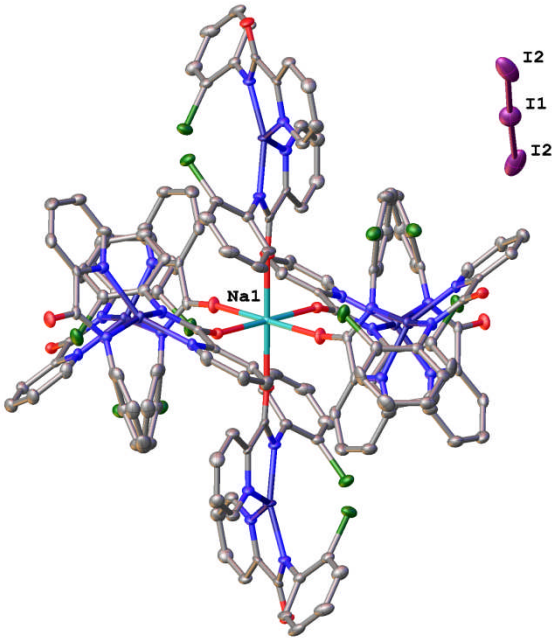


Figure 3.15: *Octahedral structure around Na in complex **$C28_{Na}$***

The effect of Na_2CO_3 in inhibiting the activation of the C-halogen bond demonstrates the crucial role of the Cs ion (and therefore of the base used) in this process. Moreover, given that

the activation of the aryl halide is supposed to be the rate-determining step in other Cu-catalysed cross couplings (such as C-O and C-N bond formation) as well, it might be possible to envisage the same role of the base in these processes. The development of these results may thus be very important in determining some of the causes of the "caesium effect" in Cu-catalysed processes, which have not, until now, been investigated.

3.8 – Summary

The results of an investigation upon complexation of CuI with picolinamide ligands, under conditions similar to those employed for catalysis, have been reported in this chapter. The interaction between ligand, CuI and Cs_2CO_3 in acetonitrile gave rise to Cu(II) complexes, possibly through oxidation by the solvent. Five different types of complexes were obtained, where the copper centre coordinates to two ligand molecules. Types **I** and **II** only differ by the stereochemical arrangement of the ligands, respectively *trans* or *cis*, in a distorted square planar geometry. Type **III** complex **C26** shows additional coordination of a water molecule to the metal centre, while type **IV** complex **C18** shows an unusual Cu-I-Cs bridging interaction, probably stabilised by the coordination of the Cs ion to the mesityl rings. No dissociation of CsI was detected in solution for this complex, so this interaction may be present during the catalytic process when using ligand **L18**. Finally, type **V** complexes were obtained with ligands *N*-(2-halophenyl) or *N*-(2,4-dihalophenyl)picolinamide ligands (halogen = Cl, Br, I). The *ortho* C-halogen bonds in these complexes are activated by the caesium base, and C-C bonds are formed between ligands, leading to mononuclear, dinuclear or trinuclear new species. C-halogen bond activation did not occur using Na_2CO_3 as base, proving the important role of the caesium base in the process. Type **II-V** complexes with picolinamide ligands have not been reported before.

3.9 – References

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Chapter 4:

Mechanistic investigations

4.1 – Introduction

Once determined that picolinamides are effective ligands in copper-catalysed arylation reactions (Chapter 2), mechanistic investigations were undertaken. Anionic ligands have not been commonly explored from the mechanistic point of view; only Lei[1, 2] and Taillefer/Jutand[3, 4] have reported experimental studies on this field. Anionic ligands can behave in a very different way than the classical neutral ligands such as phenanthroline and neutral bidentate amines, for a number of reasons. Firstly, the addition of a negative charge in the catalytic species due to the ligand would result in an extra counter-cation, if an active species similar to those with neutral ligands is to be assumed (see Chapter 1, section 1.5). Positively charged species, able to act as counter-cations in copper catalysed couplings, can be other copper species, such as those reported by Hartwig and Davies,[5-8] or can be derived from the inorganic base, as observed by Hartwig and Shyu.[7, 9] In the latter case, the role of the base would be even more important in the reaction when using anionic ligands, rather than neutral. Secondly, when Cu(I) salts react with neutral ligands in conditions similar to those employed for catalysis, Cu(I) complexes are obtained (*e.g.* Cu(I)-phenanthroline, Cu(I)-bipyridine or Cu(I)-diamine are common complexes), while with anionic ligands, Cu(II) complexes are easily formed (*e.g.* Cu(II)-amino-acid or Cu(II)-diketone complexes), and Cu(I) complexes with anionic ligands are generally obtained only when a second, neutral ligand is added.[10-13] This may occur through disproportionation or oxidation processes. The case of picolinamides has been discussed in Chapter 3, and the same behaviour was observed with aryl-substituted β-diketonate ligands in acetonitrile, during investigations performed by Mr. Elliot Steeples (Master's project, McGowan group, Leeds, 2013).

The formation of Cu(II) species with these ligands may suggest that completely different species are present at the beginning of the catalytic process, and may result in a different mechanism than the one typically accepted. Thus, mechanistic investigations on these ligands are important to improve the general knowledge of the transformations involved in the coupling process. The results of the investigations undertaken with this purpose, for the arylation of phenols in acetonitrile with picolinamide ligands, will be reported and discussed in this chapter.

4.2 – Reproducibility of the reaction

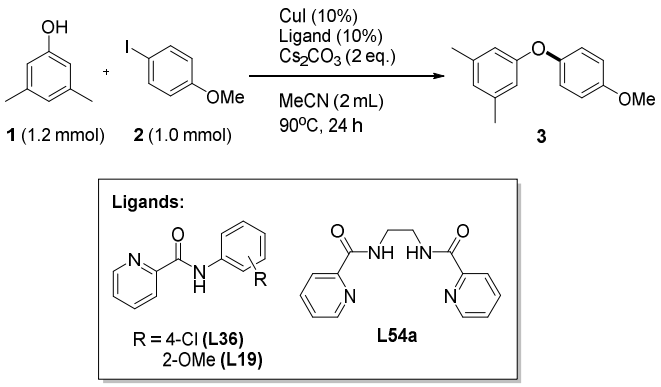
Not much information is found on the literature on reproducibility issues of copper-catalysed arylation reactions. Nonetheless, the author has been in contact, during these studies, with other researchers involved in the field, who reported serious irreproducibility problems, even using the same reaction conditions throughout their studies. In particular, Mr. Robert Cox

(PhD candidate, Lloyd-Jones group, Edinburgh), reported general irreproducibility for the arylation of potassium phenoxide, that could be solved by the addition of small amounts of phenol into the reaction; Dr. Matthew Scott (PhD, Spring group, Cambridge) reported that a phenol arylation process was dependent on the stirring rate used during the reaction, and on the different physical properties (such as particle size) of the base used, in that case Cs_2CO_3; Mr. Grant Sherborne (PhD candidate, Nguyen group, Leeds) reported irreproducibility issues in the arylation of pyrrolidinone under a nitrogen atmosphere.

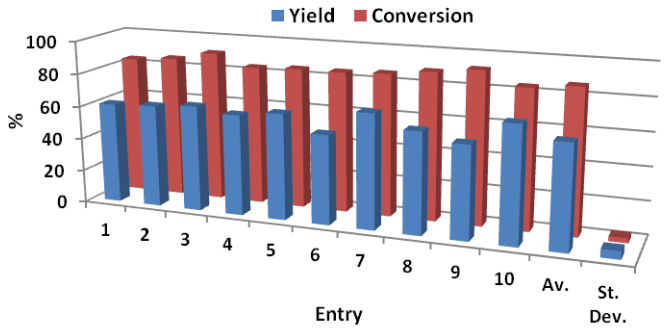
In the latter case, the irreproducibility was due to a non-adequate sampling method: no irreproducibility was observed after a more efficient method was developed. In the case of the dependence on stirring rate and base properties observed by Dr. Scott, this is explainable considering that the use of inorganic bases often results in heterogeneous systems, due to low solubility in the organic solvents used in the reaction.[14] It is thus clear that slow stirring or different surface area of the particles of the base may strongly influence the reaction outcome. These problems can be easily avoided by being consistent with the stirring rate and the chemicals employed for the reactions, in particular for the base, used in these reaction in large excess (even the hygroscopicity is important in this case). Many examples have been reported in the literature about the different performance of bases with different properties and from different commercial sources.[15-19] Similar effects have been also observed for the catalyst employed, due to impurities.[20] In the case of a heterogeneous system, even the shape and size of the reaction vessel and the stir bar used may influence the reaction.

For the reactions reported in this thesis, the same commercial sources of chemicals and solvent were always used (these are reported in experimental section, Chapter 6), and the reactions were always performed in carousel tubes of the same size and shape, and using the same type of stir bars, at a stirring rate of 1000 rpm, so to avoid irreproducibility issues related to physical variables. At the end, the reaction mixture can be sonicated for a few seconds, and the tube walls can be scratched with a spatula, which helps breaking possible chunks of solid formed during the cooling, and recovering all the product eventually deposited on the tube walls, further reducing the sources of irreproducibility. Furthermore, all the tubes used were, after the reaction, washed rigorously to remove any trace of chemicals left and possible metallic copper formed during the reaction (*vide infra*). The accurate cleaning procedure is reported in the experimental section.

During these PhD studies, some investigations on the reproducibility of the reaction have been undertaken to ascertain that the data were reliable. Some of the early experiments involved repeats with different ligands, chosen randomly among the picolinamide ligands synthesised, for the synthesis of aryl ether **3** (Scheme 4.1); these results are reported in Figures 4.1-4.3.

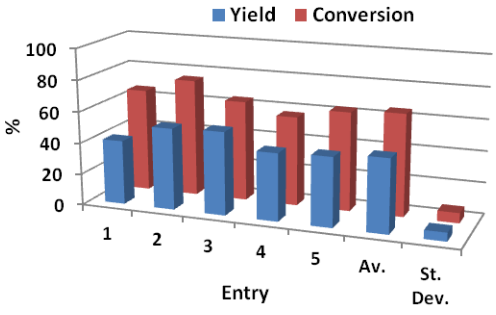


Scheme 4.1: *Synthesis of aryl ether **3***



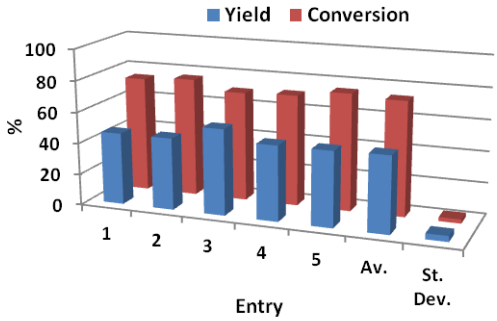
	1	2	3	4	5	6	7	8	9	10	Av.	St. Dev.
Yield	61	62	64	61	64	54	69	61	56	70	62.2	4.98
Conversion	84	86	91	84	85	85	86	89	92	84	86.6	2.99

Figure 4.1: *Synthesis of **3**: reproducibility with **L36** (^{1}H-NMR yields)*



	1	2	3	4	5	Av.	St. Dev.
Yield	41	52	53	43	44	46.6	5.50
Conversion	66	75	64	57	63	65	6.52

Figure 4.2: *Synthesis of **3**: reproducibility with **L19** (^{1}H-NMR yields)*

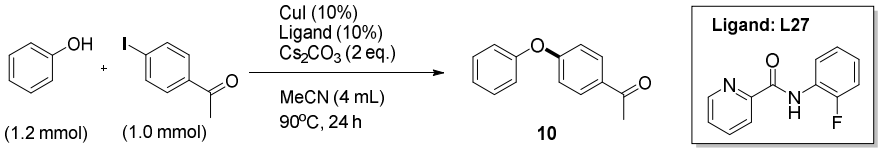


	1	2	3	4	5	Av.	St. Dev.
Yield	46	46	55	48	48	48.6	3.71
Conversion	74	76	70	71	75	73.2	2.59

Figure 4.3: *Synthesis of **3**: reproducibility with **L54a** (^{1}H-NMR yields)*

The results of 5 or 10 repeats with the three ligands do not show large differences in either yields or conversions (yields refer to the amount of aryl ether formed, conversions refer to the amount of aryl halide reacted), although differences of about 10% were observed (N.B.: a minimum of ±2% error on the ^{1}H-NMR is assumed).

Reaction profiles were also recorded to investigate the reproducibility (N.B.: all reaction profiles reported in this chapter were recorded through GC measurements, for which a minimum of ±5% error is assumed). In Figure 4.4 are reported the results for three parallel runs of the synthesis of aryl ether **10** (Scheme 4.2), while Figure 4.5 reports two repeats of the competition experiments for the formation of aryl ethers **8** and **10** (Scheme 4.3) with two ligands.



Scheme 4.2: *Synthesis of aryl ether **10***

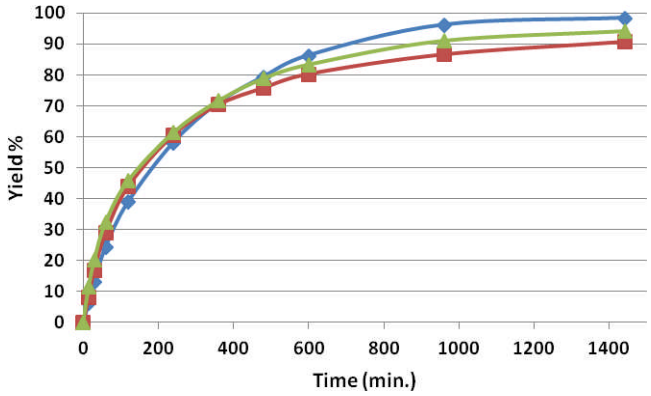
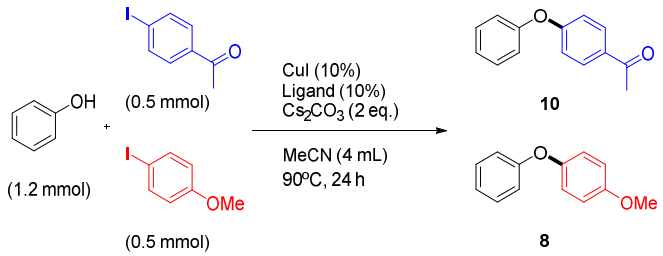
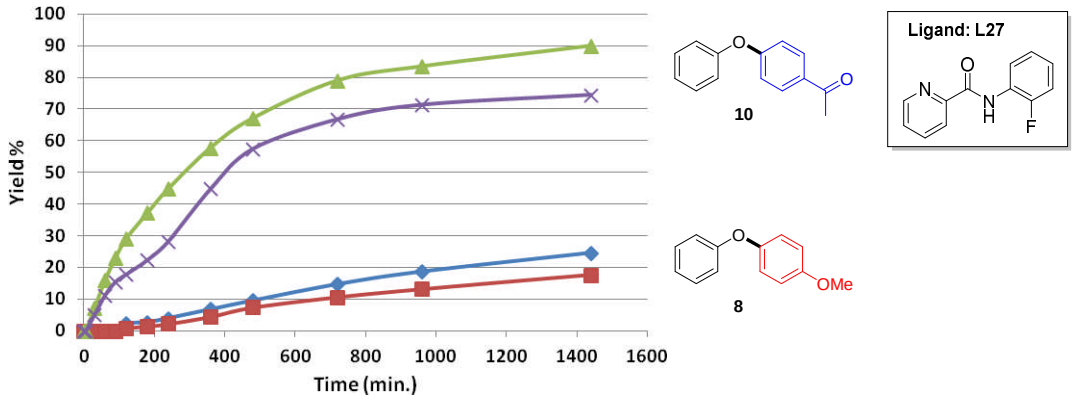


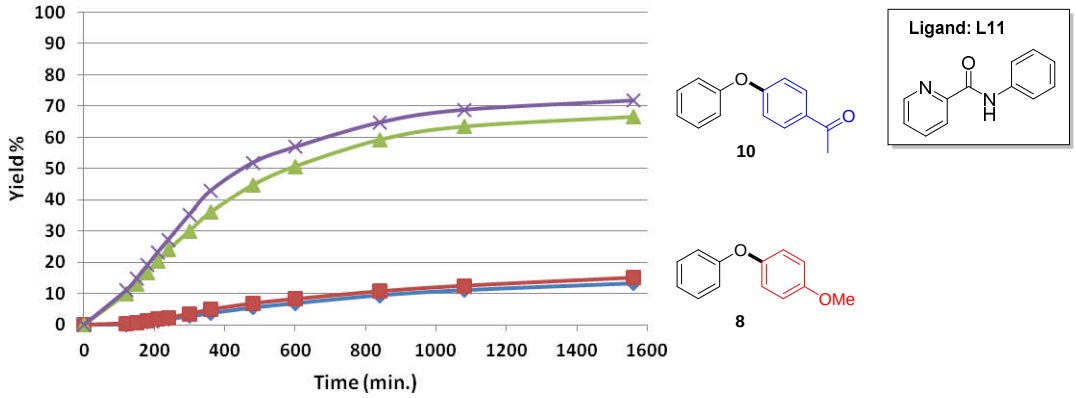
Figure 4.4: *Three parallel reaction profiles for the synthesis of aryl ether **10***



Scheme 4.3: *Competing formation of aryl ether **8** and **10***



a) L27



b) L11

Figure 4.5: *Profiles for competition experiments (esters **8** and **10**) with **L27** and **L11***

Although the profiles are not perfectly overlapping in the graphs reported, it is clear that in general the reproducibility of the reaction in these conditions is not an issue, and the results for parallel runs are comparable. The similar trends observed during the optimisation screenings in acetonitrile and in green solvents reported in Chapter 2 also demonstrate that no relevant irreproducibility issues arise in the experimental conditions explored. This is important in view of the experiments that will be reported later in this chapter.

4.3 – General observations from the catalytic reactions

As described in Chapter 1, the mechanism for copper-catalysed arylations has not been completely understood, and different mechanisms are actually possible depending on the catalytic system and the experimental conditions employed. At this point, it is useful to summarise some the typical features of the formation of aryl ethers under the optimised conditions reported in Chapter 2:

- The reactions can be performed in air, but depending on the ligand employed, air-free conditions result in better results or in very similar results (solvent: MeCN, see Chapter 2, Figures 2.2 and 2.5);

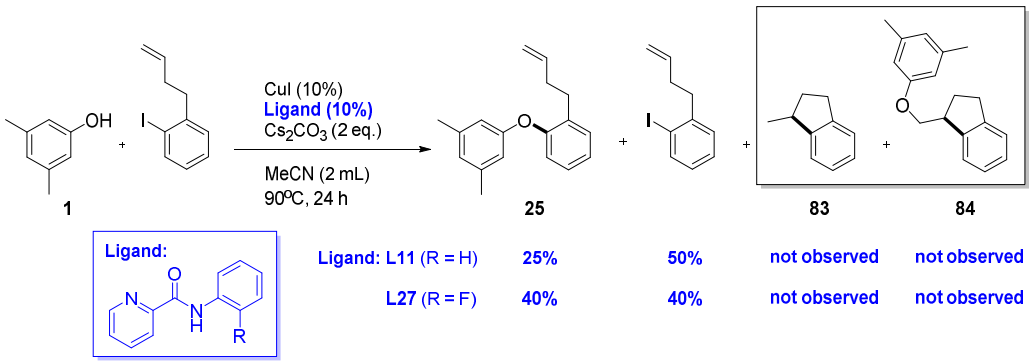
- At the end of the reactions, Cu(II)-picolinamide complexes can be recovered from the crude mixture of reactions under air, either using MeCN or *i*-PrOAc as solvent; a green colour is also observed at the beginning of these reactions;
- Although the reactions performed under air-free conditions remained generally of a clearer colour than the reactions under air (dark / brown at the end), some blue-green solid was also formed in these conditions, suggesting the formation of Cu(II) compounds under anaerobic conditions too;
- Although it was not generally observed in acetonitrile, the reactions in *i*-PrOAc under air often resulted in the formation of a copper mirror at the bottom of the tube.

These observations seem to suggest that Cu(0), Cu(I) and Cu(II) species could all be involved in the reaction, and, while atmospheric oxygen may play an important role in oxidation processes, other oxidation or reduction processes may be involved, derived from internal interactions (*e.g.* disproportionations and comproportionations).

4.4 – Radical trap / clock experiments on the aryl halide

Cu(II) species can be formed from Cu(I) during reaction occurring *via* radical mechanisms (see Chapter 1). The formation of (supposedly) Cu(II) species at the beginning of the reaction, and their recovery at the end of the catalysis, therefore, might be considered as an indication of a radical mechanism. Moreover, as radical reactions are known to be inhibited by molecular oxygen naturally present in the air, the different effect of air-free conditions depending on the ligand (Chapter 2, Figures 2.5), could in theory be associated to different degrees of radical mechanism in reactions with different ligands.

Radical clock experiments (Chapter 1, Scheme 1.13) are often performed as control reactions in Cu-catalysed couplings to ascertain the formation of free radicals from the aryl halide, according to the SET mechanism.[5-7, 21-26] Positive results were only obtained for reactions under photochemical conditions,[21] and a small amount (5%, accounting for a fourth of the converted starting material) of radical product was observed during a C-F coupling.[26] The reaction of 2-(3-butenyl)iodobenzene (the most common radical clock for these couplings) with 3,5-dimethylphenol **1** was thus performed either with unsubstituted ligand **L11** and 2-fluoropicolinamide **L27**, to investigate the possibility of a different mechanism with the two ligands. However, only the coupling product **25** could be obtained from these experiments, together with the recovery of the initial iodobenzene (Scheme 4.4).



Scheme 4.4: *Radical clock experiments on the aryl iodide (isolated yields)*

The coupling product and the starting material recovered for the two reactions account for 75-80% of the aryl iodide precursor, and the bicyclic products **83** and **84**, which are supposed to be formed under radical conditions, were not recovered or observed in the crude ^{1}H-NMR spectrum, where only the starting material and product **25** could be detected (Figure 4.6). Peaks characteristic of the radical derived product would fall between 1.2 and 1.7 ppm, and at 3.2 ppm.[27]

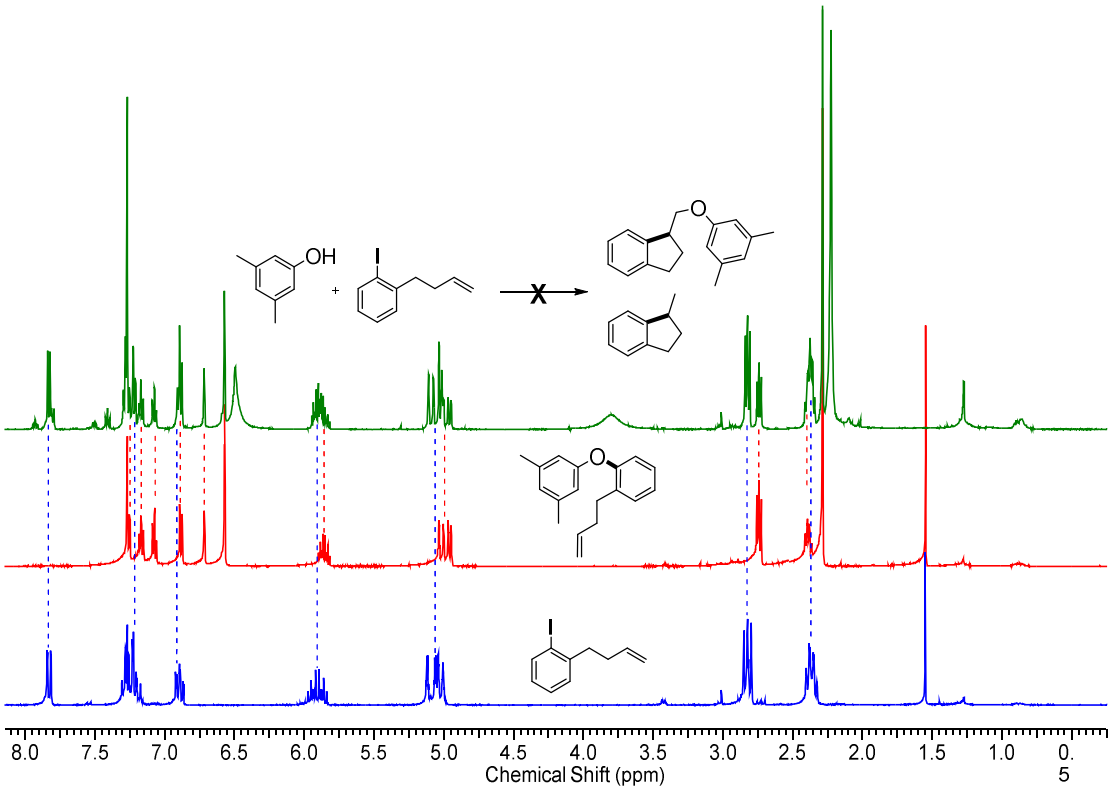
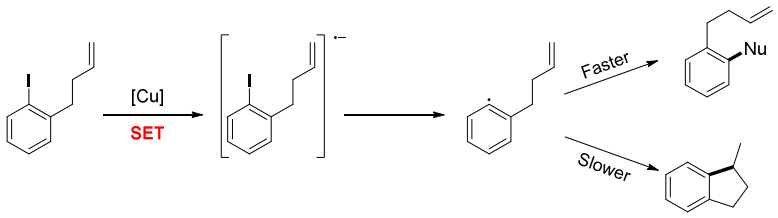


Figure 4.6: *Comparison of ^{1}H-NMR spectra of: butenyl-iodobenzene (blue), aryl ether **25** (red) and crude mixture (green)*

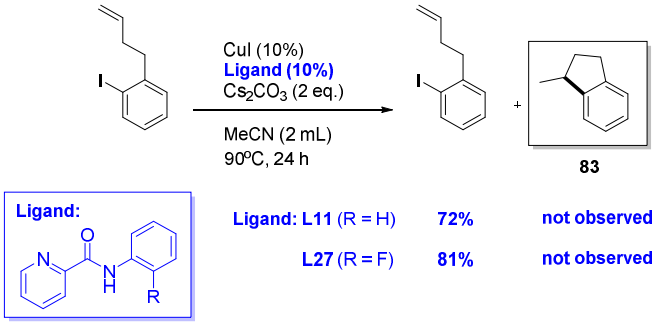
It has been suggested by different authors that, as the two reactions are competitive, after the formation of the radical derived from the SET activation of the aryl iodide, the coupling

with the nucleophile may actually take place more quickly than the radical closure (Scheme 4.5).[21, 28]



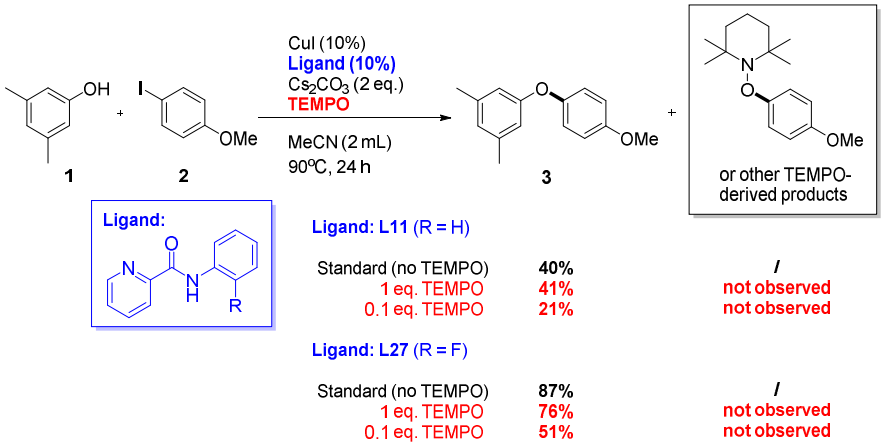
Scheme 4.5: *Competing coupling reaction and radical closure*

However, this radical cyclisation has been calculated to be very fast (the rate constant at room temperature is in the range of 10^8 – 10^9 s^{-1}),[29] and no proof supporting the hypothesis of a faster coupling has been presented. Therefore, an experiment was undertaken without the addition of phenol (Scheme 4.6). Even in this case, the radical closure product was not observed, and 72% and 81% of the starting material was recovered respectively with **L11** and **L27**.



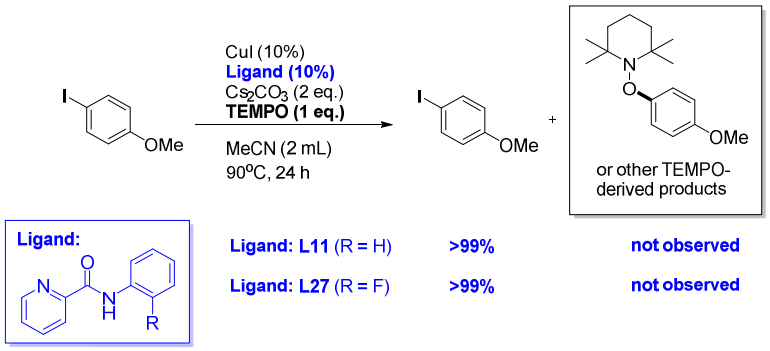
Scheme 4.6: *Radical clock experiments, no nucleophile added (isolated yields)*

Two similar series of reactions were performed with the radical trap TEMPO (Scheme 4.7). Adding 1 eq. of TEMPO to the reaction between 3,5-dimethylphenol (**1**) and 4-iodoanisole (**2**), the aryl ether **3** was obtained in similar yields than those in the standard conditions (*i.e.* without TEMPO). Interestingly, however, when only 10% of TEMPO was added, a considerable inhibition was observed with both ligands **L11** and **L27**.



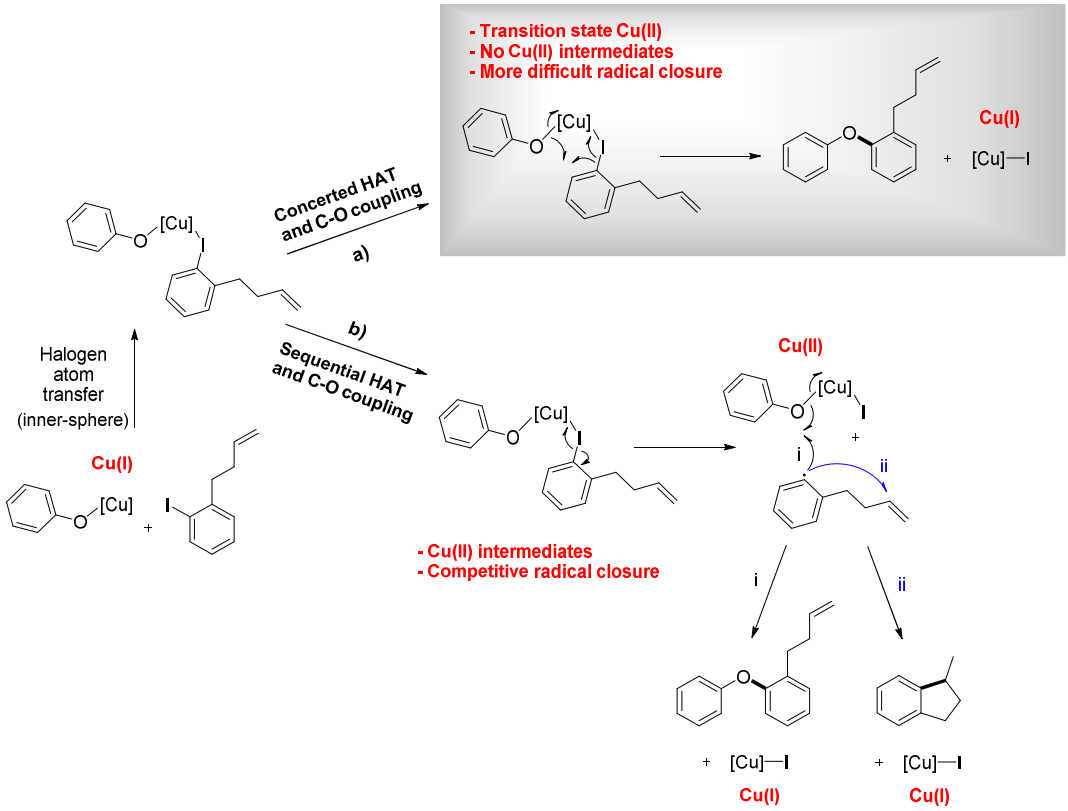
Scheme 4.7: *Radical trap experiments (GC yields)*

When one equivalent of TEMPO was used with the iodoanisole alone in the reaction conditions, all the starting material was detected after 24h (Scheme 4.8).



Scheme 4.8: *Radical trap experiments, no nucleophile added (GC yields)*

These results suggest that no free radicals from the aryl halide are formed in the reaction (Schemes 4.4, 4.6-4.8) although the inhibition of the reaction with catalytic amounts of TEMPO is not easily explainable without a deeper investigation (the oxidising properties of TEMPO also need to be considered). However, the results of these experiments do not exclude the possibility of a different mechanism, such as an inner-sphere electron transfer (Halogen Atom Transfer, HAT, Scheme 4.9), where the nucleophile-bound Cu catalyst would be connected to the aryl halide, and a concerted coupling with the nucleophile could be possible (**a**). If the C-O coupling did not occur through a concerted mechanism, a free radical would be formed through HAT, and the radical closure would become competitive (**b**).

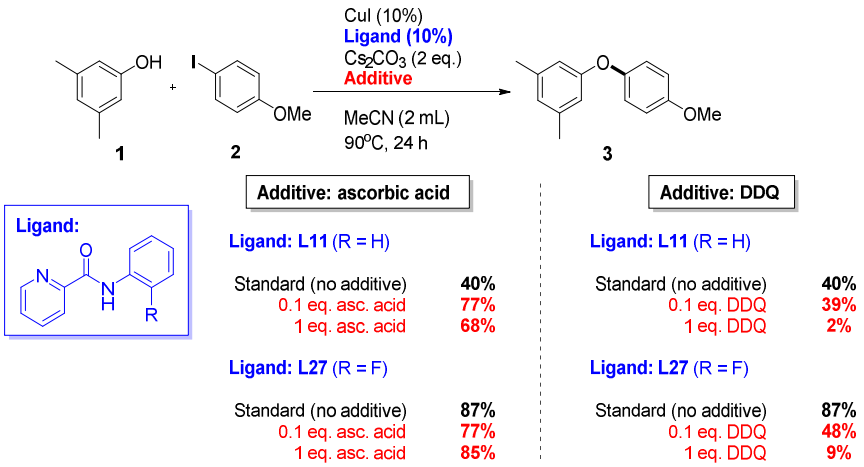


Scheme 4.9: *Possible Halogen Atom Transfer (HAT) mechanisms*

4.5 – Ligand effect on the Cu(II) / Cu(I) reduction

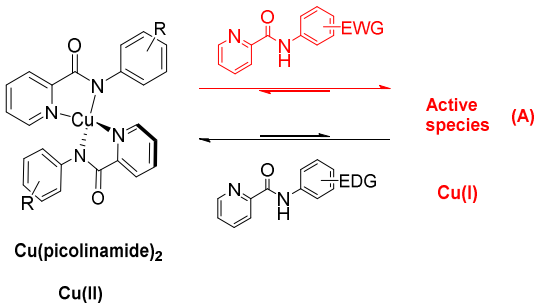
Ligands **L11** and **L27** showed the same behaviour toward the radical clock/trap experiments, suggesting that the different results obtained from the reaction under air (Chapter 2, Figure 2.5) are not due to differences in the mechanism. Therefore, the reason must be found in other properties of the ligand. The most obvious difference in the two ligands is the different electronic effect of the substituent on the phenyl ring. Hence, the question was if this effect could be enough to account for this difference, and how this variable could enter in the mechanistic process. Experiments were performed as a proof of concept.

A reductant and an oxidant were added to the reaction with the two ligands, under air. *L*-ascorbic acid and DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) were chosen respectively, being commonly used in transition metal-catalysed transformations.[30-39] The results are reported in Scheme 4.10.



Scheme 4.10: *Effect of reductant and oxidant in the reaction*

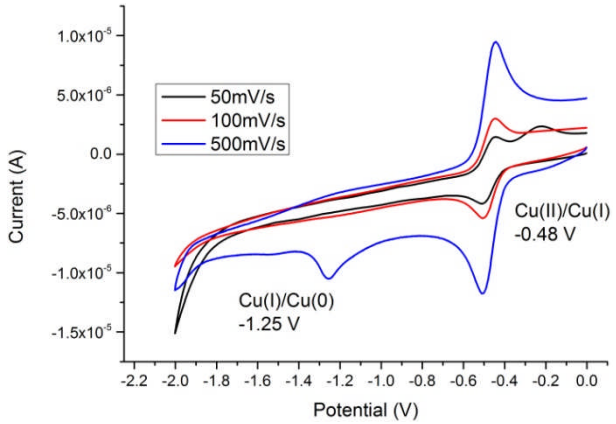
The addition of a reducing agent in the reaction with **L11** resulted in a notable increase in the yield of product **3**, while the same addition has almost no effect on the reaction with **L27**. On the contrary, the addition of a catalytic amount of oxidant (DDQ) in the reaction results in no inhibition using **L11**, while a considerable inhibition is observed with **L27**. Finally, the addition of a full equivalent of DDQ completely inhibits the reaction with both ligands. These results show that the two ligands strongly influence the redox properties of the catalytic system, suggesting in practise contrasting behaviour. Hypothesising that Cu(II) complexes such as those recovered from the catalytic reaction (see Chapter 3) may be formed during catalysis, and actually involved in the process, a possible step of the mechanism might be the reduction of the Cu(picolinamide)$_2$ complexes to the active Cu(I) species. On the basis of the results above, the different substituents on the ligand may have important repercussions on the reduction of the Cu(picolinamide)$_2$ complex to form the active Cu(I) species, thus influencing the reactivity by controlling the amount of active species present during the reaction. EWG-substituted picolinamide ligands make the reduction favoured, so the addition of a reductant in the reaction is not necessary, and has no effect on the coupling (Scheme 4.10, ligand **L27**). On the other hand, with less electron-withdrawing ligands, the formation of the Cu(II) species is more favoured, and the addition of a reductant is therefore required to form the active species and make the reaction work better (Scheme 4.10, ligand **L11**). This effect is summarised in Scheme 4.11. The process in Scheme 4.11 would also explain the effect of an oxidant in the reaction: the addition of DDQ in the reaction with EWG-substituted ligand shifts the equilibrium Cu(I)/Cu(II) toward the oxidised species, while with **L11**, being the Cu(II) already preferred, a catalytic amount of DDQ has almost no effect.



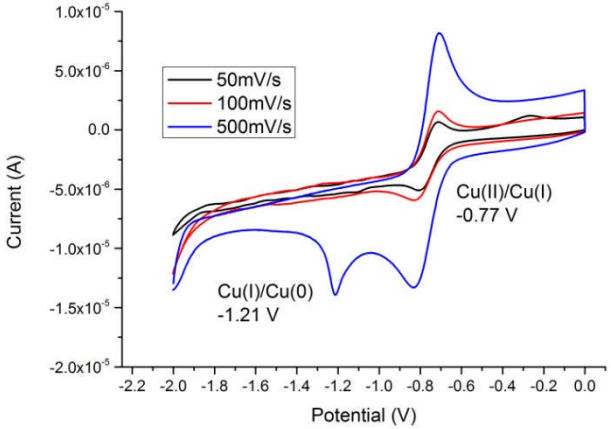
Scheme 4.11: *Possible effect of the substituents on the reduction of Cu(II) complexes*

To verify the hypothesis of such an effect on the reduction of Cu(picolinamide)$_2$ complexes, the redox behaviour of type **I-III** complexes was studied through cyclic voltammetry experiments. These measurements were performed in acetonitrile using [NBu_4][BF_4] as supporting electrolyte (0.1 M), at scan rates of 100, 500 and 1000 mV/s, between a potential window from 0 V to -2 V. The voltammograms for complexes of type **I-III** are reported in Table 4.1 (see Chapter 3 for complex types). Cyclic voltammetry for complexes **C23** (R = 3-NO_2) and **C34** (R = 3-I) could not be performed due to the low solubility of these complexes in acetonitrile under the experimental conditions.

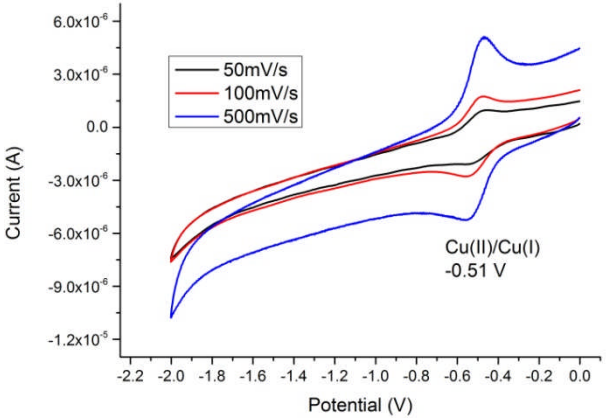
Table 4.1: *Cyclic voltammograms of type **I-III** complexes*



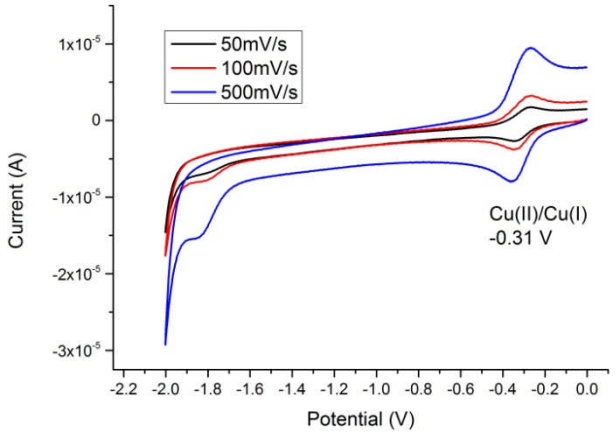
C11 (R = H)



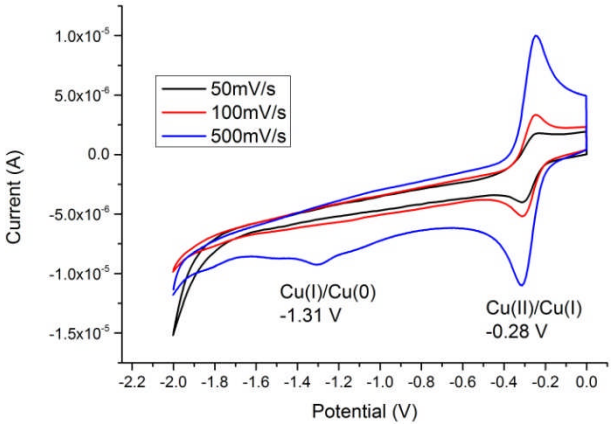
C20 (R = 2,4-OMe)



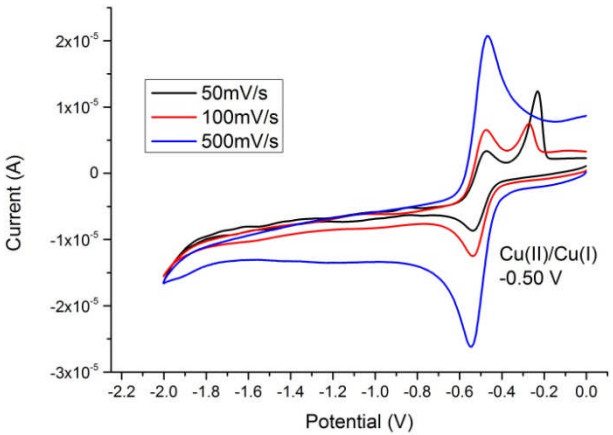
C22 (R = 2-Cl-6-Me)



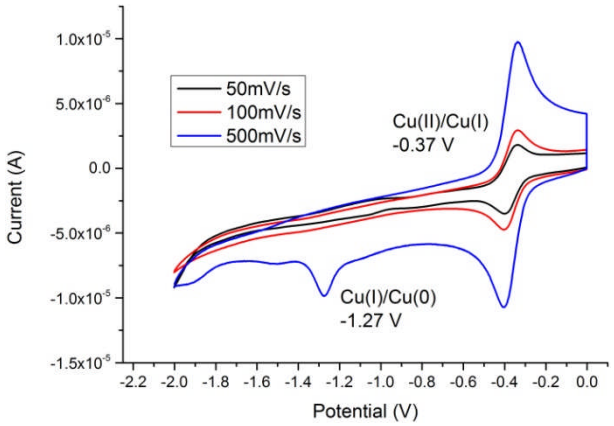
C25 (R = 4-Ac)



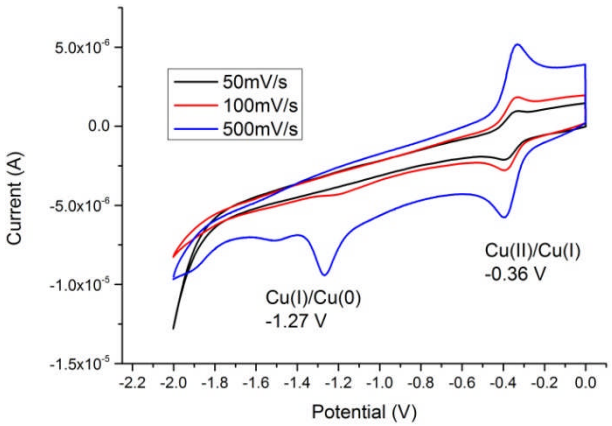
C26 (R = 3,5-CF_3)



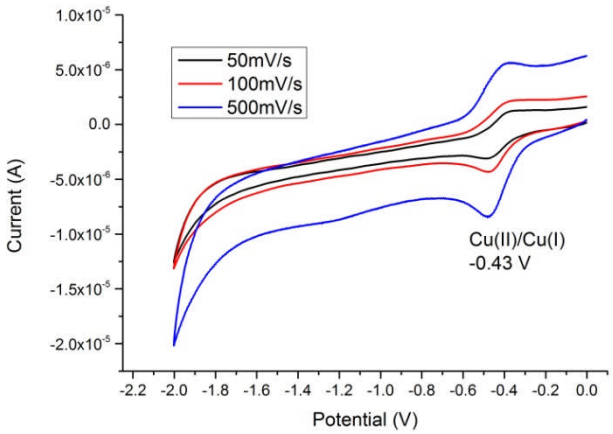
C27 (R = 2-F)



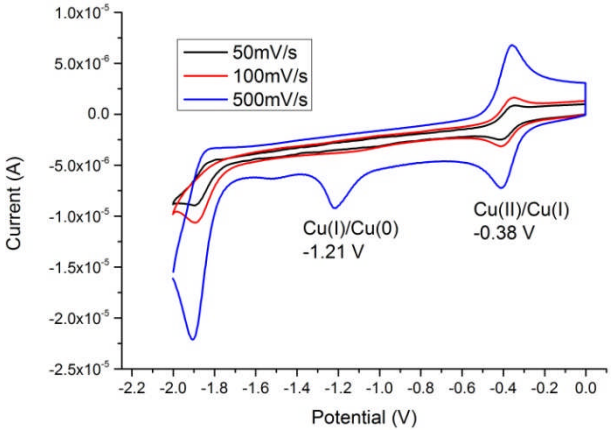
C31 (R = 3-F)



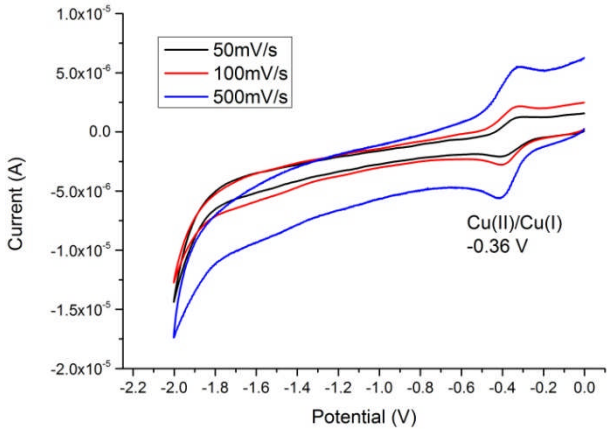
C32 (R = 3-Cl)



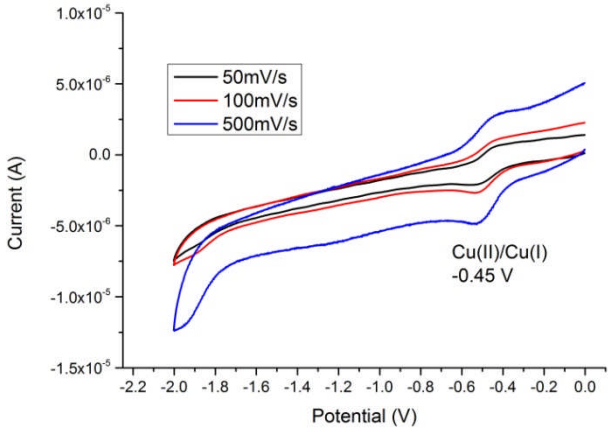
C35 (R = 4-F)



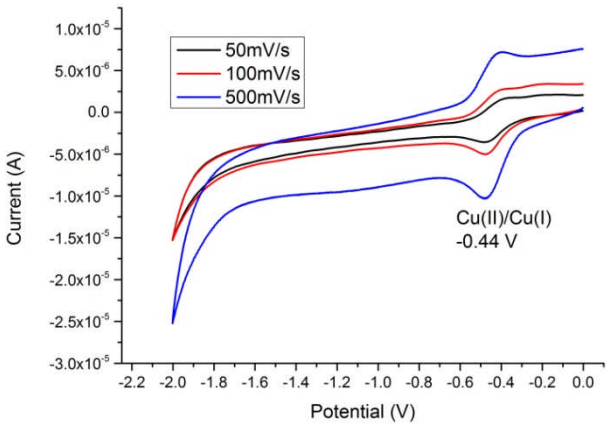
C36 (R = 4-Cl)



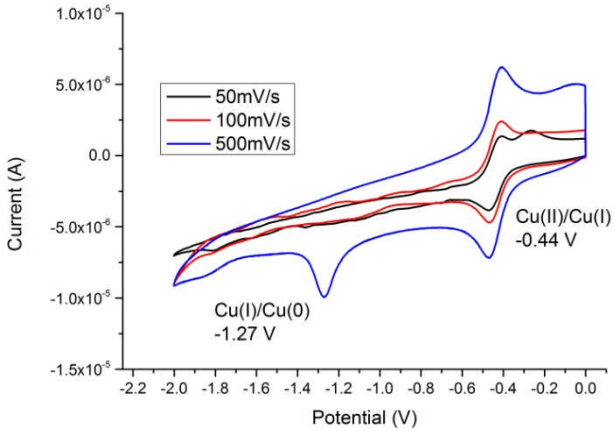
C38 (R = 4-I)



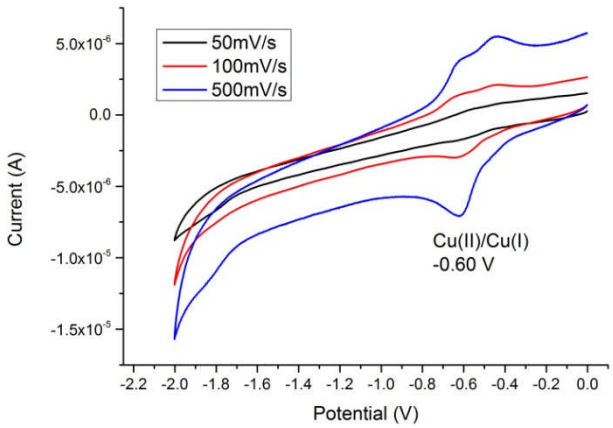
C39 (R = 2,4-F)



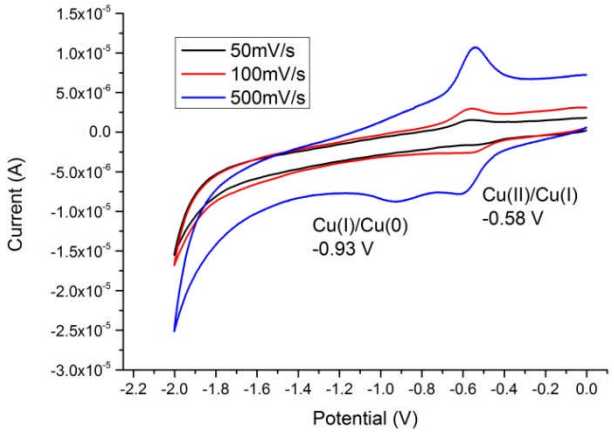
C42 (R = 2,5-F)



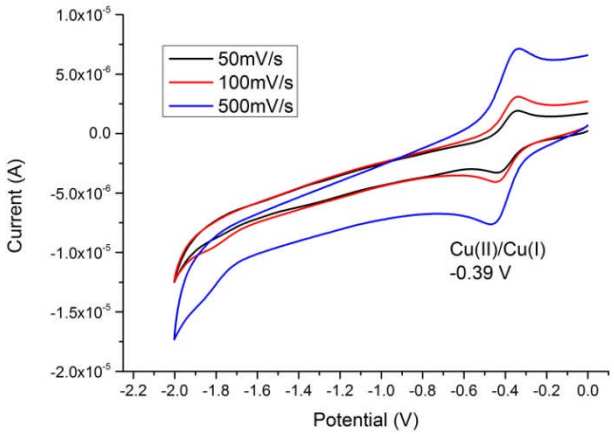
C43 (R = 2,5-Cl)



C44 (R = 2,5-Br)



C51 (R_1 = OMe)



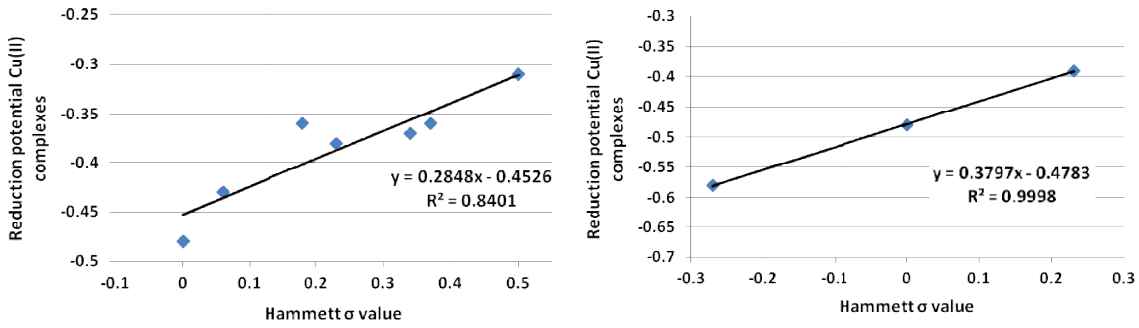
C52 (R_1 = Cl)

As can be seen in the voltammograms, a reversible reduction peak,[40] which can be attributed to the reduction to Cu(I),[41] was observed for all of the complexes, with considerably different reduction potentials, depending on the substituents on the ligand. Electron-withdrawing substituents on the ligand resulted in higher reduction potentials (favoured reduction), whereas with EDG-substituted ligands the reduction potential decreased substantially. Potential values range from from -0.77 V for complex **C20** (R = 2,4-OMe) to -0.28V for complex **C26** (R = 3,5-CF_3). The Cu(II) / Cu(I) reduction potentials for all complexes are summarised in Table 4.2.

Table 4.2: *Cu(II) / Cu(I) reduction potentials for type **I-III** complexes*

Complex (R)	Cu(II) / Cu(I) Potential (V)	Complex (R)	Cu(II) / Cu(I) Potential (V)
C11 (H)	-0.48	**C36** (4-Cl)	-0.38
C20 (2,4-OMe)	-0.77	**C38** (4-I)	-0.36
C22 (2-Cl-6-Me)	-0.51	**C39** (2,4-F)	-0.45
C25 (4-Ac)	-0.31	**C42** (2,5-F)	-0.44
C26 (3,5-CF_3)	-0.28	**C43** (2,5-Cl)	-0.44
C27 (2-F)	-0.50	**C44** (2,5-Br)	-0.60
C31 (3-F)	-0.37	**C51** (R = H, R_1 = OMe)	-0.58
C32 (3-Cl)	-0.36	**C52** (R = H, R_1 = Cl)	-0.39
C35 (4-F)	-0.43		

The correlation with Hammett σ values[42] with the reduction potential for complexes with *meta*- and *para*-substituted picolinamide ligands (substituents on the phenyl ring, R) shows that the more electron-withdrawing the substituent, the more favoured is the reduction potential (Figure 4.7a), in agreement with Scheme 4.11. The same correlation is observed for the substituents on the pyridine ring (R_1, Figure 4.7b).

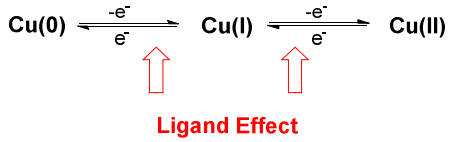


a) **b)**

Figure 4.7: *Correlation Hammett value (σ) / reduction potential: a) for meta- and para-substituents R, and b) for substituents R_1 on the pyridine (R_1 = H: complex **C11**)*

Interestingly, complexes **C11** and **C27** show a similar reduction potential (Table 4.2, -0.48 V and -0.50 V respectively), despite the effect of oxidising and reducing agents in the catalytic reactions with these ligands being quite different (see Scheme 4.10). Hammett σ values cannot be used for *ortho*-substituents, due to the steric effects these might provide, so their electronic properties cannot be directly compared in this case. Moreover, the formation of complexes of type **V** with other *ortho*-substituted ligands demonstrates that the *ortho* halogen is close enough to the copper centre to interact with it (see Chapter 3, section 3.7). The *ortho*-fluorine substituent is not involved in the activation process resulting from this closeness, but other factors may well be operating in this complex, so to explain the different activity.

Apart from the Cu(II) / Cu(I) reduction potential, other differences are observed between the cyclic voltammograms. For example, an irreversible reduction peak at *ca.* -1.2 V to -1.3 V appears at high scan rates (500 mV/s, Table 4.1) for some of the complexes. This irreversible reduction peak might be attributed to the further reduction of the Cu(I) formed to Cu(0). The appearance of this peak only at higher scan rate is explainable in that, as cyclic voltammetry is a diffusion-controlled technique,[40, 43] at high scan rate the newly formed Cu(I) species during the reduction sweep does not have enough time to diffuse far from the electrode, and a further reduction of this species occur. This peak, however, does not appear in other complexes under the same conditions, even increasing the scan rate to 1000 mV/s, or it appears at different potentials, such as in **C51** at -0.93 V. This might suggests that, in such complexes, the Cu(I) species derived from the reduction of the Cu(II) complex is somehow stabilised or destabilised against further reduction. Thus, these results suggest that at least two redox processes are affected by the ligand properties: i) the reduction of the Cu(II) species to Cu(I); and ii) the stabilisation of the Cu(I) species over further reduction to Cu(0), or possibly over disproportionation (Scheme 4.12).



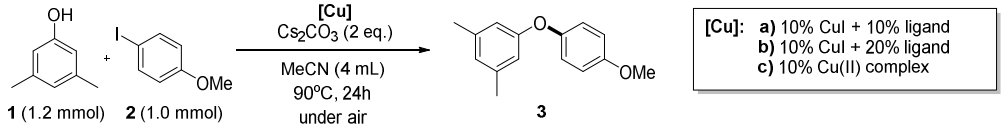
Scheme 4.12: *Ligand effects on the redox properties of the metal centre*

Another feature of the voltammograms is the presence of a second oxidation peak after the re-oxidation to Cu(II) at *ca.* -0.2 V, which is clearly visible in the CV graph of complex **C27**, with a high intensity. This peak is observed in other complexes as well, although with a much lower intensity (**C11**, **C20**, **C43**, Table 4.1). The characteristic of this peak is its disappearance at higher scan rate, opposite to the Cu(I) / Cu(0) reduction peak. This effect could be explained as a competitive oxidation of the Cu(I) species formed, possibly due to an interaction with the acetonitrile solvent. At higher scan rates the re-oxidation to the original

Cu(II) species becomes faster than the competitive process, and its corresponding peak disappears.

4.6 – Reaction profiling

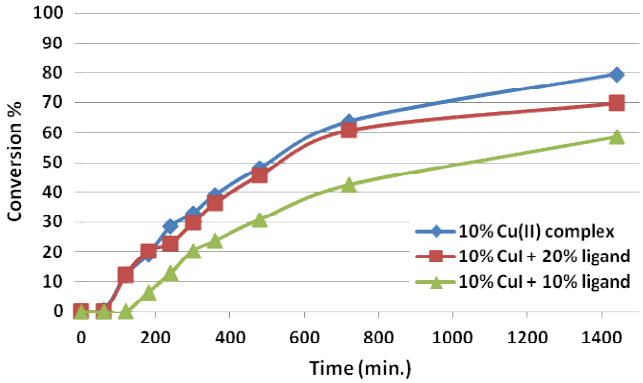
Hypothesising a Cu(I) species as active catalytic species in the formation of aryl ethers, the different reduction potentials Cu(II)/Cu(I) observed suggest that the electronic properties of the ligands can be crucial in influencing the amount of active species in the reaction. To evaluate the importance of the reduction of Cu(II) to Cu(I) in the catalytic process, the Cu(picolinamide)$_2$ complexes were tested in the synthesis of **3**, and their activity was compared with the corresponding CuI/ligand system, ratio 1/1 (as used in Chapter 2) and 1/2, for stoichiometric equivalence to the Cu(II) complexes (Scheme 4.13).



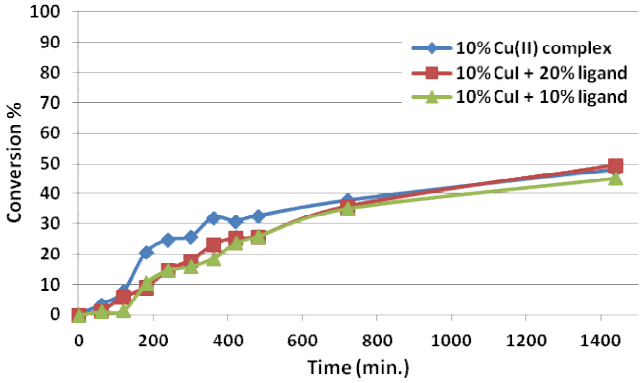
Scheme 4.13: *Synthesis of aryl ether **3**, conditions for reaction profiling*

Reaction profiles using the three catalytic systems for different ligands and complexes are reported in Table 4.3. Interestingly, the use of a 1/2 CuI/ligand ratio and of Cu(II) complexes in the catalytic process often resulted in faster reactions and higher yields of aryl ether **3**, when compared to the use of only 10% of the ligands. In other cases, the profiles were comparable for the three methods. While higher amounts of ligand are often associated with better results in the catalytic process,[44, 45] the good performance of the Cu(II) complexes is surprising, considering that Cu(I) is thought to be the active species,[5-7, 44, 46-48] and generally furnish better catalytic results. These results demonstrate that the Cu(II) complexes recovered from the reaction are not end-of-life species or deleterious off-cycle decomposition products, on the contrary, are in several cases better pre-catalysts for the arylation of phenols than the CuI / ligand precursors.

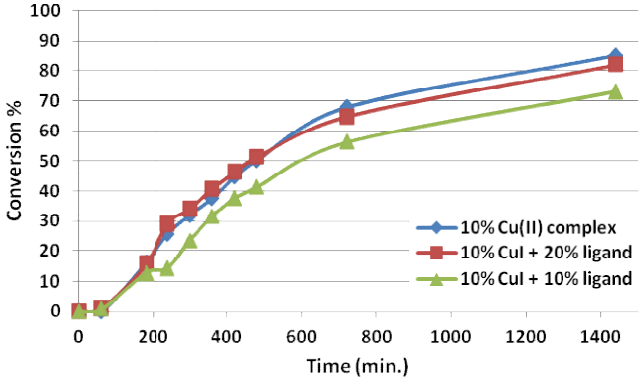
Table 4.3: *Reaction profiling with ligands and corresponding Cu(II) complexes*



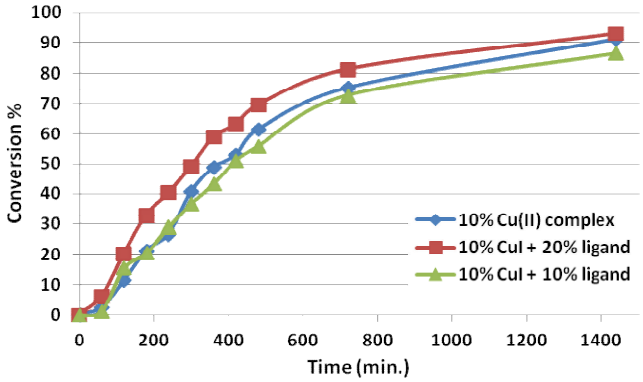
C11 (R = H)



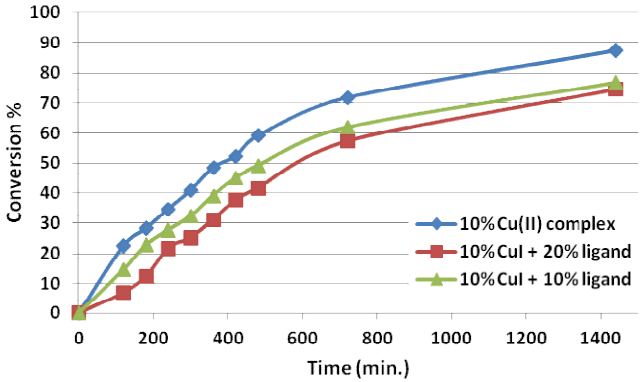
C20 (R = 2,4-OMe)



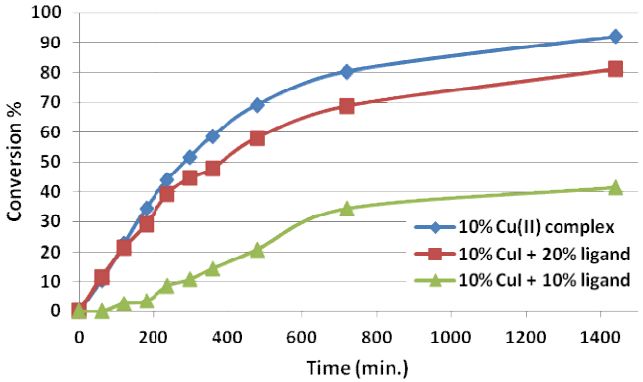
C22 (R = 2-Cl-6-Me)



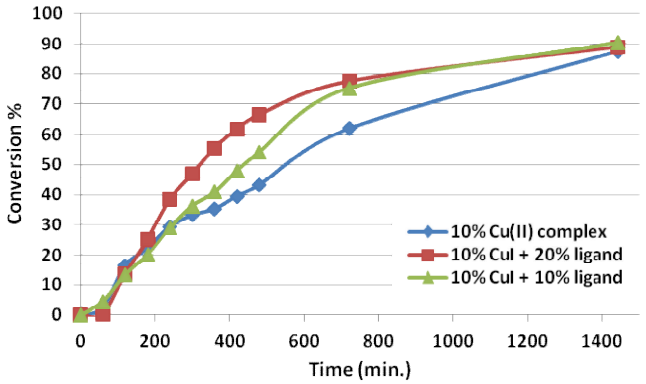
C23 (R = 3-NO_2)



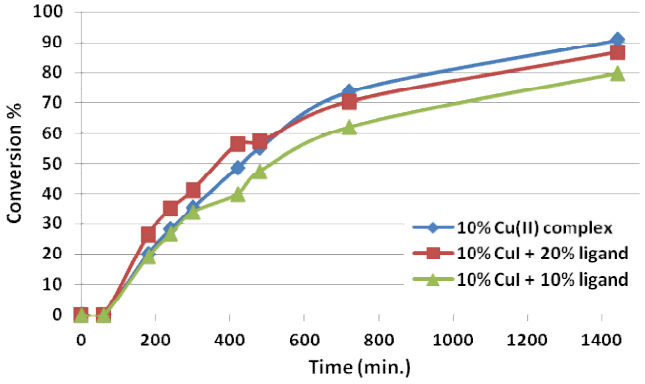
C25 (R = 4-Ac)



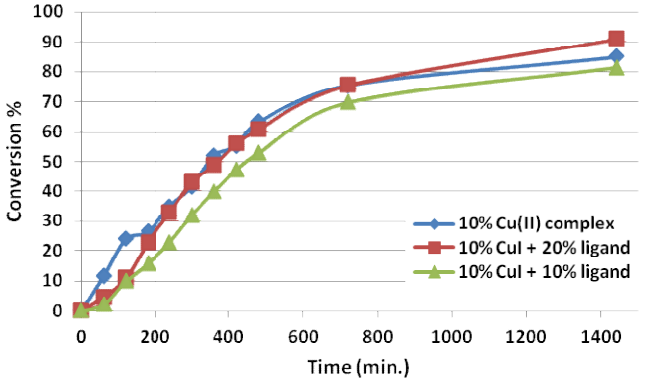
C26 (R = 3,5-CF_3)



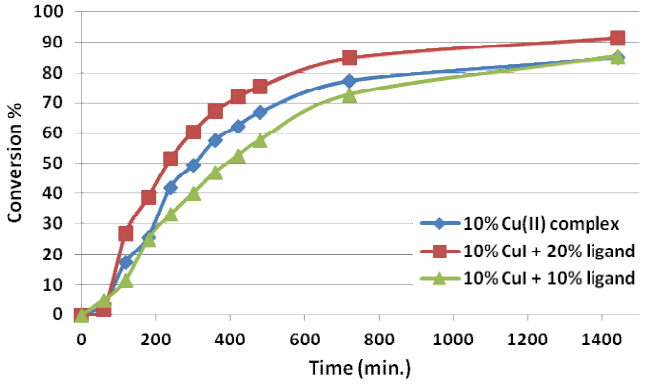
C27 (R = 2-F)



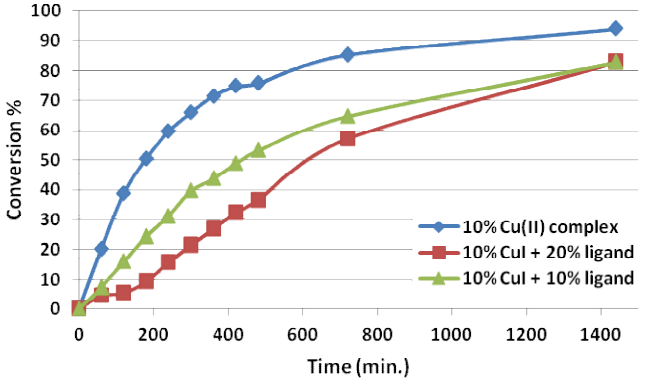
C31 (R = 3-F)



C32 (R = 3-Cl)



C34 (R = 3-I)



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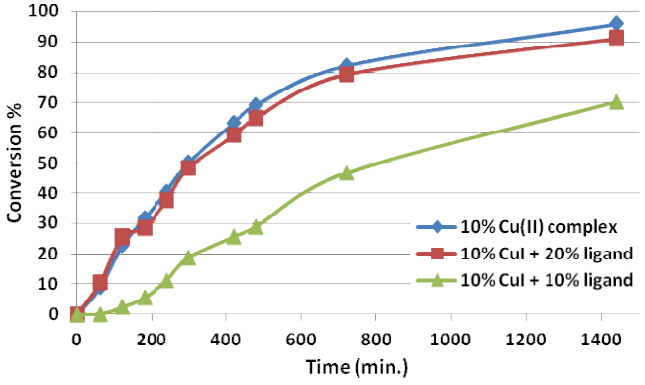

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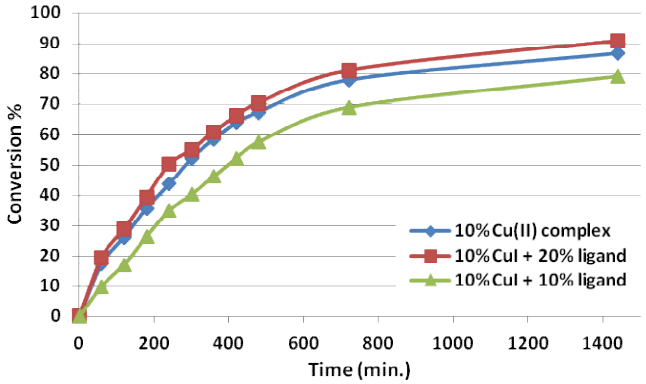
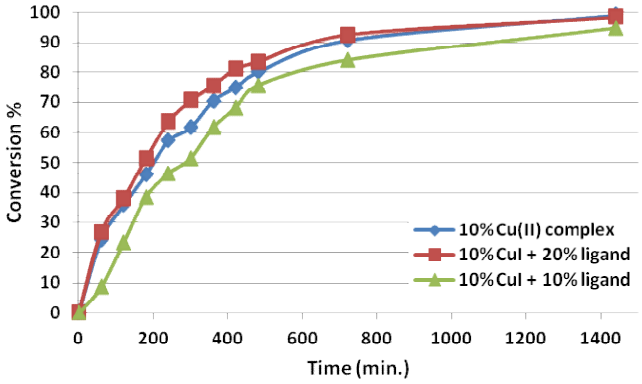
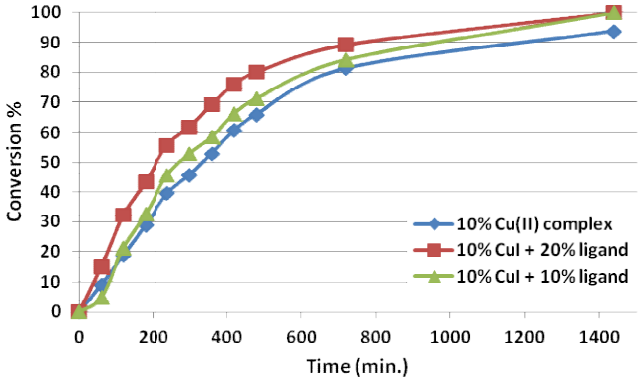


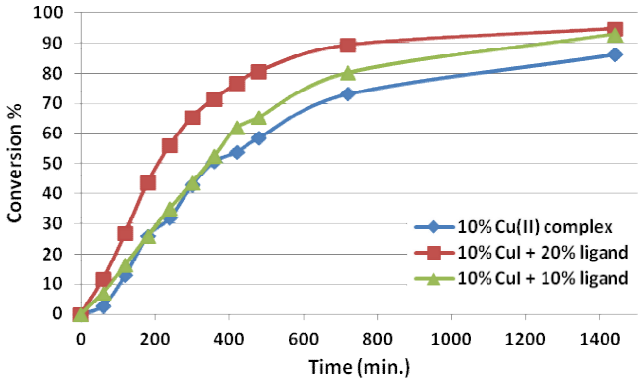
C38 (R = 4-I)



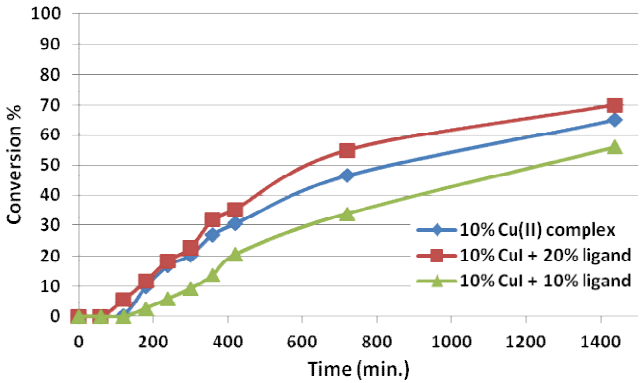
C39 (R = 2,4-F)



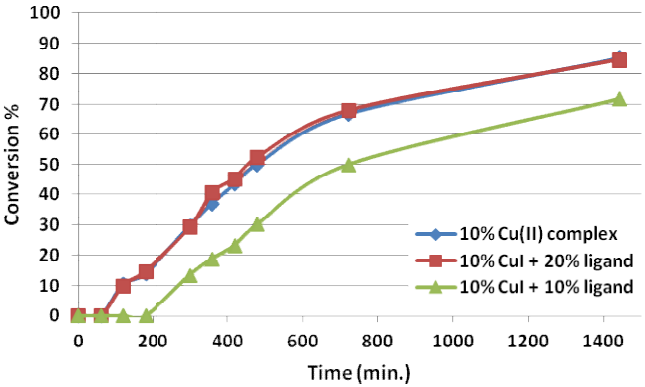
C42 (R = 2,5-F)



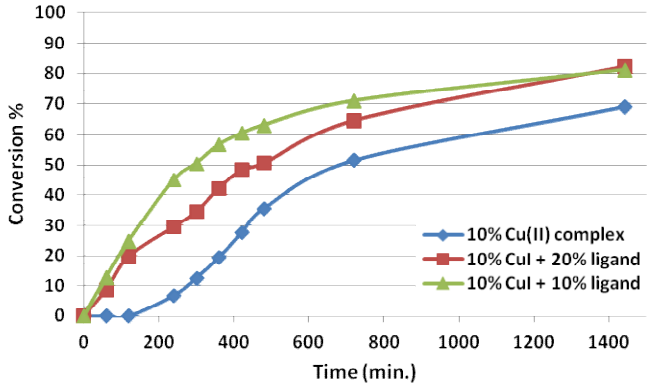
C43 (R = 2,5-Cl)



C44 (R = 2,5-Br)

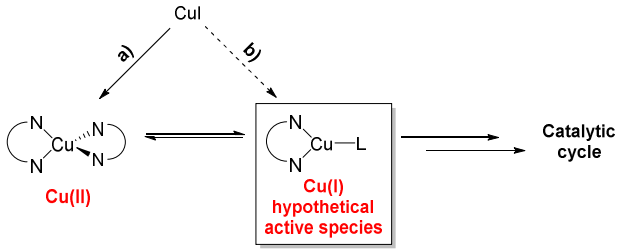


C51 (R_1 = OMe)


100
90
80
70
60
50
40
30
20
10
0
Conversion %
0
200
400
600
800
1000
1200
1400
Time (min.)
10% Cu(II) complex
10% CuI + 20% ligand
10% CuI + 10% ligand

C52 (R_1 = Cl)

Assuming a Cu(I) active species, the better results obtained with Cu(II) complexes might be explained with the formation of a different Cu(I) species than the initial CuI. A picolinamide-ligated Cu(I) species might be formed more easily from the reduction of Cu(II) complexes than from the CuI precatalyst. Thus, pathway **a** in Scheme 4.14 (CuI → Cu(II) complex → Cu(I) active species) might be faster than path **b** (CuI → Cu(I) active species), and the Cu(II) complexes might be an off-cycle resting state necessary to form the active Cu(I) species from CuI (Scheme 4.14). The formation of these complexes even under anaerobic and anhydrous conditions, and even using only one equivalent of ligand (see Chapter 3, section 3.2) is in agreement with this reasoning.



Scheme 4.14: *Possible pathways to the active Cu(I) species*

Figure 4.8 shows the correlation between the final conversions (24h) with the three methods and the reduction potentials for the complexes. Interestingly, the observed is more linear when using Cu(II) complexes than for the other two catalytic systems. Because of the presence of induction periods in some of the reactions (which may be due to a number of factors, including solubility), graphs conversion/reduction potential were also plotted at the sixth and at the twelfth hour of reaction. Even in these cases, more linear correlations for the Cu(II) complexes was observed. This suggests that the reduction potential influences more strongly the reaction rate when using Cu(II) complexes, and that the reduction to the active species may be a kinetically significant step in the mechanism.

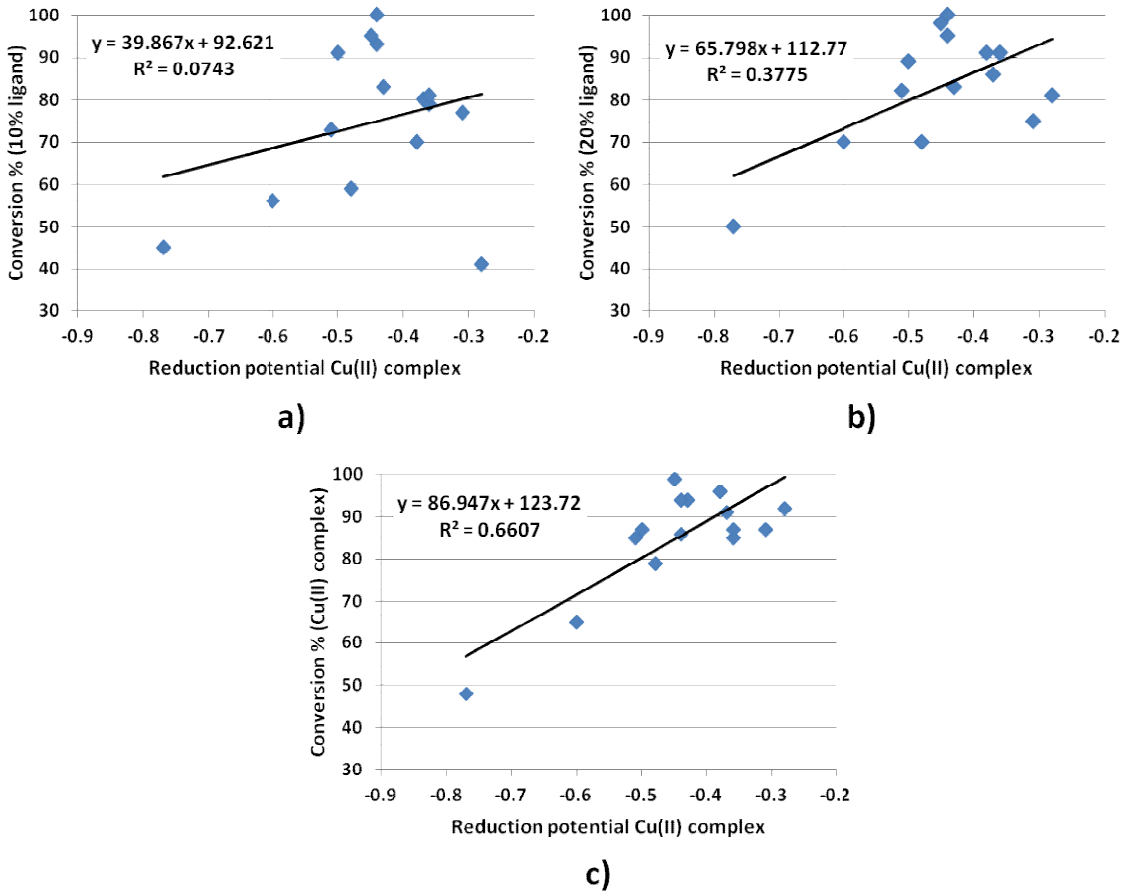


Figure 4.8: *Correlation between conversion (24h) and reduction potential (substituents R): a) 10% CuI + 10% ligand; b) 10% CuI + 20% ligand; c) 10% Cu(II) complex*

The same correlation, in the case of ligands **L51** and **L52**, substituted on the pyridine ring, when compared to the unsubstituted **L11** in the catalytic reaction, using either a 1/1 ratio or a 2/1 ratio to CuI, is not as obvious, due to the small number of examples (Figure 4.9a-b). However, a good correlation is obtained with the reduction potential when the corresponding complexes were used as pre-catalysts. The correlation is here opposite than that observed for the substituents on the phenyl ring, with the complex with higher electron potential giving the worse results (**C52**), while the electron-donating methoxy substituent in **C51** results a in better conversion (Figure 4.9c), suggesting that different effects may be involved (see following section). These data are, however, not enough to assess the role of the substituent on the pyridine ring.

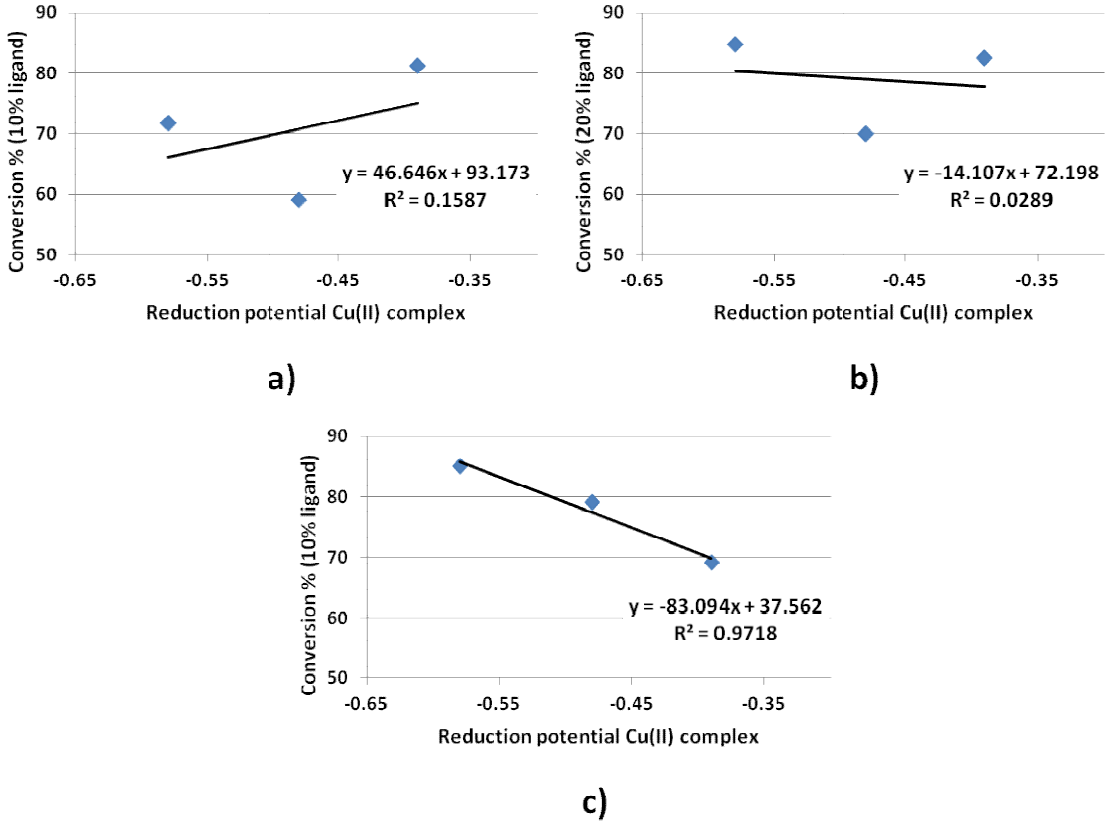
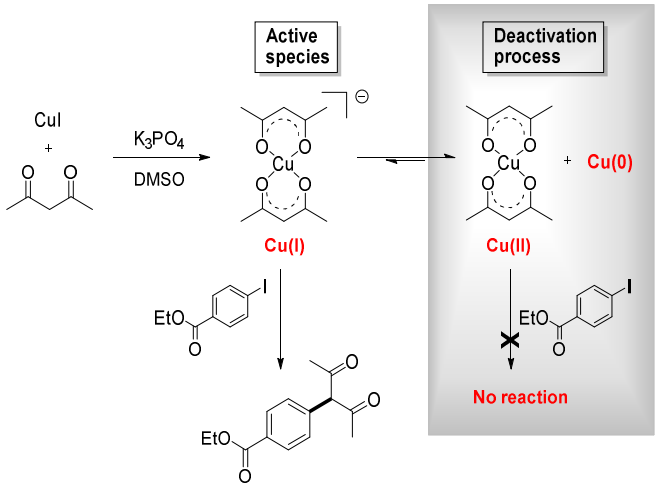


Figure 4.9: *Correlation between conversion (24h) and reduction potential (substituents R_1): a) 10% CuI + 10% ligand; b) 10% CuI + 20% ligand; c) 10% Cu(II) complex*

4.7 – Comparison with literature data

Mechanistic investigations using anionic ligands were recently reported by Lei and co-workers.[1, 2] During the coupling between a *β*-diketone (acetylacetone, acac) and an aryl iodide, the authors observed that the Cu(I) precatalyst used underwent disproportionation at an early stage of the reaction, giving metallic copper and $Cu(acac)_2$.[1] The small amount of Cu(I) left from the disproportionation acted as the only catalyst, and the Cu(II) species was reported to be inactive under the catalytic conditions, denying a possible comproportionation or reduction process to form more of the Cu(I) species (Scheme 4.15). The authors also reported that different ligands resulted in different disproportionation rates.[2]



Scheme 4.15: *Formation of Cu(II) as a catalyst deactivation process*[1]

Lei's results partially correspond to those reported so far in this chapter and in Chapter 3:

- The formation of Cu(II) species from Cu(I) precatalyst, with an anionic ligands, occurs through the initial formation of a labile Cu(I) species (*cf*. Chapter 3, section 3.2.1), which is then oxidised (picolinamides in MeCN) or disproportionates (Lei's case[1, 2] and picolinamides in DMF, Chapter 3) to give Cu(II) species;
- The equilibrium between the Cu(I) and Cu(II) species depends on the ligand substituents, in Lei's case with different disproportionation rates, in our case with different reduction potentials.

This demonstrates that some common characteristics between the two different ligand systems can be found, and that potential prediction of the behaviour of other anionic ligands can be envisaged. However, while in Lei's case the Cu(II) complex was not active as catalyst, with picolinamide ligands the Cu(II) complex behaves as an even more effective catalyst than its Cu(I) precursor.

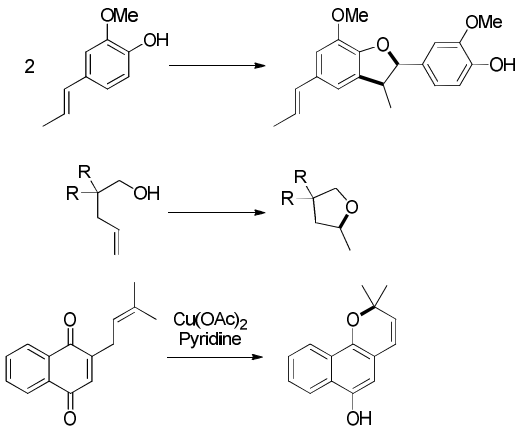
Concerning the (seemingly) opposite effects of the substituents on the two sides of the picolinamide ligand, it is interesting the comparison with Taillefer's iminopyridine ligand, discussed in Chapter 1, section 1.4.[49] The authors observed the same effect, and suggested that the electron-rich side of the ligand favoured an oxidative addition step, while the electron-withdrawing substituent on the other side aided the reductive elimination. Although no proof was given in their work or in this thesis to ascertain this hypothesis, the similarity should be considered for the future development of these ligands.

4.8 – Possible formation of phenoxy radicals

The reduction step from Cu(II) to Cu(I), necessary for the reaction to occur, needs to be possible in an oxidising environment (catalytic reactions under air). In 1964 Weingarten demonstrated how the phenol substrate in the coupling may undergo deprotonation and

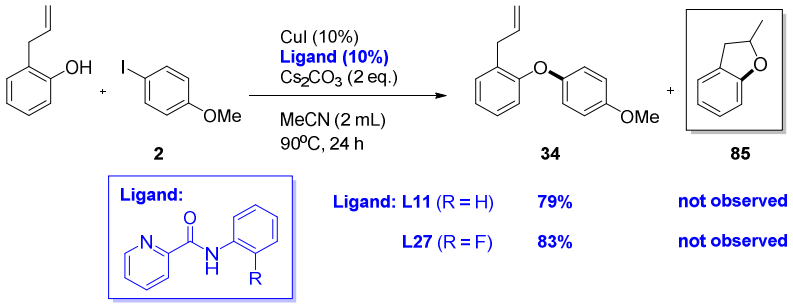
following oxidation to phenoxy radical, with consequent reduction of Cu(II) precatalysts.[48] The formation of phenoxy radicals in the reaction, however, has only ever been considered once since.[50] The oxidation of phenoxides to phenoxy radicals by Cu(II) is a very common process, for example it is at the basis of Cu-based oxidase enzymes.[51] This process usually occurs with the involvement of oxygen,[51-53] so that it would be plausible under our catalytic conditions. Furthermore, the formation of phenoxy radicals is most favoured in sterically hindered phenols,[54] which also gave good results in the coupling with aryl halides in our conditions (see Chapter 2). Phenoxy radicals generally isomerise to carbon-centred radicals, leading to dimers or polymers bound *via* C-O or C-C bonds,[54] which were not observed under our experimental conditions. However, if a concerted mechanism or an inner-sphere electron transfer from the coordinated phenoxides to the Cu catalyst was involved, this typical reactivity would not be observed (see Scheme 4.9 and discussion). Following this reasoning, radical trap and radical clock experiments analogous to those performed on the aryl halide (section 4.4) were studied on the phenol moiety.

Although intramolecular reactivity of the phenoxy radical with a close unsaturated non-aromatic moiety, such as studied in Scheme 4.4 for an aromatic radical, has not been reported in the literature, intermolecular couplings are known.[55] Intramolecular radical couplings are instead known to occur with aliphatic alcohols,[56] and Cu(II)-catalysed couplings have also been reported for substituted quinones[57] (Scheme 4.16).



Scheme 4.16: *Intermolecular or intramolecular couplings of phenoxy or alkoxy radicals with unsaturated moieties*

Thus, the coupling between 2-allylphenol and 4-iodoanisole (**2**) was envisaged as potentially interesting control reaction (Scheme 4.17). However, either using **L11** or **L27**, aryl ether **34** was obtained in high yields, and no radical-derived product **85** was observed in the crude mixture (Figure 4.10).



Scheme 4.17: *Radical clock experiments on the phenol (isolated yields)*

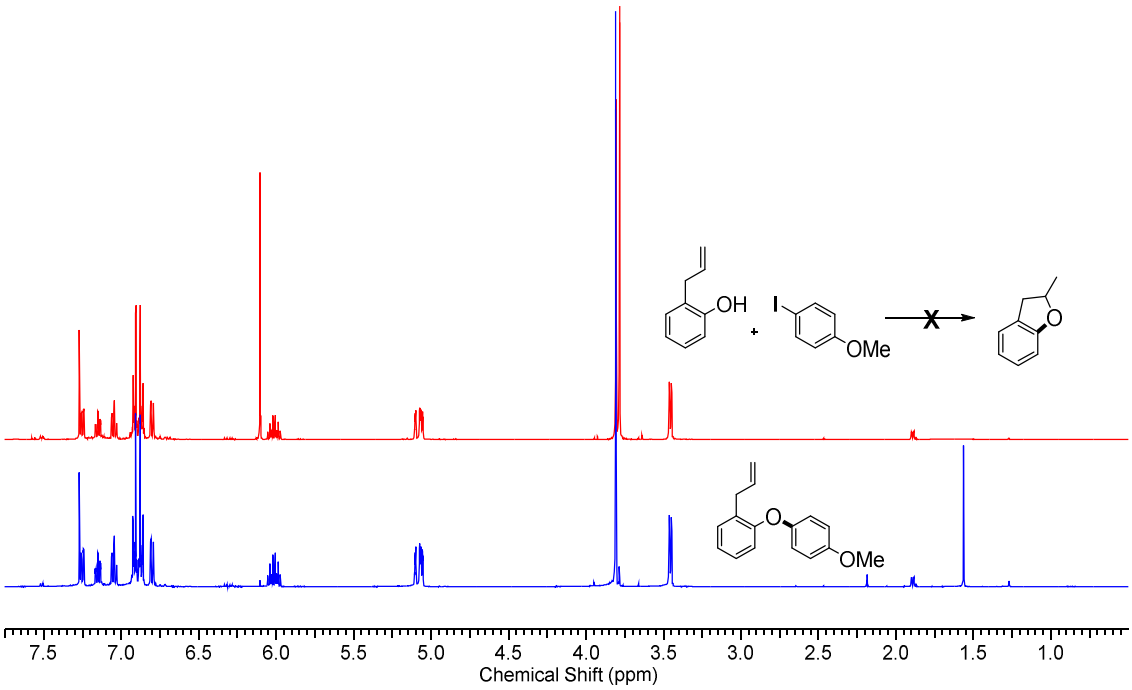
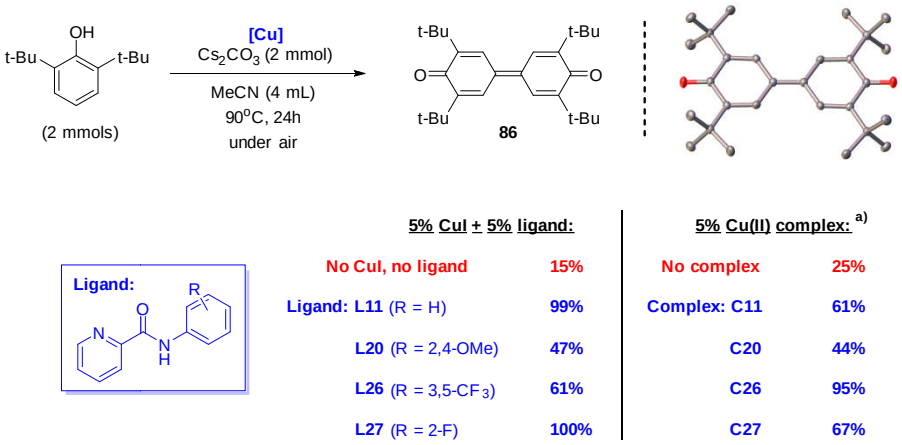


Figure 4.10: *Comparison of ^{1}H-NMR spectra of: aryl ether **34** (blue) and crude mixture (red)*

Reactions with **L11** and **L27** of either 3,5-dimethylphenol (**1**) or 2-allylphenol in the absence of aryl iodide resulted respectively in *ca.* 30% and 50-60% of unreacted phenol after 24 h (GC data). Similar results were obtained adding 1 eq. of TEMPO to the reaction. The relatively small amounts of phenol left in the reaction crude are likely due to deprotonation and formation of salts.

Another experiment was performed to investigate the formation of phenoxy radicals under our catalytic conditions. 2,6-Di-*tert*-butylphenol was used as a probe in reactions without any aryl halide, in the presence or absence of copper catalysts. The choice of this substrate was driven by their known ability to stabilise radicals and form the corresponding dimer **86**,[54] which can be easily identified by ^{1}H-NMR (Scheme 4.18). The formation of dimers is known to proceed via the rearranged phenoxide radical,[54] thus its presence would be an indication of the oxidation of the phenol to phenoxy radical.



Scheme 4.18: *Dimerisation of 2,6-di-tert-butylphenol (^{1}H-NMR yields); a) reactions on 1 mmol scale*

Performing the reaction in air, small amounts of **85** are formed even in the absence of copper and ligand, but the addition of CuI/ligand (ligands **L11**, **L20**, **L26** and **L27**) considerably increases the amount of **85** produced. These results suggest that CuI/ligand catalytic system in the reaction can lead to the formation of the phenoxy radical. The use of the corresponding Cu(II) complexes **C11**, **C20**, **C26** and **C27**, also resulted in the formation of the dimeric product, showing that these species might catalyse the oxidation of phenol **22**. In this case, a good correlation between yields and reduction potential of the complexes is also observed (Figure 4.11).

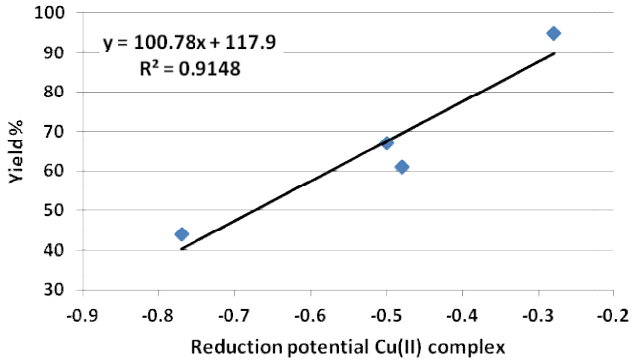


Figure 4.11: *Correlation between reduction potentials and yield of dimer **85** for Cu(II)complexes*

Thus, these results are in agreement with a possible reduction step at the expense of the phenol, when Cu(II) species are used as catalysts. Although this step would depend on the phenol used in the reaction, the good yields obtained for the C-O coupling with similarly substituted phenols (such as 2,4-di-*tert*-butylphenol or 2,4-di-*tert*-amylphenol, see Chapter 2, Scheme 2.7), also susceptible to radical dimerisation,[53] indicates this as a possible reduction step to form the active Cu(I) species.

A final clue about the effect of the phenol on the reduction of Cu species was obtained by Miss Jessica Lamb (University of Leeds), during the study of Cu(I) complexes with iminopyridine ligands **L53** (see Chapter 2, Scheme 2.6), which are known to stabilise Cu(I) complexes. Reaction of **L53** ligands, in particular **L53a**, with CuI in acetonitrile, quickly gives the corresponding Cu(I) species as dinuclear complexes.[47, 58] When sodium phenoxides are added, under inert conditions, to an acetonitrile solution of these species (especially with **L53a**), a copper mirror is deposited after a few hours on the walls of the flask, thus accounting for a reduction of Cu(I) to Cu(0) or a disproportionation process. The phenomenon is reproducible, but strongly dependent on the ligand and the phenol substituents.[58] This result, other than being a confirmation of the effect of phenoxide anions on the redox properties of the metal, has also relevance for the mechanism of the reaction with neutral ligands, for which no one-electron processes have been considered in the recent literature.

4.9 – Profiling with Cs complex, effect of 18-crown-6 in the reaction

Complex **C18** (R = 2,4,6-trimethyl), type **IV**, was also tested in the catalysis. Due to the different structure of the complex, the results are reported in this separate section. This complex contains one unit of CsI on top of the Cu(picolinamide)$_2$ complex. The presence of the CsI unit, being this one of the products of the catalytic reaction under our conditions, was thought to inhibit the reaction, when compared to the standard CuI / ligand system. Surprisingly, instead, when the complex was compared with the corresponding CuI / ligand system (ratio 1/2), it proved more catalytically active, although considerably less than CuI /ligand 1/1 (Figure 4.12).

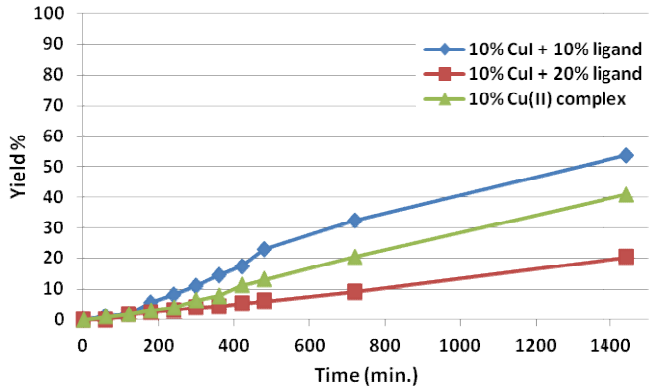
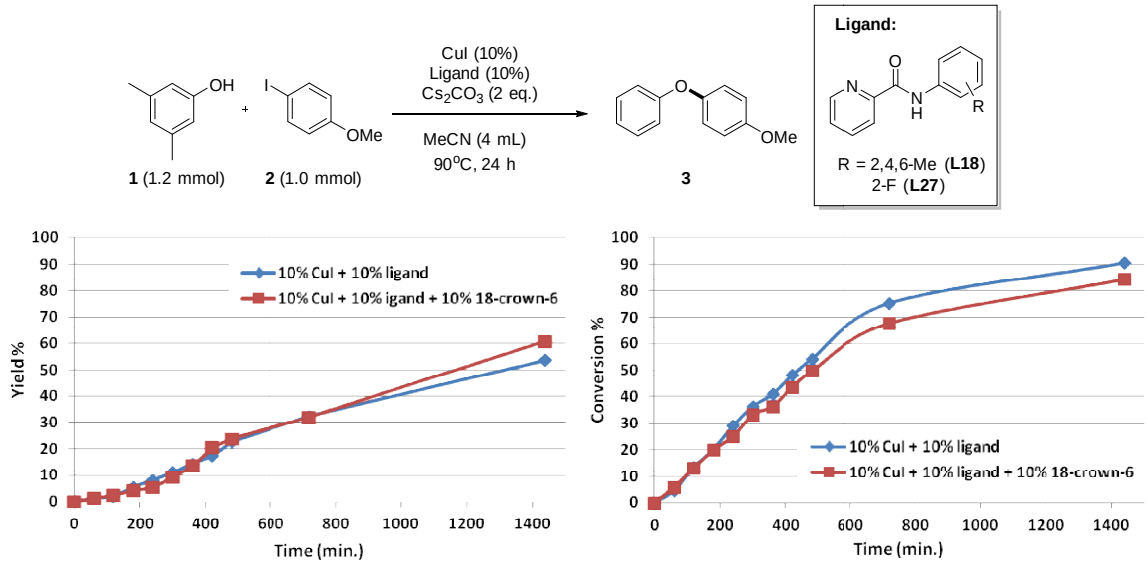


Figure 4.12: *Reaction profile with type **IV** complex **C18** and corresponding CuI / ligand precatalysts*

The higher activity of the complex suggests that the inclusion of the CsI unit might actually be beneficial for the catalytic process, thus suggesting, as in Chapter 3 (Scheme 3.8), the possibility of this complex being some sort of "frozen intermediate" for the synthesis of Cu(picolinamide)$_2$ complexes, which, as discussed in section 4.6, are active catalysts.

A preliminary experiment to try to assess the role of the caesium base was undertaken. The use of crown ether has been exploited to improve the reactivity in several processes

involving alkaline metal cations. The crown ether used for the purpose, generally 18-crown-6, coordinates to the cation, making its counterpart a naked, more reactive nucleophile.[14, 59-61] The addition of a crown ether in this case would show if purely a size effect would be sufficient to explain the better performance of the Cs base, or if other effects may involved too. The reaction profile for the synthesis of **3** using a catalytic amount of 18-crown-6 in the reaction with **L18** is shown in Figure 4.13a. As can be seen, almost no effect is observed, and the profile is almost overlapping the one without any additive. A similar result was obtained in a reaction with **L27**, performed for comparison (Figure 4.13b). Although no further experiments have been performed on the matter, these experiments suggest that the reaction is not particularly sensitive to the crown ether, and the caesium base might have other effects on the catalytic process.



a) L18 (R = 2,4,6-Me) **b) L27** (R = 2-F)

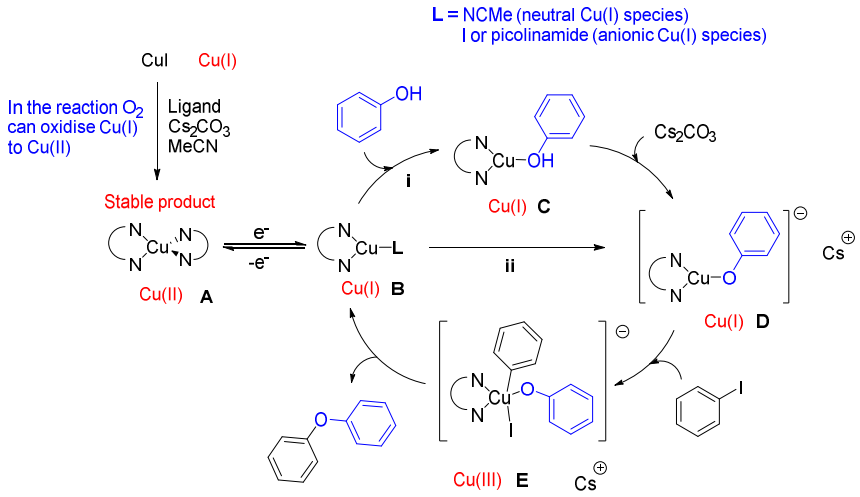
Figure 4.13: *Effect of the addition of 18-crown-6 to the reaction with **L18** (a) and **L27** (b)*

4.10 – Summary – proposed mechanism

In this chapter, mechanistic investigations on the role of the picolinamide ligand in the catalytic arylation of phenols have been reported. Radical trap and radical clock experiments show that no free radicals from the aryl iodide are involved in the process, although inner-sphere electron-transfer mechanism and concerted coupling could not be excluded. However, in the absence of other evidence for electron transfer processes, an oxidative addition / reductive elimination cycle can be suggested. Cyclic voltammetry experiments showed how the ligand properties strongly influence the redox chemistry of the metal centre, in particular with effects on the reduction Cu(II)/Cu(I) and Cu(I)/Cu(0). The catalytic performance of Cu(II) complexes seems to be related at least to the Cu(II)/Cu(I) reduction potential, suggesting a Cu(I) active species. This reduction may take place at the expenses of the excess phenoxide present in the reaction, which may be oxidised to a phenoxy radical. Nonetheless, further investigations on

different fronts are needed to clarify the presence and reactivity of phenoxy radicals in the catalytic process.

Scheme 4.19 shows a possible mechanistic scenario for the arylation of phenols, based on the results reported. The CuI used in the reaction is readily oxidised to the Cu(II) species **A**, which can be reduced to the active Cu(I) species, whose hypothetical structure is described as **B**. **B** is a ligated species which can be either neutral (**L** = acetonitrile) or anionic (**L** = I or another picolinamide ligand); in the latter case, a Cs ion may act as a counteraction. The formation of the Cu(I) species **B** may occur through oxidation of the excess phenoxide ion present in the reaction to phenoxy radical, or it may occur through disproportionation, as reported by Lei,[1] and as may be suggested by the formation of metallic copper in the reaction in acetate solvents (see Chapter 2). The arylation reaction proceeds through coordination of the phenol to the metal centre, either before (pathway **i**) or after deprotonation (pathway **ii**), followed by an (hypothetical) oxidative addition / reductive elimination process through the intermediate **E**. This intermediate, if the anionic character of the ligand is to be maintained, would necessarily be negatively charged, in which case the Cs ion may again be involved in stabilising interactions with the Cu complex. Species **B**, re-formed at the end of the catalytic process, is itself re-oxidised to the Cu(II) species **A**, which can be recovered from the crude solution.



Scheme 4.19: *Proposed mechanism for the arylation of phenols using picolinamide ligands*

4.11 – References

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Chapter 5:

Conclusions and future work

5.1 – General conclusions

This thesis has reported upon the results of an investigation on the use of picolinamide ligands in Cu-catalysed arylation processes. A screening of a number of different ligands and the comparison with other classes of ligands used in this process proved the picolinamide backbone an effective ligand type for these transformations.

Picolinamide ligands are effective in copper-catalysed arylation reactions, either for the synthesis of aryl ethers (arylation of phenols) and for the arylation of amides, including lactams. A range of EWG and EDG substituted substrates are tolerated in the catalytic process with these ligands, and steric hindrance on the phenol in the synthesis of aryl ethers is also very well tolerated. Limitations are the low yields obtained with sterically hindered aryl halides, and the use of potentially coordinating substrates, such as amino-phenols and heterocyclic substrates where the heteroatom is close to the reactive site in the nucleophile of the aryl halide. Steric hindrance and heterocyclic or chelating substrates are common limitations for copper-catalysed arylation strategies in homogeneous thermal conditions.

The first investigation on the use of green organic solvents as media for these transformations has been undertaken, giving very good results in the arylation of phenols and amides. The substrate scope for the arylation of phenols in acetate solvents proved similar to that observed in acetonitrile, while the yields obtained were in many cases higher than in acetonitrile. These results are important in view of potential industrial applications.

The synthesis of copper complexes with picolinamide ligands was explored in acetonitrile. The use of experimental conditions similar to those employed for the catalytic process resulted in five different types of Cu(II)-picolinamide complexes, four of which have never been reported before in the literature. Among these, a complex showing inclusion of a Cs ion from the base used (Cs_2CO_3) was obtained (type **IV** complex), whose study can give important information about the role of the base in the catalytic process. Another type of complexes (type **V**) was obtained using *ortho*-halogenated picolinamide ligands, in which the C-halogen bond is activated by the CuI at room temperature to furnish homo-coupling products between two molecules of ligands, attached either to the same Cu centre, or to two different Cu centres. The activation of the C-halogen bonds was not observed when using Na_2CO_3 as base, demonstrating a crucial role of the Cs ion in the activation process. Both types of complexes are novel.

The preformed Cu(II) complexes were employed in the catalytic reaction, and showed to be, in several cases, more effective than the corresponding CuI/ligand systems under the same reaction conditions. Studying their electrochemical properties, a plausible role of the ligand was

suggested to explain the results obtained. The reduction potential of Cu(II) complexes seems to be an important factor in the catalytic process, as higher reduction potentials favour the catalysis. This may be attributed to the necessity of a Cu(I) active species to be formed during the reaction. These experiments were undertaken to assess a structure-activity relationship for these ligands. Other mechanistic investigations included a series of control reactions to ascertain the radical character of the mechanism; these experiments ruled out free-radical, outer-sphere pathways, although inner-sphere electron-transfer processes could not be excluded. In this short chapter are reported a few ideas on further investigation based on the results reported in this thesis.

5.2 – Future work

5.2.1 – Ligand/catalyst design

Variation of the picolinamide moiety has been investigated, in this thesis, mostly through variation of the substituent on the *N*-phenyl ring, which resulted in very different catalytic results and properties. Variation of the substituent in the *para* position (the most important for influencing the coordination properties) on the pyridine ring has been also preliminarily investigated. A more detailed investigation on the effect of different substituents on the pyridine ring could prove an important improvement in the ligand design. Due to the high prices of the substituted picolinic acids, however, a different synthetic pathway to the picolinamide ligands might prove necessary for this purpose.

Another possible modification area of the picolinamide backbone is the area around the carbonyl group. This can be changed in different ways, providing different chelating groups which can influence the catalytic properties. The possible modifications available on the picolinamide backbone are summarised in Figure 5.1.

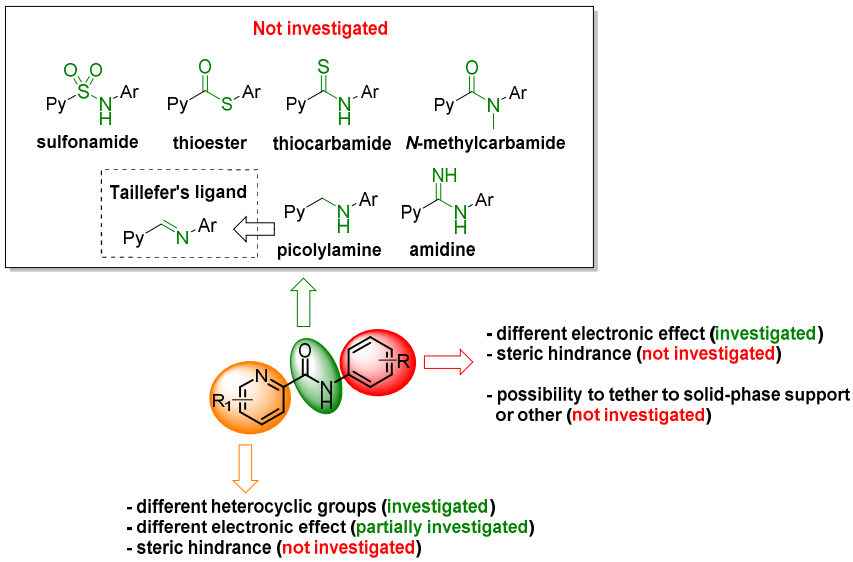
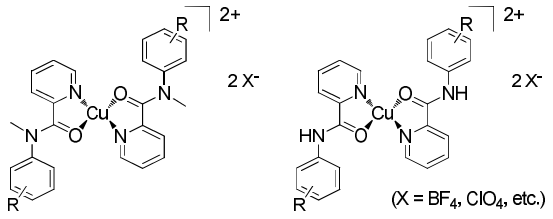


Figure 5.1: *Further ligand modifications*

Because Cu(II)-picolinamide complexes were effective catalytic species, the investigation of differently coordinated Cu(II) species may be of interest. A logical modification would be the *N,O* coordination of the ligand to the metal centre, furnishing ionic complexes, which would increase the solubility in polar solvents. These complexes can be prepared in the absence of a base using a Cu(II) salt and: i) neutral ligands, for example *N*-methyl-*N*-phenylpicolinamides (Figure 5.2a); or ii) large counterions without *N*-methyl substitution on the ligand (Figure 5.2b). *N,O* coordination with the ligands reported in this thesis, in the absence of the base and starting from CuI, did not occur, while it occurs swiftly using $Cu(BF_4)_2$ as the copper source. A comparison between the neutral and the corresponding ionic complexes may give important insights on the role of the ligand in the catalysis.



a) **b)**

Figure 5.2: *Ionic N,O coordination complexes*

5.2.2 – Applications

Design of Experiments (DoE), combined with Principal Component Analysis (PCA), is an excellent way of optimising the reaction conditions and discover the relationships between ligands, solvents, and bases.[1] In particular, this would be of interest for carrying on the investigations on green solvents and design an effective, greener process, and it would be of help in effective ligand design.

The C-C bond formation between two ligands attached to the metal centre occurring at room temperature reported in Chapter 3 showed that a group-directed C-halogen activation process occurs easily using Cs_2CO_3 as a base. The substrate scope of the process may be explored to investigate if other C-C bonds can be formed. To our knowledge, although picolinamide-directed C-H activations are common in the chemical literature, no picolinamide-directed C-halogen bond activation processes have been reported.

5.2.3 – Mechanistic investigations

A few papers in the literature report the synthesis of flexible tetradentate picolinamide ligands, where two *N*-phenylpicolinamide units are linked through a $–O(CH_2)_nO–$ or a $–S(CH_2)_nS–$ spacer attached to the phenyl rings (Figure 5.3a,b), and corresponding complexes with Cu(II).[2, 3] Although these ligands may potentially behave as hexadentate ligands, wrapping around the metal centre in an octahedral geometry, they may also act as tetradentate ligands. In these cases, a geometry similar to that obtained with simple bidentate picolinamide ligands is

observed. Variation of these ligands, in particular with ethereal spacer, could be of interest for the elucidation of the mechanism of the Cu-catalysed couplings, and for trapping intermediates involving Cs ions.

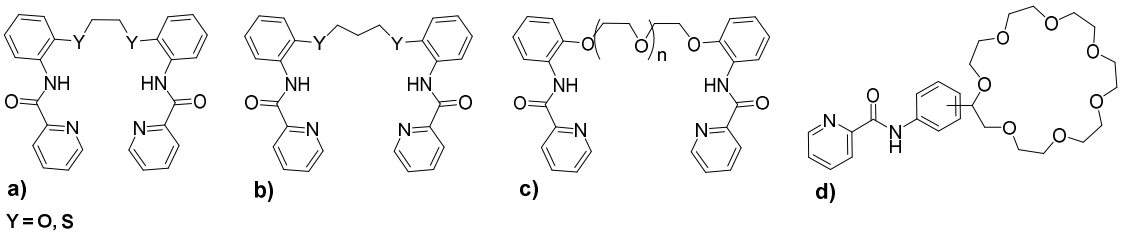


Figure 5.3: *Picolinamide ligands with ether spacers*

The complex **C18**, showing a Cu-I-Cs interaction, only observed with the *N*-mesithyl picolinamide ligand **L18**, suggests that this group has a crucial role in stabilising this interaction through coordination to the Cs ion (Chapter 3). In a similar complex, obtained using *N,N*-dimethylglycine in the Nguyen group at the University of Leeds, the Cs ion is coordinated to a number of oxygen donors from the ligand.[4] This experimental evidence can be thus exploited to stabilise potential reaction intermediates using modified ligands similar to those above. If an ethereal spacer could be attached to the ligand, wide enough to accommodate entirely or partially the Cs ion (a crown ether-like spacer, Figure 5.3c), this ligand could be an invaluable mechanistic tool. Moreover, this modification may also increase the solubility of the Cs base, allowing easier mechanistic investigations in solution. A crown ether could otherwise be attached to the ligand as in Figure 5.3d. However, a copper complex with a tetradentate ligand would have higher stability, useful to isolate intermediates.

In situ NMR techniques could be useful in elucidating the mechanism of the copper-catalysed formation of aryl ethers. These are not commonly used for these reactions, due to the often considerable amount of solid formed during the reaction (mostly from the inorganic base). However, if a soluble system could be developed, with organic bases or very polar solvents, such as DMSO, the utilisation of NMR techniques will be feasible. In particular, ^{133}Cs-NMR would help elucidating the role of the Caesium base in the reaction. Other *in situ* techniques, such as IR and ESI-MS would be useful when Cu(II) species such as Cu(II)-picolinamide complexes are involved as initial pre-catalysts. *In situ* techniques could also be used to study the formation of the Cu(II) complexes in acetonitrile, clarifying the oxidation mechanism and the possible formation of intermediates such as complex **C18** in the process.

The role of the caesium base in the catalytic coupling can also be investigated by comparison with other alkali metal bases and crown ethers, both in the catalytic reaction and in the synthesis of complexes. Some preliminary results have been reported in this thesis, but a deeper investigation is needed for significant results.

5.3 – References

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Chapter 6:

Experimental section

6.1 – General remarks and instrumentation

^{1}H-NMR spectra were acquired using a Bruker Avance 300, 400 or 500 MHz spectrometer. Chemical shifts (δ) are expressed in ppm and referred to the solvent signal, used as internal reference ($CDCl_3$ was used as solvent, if not otherwise specified; $CDCl_3$: 7.27 ppm; DMSO-d_6: 2.50 ppm). ^{13}C-NMR spectra were recorded using a Bruker Avance 300, 400 or 500 (75, 100 or 125 MHz) spectrometer. Chemical shifts (δ) are expressed in ppm and referred to the solvent signal, used as internal reference ($CDCl_3$: 77.0 ppm, DMSO-d_6: 39.5 ppm). Microanalyses were obtained by Mr. Ian Blakeley or Ms. Tanya Marinko-Covell at the University of Leeds Microanalytical Service using a Carlo Erba 1108 Elemental Analyzer. Electrospray (ESI) and electron-impact (EI) mass spectra were recorded by Ms. Tanya Marinko-Covell, Dr. Stuart Warriner or the author at the University of Leeds Mass Spectrometry Service, on a Waters GCT-Premier instrument (EI, direct injection), or on a Bruker Daltonics MicroTOF instrument (ESI). APCI spectra were recorded by Ms. Moya McCarron at the University of Liverpool Mass Spectrometry Service on an Agilent QTOF 7200 instrument. Infrared spectra were recorded by the author on a Perkin-Elmer SpectrumOne FT-IR spectrometer. Melting points were determined with an Electrothermal digital melting point apparatus in open capillary tubes, and are uncorrected. Purification by column chromatography was carried out using Merck Geduran Si 60 Silicagel, or pre-packed Biotage cartridges for automatic chromatography apparatus.

GC analyses were performed using a Bruker 430-GC equipped with a CP-8400 autosampler and a BR-5 column (30 m x 0.25 mm (ID) x 0.25 µm film thickness) with carrier gas (H_2) flow rate of 2.0 mL/min and a temperature ramp from 50 to 310 °C at 20 °C/min. Single point calibration was performed through analysis of standard solutions containing known amounts of analyte (AN) and internal standard (IS). Internal response factors (IRF) were calculated for the analytes using the following equation:

$IRF_{AN} = (area_{IS} \times [AN]) / ([IS] \times area_{AN})$.

The following equation was then used to calculate the analyte concentration in reaction samples:

$[AN] = (area_{AN} \times [IS] \times IRF_{AN}) / area_{IS}$.

Single crystal X-ray data were collected by the author, Dr. Chris Pask or Dr. Helena Shepherd using one of the following: i) Bruker X8 Apex diffractometer connected to an Oxford Cryostream low temperature device using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å); ii) Agilent SuperNova diffractometer equipped with an Atlas CCD detector using

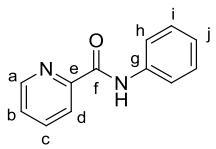
mirror monochromated Mo-Kα (λ = 0.71073 Å) or Cu-Kα (λ = 1.54184 Å). The structures were solved using SHELXS direct methods,[1] and the structural model refined by full matrix least squares on F2 using SHELXL97.[1] Squeezed structures were obtained with Platon.[2] Molecular graphics and preparation of tables of bond lengths was carried out using Olex2.[3]

Cleaning procedure for catalysis tubes: Glass tubes used for catalytic reactions were cleaned thoroughly after use. They were initially scrubbed with soapy water, followed by a three-time rinse with acetone, and a soak in a base bath for 10-15 hours (KOH approx. 1 M in water/isopropanol). When taken out of the base bath, the tubes were rinsed with abundant water and placed into an acid bath for 1-5 hours (HCl 37% approx. 1 L per 8-10 L of water). Finally, the tubes were rinsed thoroughly with water and then with acetone (three times), before being placed to dry in the oven.

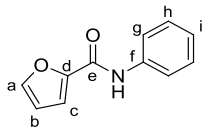
6.2 – Experimental for Chapter 2

6.2.1 – Synthesis of bidentate amidic ligands

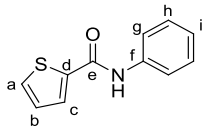
General procedure: The ligands were prepared through a modified ligand procedure.[4] In a round-bottom flask equipped with a condenser 1 eq. of carboxylic acid was stirred with pyridine at room temperature, then 1 eq. of the amine and 1 eq. of triphenyl phosphite were added to the solution. The mixture was heated to reflux (120°C) and left for 20h. At the end of the reaction the solution was left to cool to room temperature and an excess of distilled water was added, stirring the mixture for an additional hour. Unless otherwise specified, the crude product precipitated out, and was successively filtered, washed with water and purified by recrystallisation from hot MeOH.



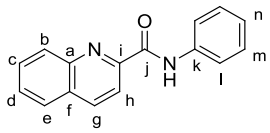
***N*-Phenylpicolinamide (L11).**[5] Prepared using 10.0 g (81 mmols) of picolinic acid and 40 mL of pyridine. The organic layer was separated and dried over $MgSO_4$. A precipitate formed when cooled to -20°C: filtered, washed with water and crystallised from hot MeOH as white crystals, yield 29% (4.70 g, 24 mmols). **^{1}H-NMR (500MHz) δ:** 10.06 (s, 1H, NH); 8.64 (d, 1H, H_a, J_{a-b} = 4.8 Hz); 8.32 (d, 1H, H_d, J_{d-c} =7.8 Hz); 7.93 (dt, 1H, H_c, J_{c-a} = 1.7 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.80 (d, 2H, H_h, J_{h-i} = 7.6 Hz); 7.50 (ddd, 1H, H_b, J_{b-d} = 1.1 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 7.40 (t, 2H, H_i, J_{i-h} = J_{i-j} = 7.9 Hz); 7.17 (t, 1H, H_j, J_{j-i} = 7.3 Hz). **^{13}C{^{1}H}-NMR (75MHz) δ:** 161.9 (C_f); 149.8 (C_e); 147.9 (C_a); 137.8 (C_g); 137.7 (C_c); 129.1 (C_i); 126.4 (C_b); 124.3 (C_j); 122.4 (C_d); 119.7 (C_h). **M/z (HRMS-ESI+):** calcd for $C_{12}H_{10}N_2NaO$ $[M+Na]^+$: 221.0685. Found: 221.0683. **Anal:** calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.20; H, 5.10; N, 14.10.



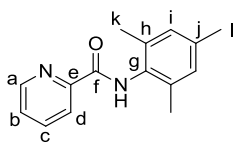
***N*-Phenylfuran-2-carboxamide (L13).**[6] Prepared using 5.0 g (45 mmols) of furan-2-carboxylic acid and 10 mL of pyridine. The mixture was extracted with DCM, and the organic fraction dried over $MgSO_4$ and concentrated. A solid product was obtained: filtered, washed with water and crystallised from hot MeOH as pale yellow crystals, yield 31% (2.59 g, 14 mmols). **^{1}H-NMR (500MHz) δ:** 8.08 (s, 1H, NH); 7.66 (d, 2H, H_g, J_{g-h} = 7.8 Hz); 7.53 (broad s, 1H, H_c); 7.38 (t, 2H, H_h, J_{h-g} = J_{h-i} = 7.9 Hz); 7.26 (d, 1H, H_a, J_{a-b} = 3.4 Hz); 7.16 (t, 1H, H_i, J_{i-h} = 7.6 Hz); 6.58 (dd, 1H, H_b, J_{b-a} = 3.4 Hz, J_{b-c} = 1.6 Hz). **^{13}C{^{1}H}-NMR (75MHz) δ:** 156.0 (C_e); 147.8 (C_d); 144.1 (C_c); 137.4 (C_f); 129.1 (C_h); 124.5 (C_i); 119.9 (C_g); 115.2 (C_a); 112.6 (C_b). **M/z (HRMS-ESI+):** calcd. for $C_{11}H_{10}NO_2$ $[M+H]^+$: 188.0706. Found: 188.0713.



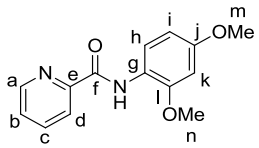
***N*-Phenylthiophene-2-carboxamide (L15).**[6] Prepared using 5.0 g (39 mmols) of thiophene-2-carboxylic acid and 10 mL of pyridine. White crystals, yield 78% (6.16 g, 30 mmols). **^{1}H-NMR (500MHz) δ:** 7.62 (m, 3H, $H_{c,g}$); 7.57 (d, 1H, H_a, J_{a-b} = 4.8 Hz); 7.38 (t, 2H, H_h, J_{h-g} = J_{h-i} = 7.9 Hz); 7.16 (t, 1H, H_i, J_{i-h} = 7.5 Hz); 7.15 (m, 1H, H_b, J_{b-c} = 4.1 Hz, J_{b-a} = 4.6 Hz). [N.B. NH peak not visible]. **^{1}H-NMR (500MHz) δ (DMSO-d_6):** 10.21 (s, 1H, NH); 8.03 (d, 1H, H_c, J_{c-b} = 3.7 Hz); 7.86 (d, 1H, H_a, J_{a-b} = 5.0 Hz); 7.72 (d, 2H, H_g, J_{g-h} = 7.8 Hz); 7.35 (t, 2H, H_h, J_{h-g} = J_{h-i} = 7.8 Hz); 7.23 (m, 1H, H_b); 7.10 (t, 1H, H_i, J_{i-h} = 7.3 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 159.9 (C_e); 139.3 (C_d); 137.6 (C_f); 130.7 (C_a); 129.1 ($C_{h,l}$); 128.4 (C_c); 127.8 (C_b); 124.6 (C_i); 120.2 ($C_{g,m}$). **M/z (EI)**: 203 (M^+), 111 (100), 94, 69, 65, 39. **M/z (HRMS-EI):** calcd. for $C_{11}H_9NOS$ $[M]^+$: 203.0405. Found: 203.0403. **IR ν (cm^{-1}):** 3301 (NH); 3088 (Ar CH); 1630; 1594; 1536; 1486; 1444; 1322; 1269. **Anal:** calcd. for $C_{11}H_9NOS$: C, 65.00; H, 4.46; N, 6.89. Found: C, 64.70; H, 4.40; N, 6.70.



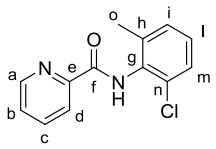
***N*-Phenylquinoline-2-carboxamide (L17).**[7] Prepared using 3.0 g (17 mmols) of quinaldic acid and 10 mL of pyridine. Pink solid, yield 81% (3.41 g, 14 mmols). **^{1}H-NMR (500MHz) δ:** 10.26 (broad s, 1H, NH); 8.45-8.35 (m, 2H, $H_{g,h}$); 8.21 (d, 1H, H_e, J_{e-d} = 8.1 Hz); 7.93 (d, 1H, H_b, J_{b-c} = 7.7 Hz); 7.88 (d, 2H, H_l, J_{l-m} = 7.9 Hz); 7.83 (t, 1H, H_d, J_{d-c} = J_{d-e} = 7.5 Hz); 7.66 (t, 1H, H_c, J_{c-b} = J_{c-d} = 7.5 Hz); 7.44 (t, 2H, H_m, J_{m-l} = J_{m-n} = 7.9 Hz); 7.19 (t, 1H, H_n, J_{n-m} = 7.5 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 162.2 (C_j); 149.9 (C_i); 146.4 (C_a); 138.0 (C_k); 137.8 (C_g); 130.3 (C_d); 129.8 (C_e); 129.1 (C_m); 128.1 ($C_{c,f}$); 127.8 (C_b); 124.4 (C_n); 119.9 (C_l); 119.0 (C_h). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{13}N_2O$ $[M+H]^+$: 249.1022. Found: 249.1020. **Anal:** calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.30; H, 4.90; N, 11.20.



***N*-Mesitylpicolinamide (L18).**[5] Prepared using 5.0 g (41 mmols) of picolinic acid and 15 mL of pyridine. The mixture was extracted with DCM, the organic fraction dried over $MgSO_4$ and concentrated; a solid product was obtained; filtered, washed with water and crystallised from hot MeOH as a white solid, yield 20% (2.0 g, 8 mmols). **^{1}H-NMR (300MHz) δ:** 9.40 (broad s, 1H, NH); 8.64 (ddd, 1H, H_a, J_{a-d} = 0.9 Hz, J_{a-c} = 1.6 Hz, J_{a-b} = 4.8 Hz); 8.31 (dt, 1H, H_d, J_{d-a} = J_{d-b} = 1.0 Hz, J_{d-c} = 7.8 Hz); 7.91 (dt, 1H, H_c, J_{c-a} = 1.8 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.50 (ddd, 1H, H_b, J_{b-d} = 1.2 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.5 Hz); 6.96 (s, 2H, H_i); 2.31 (s, 3H, H_l); 2.26 (s, 6H, H_k). **^{13}C{^{1}H}-NMR (75MHz) δ:** 162.5 (C_f); 149.9 (C_e); 148.1 (C_a); 137.5 (C_c); 136.8 (C_j); 135.1 (C_h); 131.1 (C_g); 128.9 (C_i); 126.3 (C_b); 122.5 (C_d); 20.9 (C_l); 18.4 (C_k). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{16}N_2NaO$ $[M+Na]^+$: 263.1155. Found: 263.1157. **Anal:** calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.90; H, 6.80; N, 11.70.

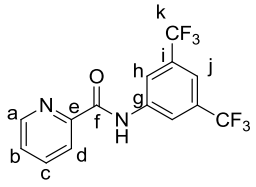


***N*-(2,4-Dimethoxyphenyl)picolinamide (L20).**[8] Prepared using 5.0 g (41 mmols) of picolinic acid and 10 mL of pyridine. The mixture was extracted with DCM, the organic fraction dried over $MgSO_4$ and concentrated, then stored at -20°C. A black solid product was obtained: filtered, washed with water and crystallised from hot MeOH as a black solid, yield 84% (8.90 g, 35 mmols). **^{1}H-NMR (300MHz) δ:** 10.38 (s, 1H, NH); 8.65 (m, 1H, H_a, J_{a-b} = 4.2 Hz); 8.50 (m, 1H, H_h);8.29 (dd, 1H, H_d, J_{d-b} = 0.9 Hz, J_{d-c} = 7.8 Hz); 7.90 (dt, 1H, H_c, J_{c-a} = 1.7 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.46 (ddd, 1H, H_b, J_{b-d} = 1.1 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 6.55 (m, 2H, $H_{i,k}$); 3.95 (s, 3H, H); 3.83 (s, 3H, H). **^{13}C{^{1}H}-NMR (125MHz) δ:** 161.6 (C_f); 156.6 (C_j); 150.4 (C_l); 150.1 (C_e); 148.1 (C_a); 137.4 (C_c); 126.0 (C_b); 122.2 (C_d); 121.2 (C_g); 120.4 (C_h); 103.7 (C_i); 98.7 (C_k); 55.8(C_m); 55.5 (C_n). **M/z (HRMS-ESI+):** calcd for $C_{14}H_{15}N_2O_3$ $[M+H]^+$: 259.1077. Found: 259.1081. **IR ν (cm^{-1}):** 3355 (NH); 3060 (Ar CH); 2990 (Me CH); 1947 (Me CH); 2843; 1868 (overtone); 1674 (CO); 1592; 1531; 1495; 1463; 1439; 1417; 1288; 1260; 1207. **M.p.:** 121-123°C.

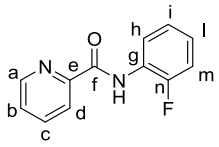


***N*-(2-Chloro-6-methylphenyl)picolinamide (L22).**[9] Prepared using 10.0 g (81 mmols) of picolinic acid and 20 mL of pyridine. The mixture was extracted with DCM, and the organic fraction dried over $MgSO_4$ and concentrated. The resulting product was purified by chromatography (Petroleum ether/Et_2O: 90/10). Obtained as a white powder, yield 30% (5.99 g, 24 mmols). **^{1}H-NMR (500MHz) δ:** 9.70 (s, 1H, NH); 8.68 (d, 1H, H_a, J_{a-b} = 4.8 Hz); 8.31 (d, 1H, H_d, J_{d-c} =7.8 Hz); 7.93 (dt, 1H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.52 (ddd, 1H, H_b, J_{b-d} = 1.1 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 7.34 (d, 1H, H_m, J_{m-l} = 7.6 Hz); 7.21 (bd, 1H, H_i, J_{i-l} = 7,4 Hz); 7.17 (t, 1H, H_l, J_{l-I} = J_{l-m}= 7.7 Hz); 2.37 (s, 3H, H_o). **^{13}C{^{1}H}-NMR (125MHz) δ:** 162.3 (C_f); 149.5 (C_e); 148.3 (C_a); 138.0 (C_g); 137.5 (C_c); 132.7 (C_h); 131.5 (C_n); 129.3 (C_i); 127.7 (C_l); 127.1 (C_m); 126.6

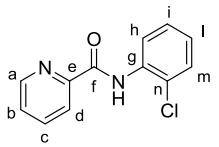
(C_b); 122.7 (C_d); 19.2 (C_o). **M/z (EI)**: 218, 212, 211 ([M-Cl]$^+$, 100), 79, 78, 51. **M/z (HRMS-ESI+):** calcd. for $C_{13}H_{11}ClN_2NaO$ [M+Na]$^+$: 269.0452. Found: 269.0452. **IR ν (cm^{-1}):** 3331 (NH); 3060 (Ar CH); 2924 (Me); 1683 (CO); 1589; 1568; 1494; 1469; 1435; 1281; 1233. **Anal**: calcd. for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.00; H, 4.45; N, 11.30. **M.p.:** 107-108 °C.



***N*-(3,5-Bis(trifluoromethyl)phenyl)picolinamide (L26).** Prepared using 2.0 g (16 mmols) of picolinic acid and 10 mL of pyridine. White crystals, yield 75% (4.00 g, 12 mmols). **^{1}H-NMR (500MHz) δ:** 10.36 (s, 1H, NH); 8.65 (d, 1H, H_a, J_{a-b} = 4.3 Hz); 8.32 (broad s, 3H, $H_{d,h}$); 7.97 (dt, 1H, H_c, J_{c-a} = 1.5 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.65 (s, 1H, H_j); 7.56 (m, 1H, H_b).**^{13}C{^{1}H}-NMR (125MHz) δ:** 162.4 (C_f); 148.7 (C_e); 148.1 (C_a); 139.2 (C_g); 138.0 (C_c); 132.5 (q, C_i, $^2J_{C-F}$ = 33.1 Hz); 127.1 (C_b); 123.1 (q, C_k, $^1J_{C-F}$ = 273.0 Hz); 122.7 (C_d); 119.3 (q, C_h, $^3J_{C-F}$ = 3.1 Hz); 117.5 (sept, C_j, $^3J_{C-F}$ = 4.2 Hz). **M/z (HRMS-ESI+):** calcd for $C_{14}H_9F_6N_2O$ [M+H]$^+$: 335.0614. Found: 335.0618. **Anal:** calcd. for $C_{14}H_8F_6N_2O$: C, 50.31; H, 2.41; N, 8.38. Found: C, 50.20; H, 2.36; N, 8.25. **M.p.:** 158-160°C.

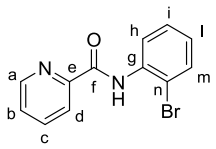


***N*-(2-Fluorophenyl)picolinamide (L27).**[5] Prepared using 10.0 g (81 mmols) of picolinic acid and 20 mL of pyridine. Off-white crystals, yield 80% (14.07 g, 65 mmols). **^{1}H-NMR (500MHz) δ:** 10.36 (s, 1H, NH); 8.67 (d, 1H, H_a, J_{a-b} = 4.5 Hz); 8.59 (t, 1H, H_h, J_{h-i} = J_{h-n} ≈ 8.3 Hz); 8.31 (d, 1H, H_d, J_{d-c} = 8.0 Hz); 7.93 (dt, 1H, H_c, J_{c-a}=1.6 Hz, J_{c-b}= J_{c-d}=7.7 Hz); 7.52 (ddd, 1H, H_b, J_{b-d}= 0.8 Hz, J_{b-a}= 4.6 Hz, J_{b-c}=7.2 Hz); 7.21 (dt, 1H, H_i, J_{i-n} = 0.9 Hz, J_{i-h} = J_{i-l} = 7.9 Hz); 7.17 (m, 1H, H_m, J = 1.3 Hz, J_{m-n} = 10.9 Hz,); 7.11 (m, 1H, H_l, J = 1.3 Hz, J_{l-n} = 6.4 Hz).**^{13}C{^{1}H}-NMR (125MHz) δ:**162.1 (C_f); 152.9 (d, C_n, $^1J_{C-F}$ = 245.0 Hz); 149.6 (C_e); 148.2 (C_a); 137.7 (C_c); 126.6 (C_b); 126.4 (d, C_g, $^2J_{C-F}$ = 9.4 Hz); 124.6 (d, C_i, $^4J_{C-F}$ = 4.1 Hz); 124.3 (d, C_l, $^3J_{C-F}$ = 8.3 Hz); 122.4 (C_d); 121.3 (C_h); 114.9 (d, C_m, $^2J_{C-F}$ = 18.7 Hz). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9FN_2NaO$ [M+Na]$^+$: 239.0591. Found: 239.0598. **Anal:** calcd. for $C_{12}H_9FN_2O$: C, 66.66; H, 4.20; N, 12.96. Found: C, 66.20; H, 4.25; N, 12.90.

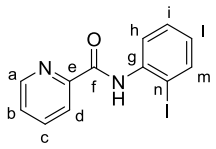


***N*-(2-Chlorophenyl)picolinamide (L28).**[10] Prepared using 10.0 g (81 mmols) of picolinic acid and 20 mL of pyridine. White crystals, yield 74% (13.94 g, 60 mmols). **^{1}H-NMR (500MHz) δ:** 10.73 (s, 1H, NH); 8.68 (m, 2H, $H_{a,h}$, J_{h-i} = 7.8 Hz); 8.31 (d, 1H, H_d, J_{d-c}= 8.0 Hz); 7.93 (dt, 1H, H_c, J_{c-a} = 1.6 Hz, J_{c-b}= J_{c-d}=7.8 Hz); 7.52 (ddd, 1H, H_b, J_{b-d}=1.1 Hz, J_{b-a}=4.8 Hz, J_{b-c}=7.6 Hz); 7.44 (dd, 1H, H_m, J_{m-i} = 1.4 Hz, J_{m-l} = 8.0 Hz); 7.35 (dt, 1H, H_l, J_{l-h} = 1.0 Hz, J_{l-i} = J_{l-m} = 8.3 Hz); 7.09 (dt, 1H, H_i, J_{i-m} = 1.4 Hz, J_{i-h} =J_{i-l} = 7.8 Hz). **^{13}C{^{1}H}-NMR (75MHz) δ:** 162.1 (C_f); 149.7 (C_e); 148.3 (C_a); 137.6 (C_c); 134.7 (C_g); 129.2 (C_m); 127.7 (C_l); 126.6 (C_b); 124.6 (C_i); 123.5 (C_n); 122.4

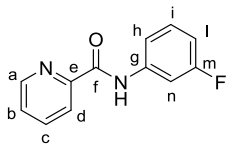
(C_d); 121.1 (C_h). **M/z (EI)**: 234, 233, 232 (M^+), 198, 197 ([M-Cl]$^+$, 100), 99, 79, 78, 52, 51. **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9ClN_2NaO$ [M+Na]$^+$: 255.0296. Found: 255.0292. **Anal:** calcd. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.80; H, 3.90; N, 12.00.



***N*-(2-Bromophenyl)picolinamide (L29).**[11] Prepared using 10.0 g (81 mmols) of picolinic acid and 20 mL of pyridine. Off-white crystals, yield 70% (15.81 g, 57 mmols). **^{1}H-NMR (500MHz) δ:** 10.73 (s, 1H, NH); 8.70 (bs, 1H, H_a); 8.65 (dd, 1H, H_h, J_{h-l} = 1.4 Hz, J_{h-i} = 8.2 Hz); 8.33 (bs, 1H, H_d); 7.93 (dt, 1H, H_c, J_{c-a} = 1.4 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.61 (dd, 1H, H_m, J_{m-i} = 1.4 Hz, J_{m-l} = 8.0 Hz); 7.52 (bs, 1H, H_b); 7.39 (dt, 1H, H_i, J_{i-m} = 1.4 Hz, J_{i-h} = J_{i-l} = 7.1 Hz); 7.02 (dt, 1H, H_l, J_{l-h} = 1.6 Hz, J_{l-i} = J_{l-m} = 7.7 Hz).**^{13}C{^{1}H}-NMR (75MHz) δ:** 162.2 (C_f); 149.7 (C_e); 148.3 (C_a); 137.6 (C_c); 135.9 (C_g); 132.4 (C_m); 128.3 (C_i); 126.6 (C_b); 125.1 (C_l); 122.4 (C_d); 121.3 (C_h); 113.9 (C_n). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9BrN_2NaO$ [M+Na]$^+$: 298.9790. Found: 298.9781. **Anal**: calcd. for $C_{12}H_9BrN_2O$: C, 52.01; H, 3.27; N, 10.11. Found: C, 51.95; H, 3.20; N, 10.20.

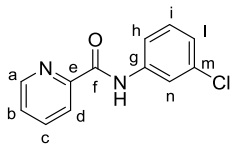


***N*-(2-Iodophenyl)picolinamide (L30).** Prepared using 652 mg (4.6 mmols) of picolinic acid and 3 mL of pyridine. Off-white crystals, yield 68% (1.01 g, 3.1 mmols). **^{1}H-NMR (500MHz) δ:** 10.55 (s, 1H, NH); 8.71 (d, 1H, H_a, J_{a-b} = 4.6 Hz); 8.54 (dd, 1H, H_h, J_{h-l} = 1.6 Hz, J_{h-i} = 8.2 Hz); 8.31 (d, 1H, H_d, J_{d-c} = 7.8 Hz); 7.93 (dt, 1H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.86 (dd, 1H, H_m, J_{m-i} = 1.3 Hz, J_{m-l} = 7.9 Hz); 7.52 (ddd, 1H, H_b, J_{b-d} = 1.1 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 7.42 (dt, 1H, H_i, J_{i-m} = 1.4 Hz, J_{i-h} = J_{i-l} ≈ 7.1 Hz); 6.89 (dt, 1H, H_l, J_{l-h} = 1.6 Hz, J_{l-i} = J_{l-m} = 7.7 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 162.4 (C_f); 149.7 (C_e); 148.3 (C_a); 139.1 (C_m); 138.6 (C_g); 137.7 (C_c); 129.2 (C_i); 126.6 (C_b); 125.9 (C_l); 122.5 (C_d); 121.5 (C_h); 89.7 (C_n). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9IN_2NaO$ [M+Na]$^+$: 346.9652. Found: 346.9644. **IR ν (cm^{-1}):** 3269 (NH); 3104; 3063 (Ar CH); 1689 (CO); 1572; 1532; 1465; 1438; 1429; 1301; 1272; 1232. **Anal**: calcd. for $C_{12}H_9IN_2O$: C, 44.47; H, 2.80; N, 8.64. Found: C, 44.60; H, 2.75; N, 8.40. **M.p.:** 137-139 °C.

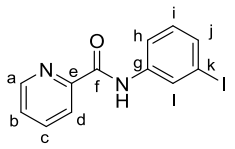


***N*-(3-Fluorophenyl)picolinamide (L31).**[12] Prepared using 5.0 g (41 mmols) of picolinic acid and 10 mL of pyridine. The organic layer was separated and dried over $MgSO_4$. Stored at -20°C, it led to precipitation of the crude product: washed with water and crystallised from hot MeOH as off-white crystals, yield 71% (6.21 g, 29 mmols). **^{1}H-NMR (500MHz) δ:** 10.12 (s, 1H, NH);8.63 (d, 1H, H_a, J_{a-b}=4.6 Hz); 8.32 (d, 1H, H_d, J_{d-c}= 8.0 Hz);7.94 (dt, 1H, H_c, J_{c-a}=1.4 Hz, J_{c-b}= J_{c-d}=7.6 Hz); 7.77 (dt, 1H, H_n, J_{n-h}= J_{n-l}= 2.1 Hz, J_{n-m}= 11.0 Hz); 7.52 (dd, 1H, H_b, J_{b-a}= 4.8 Hz, J_{b-c}=7.3 Hz); 7.42 (m, 1H, H_h, J_{h-m} = 0.7 Hz, J_{h-i} = 8.1 Hz); 7.33 (dt, 1H, H_i, J_{i-m} = 6.4 Hz, J_{i-h} = J_{i-l} = 8.2 Hz); 6.86 (dt, 1H, H_l, J_{l-n} = 2.4 Hz, J_{l-i} = J_{l-m} = 8.3 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 163.1 (d, C_m, $^1J_{C-F}$ = 245.0 Hz); 162.0 (C_f); 149.4 (C_e); 147.9 (C_a); 139.3 (d, C_g, $^3J_{C-F}$ = 10.4 Hz);

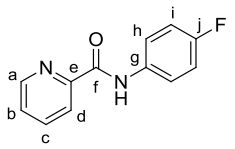
137.8 (C_c); 130.1 (d, C_i, $^3J_{C-F}$ = 9.3 Hz); 126.7 (C_b); 122.5 (C_d); 115.0 (d, C_h, $^4J_{C-F}$ = 2.1 Hz); 111.0 (d, C_l, $^2J_{C-F}$ = 21.8 Hz); 107.1 (d, C_n, $^2J_{C-F}$ = 25.9 Hz). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9FN_2NaO$ $[M+Na]^+$: 239.0591. Found: 239.0594.



***N*-(3-Chlorophenyl)picolinamide (L32).**[10] Prepared using 10.0 g (81 mmols) of picolinic acid and 20 mL of pyridine. The organic layer was separated and the crude product precipitated out: filtered, washed with water and crystallised from hot MeOH as off-white crystals, yield 70% (13.14 g, 57 mmols). **^{1}H-NMR (500MHz) δ:** 10.10 (s, 1H, NH); 8.63 (d, 1H, H_a, J_{a-b}= 4.8 Hz); 8.32 (d, 1H, H_d, J_{d-c}= 7.8 Hz); 7.95 (m, 2H, $H_{c,n}$, J_{c-a}= 1.6 Hz, J_{c-b}= J_{c-d}= 7.8 Hz); 7.64 (dt, 1H, H_h, J_{h-l} = J_{h-n} = 1.0 Hz, J_{h-i} = 8.2 Hz); 7.52 (ddd, 1H, H_b, J_{b-d} = 1.1 Hz, J_{b-a}= 4.8 Hz, J_{b-c} = 7.6 Hz); 7.32 (t, 1H, H_i, J_{i-h} = J_{i-l} = 8.2 Hz); 7.14 (dt, 1H, H_l, J_{l-h} = J_{l-n} = 1.0 Hz, J_{l-i} = 8.0 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 162.0 (C_f); 149.4 (C_e); 147.9 (C_a); 138.9 (C_g); 137.8 (C_c); 134.8 (C_m); 130.0 (C_i); 126.7 (C_b); 124.3 (C_l); 122.5 (C_d); 119.7 (C_n); 117.6 (C_h). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9ClN_2NaO$ $[M+Na]^+$: 255.0296. Found: 255.0302. **Anal:** calcd. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.60; H, 3.90; N, 11.95.

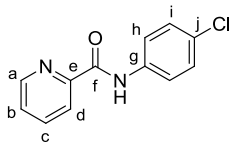


***N*-(3-Iodophenyl)picolinamide (L34).** Prepared using 2.8 g (23 mmols) of picolinic acid and 7 mL of pyridine. White fluffy solid, yield 90% (6.68 g, 21 mmols). **^{1}H-NMR (500MHz) δ:** 10.03 (s, 1H, NH); 8.63 (d, 1H, H_a, J_{a-b} = 4.6 Hz); 8.30 (d, 1H, H_d, J_{d-c} = 7.8 Hz); 8.22 (d, 1H, H_l, J_{l-j} = 1.8 Hz); 7.94 (dt, 1H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.78 (d, 1H, H_h, J_{h-i} = 8.3 Hz); 7.54-7.48 (m, 2H, $H_{b,j}$); 7.12 (t, 1H, H_i, J_{i-h} = J_{i-j} = 8.0 Hz). **^{13}C{^{1}H} -NMR (125MHz) δ:** 161.9 (C_f); 149.4 (C_e); 147.9 (C_a); 138.9 (C_g); 137.8 (C_c); 133.3 (C_j); 130.5 (C_i); 128.3 (C_l); 126.7 (C_b); 122.5 (C_d); 118.8 (C_h); 94.2 (C_k). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_{10}IN_2O$ $[M+H]^+$: 324.9832. Found: 324.9843. **Anal:** calcd. for $C_{12}H_9IN_2O$: C, 44.47; H, 2.80; N, 8.64. Found: C, 44.70; H, 2.75; N, 8.40. **M.p.:** 144-146°C.

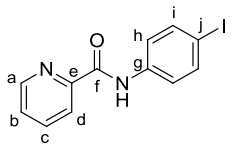


***N*-(4-Fluorophenyl)picolinamide (L35).**[5] Prepared using 10.0 g (81 mmols) of picolinic acid and 20 mL of pyridine. Yellow crystals, yield 53% (9.27 g, 43 mmols). **^{1}H-NMR (500MHz) δ:** 10.05 (s, 1H, NH); 8.63 (d, 1H, H_a, J_{a-b} = 4.6 Hz); 8.32 (d, 1H, H_d, J_{d-c} = 7.6 Hz); 7.94 (dt, 1H, H_c, J_{c-a} = 1.4 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.77 (dd, 2H, H_h, J_{h-i} = 8.9 Hz); 7.52 (dd, 1H, H_b, J_{b-a} = 5.2 Hz, J_{b-c} =7.0 Hz); 7.09 (d, 2H, H_i, J_{i-h} = 8.6 Hz). **^{13}C{^{1}H}-NMR (75MHz) δ:**161.9 (C_f); 154.4 (d, C_j, $^1J_{C-F}$ = 243.8 Hz); 149.6 (C_e); 147.9 (C_a); 137.8 (C_c); 133.8 (d, C_g, $^4J_{C-F}$ = 2.5 Hz); 126.5 (C_b); 122.4 (C_d); 121.3 (d, C_h, $^3J_{C-F}$ = 7.4 Hz); 115.7 (d, C_i, $^2J_{C-F}$ = 23.0 Hz). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9FN_2NaO$ $[M+Na]^+$: 239.0591. Found: 239.0592. **IR ν (cm^{-1}):** 3343 (NH); 3067

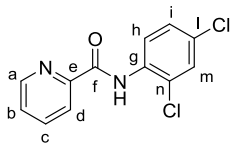
(Ar CH); 1892; 1682; 1607; 1591; 1572; 1513; 1408; 1299; 1209. **Anal:** calcd. for $C_{12}H_9FN_2O$: C, 66.66; H, 4.20; N, 12.96. Found: C, 66.20; H, 4.20; N, 12.70.



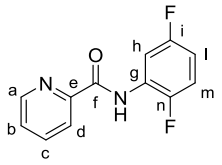
***N*-(4-Chlorophenyl)picolinamide (L36).**[11] Prepared using 10.0 g (81 mmols) of picolinic acid and 25 mL of pyridine. Off-white crystals, yield 78% (14.70 g, 63 mmols). **^{1}H-NMR (500MHz) δ:** 10.06 (s, 1H, NH); 8.63 (d, 1H, H_a, J_{a-b} = 4.6 Hz); 8.31 (d, 1H, H_d, J_{d-c} = 7.8 Hz); 7.93 (dt, 1H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.76 (d, 2H, H_h, J_{h-i} = 8.9 Hz); 7.52 (ddd, 1H, H_b, J_{b-d} = 1.1 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 7.36 (d, 2H, H_i, J_{i-h} = 8.7 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 161.9 (C_f); 149.5 (C_e); 147.9 (C_a); 137.8 (C_c); 136.3 (C_g); 129.2 (C_l); 129.1 (C_i); 126.6 (C_b); 122.5 (C_d); 120.9 (C_h). **M/z (EI):** 234, 233, 232 (M^+), 231, 106, 99, 79, 78 (100), 63, 52, 51. **M/z (HRMS-EI):** calcd. for $C_{12}H_9N_2OCl$ $[M]^+$: 232.0403. Found: 232.0404. **IR ν (cm^{-1}):** 3412; 3332 (NH); 3245; 3099; 3057 (CH); 1894; 1768; 1685; 1593; 1495; 1435; 1398; 1295; 1230. **Anal:** calcd. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.60; H, 3.80; N, 12.10.



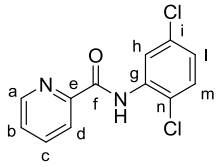
***N*-(4-Iodophenyl)picolinamide (L38).**[13] Prepared using 3.0 g (24 mmols) of picolinic acid and 10 mL of pyridine. White crystals, yield 82% (6.47 g, 20 mmols). **^{1}H-NMR (500MHz) δ:** 10.04 (s, 1H, NH); 8.61 (ddd, 1H, H_a, J_{a-b} = 4.9 Hz, J_{a-c} = 1.7 Hz, J_{a-d} = 0.9 Hz); 8.29 (dt, 1H, H_d, J_{d-c} = 7.9 Hz, J_{d-b} = J_{d-a} = 1.0 Hz); 7.92 (dt, 1H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.69 (m, 2H, H_h); 7.58 (m, 2H, H_i); 7.50 (ddd, 1H, H_b, J_{b-d} = 1.2 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.5 Hz). **^{13}C{^{1}H} -NMR (125MHz) δ:** 162.0 (C_f); 149.5 (C_e); 147.9 (C_a); 138.0 (C_h); 137.8 (C_c); 137.5 (C_g); 126.6 (C_b); 122.5 (C_d); 121.5 (C_i); 87.5 (C_j). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9IN_2ONa$ $[M+Na]^+$: 346.9652. Found: 346.9651. **Anal:** calcd. for $C_{12}H_9IN_2O$: C, 44.47; H, 2.80; N, 8.64. Found: C, 44.65; H, 2.80; N, 8.50. **M.p.:** 163-165°C.



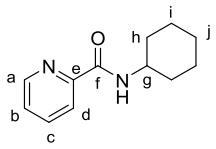
***N*-(2,4-Dichlorophenyl)picolinamide (L40).**[10] Prepared using 9.0 g (62 mmols) of picolinic acid and 20 mL of pyridine. White crystals, yield 64% (10.60 g, 40 mmols). **^{1}H-NMR (500MHz) δ:** 10.71 (s, 1H, NH); 8.68 (dt, 1H, H_a, J_{a-c} = 1.3 Hz, J_{a-b} = 4.5 Hz,); 8,65 (d, 1H, H_h, J_{h-i} = 8.9 Hz); 8.30 (d, 1H, H_d, J_{d-c} = 7.8 Hz); 7.95 (dt, 1H, H_c, J_{c-b} = J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.53 (ddd, 1H, H_b, J_{b-d} = 0.7 Hz, J_{b-a} = 4.6 Hz, J_{b-c} = 7.5 Hz); 7.46 (d, 1H, H_m, J_{m-i} = 2.3 Hz); 7.33 (dd, 1H, H_i, J_{i-m} = 2.3, J_{i-h}=8.9 Hz). **^{13}C{^{1}H}-NMR (75MHz) δ:** 162.2 (C_f); 149.5 (C_e); 148.3 (C_a); 137.7 (C_c); 133.5 (C_g); 129.0 (C_l); 128.9 (C_m); 127.9 (C_i); 126.8 (C_b); 124.0 (C_n); 122.5 (C_d); 121.7 (C_h). **M/z (EI)**: 266 (M^+), 233, 231 ($[M-Cl]^+$, 100), 106, 79, 78, 52, 51. **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9Cl_2N_2O$ $[M+H]^+$: 267.0086. Found: 267.0085. **Anal:** calcd. for $C_{12}H_8Cl_2N_2O$: C, 53.96; H, 3.02; N, 10.49. Found: C, 54.00; H, 3.10; N, 10.60.



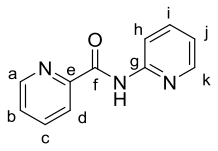
***N*-(2,5-Difluorophenyl)picolinamide (L42).**[11] Prepared using 10.0 g (81 mmols) of picolinic acid and 20 mL of pyridine. White crystals, yield 69% (13.01 g, 56 mmols). **^{1}H-NMR (500MHz) δ:** 10.40 (s, 1H, NH); 8.67 (d, 1H, H_a, J_{a-b} = 4.4 Hz); 8.44 (ddd, 1H, H_h, J_{h-l} = 3.2 Hz, J_{h-n} = 6.5 Hz, J_{h-I} = 10.0 Hz); 8.30 (d, 1H, H_d, J_{d-c} = 7.8 Hz); 7.94 (dt, 1H, H_c, J_{c-a} = 1.7 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.53 (ddd, 1H, H_b, J_{b-d} = 1.0 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.4 Hz); 7.10 (ddd, 1H, H_m, J_{m-l} = 5.0 Hz, J_{m-l} = 9.2 Hz, J_{m-n} = 10.0 Hz); 6.78 (m, 1H, H_l). **^{13}C{^{1}H}-NMR (75MHz) δ:** 162.2 (C_f); 158.7 (dd, C_i, $^{4}J_{C-F}$ = 2.5 Hz, $^{1}J_{C-F}$ = 241.4 Hz); 149.2 (C_e); 148.8 (d, C_n, $^{1}J_{C-F}$ = 236.4 Hz); 148.2 (C_a); 137.7 (C_c); 127.3 (d, C_g, $^{2}J_{C-F}$ = 13.1 Hz); 126.8 (C_b); 122.5 (C_d); 115.3 (dd, C_m, $^{3}J_{C-F}$ = 9.9 Hz, $^{2}J_{C-F}$ = 21.2 Hz); 110.1 (dd, C_l, $^{3}J_{C-F}$ = 8.1 Hz, $^{2}J_{C-F}$ = 24.2 Hz); 108.4 (d, C_h, $^{2}J_{C-F}$ = 31.7 Hz). **M/z (EI):** 235, 234 (M^+), 215, 106, 101, 79, 78 (100), 69, 52, 51. **M/z (HRMS-EI):** calcd. for $C_{12}H_8F_2N_2O$ $[M]^+$: 234.0605. Found: 234.0613. **Anal:** calcd. for $C_{12}H_8F_2N_2O$: C, 61.54; H, 3.44; N, 11.96. Found: C, 61.30; H, 3.40; N, 11.90.



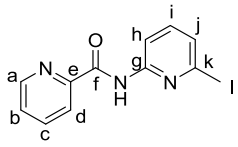
***N*-(2,5-Dichlorophenyl)picolinamide (L43).**[10] Prepared using 10.0 g (81 mmols) of picolinic acid and 20 mL of pyridine. Off-white crystals, yield 62% (13.41 g, 50 mmols). **^{1}H-NMR (500MHz) δ:** 10.75 (s, 1H, NH); 8.78 (d, 1H, H_h, J_{h-l} = 2.3 Hz); 8,68 (d, 1H, H_a, J_{a-b} = 4.8 Hz); 8.30 (d, 1H, H_d, J_{d-c} = 7.8 Hz); 7.95 (dt, 1H, H_c, J_{c-a} = 1.6 Hz, J_{c-d} = J_{c-b} = 7.8 Hz); 7.54 (ddd, 1H, H_b, J_{b-d} = 1.2 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 7.36 (d, 1H, H_m, J_{m-l} = 8.5 Hz); 7.07 (dd, 1H, H_l, J_{l-h} = 2.5 Hz, J_{l-m} = 8.8 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 162.2 (C_f); 149.3 (C_e); 148.3 (C_a); 137.7 (C_c); 135.6 (C_g); 133.5 (C_i); 129.8 (C_m); 126.8 (C_b); 124.5 (C_l); 122.5 (C_d); 121.5 (C_n); 120.9 (C_h). **M/z (EI)**: 233, 231([M-Cl]$^+$, 100), 133, 79, 78, 51. **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9Cl_2N_2O$ $[M+H]^+$: 267.0086. Found: 267.0082. **Anal:** calcd. for $C_{12}H_8Cl_2N_2O$: C, 53.96; H, 3.02; N, 10.49. Found: C, 53.60; H, 2.90; N, 10.40.



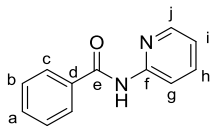
***N*-Cyclohexylpicolinamide (L45).**[14] Prepared using 2.0 g (16 mmols) of picolinic acid and 5 mL of pyridine. The mixture was extracted with DCM, and the organic fraction dried over $MgSO_4$ and concentrated. The crude product was purified through chromatography (biotage, gradient Hexane/ AcOEt). White solid, yield 89% (2.91 g, 14 mmols). **^{1}H-NMR (400MHz) δ:** 8.55 (d, 1H, H_a, J_{a-b} = 4.8 Hz); 8.21 (d, 1H, H_d, J_{d-c} = 7.9 Hz); 7.96 (broad s, 1H, NH); 7.85 (dt, 1H, H_c, J_{c-a} = 1.7 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 4.42 (ddd, 1H, H_b, J_{b-d} = 1.3 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 3.98 (m, 1H, H_g); {[2.05-2.00 (2H); 1.82-1.75 (2H); 1.70-1.63 (1H); 1.51-1.19 (5H)], multiplets, 10H, $H_{h,i,j}$}. **^{13}C{^{1}H}-NMR (100MHz) δ:** 163.3 (C_f); 150.3 (C_e); 147.9 (C_a); 137.3 (C_c); 125.9 (C_b); 122.2 (C_d); 48.1 (C_g); 33.1 (C_h); 25.6 (C_j); 24.9 (C_i). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_{16}N_2NaO$ $[M+Na]^+$: 227.1155. Found: 227.1156. **Anal:** calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.10; H, 8.00; N, 13.80.



***N*-(2-Pyridyl)picolinamide (L46).**[15] Prepared using 2.0 g (16 mmols) of picolinic acid and 5 mL of pyridine. The mixture was extracted with DCM, and the organic fraction driedover $MgSO_4$ and concentrated. A solid product was obtained: filtered, washed with water and hexane, and crystallised from hot MeOH. White crystals, yield 48% (1.52 g, 8 mmols)**. ^{1}H-NMR (500MHz) δ:** 10.93 (bs, 1H, NH); 8.69 (d, 1H, H_a, J_{a-b} = 4.4 Hz); 8.54 (d, 1H, H_h, J_{h-i} = 8.0 Hz); 8.37 (d, 1H, H_k, J_{k-j} = 4.6 Hz); 8.30 (d, 1H, H_d, J_{d-c} = 7.8 Hz); 7.93 (dt, 1H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.87 (bt, 1H, H_i, J_{i-h} = J_{i-j} = 7.3 Hz); 7.52 (dd, 1H, H_b, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 7.15 (m, 1H, H_j). **^{13}C{^{1}H}-NMR (75MHz) δ:** 162.6 (C_f); 151.1 (C_g); 149.3 (C_e); 148.3 (C_a); 148.0 (C_k); 138.4 (C_i); 137.5 (C_c); 126.7 (C_b); 122.4 (C_d); 119.8 (C_j); 114.0 (C_h). **M/z (HRMS-ESI+):** calcd. for $C_{11}H_{10}N_3O$ $[M+H]^+$: 200.0818. Found: 200.0827.

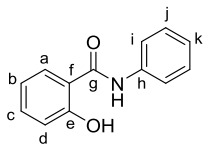


***N*-(6-Methylpyridin-2-yl)picolinamide (L47).**[15] Prepared using 5.0 g (41 mmols) of picolinic acid and 10 mL of pyridine. The mixture was extracted with DCM, and the organic layer separated and dried over $MgSO_4$. When stored at -20°C, a solid product formed: filtered, washed with water and crystallised from hot MeOH, furnishing yellow crystals of the product, yield 38% (3.35 g, 16 mmols). **^{1}H-NMR (500MHz) δ:** 10.50 (s, 1H, NH); 8.64 (d, 1H, H_a, J_{a-b} = 4.6 Hz); 8.29 (d, 1H, H_d, J_{d-c} = 7.8 Hz); 8.24 (d, 1H, H_h, J_{h-i} = 8.2 Hz); 7.91 (dt, 1H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.66 (t, 1H, H_i, J_{i-h} = J_{i-j} = 7.9 Hz); 7.49 (ddd, 1H, H_b, J_{b-d} = 1.0 Hz, J_{b-a} = 4.7 Hz, J_{b-c} = 7.6 Hz); 6.94 (d, 1H, H_j, J_{j-i} = 7.6 Hz); 2.52 (s, 3H, H_l). **^{13}C{^{1}H} -NMR (125MHz) δ:** 162.5 (C_f); 157.1 (C_g); 150.5 (C_k); 149.4 (C_e); 148.2 (C_a); 138.6 (C_i); 137.5 (C_c); 126.6 (C_b); 122.4 (C_d); 119.3 (C_j); 110.8 (C_h); 24.1 (C_l). **M/z (EI):** 213 (M^+), 185, 184, 135, 92, 78. **M/z (HRMS-ESI+):** calcd. for $C_{12}H_{12}N_3O$ $[M+H]^+$: 214.0975. Found: 214.0981. **IR ν (cm^{-1}):** 3341 (NH); 3060 (Ar CH); 1685 (CO); 1525; 1459; 1398; 1282; 1255; 1236. **Anal:** calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.25; H, 5.15; N, 19.35. **M.p.:** 96-98°C.

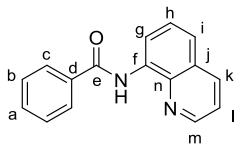


***N*-(2-Pyridyl)benzamide (L48).**[16] Prepared using 1.0 g (8 mmols) of benzoic acid and 5 mL of pyridine. The mixture was extracted with DCM, and the organic layer separated, dried over $MgSO_4$ and concentrated. The crude product was purified through chromatography (biotage, gradient Hexane/AcOEt 90/10 to 40/60). White solid, yield 61% (1.00 g, 5 mmols). **^{1}H-NMR (500MHz) δ:** 8.66 (broad s, 1H, NH); 8.41 (d, 1H, H_g, J_{g-h} = 8.4 Hz); 8.29 (d, 1H, H_j, J_{j-i} = 4.6 Hz); 7.94 (d, 2H, H_c, J_{c-b} = 7.5 Hz); 7.77 (dt, 1H, H_h, J_{h-j} = 1.6 Hz, J_{h-g} = J_{h-i} = 7.9 Hz); 7.59 (t, 1H, H_a, J_{a-b} = 7.4 Hz); 7.51 (t, 2H, H_b, J_{b-a} = J_{b-c} = 7.5 Hz); 7.08 (dd, 1H, H_i, J_{i-j} = 5.4 Hz, J_{i-h} = 6.8 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.6 (C_e); 151.7 (C_f); 147.6(C_j); 138.5 (C_h); 134.5 (C_d); 132.2 (C_a); 128.9 (C_b);

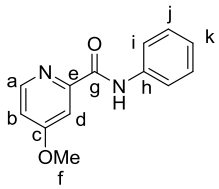
127.3 (C_c); 119.9 (C_i); 114.4 (C_g). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_{10}N_2NaO$ $[M+Na]^+$: 221.0685. Found: 221.0982.



***N*-Phenylsalicylamide (L49).**[17] Prepared using 2.0 g (14 mmols) of salicylic acid and 5 mL of pyridine. The mixture was extracted with DCM, and the organic layer separated, dried over $MgSO_4$ and concentrated. A solid product was obtained: filtered, washed with water and crystallised from hot MeOH. Off-white solid, yield 22% (662 mg, 3 mmols). **^{1}H-NMR (500MHz) δ:** 11.99 (broad s, 1H, OH); 7.97 (broad s, 1H, NH); 7.59 (d, 2H, H_i, J_{i-j} = 7.5 Hz); 7.54 (dd, 1H, H_a, J_{a-c} = 1.4 Hz, J_{a-b} = 8.0 Hz); 7.48-7.43 (m, 1H, H_c); 7.41 (t, 2H, H_j, J_{j-i} = J_{j-k} = 8.0 Hz); 7.22 (t, 1H, H_k, J_{k-j} = 7.5 Hz); 7.05 (dd, 1H, H_d, J_{d-b} = 1.1 Hz, J_{d-c} = 8.3 Hz); 6.95-6.90 (m, 1H, H_b). **^{13}C{^{1}H}-NMR (125MHz) δ:** 168.5 (C_g); 162.1 (C_e); 136.8 (C_h); 134.6 (C_c); 129.2 (C_j); 125.4 ($C_{a,k}$); 121.3 (C_i); 119.1 (C_b); 118.9 (C_d); 114.8 (C_f). **M/z (HRMS-ESI+):** calcd. for $C_{13}H_{12}NO_2$ $[M+H]^+$: 214.0863. Found: 214.0860. **Anal:** calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.10; H, 5.25; N, 6.30.

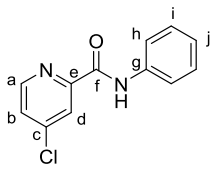


***N*-(8-Quinolyl)benzamide (L50).**[18] Prepared using 2.0 g (16 mmols) of benzoic acid and 5 mL of pyridine. The mixture was extracted with DCM, and the organic layer dried over $MgSO_4$ and concentrated. The crude product was purified through chromatography (biotage, gradient Hexane/AcOEt : 90/10 to 40/60). White solid, yield 21% (860 mg, 3 mmols). **^{1}H-NMR (500MHz) δ:** 10.77 (s, 1H, NH); 8.96 (dd, 1H, H_g, J_{g-i} = 1.3 Hz, J_{g-h} = 7.5 Hz); 8.87 (dd, 1H, H_m, J_{m-k} = 1.7 Hz, J_{m-l} = 4.2 Hz); 8.20 (dd, 1H, H_k, J_{k-m} = 1.6 hz, J_{k-l} = 8.3 Hz); 8.11 (m, 2H, H_c); 7.63-7.55 (m, 5H, $H_{a,b,h,i}$); 7.50 (dd, 1H, H_l, J_{l-m} = 4.2 Hz, J_{l-k} = 8.3 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.5 (C_e); 148.3 (C_m); 138.8 (C_f); 136.4 (C_k); 135.2 (C_d); 134.6 (C_n); 131.8 (C_a); 128.8 (C_b); 128.0 (C_j); 127.5 (C_h); 127.3 (C_c); 121.7 ($C_{i,l}$); 116.5 (C_g). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{13}N_2O$ $[M+H]^+$: 249.1022. Found: 249.1024. **Anal:** calcd. for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.80; H, 5.00; N, 11.30.



***N*-Phenyl-4-methoxypicolinamide (L51).**[13] Prepared using 0.2 g (1.3 mmols) of 4-methoxypicolinic acid and 2 mL of pyridine. The mixture was extracted with DCM, and the organic layer dried over $MgSO_4$ and concentrated. The product was purified through chromatography (gradient Hexane/AcOEt : 90/10 to 30/70). Off-white solid, yield 98% (295 mg, 1.3 mmols). **^{1}H-NMR (500MHz) δ:** 10.08 (broad s, 1H, NH); 8.41 (d, 1H, H_a, J_{a-b}= 5.5 Hz); 7.84 (d, 1H, H_d, J_{d-b} = 2.3 Hz); 7.79 (d, 2H, H_i, J_{i-j} = 8.0 Hz); 7.40 (t, 2H, H_j, J_{j-i} = J_{j-k} = 7.8 Hz); 7.16 (t, 1H, H_k, J_{k-j} = 7.3 Hz) 6.97 (dd, 1H, H_b, J_{b-d} = 2.4 Hz, J_{b-a} = 5.6 Hz); 3.94 (s, 3H, H_f). **^{13}C{^{1}H}-NMR (125MHz) δ:** 167.2 (C_c); 161.9 (C_g); 151.8 (C_e); 149.0 (C_a); 137.7 (C_h); 129.0 (C_j); 124.3

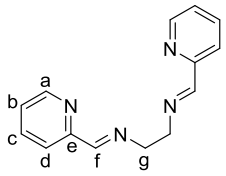
(C_k); 119.6 (C_i); 113.2 (C_b); 107.6 (C_d); 55.6 (C_f). **M/z (HRMS-ESI+):** calcd. for $C_{13}H_{12}N_2NaO_2$ $[M+Na]^+$: 251.0791. Found: 251.0789.



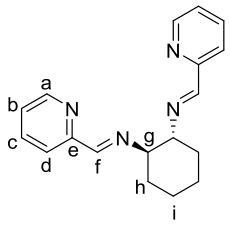
***N*-Phenyl-4-Chloropicolinamide (L52).**[13] Prepared according to an alternative procedure.[19] In a round-bottom flask 300 mg (1.9 mmols). of 4-chloropicolinic acid acid was stirred at 0°C with triethylamine (0.4 mL, 1.9 mmols), aniline (0.2 mL, 1.9 mmols) and DCM (4 mL). After dropwise addition of $POCl_3$ (0.6 mL, 1.9 mmols), the solution was stirred for 30 minutes at 0°C, then left to warm to room temperature, further stirring for 2 hours. The reaction was quenched with water at 0°C, the organic layer was separated and evaporated, yielding an off-white solid. Crystallisation from hot MeOH afforded the product as an off-white solid, yield 90% (399 mg, 1.7 mmols). **^{1}H-NMR (500MHz) δ:** 9.92 (broad s, 1H, NH); 8.53 (d, 1H, H_a, J_{a-b}= 5.3 Hz); 8.32 (d, 1H, H_d, J_{d-b} = 1.4 Hz); 7.77 (d, 2H, H_h, J_{h-i} = 7.8 Hz); 7.50 (dd, 1H, H_b, J_{b-d} = 2.0 Hz, J_{b-a} = 5.3 Hz); 7.41 (t, 2H, H_i, J_{i-h} = J_{i-j} = 7.8 Hz); 7.18 (t, 1H, H_j, J_{j-i} = 7.5 Hz). **^{13}C{^{1}H}-NMR (75MHz) δ:** 160.8 (C_f); 151.3 (C_e); 148.9 (C_a); 146.3 (C_c); 137.4 (C_g); 129.1 (C_i); 126.6 (C_b); 124.6 (C_j); 123.1 (C_d); 119.7 (C_h). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_9ClN_2NaO$ $[M+Na]^+$: 255.0296. Found: 255.0294.

6.2.2 – Synthesis of tetradentate iminopyridine ligands

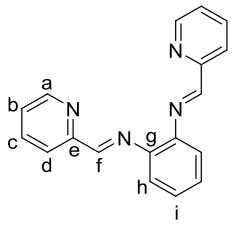
General procedure: The ligands were prepared through a modified literature procedure.[20] A solution of 20 mmols (1.9 mL) of pyridine-2-carbaldehyde in 10 mL of methanol/ethanol was added to a stirred solution of di-amine (10 mmols) in 10 mL of methanol/ethanol. Unless otherwise stated, the solution was taken to reflux for three hours under a nitrogen atmosphere, then the crude solution was evaporated, and the crude solid re-crystallised from hot methanol.



***N*^{1},*N*^{2}-bis(pyridin-2-ylmethylene)ethane-1,2-diamine (L53a).**[21] Prepared using methanol as solvent. The crude solid was re-crystallised from hot methanol. Fibrous yellow-orange crystals were obtained, washed with hexane. Yield 100% (2.38 g, 10 mmols). **^{1}H-NMR (500MHz) δ:** 8.63 (m, 2H, H_a); 8.42 (s, 2H, H_f); 7.98 (d, 2H, H_d, J_{d-c} = 7.8 Hz); 7.73 (dt, 2H, H_c, J_{c-a} = 1.5 Hz, J_{c-b} = J_{c-d} = 7.6 Hz); 7.30 (ddd, 2H, H_b, J_{b-d} = 1.2 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 4.07 (s, 4H, H_g). **^{13}C{^{1}H}-NMR (125MHz) δ:** 163.4 (C_f); 154.4 (C_e); 149.4 (C_a); 136.5 (C_c); 124.7 (C_b); 121.3 (C_d); 61.3 (C_g). **M/z (HRMS-ESI+):** calcd for $C_{14}H_{15}N_4$ $[M+H]^+$: 239.1291. Found: 239.1282.



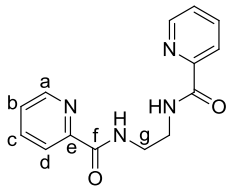
(±)-*N*^{1},*N*^{2}-*trans*-bis(pyridin-2-ylmethylene)cyclohexane-1,2-diamine (L53b).[22] Prepared using methanol as solvent. The crude solid was re-crystallised from hot methanol. Big pale yellow crystals were obtained, washed with water and hexane. Yield 93% (2.70 g, 9 mmols). **^{1}H-NMR (500MHz) δ:** 8.56 (m, 2H, H_a); 8.32 (s, 2H, H_f); 7.89 (dd, 2H, H_d, J_{d-b}= 0.9 Hz, J_{d-c}= 7.8 Hz); 7.65 (dt, 2H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.8 Hz); 7.22 (ddd, 2H, H_b, J_{b-d} = 1.2 Hz, J_{b-a}= 4.8 Hz, J_{b-c} = 7.5 Hz); 3.55 (m, 2H, H_g); 1.85 (m, 6H, $H_{h,i}$); 1.52 (m, 2H, H_i). **^{13}C{^{1}H}-NMR (125MHz) δ:** 161.4 (C_f); 154.7 (C_e); 149.2 (C_a); 136.4 (C_c); 124.4 (C_b); 121.3 (C_d); 73.5 (C_g); 32.7 (C_h); 24.3 (C_i). **M/z (HRMS-ESI+):** calcd for $C_{18}H_{21}N_4$ $[M+H]^+$: 293.1761. Found: 293.1770.



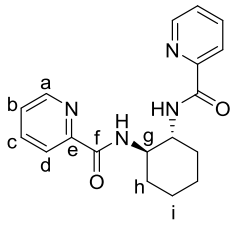
***N*^{1},*N*^{2}-bis(pyridin-2-ylmethylene)benzene-1,2-diamine (L53c).**[20] Prepared using ethanol as solvent. The reaction was performed at room temperature. The crude solution was evaporated and purified by column chromatography using methanol as eluent. Yellow powder, yield 63% (1.80 g, 6 mmols). **^{1}H-NMR (300MHz) δ:** 8.72 (d, 2H, H_a, J_{a-b} = 4.5 Hz); 8.66 (s, 2H, H_f); 8.22 (d, 2H, H_d, J_{d-c} = 7.9 Hz); 7.83 (dt, 2H, H_c, J_{c-a} = 1.0 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.40-7.36 (m, 2H, H_b); 7.38 (m, 4H, $H_{h,i}$). **^{13}C{^{1}H}-NMR (125MHz) δ:** 160.2 (C_f); 154.6 (C_e); 149.7 (C_a); 149.5 (C_g); 136.7 (C_c); 125.1 (C_b); 122.2 ($C_{h,i}$); 121.9 (C_d). **M/z (HRMS-ESI+):** calcd for $C_{18}H_{15}N_4$ $[M+H]^+$: 287.1291. Found: 287.1287.

6.2.3 – Synthesis of tetradentate picolinamide ligands

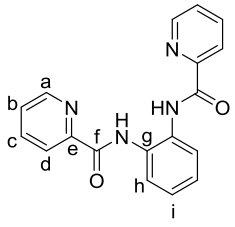
General procedure: The general procedure for these ligands is similar to the one used for the synthesis of bidentate amidic ligands,[4] but 2 eq. of picolinic acid and triphenyl phosphite were used. Unless otherwise stated, after the addition of water the crude product precipitated out, and was recrystallised from hot methanol.



***N*,*N*'-(Ethane-1,2-diyl)dipicolinamide (L54a).**[23] Prepared using 4.9 g (40 mmols) of picolinic acid and 20 mL of pyridine. Off-white crystals, yield 80% (4.32 g, 16 mmols). **^{1}H-NMR (500MHz) δ:** 8.58 (d, 2H, H_a, J_{a-b} = 4.8 Hz); 8.44 (s, 2H, NH); 8.22 (d, 2H, H_d, J_{d-c} = 7.8 Hz); 7.86 (dt, 2H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.44 (ddd, 2H, H_b, J_{b-d} = 1.2 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 3.77 (m, 4H, H_g). **^{13}C{^{1}H}-NMR (75MHz) δ:** 165.0 (C_f); 149.7 (C_e); 148.1 (C_a); 137.1 (C_c); 126.2 (C_b); 122.2 (C_d); 39.5 (C_g). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{15}N_4O_2$ $[M+H]^+$: 271.1189. Found: 271.1191. **Anal:** calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 61.95; H, 5.20; N, 20.90.



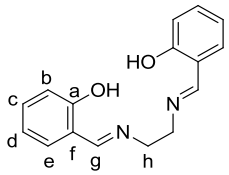
(±)-*N,N'*-(*Trans*-cyclohexane-1,2-diyl)dipicolinamide (L54b).[24] Prepared using 4.9 g (40 mmols) of picolinic acid and 20 mL of pyridine. The crude mixture was extracted with DCM, and the organic layer was separated, dried over $MgSO_4$ and concentrated. A solid product was obtained: filtered, washed with water and crystallised from hot methanol. Off-white crystals, yield 57% (3.67 g, 11 mmols). **^{1}H-NMR (500MHz) δ:** 8.53 (d, 2H, H_a, J_{a-b} = 4.8 Hz); 8.26 (s, 2H, NH); 8.08 (d, 2H, H_d, J_{d-c} = 7.8 Hz); 7.75 (dt, 2H, H_c, J_{c-a} = 1.8 Hz, J_{c-b} = J_{c-d} = 7.7 Hz); 7.35 (ddd, 2H, H_b, J_{b-d} = 1.1 Hz, J_{b-a} = 4.8 Hz, J_{b-c} = 7.6 Hz); 4.08 (broad s, 2H, H_g); 2.25-1.45 (3 multiplets, 8H, $H_{h,i}$). **^{13}C{^{1}H}-NMR (75MHz) δ:** 164.5 (C_f); 149.7 (C_e); 148.1 (C_a); 137.0 (C_c); 125.9 (C_b); 122.1 (C_d); 53.3 (C_g); 32.6 (C_h); 24.8 (C_i). **M/z (HRMS-ESI+):** calcd. for $C_{18}H_{21}N_4O_2$ $[M+H]^+$: 325.1659. Found: 325.1664.



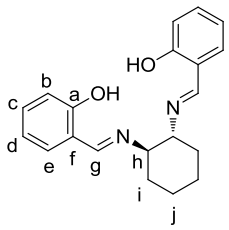
***N,N'*-(1,2-Phenylene)dipicolinamide (L54c).**[25] Prepared using 10 g (81 mmols) of picolinic acid, and 50 mL of pyridine. White crystals, yield 51% (6.53 g, 21 mmols). **^{1}H-NMR (500MHz) δ:** 10.29 (s, 2H, NH); 8.58 (d, 2H, H_a, J_{a-b} = 4.6 Hz); 8.34 (d, 2H, H_d, J_{d-c} = 7.8 Hz); 7.91 (m, 4H, $H_{c,h}$, $J_{c-a} \approx$ 1.5 Hz, J_{c-b} = $J_{c-d} \approx$ 7.8 Hz); 7.48 (ddd, 2H, H_b, J_{b-d} = 0.8 Hz, J_{b-a} = 4.6 Hz, J_{b-c} = 7.3 Hz); 7.32 (dd, 2H, H_i, J = 3.5 Hz, J = 6.0 Hz). **^{1}H-NMR (500MHz) δ (DMSO-d_6):** 10.72 (s, 2H, NH); 8.64 (d, 2H, H_a, J_{a-b} = 4.8 Hz); 8.17 (d, 2H, H_d, J_{d-c} = 7.8 Hz); 8.06 (dt, 2H, H_c, J_{c-a} = 1.6 Hz, J_{c-b} = J_{c-d} = 7.8 Hz); 7.77 (m, 2H, H_h); 7.66 (ddd, 2H, H_b, J_{b-d} = 0.9 Hz, J_{b-a} = 4.9 Hz, J_{b-c} = 7.7 Hz); 7.30 (m, 2H, H_i). **^{13}C{^{1}H}-NMR (125MHz) δ:** 162.9 (C_f); 149.7 (C_e); 148.4 (C_a); 137.5 (C_c); 130.1 (C_g); 126.4 (C_b); 126.1 (C_i); 124.7 (C_h); 122.5 (C_d). **M/z (EI):** 319, 318 (M^+), 300, 272, 271, 240, 222, 212, 197, 196, 195, 131, 106, 94, 79, 78(100), 69, 52, 51. **M/z (HRMS-EI):** calcd. for $C_{18}H_{14}N_4O_2$ $[M]^+$: 318.1117. Found: 318.1103. **IR ν (cm^{-1}):** 3316 (NH); 3062 (CH); 1917; 1889; 1798; 1666; 1589; 1519; 1431; 1298; 1235. **Anal:** calcd. for $C_{18}H_{14}N_4O_2$: C, 67.92; H, 4.43; N, 17.60. Found: C, 67.50; H, 4.40; N, 17.70.

6.2.4 – Synthesis of tetradentate salen ligands

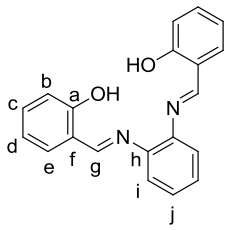
General procedure: The ligands were prepared through a modified ligand procedure.[26] A solution of 9.4 mmols (1.0 mL) of salicylaldehyde in 4 mL of water/methanol was stirred under nitrogen at room temperature. To this solution, half equivalent (4.7 mmols) of amine was added, and the resulting solution was left to stir for 16h, then the solid product formed was filtered, and washed with water and hexane.



2,2'-((1*E*,1'*E*)-(ethane-1,2-diylbis(azanylylidene)) bis(methanylylidene))diphenol (L55a).[27] Prepared using water as solvent. Yellow solid, yield 94% (1.18 g, 4.4 mmols). **^{1}H-NMR (500MHz) δ:** 8.37 (s, 2H, H_g); 7.30 (m, 2H, H_c); 7.24 (dd, 2H, H_e, J_{e-c} = 1.7 Hz, J_{e-d} = 7.7 Hz); 6.95 (d, 2H, H_b, J_{b-c} = 8.3 Hz); 6.87 (dt, 2H, H_d, J_{d-b} = 1.1 Hz, J_{d-c} = J_{d-e} = 7.5 Hz); 3.96 (s, 2H, H_h) [N.B. OH peak not visible]. **^{13}C{^{1}H}-NMR (125MHz) δ:** 166.5 (C_g); 161.2 (C_a); 132.4 (C_c); 131.5 (C_e); 118.8 (C_f); 118.7 (C_d); 117.1 (C_b); 59.8 (C_h). **M/z (HRMS-ESI+):** calcd for $C_{16}H_{17}N_2O_2$ $[M+H]^+$: 269.1285. Found: 269. 1289. **Anal:** calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.40; H, 6.00; N, 10.50.



2,2'-((1*E*,1'*E*)-((cyclohexane-1,2-diylbis(azanylylidene)) bis(methanylylidene))diphenol (L55b).[22] Prepared using water as solvent. Yellow powder, yield 90% (1.36 g, 4.2 mmols). **^{1}H-NMR (500MHz) δ:** 8.27 (s, 2H, H_g); 7.26-7.22 (m, 2H, H_c); 7.15 (dd, 2H, H_e, J_{e-c} = 1.6 Hz, J_{e-d} = 7.6 Hz); 6.89 (d, 2H, H_b, J_{b-c} = 8.3 Hz); 6.80 (t, 2H, H_d, J_{d-c} = J_{d-e} = 7.5 Hz); 3.37-3.29 (m, 2H, H_h); 2.00-1.45 (4 multiplets, 8H, $H_{i,j}$) [N.B. OH peak not visible]. **^{13}C{^{1}H}-NMR (125MHz) δ:** 164.8 (C_g); 161.1 (C_a); 132.2 (C_c); 131.5 (C_e); 118.8 (C_f); 118.6 (C_d); 116.9 (C_b); 72.7 (C_h); 33.1 (C_i); 24.3 (C_j). **M/z (HRMS-ESI+):** calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$: 323.1754. Found: 323.1751. **Anal:** calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.10; H, 6.90; N, 8.80.

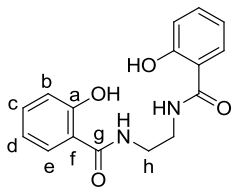


2,2'-((1*E*,1'*E*)-(1,2-phenylenebis(azanylylidene)) bis(methanylylidene))diphenol (L55c).[28] Prepared using methanol as solvent. Orange powder, yield 77% (1.14 g, 3.6 mmols). **^{1}H-NMR (500MHz) δ:** 8.65 (s, 2H, H_g); 7.41-7.34 (m, 6H, $H_{c,e,i}$); 7.27-7.23 (m, 2H, H_j); 7.06 (d, 2H, H_b, J_{b-c} = 8.3 Hz); 6.93 (t, 2H, H_d, J_{d-c} = J_{d-e} = 7.5 Hz) [N.B. OH peak not visible]. **^{13}C{^{1}H}-NMR (125MHz) δ:** 163.7 (C_g); 161.4 (C_a); 142.6 (C_h); 133.4 (C_c); 132.3 (C_e); 127.7 (C_i); 119.7 (C_j); 119.2 (C_f); 119.0 (C_d); 117.6 (C_b). **M/z (HRMS-ESI+):** calcd for $C_{20}H_{17}N_2O_2$ $[M+H]^+$: 317.1285. Found: 317.1299.

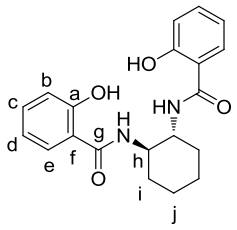
6.2.5 – Synthesis of tetradentate bis(hydroxy-benzamido) ligands

General procedure: The ligands were prepared through a modified ligand procedure.[29] Acetylsalicyloyl chloride (10 mmols) was added to a solution of diamine (5.0 mmols) in 10-15 mL of dioxane. The mixture was stirred at room temperature for 20 hours. At the end, 1 mL of conc. HCl was slowly added to the solution, which was stirred again at room temperature for 4 hours, followed by the addition of 40 mL of water and another hour of stirring. The precipitate obtained was filtered and washed with water and acetonitrile, then recrystallised from hot

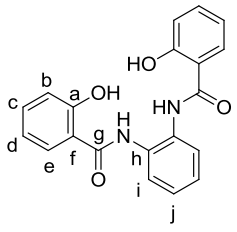
acetonitrile. These ligands were synthesised and partially characterised by Miss Jessica Lamb (University of Leeds).



***N,N'*-(ethane-1,2-diyl)bis(2-hydroxybenzamide) (L56a).**[30] White powder, yield 90% (1.35 g, 5 mmols). **^{1}H-NMR (500MHz) δ:** 12.15 (broad s, 2H, OH); 7.43-7.40 (m, 4H, $H_{c,e}$); 7.32 (broad s, 2H, NH); 6.99 (d, 2H, H_b, $J_{b\text{-}c}$ = 8.7 Hz); 6.88 (t, 2H, H_d, $J_{d\text{-}c}$ = $J_{d\text{-}e}$ = 7.6 Hz); 3.84-3.64 (m, 4H, H_h). **^{13}C{^{1}H}-NMR (125MHz) δ:** 171.4 (C_g); 161.5 (C_a); 134.6 (C_c); 125.7 (C_e); 119.0 (C_d); 118.7 (C_b); 113.7 (C_f); 40.6 (C_h). **M/z (HRMS-ESI+):** calcd for $C_{16}H_{16}N_2NaO_4$ $[M+Na]^+$: 323.1002. Found: 323.1001.



***N,N'*-((cyclohexane-1,2-diyl)bis(2-hydroxybenzamide) (L56b).**[30] White powder, yield 47% (0.83 g, 2 mmols). **^{1}H-NMR (500MHz) δ (DMSO-d_6):** 12.36 (s, 2H, OH); 8.61 (d, 2H, NH, $J_{NH\text{-}h}$ = 7.5 Hz); 7.76 (dd, 2H, H_e, $J_{e\text{-}c}$ = 1.3 Hz, $J_{e\text{-}d}$ = 7.9 Hz); 7.36-7.29 (m, 2H, H_c); 6.86-6.79 (m, 4H, $H_{b,d}$); 4.02 (m, 2H, H_h); 1.98-1.29 (4 multiplets, 8H, $H_{i,j}$). **^{13}C{^{1}H}-NMR (125MHz) δ (DMSO-d_6):** 168.5 (C_g); 159.7 (C_a); 133.5 (C_c); 127.9 (C_e); 118.4 (C_d); 117.1 (C_b); 115.4 (C_f); 52.1 (C_h); 31.5 (C_i); 24.5 (C_j). **M/z (HRMS-ESI+):** calcd for $C_{20}H_{23}N_2O_4$ $[M+H]^+$: 355.1652. Found: 355.1652.

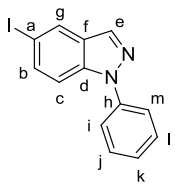


***N,N'*-(1,2-phenylene)bis(2-hydroxybenzamide) (L56c).**[29] Pink powder, yield 48% (0.83 g, 2 mmols). **^{1}H-NMR (500MHz) δ (DMSO-d_6):** 11.73 (s, 2H, OH); 10.42 (s, 2H, NH); 8.02 (dd, 2H, H_e, $J_{e\text{-}c}$ = 1.2 Hz, $J_{e\text{-}d}$ = 8.0 Hz); 7.83-7.79 (m, 2H, H_i); 7.46-7.40 (m, 2H, H_c); 7.31-7.27 (m, 2H, H_j); 6.99-6.94 (m, 4H, $H_{b,d}$). **^{13}C{^{1}H}-NMR (125MHz) δ (DMSO-d_6):** 166.2 (C_g); 158.1 (C_a); 133.4 (C_c); 130.9 (C_h); 129.2 (C_e); 125.4 (C_i); 125.2 (C_j); 123.0 (C_f); 119.0 (C_d); 117.0 (C_b). **M/z (HRMS-ESI+):** calcd for $C_{20}H_{16}N_2NaO_4$ $[M+Na]^+$: 371.1002. Found: 371.1002.

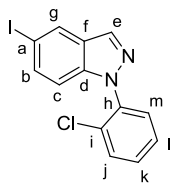
6.2.6 – Synthesis of iodoindazole derivatives (precursors to aryl ethers 16-19)

General procedure: Indazole compounds were prepared through a modified ligand procedure.[31, 32] In a round-bottom flask equipped with a condenser were introduced 5-iodo-2-fluorobenzaldehyde (1 eq.), 1-arylhydrazine derivative (1.1 eq.), potassium carbonate (2 eq. if using hydrazines, 3 eq. if using their hydrochloric salt), together with DMF (100 mL per 20 mmols of aldehyde). When pure liquid hydrazines were used, they were added slowly to the stirred solution with a syringe, after the addition of solvent. The mixture was heated to reflux and stirred for 16h. The reaction was then left to cool to room temperature, quenched with an excess of aqueous NH_4Cl and stirred for an additional hour. A semi-solid precipitate was

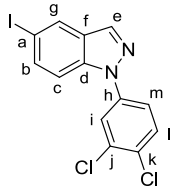
obtained, which was filtered, washed with water and dissolved in ethyl acetate. The aqueous solution was extracted once with ethyl acetate, and the organic solutions were then combined and washed once with water. The crude was then evaporated and purified by chromatography, followed by recrystallisation.



5-Iodo-1-phenyl-1*H*-indazole. Prepared using 5.0 g (20 mmols) of 5-iodo-2-fluorobenzaldehyde and 1-phenylhydrazine. The crude product was purified by chromatography (Petroleum ether/Et_2O: 90/10) and crystallised from hot MeCN. Small colourless crystals, yield 35% (2.2 g). **^{1}H-NMR (500MHz) δ:** 8.18 (m, 1H, H_g); 8.13 (s, 1H, H_e); 7.70 (d, 2H, $H_{i,m}$, $J_{i-j} = J_{m-l}$ = 7.6 Hz); 7.66 (dd, 1H, H_b, J_{b-c} = 8.9 Hz, J_{b-g} = 1.6 Hz); 7.56 (t, 2H, $H_{j,l}$, $J_{j-i} = J_{j-k} = J_{l-k} = J_{l-m}$ = 7.9 Hz); 7.54 (d, 1H, H_c, J_{c-b} = 9.0 Hz); 7.40 (t, 1H, H_k, $J_{k-j} = J_{k-l}$ = 7.5 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 139.7 (C_h); 137.9 (C_d); 135.4 (C_b); 134.2 (C_e); 130.2 (C_g); 129.5 ($C_{j,l}$); 127.7 (C_f); 127.1 (C_k); 122.8 ($C_{i,m}$); 112.2 (C_c); 84.6 (C_a). **M/z (HRMS-EI):** calcd. for $C_{13}H_9IN_2$ $[M]^+$: 319.9811. Found: 319.9814. **IR ν (cm^{-1}):** 3057; 3034; 2658; 2319; 1947; 1871; 1751; 1677; 1599; 1483; 1458; 1384; 1281. **Anal:** calcd. for $C_{13}H_9IN_2$: C, 48.77; H, 2.83; N, 8.75. Found: C, 49.05; H, 2.65; N, 8.65. **M.p.:** 121-122°C.



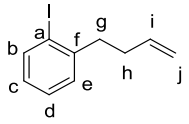
1-(2-Chlorophenyl)-5-iodo-1*H*-indazole. Prepared using 5.0 g (20 mmols) of 5-iodo-2-fluorobenzaldehyde and 1-(2-chlorophenyl)hydrazine hydrochloride. The crude product was purified by chromatography (Petroleum ether/Et_2O: 80/20) and crystallised from hot MeOH. Orange crystals, yield 72% (5.1 g). **^{1}H-NMR (500MHz) δ:** 8.19 (m, 1H, H_g); 8.17 (s, 1H, H_e); 7.64 (dd, 1H, H_b, J_{b-g} = 1.5 Hz, J_{b-c} = 8.8 Hz); 7.63-7.61 (m, 1H, H_m); 7.52-7.50 (m, 1H, H_j); 7.47-7.45 (m, 2H, $H_{k,l}$); 7.05 (d, 1H, H_c, J_{c-b} = 8.9 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 139.4 (C_h); 136.6 (C_d); 135.2 (C_b); 134.5 (C_e); 131.4 (C_i); 130.7 (C_m); 130.1 (C_l); 130.0 (C_g); 129.4 (C_j); 127.7 (C_k); 126.7 (C_f); 112.4 (C_c); 84.7 (C_a). **M/z (HRMS-ESI+):** calcd for $C_{13}H_9ClIN_2$ $[M+H]^+$: 354.9493. Found: 354.9500. **IR ν (cm^{-1}):** 3069; 1873; 1735; 1661; 1589; 1495; 1449; 1409; 1382; 1336; 1280; 1257. **Anal:** calcd. for $C_{13}H_8ClIN_2$: C, 44.04; H, 2.27; N, 7.90. Found: C, 44.20; H, 2.20; N, 7.80. **M.p.:** 101-103 °C.



1-(3,4-Dichlorophenyl)-5-iodo-1*H*-indazole. Prepared using 1.0 g (4 mmols) of 5-iodo-2-fluorobenzaldehyde and 1-(3,4-dichlorophenyl)hydrazine hydrochloride. The crude product was purified by chromatography (Petroleum ether/Et_2O: 90/10) and crystallised from hot MeOH. Off-white fluffy solid, yield 39% (0.6 g). **^{1}H-NMR (500MHz) δ:** 8.19 (m, 1H, H_g); 8.14 (s, 1H, H_e); 7.86 (d, 1H, H_i, J_{i-m} = 2.4 Hz); 7.72 (dd, 1H, H_b, J_{b-g} = 1.5 Hz, J_{b-c} = 8.8 Hz); 7.62 (d, 1H, H_l, J_{l-m} = 8.5 Hz); 7.59 (dd, 1H, H_m, J_{m-i} = 2.4 Hz, J_{m-l} = 8.7 Hz); 7.51 (d, 1H, H_c, J_{c-b} = 9.0 Hz).

$^{13}C\{^1H\}$-NMR (125MHz) δ: 139.1 (C_h); 137.7 (C_d); 136.0 (C_b); 135.1 (C_e); 133.6 (C_j); 131.2 (C_g); 130.7 (C_k); 130.5 (C_l); 128.0 (C_f); 124.2 (C_i); 121.4 (C_m); 111.9 (C_c); 85.2 (C_a). **M/z (HRMS-EI):** calcd for $C_{13}H_7Cl_2IN_2$ $[M]^+$: 387.9018. Found: 387.9031. **IR ν (cm^{-1}):** 3092 (ar CH); 1592; 1492;1435; 1390; 1334; 1282. **Anal:** calcd. for $C_{13}H_7Cl_2IN_2$: C, 40.14; H, 1.81; N, 7.20. Found: C, 40.95; H, 1.55; N, 6.80. **M.p.:** 150-152 °C.

6.2.7 – Synthesis of 2-(3-butenyl)-iodobenzene[33] (precursor to aryl ether 25)

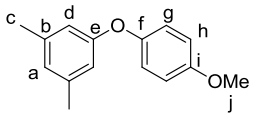


Prepared according to a modified literature procedure.[34] 2-Iodobenzyl bromide (1 g, 3.4 mmols) wad added into 10 mL of anhydrous THF at 0°C in a round bottom flask. To the stirred solutions, allylmagnesium bromide (5 mL, 1M in THF, 1.5 eq.) was added dropwise through syringe, under inert atmosphere. The solution was left to rise to room temperature and then heated under reflux for 16h. After cooling to room temperature, the reaction was then quenched with a saturated aqueous solution of ammonium chloride, and extracted with Et_2O. The organic solution was concentrated and the product was purified by chromatography using petrol/Et_2O : 90/10 as eluent. The product was obtained as colourless oil, yield 64% (560 mg, 2.2 mmols). **^{1}H-NMR (300MHz) δ:** 7.83 (dd, 1H, H_b, J_{b-d} = 1.1 Hz, J_{b-c} = 7.9 Hz); 7.31-7.17 (m, 2H, $H_{d,e}$); 6.89 (dt, 1H, H_c, J_{c-e} = 1.9 Hz, J_{c-b} = J_{c-d} = 7.6 Hz); 5.90 (ddt, 1H, H_i, J_{i-h} = 6.5 Hz, $J_{i-j(cis)}$ = 10.3 Hz, $J_{i-j(trans)}$ = 17.0 Hz); 5.09 (dq, 1H, H_j, $J_{j-j(gem)}$ = J_{j-h} = 1.7 Hz, $J_{j-i(trans)}$ = 17.2 Hz); 5.02 (m, 1H, H_j); 2.82 (m, 2H, H_g); 2.40-2.33 (m, 2H, H_h). **$^{13}C\{^1H\}$-NMR (75MHz) δ:** 144.3 (C_f); 139.5 (C_b); 137.5 (C_i); 129.4 (C_e); 128.2 (C_d); 127.7 (C_c); 115.2 (C_j); 100.5 (C_a); 40.2 (C_g); 34.1 (C_h). **M/z (HRMS-EI):** calcd for $C_{10}H_{11}I$ $[M]^+$: 257.9906. Found: 257.9909.

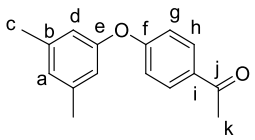
6.2.8 – Synthesis of aryl ethers through Cu-catalysed coupling

General procedure: All catalytic reactions were performed in 25 mL glass tubes in a Radleys Standard carousel. An oven dried tube was charged with the phenol (1.2 mmol), the aryl iodide (1.0 mmol), caesium carbonate (652 mg, 2 mmol), CuI (19 mg, 0.1 mmol) and ligand (0.1 mmol). The solvent (2 mL) was then added, the tube was placed in the carousel (preheated at a temperature slightly higher than the solvent's boiling point) and the reaction was stirred for 24 h (1000 rpm). At the end of the reaction the tube was cooled to room temperature, then the crude was diluted with ≈ 2mL DCM, filtered through celite and washed thoroughly with DCM (≈ 50 mL). 1 mL of a 0.5 M solution of 1,3,5-trimethoxybenzene or *para*-cymene (internal standard) in DCM was added, and the crude solution was analysed through gas chromatography. Isolated compounds were purified by column chromatography. Yields are not reported below, as different yields were obtained for the compounds depending on the conditions. The different conditions tested are described in Chapter 2.

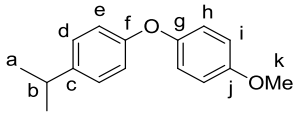
Chemicals used for ligand screening and optimisation in MeCN (Chapter 2, section 2.4): Sigma Aldrich CuI (98%); Alfa Aesar Cs_2CO_3 (99+% metal basis); Alfa Aesar 4-iodoanisole (98+%); Acros Organics 3,5-dimethylphenol (99+%); VWR BDH Prolabo HiPerSolv CHROMANORM (min 99.9%, HPLC grade) acetonitrile. **Chemicals used for screening in green solvents (Chapter 2, section 2.6):** Sigma Aldrich CuI (98%); Alfa Aesar Cs_2CO_3 (99+% metal basis), Alfa Aesar K_3PO_4 (97% anhydrous, granular); Alfa Aesar 4-iodoanisole (98+%); Acros Organics 3,5-dimethylphenol (99+%). **Solvents:** Sigma Aldrich MeOAc (for HPLC, ≥99.8%); VWR Prolabo EtOAc (GPR Rectapur, min 99.0%); Sigma Aldrich *n*-PrOAc (99%); Alfa Aesar *i*-PrOAc (99+%); Sigma Aldrich *n*-BuOAc (anhydrous, ≥99%); Sigma Aldrich *t*-BuOAc (≥99%); Alfa Aesar *i*-BuOAc (98%); Sigma Aldrich *n*-AmOAc (99%); Sigma Aldrich *i*-AmOAc (reagent grade, 98%); Merck Isosorbide Dimethyl ether (for synthesis, ≥98%); Sigma Aldrich Glyceryl Triacetate (>99%); Sigma Aldrich Diethyl carbonate (>99%).



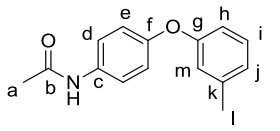
1-(4-Methoxyphenoxy)-3,5-dimethylbenzene (3).[35] Purified by column chromatography (Petroleum ether/Et_2O : 95/5); white solid. **^{1}H-NMR (500MHz) δ:** 6.98 (d, 2H, H_g, J_{g-h} = 8.9 Hz); 6.89 (d, 2H, H_h, J_{h-g} = 9.2 Hz); 6.70 (s, 1H, H_a); 6.57 (s, 2H, H_d); 3.82 (s, 1H, H_j); 2.28 (s, 6H, H_c). **^{13}C{^{1}H}-NMR (125MHz) δ:** 158.5 (C_e); 155.7 (C_i); 150.3 (C_f); 139.4 (C_b); 124.2 (C_a); 120.8 (C_g); 115.3 (C_d); 114.8 (C_h); 55.6 (C_j); 21.3 (C_c). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{17}O_2$ $[M+H]^+$: 229.1223. Found: 229.1218.



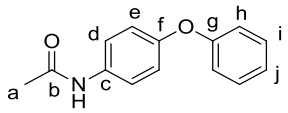
1-(4-(3,5-Dimethylphenoxy)phenyl)ethanone (4).[36] Purified by column chromatography (Petroleum ether/Et_2O : 85/15); white solid. **^{1}H-NMR (300MHz) δ:** 7.94 (d, 2H, H_h, J_{h-g} = 8.7 Hz); 7.00 (d, 2H, H_g, J_{g-h} = 8.9 Hz); 6.85 (s, 1H, H_a); 6.69 (s, 2H, H_d); 2.58 (s, 3H, H_k); 2.32 (s, 6H, H_c). **^{13}C{^{1}H}-NMR (75MHz) δ:** 196.8 (C_j); 162.2 (C_i); 155.4 (C_e); 139.9 (C_b); 131.7 (C_f); 130.5 (C_h); 126.3 (C_a); 117.8 (C_d); 117.2 (C_g); 26.4 (C_k); 21.3 (C_c). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{17}O_2$ $[M+H]^+$: 241.1223. Found: 241.1222.



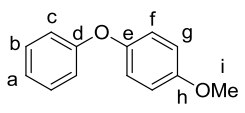
1-Isopropyl-4-(4-methoxyphenoxy)benzene (5). Purified by column chromatography (Petroleum ether/Et_2O : 95/5); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.16 (d, 2H, H_d, J_{d-e} = 8.5 Hz); 6.98 (d, 2H, H_i, J_{i-h} = 9.2 Hz); 6.89 (d, 2H, H_e, J_{e-d} = 8.8 Hz); 6.88 (d, 2H, H_h, J_{h-i} = 9.0 Hz); 3.81 (s, 3H, H_k); 2.90 (sept, 1H, H_b, J_{b-a} = 7.0 Hz); 1.25 (d, 6H, H_a, J_{a-b} = 7.1 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 156.3 (C_f); 155.7 (C_j); 150.6 (C_g); 143.1 (C_c); 127.4 (C_d); 120.5 (C_h); 117.6 (C_e); 114.8 (C_i); 55.7 (C_k); 33.4 (C_b); 24.1 (C_a). **M/z (HRMS-EI):** calcd. for $C_{16}H_{18}O_2$ $[M]^+$: 242.1307. Found: 242.1316.



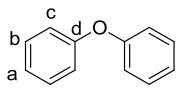
N-(4-(*m*-Tolyloxy)phenyl)acetamide (6). Purified by column chromatography (Petroleum ether/Et_2O : 85/15 to 0/100); white solid. **^{1}H-NMR (500MHz) δ:** 7.45 (d, 2H, H_d, J_{d-e} = 8.8 Hz); 7.22-7.19 (m, 2H, $H_{i,NH}$); 6.98 (d, 2H, H_e, J_{e-d} = 9.0 Hz); 6.91 (d, 1H, H_j, J_{j-i} = 7.5 Hz); 6.81-7.78 (m, 2H, $H_{h,m}$); 2.33 (s, 3H, H_l); 2.18 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 168.2 (C_b); 157.5 (C_g); 153.7 (C_f); 139.9 (C_k); 133.2 (C_c); 129.4 (C_i); 123.9 (C_j); 121.7 (C_d); 119.6 (C_e); 119.1 (C_m); 115.5 (C_h); 24.4 (C_a); 21.4 (C_l). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{16}NO_2$ $[M+H]^+$: 242.1175. Found: 242.1181.



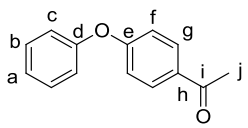
N-(4-Phenoxyphenyl)acetamide (7).[37] Purified by column chromatography (Petroleum ether/Et_2O : 95/5 to 0/100); off-white solid. **^{1}H-NMR (500MHz) δ:** 7.46 (d, 2H, H_d, J_{d-e} = 8.8 Hz); 7.33 (t, 2H, H_i, J_{i-h} = J_{i-j} = 7.9 Hz); 7.21 (broad s, 1H, H_{NH}); 7.09 (t, 1H, H_j, J_{j-i} = 7.4 Hz); 7.00-6.98 (m, 4H, $H_{e,h}$); 2.18 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 168.2 (C_b); 157.5 (C_g); 153.5 (C_f); 133.3 (C_c); 129.7 (C_i); 123.1 (C_j); 121.7 (C_d); 119.6 (C_e); 118.5 (C_h); 24.4 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{13}NNaO_2$ $[M+Na]^+$: 250.0838. Found: 250.0841.



1-Methoxy-4-phenoxybenzene (8).[35] Purified by column chromatography (Petroleum ether); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.33-7.29 (m, 2H, H_b); 7.05 (t, 1H, H_a, J_{a-b} = 7.4 Hz); 7.00 (d, 2H, H_f, J_{f-g} = 9.0 Hz); 6.96 (d, 2H, H_c, J_{c-b} = 7.7 Hz); 6.90 (d, 2H, H_g, J_{g-f} = 9.0 Hz); 3.82 (s, 3H, H_i). **^{13}C{^{1}H}-NMR (125MHz) δ:** 158.5 (C_d); 155.9 (C_h); 150.2 (C_e); 129.6 (C_b); 122.4 (C_a); 120.8 (C_f); 117.6 (C_c); 114.9 (C_g); 55.7 (C_i). **M/z (HRMS-ESI+):** calcd. for $C_{13}H_{12}NaO_2$ $[M+Na]^+$: 223.0735. Found: 223.0717.

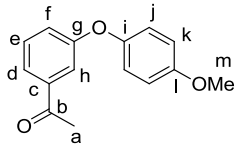


Oxydibenzene (9).[35] Purified by column chromatography (Hexane); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.35 (t, 4H, H_b, J_{b-a} = J_{b-c} = 7.8 Hz); 7.11 (t, 2H, H_a, J_{a-b} = 7.3 Hz); 7.03 (d, 4H, H_c, J_{c-b} = 7.7 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 157.3 (C_d); 129.7 (C_b); 123.2 (C_a); 118.9 (C_c). **M/z (HRMS-CI):** calcd. for $C_{12}H_{11}O$ $[M+H]^+$: 171.0804. Found: 171.0809.

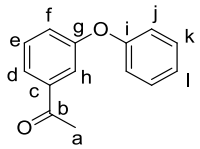


1-(4-Phenoxyphenyl)ethanone (10).[38] Purified by column chromatography (Hexane/AcOEt : 100/0 to 95/5); yellow oil. **^{1}H-NMR (500MHz) δ:** 7.95 (d, 2H, H_g, J_{g-f} = 9.0 Hz); 7.41 (t, 2H, H_b, J_{b-a} = J_{b-c} = 8.0 Hz); 7.22 (t, 1H, H_a, J_{a-b} = 7.5 Hz); 7.08 (d, 2H, H_c, J_{c-b} = 7.7 Hz); 7.01 (d, 2H, H_f, J_{f-g} = 8.8 Hz); 2.58 (s, 3H, H_j). **^{13}C{^{1}H}-NMR (125MHz) δ:** 196.7 (C_i); 162.0 (C_h); 155.5 (C_d); 131.9

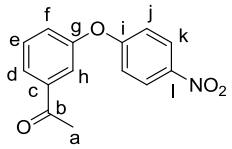
(C_e); 130.6 (C_g); 130.0 (C_b); 124.6 (C_a); 120.1 (C_c); 117.3 (C_f); 26.4 (C_j). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{12}NaO_2$ $[M+Na]^+$: 235.0729. Found: 235.0732.



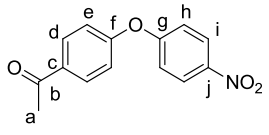
1-(3-(4-Methoxyphenoxy)phenyl)ethanone (11). Purified by column chromatography (Hexane/ AcOEt : 90/10); brown oil. **^{1}H-NMR (500MHz) δ:** 7.63 (d, 1H, H_d, J_{d-e} = 7.6 Hz); 7.52 (s, 1H, H_h); 7.39 (t, 1H, H_e, J_{e-d} = J_{e-f} = 7.9 Hz); 7.15 (dd, 1H, H_f, J_{f-h} = 2.5 Hz, J_{f-e} = 8.2 Hz); 7.00 (d, 2H, H_j, J_{j-k} = 9.2 Hz); 6.91 (d, 2H, H_k, J_{k-j} = 9.2 Hz); 3.83 (s, 3H, H_m); 2.57 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 197.5 (C_b); 158.9 (C_g); 156.3 (C_l); 149.5 (C_i); 138.8 (C_c); 129.8 (C_e); 122.4 (C_d); 122.1 (C_f); 121.0 (C_j); 116.8 (C_h); 115.1 (C_k); 55.6 (C_m); 26.7 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{14}NaO_3$ $[M+Na]^+$: 265.0835. Found: 265.0839.



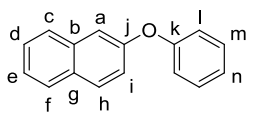
1-(3-Phenoxyphenyl)ethanone (12).[39] Purified by column chromatography (Hexane/ AcOEt : 90/10); yellow oil. **^{1}H-NMR (500MHz) δ:** 7.69 (d, 1H, H_d, J_{d-e} = 7.7 Hz); 7.59 (s, 1H, H_h); 7.44 (t, 1H, H_e, J_{e-d} = J_{e-f} = 7.9 Hz); 7.37 (t, 2H, H_k, J_{k-j} = J_{k-l} = 7.9 Hz); 7.22 (dd, 1H, H_f, J_{f-h} = 2.4 Hz, J_{f-e} = 8.1 Hz); 7.15 (t, 1H, H_l, J_{l-k} = 7.3 Hz); 7.03 (d, 2H, H_j, J_{j-k} = 7.8 Hz); 2.59 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 197.4 (C_b); 157.5 (C_g); 156.6 (C_i); 138.9 (C_c); 129.9 ($C_{e,k}$); 123.8 (C_l); 123.3 (C_f); 123.1 (C_d); 119.1 (C_j); 118.1 (C_h); 26.7 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{12}NaO_2$ $[M+Na]^+$: 235.0729. Found: 235.0732.



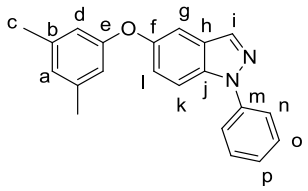
1-(3-(4-Nitrophenoxy)phenyl)ethanone (13).[40] Purified by column chromatography (Petroleum ether/Et_2O : 90/10); yellow solid. **^{1}H-NMR (500MHz) δ:** 8.24 (d, 2H, H_k, J_{k-j} = 9.2 Hz); 7.84 (d, 1H, H_d, J_{d-e} = 7.6 Hz); 7.68 (s, 1H, H_h); 7.56 (t, 1H, H_e, J_{e-d} = J_{e-f} = 7.9 Hz); 7.32 (ddd, 1H, H_f, J_{f-d} = 0.6 Hz, J_{f-h} = 2.3 Hz, J_{f-e} = 8.0 Hz); 7.04 (d, 2H, H_j, J_{j-k} = 9.2 Hz); 2.62 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 196.9 (C_b); 162.7 (C_i); 155.2 (C_g); 143.0 (C_l); 139.3 (C_c); 130.6 (C_e); 126.1 (C_k); 125.3 (C_d); 125.0 (C_f); 119.8 (C_h); 117.4 (C_j); 26.7 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{12}NO_4$ $[M+H]^+$: 258.0761. Found: 258.0761.



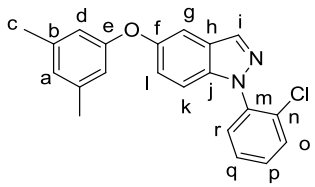
1-(4-(4-Nitrophenoxy)phenyl)ethanone (14).[41] Purified by column chromatography (Petroleum ether/Et_2O : 95/5 to 80/20); yellow solid. **^{1}H-NMR (500MHz) δ:** 8.26 (d, 2H, H_i, J_{i-h} = 9.2 Hz); 8.04 (d, 2H, H_d, J_{d-e} = 8.7 Hz); 7.14 (d, 2H, H_e, J_{e-d} = 8.7 Hz); 7.11 (d, 2H, H_h, J_{h-i} = 9.2 Hz); 2.62 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 196.5 (C_b); 161.7 (C_g); 159.1 (C_f); 143.6 (C_j); 133.9 (C_c); 130.9 (C_d); 126.1 (C_i); 119.5 (C_e); 118.4 (C_h); 26.5 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{12}NO_4$ $[M+H]^+$: 258.0761. Found: 258.0763.



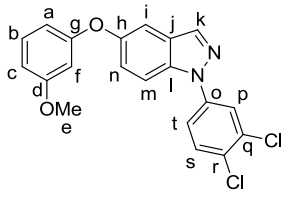
2-Phenoxynaphthalene (15).[38] Purified by column chromatography (Petroleum ether/Et_2O : 100/0 to 95/5); white solid. **^{1}H-NMR (500MHz) δ:** 7.86- 7.83 (m, 2H, $H_{c,h}$); 7.72 (d, 1H, H_f, J_{f-e} = 8.1 Hz); 7.47 (dt, 1H, H_e, J_{e-c} = 1.2 Hz, J_{e-d} = J_{e-f} = 7.5 Hz); 7.43-7.37 (m, 3H, $H_{d,m}$); 7.33 (d, 1H, H_a, J_{a-i} = 2.0 Hz); 7.28 (dd, 1H, H_i, J_{i-a} = 2.6 Hz, J_{i-h} = 9.0 Hz); 7.16 (t, 1H, H_n, J_{n-m} = 7.5 Hz); 7.10 (dd, 2H, H_l, J_{l-n} = 1.0 Hz, J_{l-m} = 7.8 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 157.2(C_k); 155.1 (C_j); 134.3 (C_g); 129.9 (C_h); 129.8 (C_m); 129.7(C_b); 127.7 (C_c); 127.1 (C_f); 126.5 (C_e); 124.7 (C_d); 123.4 (C_n); 120.0 (C_i); 119.1 (C_l); 114.1 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{13}O$ $[M+H]^+$: 221.0961. Found: 221.0962.



5-(3,5-Dimethylphenoxy)-1-phenyl-1H-indazole (16). Purified by column chromatography (Petroleum ether/Et_2O : 90/10); orange solid. **^{1}H-NMR (300MHz) δ:** 8.13 (s, 1H, H_i); 7.76-7.72 (m, 3H, $H_{k,n}$); 7.56 (t, 2H, H_o, J_{o-p} = J_{o-n} = 7.9 Hz); 7.41-7.35 (m, 2H, $H_{g,p}$); 7.21 (dd, 1H, H_l, J_{l-g} = 2.3 Hz, J_{l-k} = 9.1 Hz); 6.75 (s, 1H, H_a); 6.64 (s, 2H, H_d); 2.30 (s, 6H, H_c). **^{13}C{^{1}H}-NMR (75MHz) δ:** 158.2 (C_e); 151.8 (C_f); 140.1 (C_m); 139.6 (C_b); 135.8 (C_j); 135.0 (C_i); 129.5 (C_o); 126.7 (C_p); 125.9 (C_h); 124.7 (C_a); 122.6 (C_n); 121.3 (C_l); 115.8 (C_d); 111.5 (C_k); 109.8 (C_g); 21.3 (C_c). **M/z (HRMS-EI):** calcd. for $C_{21}H_{18}N_2O$ $[M]^+$: 314.1419. Found: 314.1414.

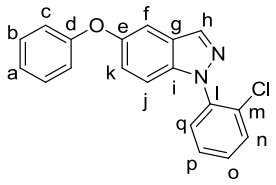


1-(2-Chlorophenyl)-5-(3,5-dimethylphenoxy)-1H-indazole (17). Purified by column chromatography (Petroleum ether/Et_2O : 95/5); yellow solid. **^{1}H-NMR (500MHz) δ:** 8.17 (s, 1H, H_i); 7.63 (m, 1H, H_r); 7.54 (m, 1H, H_o); 7.45 (m, 2H, $H_{p,q}$); 7.35 (d, 1H, H_g, J_{g-l} = 1.9 Hz); 7.24 (d, 1H, H_k, J_{k-l} = 9.0 Hz); 7.18 (dd, 1H, H_l, J_{l-g} = 2.1 Hz, J_{l-k} = 9.0 Hz); 6.75 (s, 1H, H_a); 6.65 (s, 2H, H_d); 2.30 (s, 6H, H_c). **^{13}C{^{1}H}-NMR (125MHz) δ:** 158.1 (C_e); 151.8 (C_f); 139.6 (C_b); 137.4 (C_j); 137.0 (C_m); 135.3 (C_i); 131.4 (C_n); 130.8 (C_r); 129.9 (C_q); 129.4 (C_o); 127.7 (C_p); 124.8 (C_a); 124.7 (C_g); 121.2 (C_k); 115.9 (C_d); 111.6 (C_l); 109.5 (C_g); 21.3 (C_c). **M/z (HRMS-ESI+):** calcd. for $C_{21}H_{18}ClN_2O$ $[M+H]^+$: 349.1102. Found: 349.1114.

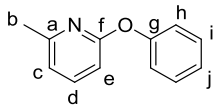


1-(3,4-Dichlorophenyl)-5-(3-methoxyphenoxy)-1H-indazole (18). Purified by column chromatography (Petroleum ether/Et_2O : 95/5); yellow oil. **^{1}H-NMR (500MHz) δ:** 8.14 (s, 1H, H_k); 7.90 (dd, 1H, H_p, J_{p-t} = 2.1 Hz, J_{p-s} = 0.6 Hz); 7.71 (dd, 1H, H_m, J_{m-i} = 0.6 Hz, J_{m-n} = 9.0 Hz); 7.64-7.60 (m, 2H, $H_{s,t}$); 7.39 (d, 1H, H_i, J_{i-n} = 2.4 Hz); 7.27 (dd, 1H, H_n, J_{n-i} = 2.2 Hz, J_{n-m} = 9.1 Hz); 7.26-7.23 (m, 1H, H_b); 6.67 (ddd, 1H, H_c, J_{c-a} = 1.1 Hz, J_{c-f} = 2.2 Hz, J_{c-b} = 8.3 Hz); 6.61-6.57 (m, 2H, $H_{a,f}$); 3.80 (s, 3H, H_e). **^{13}C{^{1}H}-NMR (125MHz) δ:**

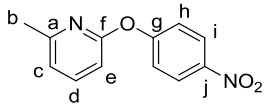
161.1 (C_g); 159.2 (C_d); 151.9 (C_h); 139.5 (C_o); 136.0 (C_k); 135.6 (C_l); 133.5 (C_q); 131.1 (C_s); 130.3 (C_r); 130.2 (C_b); 126.3 (C_j); 123.9 (C_p); 121.8 (C_n); 121.1 (C_t); 111.3 (C_m); 110.3 (C_i); 110.2 (C_a); 108.7 (C_c); 104.4 (C_f); 55.4 (C_e). **M/z (HRMS-ESI+):** calcd. for $C_{20}H_{14}Cl_2N_2O_2$ $[M+H]^+$: 385.0505. Found: 385.0506.



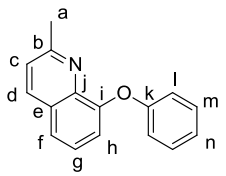
1-(2-Chlorophenyl)-5-phenoxy-1H-indazole (19). Purified by column chromatography (Petroleum ether/Et_2O : 97/3); orange oil. **^{1}H-NMR (500MHz) δ:** 8.17 (s, 1H, H_h); 7.65-7.61 (m, 1H, H_q); 7.56-7.53 (m, 1H, H_n); 7.47-7.44 (m, 2H, $H_{o,p}$); 7.39-7.38 (m, 1H, H_f); 7.37-7.34 (m, 2H, H_b); 7.25 (dd, 1H, H_j, J_{j-f} = 0.7 Hz, J_{j-k} = 9.0 Hz); 7.22-7-19 (m, 1H, H_k); 7.11 (dt, 1H, H_a, J_{a-c} = 1.1 Hz, J_{a-b} = 7.4 Hz); 7.04 (dd, 2H, H_c, J_{c-a} = 1.0 Hz, J_{c-b} = 7.7 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 158.2 (C_d); 151.7 (C_e); 137.5 (C_i); 137.1 (C_l); 135.3 (C_h); 131.5 (C_m); 130.8 (C_q); 129.9 (C_p); 129.7 (C_b); 129.4 (C_n); 127.7 (C_o); 124.8 (C_g); 122.9 (C_a); 121.2 (C_k); 118.1 (C_c); 111.7 (C_j); 109.6 (C_f). **M/z (HRMS-ESI+):** calcd. for $C_{19}H_{14}ClN_2O$ $[M+H]^+$: 321.0789. Found: 321.0795.



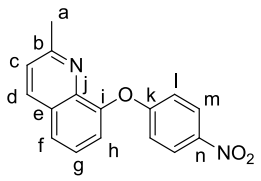
2-Methyl-6-phenoxypyridine (20).[42] Purified by column chromatography (Petroleum ether/Et_2O : 100/0 to 95/5); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.54 (t, 1H, H_d, J_{d-c} = J_{d-e} = 7.8 Hz); 7.38 (t, 2H, H_i, J_{i-h} = J_{i-j} = 7.9 Hz); 7.18 (t, 1H, H_j, J_{j-i} = 7.5 Hz); 7.14 (d, 2H, H_h, J_{h-i} = 7.5 Hz); 6.88 (d, 1H, H_c, J_{c-d} = 7.5 Hz); 6.58 (d, 1H, H_e = 8.1 Hz); 2.47 (s, 3H, H_b). **^{13}C{^{1}H}-NMR (125MHz) δ:** 163.1 (C_f); 157.6 (C_a); 154.7 (C_g); 139.5 (C_d); 129.6 (C_i); 124.3 (C_j); 120.7 (C_h); 118.0 (C_c); 107.5 (C_e); 24.1 (C_b). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_{12}NO$ $[M+H]^+$: 186.0919. Found: 186.0937.



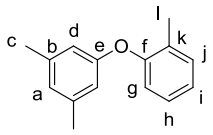
2-Methyl-6-(4-nitrophenoxy)pyridine (21). Purified by column chromatography (Petroleum ether/Et_2O : 95/5); yellow oil. **^{1}H-NMR (500MHz) δ:** 8.25 (d, 2H, H_i, J_{i-h} = 9.3 Hz); 7.67 (t, 1H, H_d, J_{d-c} = J_{d-e} = 7.7 Hz); 7.23 (d, 2H, H_h, J_{h-i} = 9.3 Hz); 7.00 (d, 1H, H_c, J_{c-d} = 7.4 Hz); 6.81 (d, 1H, H_e, J_{e-d} = 8.1 Hz); 2.47 (s,3H, H_b). **^{13}C{^{1}H}-NMR (125MHz) δ:** 161.2 (C_f); 160.3 (C_g); 157.8 (C_a); 143.6 (C_j); 140.2 (C_d); 125.5 (C_i); 119.9 (C_h); 119.7 (C_c); 109.6 (C_e); 24.0 (C_b). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_{11}N_2O_3$ $[M+H]^+$: 231.0764. Found: 231.0770.



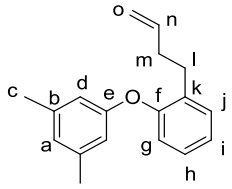
2-Methyl-8-phenoxyquinoline (22).[43] Purified by column chromatography (Hexane/AcOEt : 95/5); yellow solid. **^{1}H-NMR (500MHz) δ:** 8.07 (d, 1H, H_d, J_{d-c} = 8.3 Hz); 7.49 (dd, 1H, H_f, J_{f-h} = 1.1 Hz, J_{f-g} = 8.1 Hz); 7.40-7.32 (m, 4H, $H_{c,g,m}$); 7.20-7.13 (m, 3H, $H_{l,n}$); 7.02 (dd, 1H, H_h, J_{h-f} = 1.3 Hz; J_{h-g} = 7.7 Hz); 2.79 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 158.9 (C_b); 157.2 (C_k); 153.8 (C_i); 140.4 (C_j); 136.1 (C_d); 129.7 (C_m); 128.0 (C_e); 125.4 (C_g); 123.7 (C_n); 122.8 (C_c); 121.9 (C_f); 120.3 (C_l); 115.4 (C_h); 25.8 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{14}NO$ $[M+H]^+$: 236.1075. Found: 236.1107.



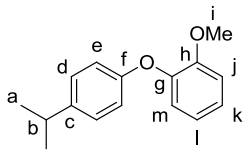
2-Methyl-8-(4-nitrophenoxy)quinoline (23). Purified by column chromatography (Hexane/AcOEt : 95/5); white needle-shaped crystals. **^{1}H-NMR (500MHz) δ:** 8.19 (d, 2H, H_m, J_{m-l} = 9.2 Hz); 8.11 (d, 1H, H_d, J_{d-c} = 8.5 Hz); 7.71 (d, 1H, H_f, J_{f-g} = 8.0 Hz); 7.50 (t, 1H, H_g, J_{g-f} = J_{g-h} = 7.8 Hz); 7.39 (dd, 1H, H_h, J_{h-f} = 0.9 Hz, J_{h-g} = 7.6 Hz); 7.35 (d, 1H, H_c, J_{c-d} = 8.5 Hz); 7.03 (d, 2H, H_l, J_{l-m} = 9.4 Hz); 2.66 (s, 3H, H_a). **^{13}C{^{1}H}- NMR (125MHz) δ:** 164.3 (C_k); 159.7 (C_b); 150.2 (C_i); 142.5 (C_n); 140.8 (C_j); 136.2 (C_d); 128.3 (C_e); 125.7 (C_m); 125.6 (C_g); 125.1 (C_f); 123.0 (C_c); 120.1 (C_h); 117.3 (C_l); 25.7 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{13}N_2O_3$ $[M+H]^+$: 281.0926. Found: 281.0957.



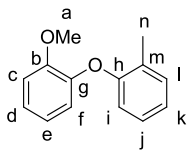
1,3-Dimethyl-5-(*o*-tolyloxy)benzene (24).[35] Purified by chromatography (Biotage, Hexane); colourless oil. **^{1}H-NMR (400MHz) δ:** 7.26 (m, 1H, H_j); 7.17 (m, 1H, H_h); 7.07 (dt, 1H, H_i, J_{i-g} = 1.2 Hz, J_{i-h} = J_{i-j} = 7.4 Hz); 6.91 (d, 1H, H_g, J_{g-h} = 8.1 Hz); 6.70 (s, 1H, H_a); 6.54 (s, 2H, H_d); 2.28 (s, 6H, H_c); 2.25 (s, 3H, H_l). **^{13}C{^{1}H}-NMR (100MHz) δ:** 157.8 (C_e); 154.6 (C_f); 139.5 (C_b); 131.3 (C_h); 129.9 (C_k); 127.0 (C_j); 124.1 (C_a); 123.7 (C_i); 119.7 (C_g); 115.0 (C_d); 21.3 (C_c); 16.2 (C_l). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{17}O$ $[M+H]^+$: 213.1274. Found: 213.1270.



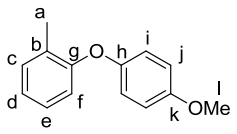
1-(2-(But-3-en-1-yl)phenoxy)-3,5-dimethylbenzene (25). Purified by column chromatography (Petroleum ether); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.26 (dd, 1H, H_j, J_{j-h} = 1.6 Hz, J_{j-i} = 7.6 Hz); 7.17 (dt, 1H, H_h, J_{h-j} = 1.7 Hz, J_{h-g} = J_{h-i} =7.7 Hz); 7.07 (dt, 1H, H_i, J_{i-g} = 1.3 Hz, J_{i-h} = J_{i-j} = 7.5 Hz); 6.88 (d, 1H, H_g, J_{g-h} = 8.1 Hz); 6.71 (s, 1H, H_a); 6.57 (s, 2H, H_d); 5.86 (ddt, 1H, H_n, J_{n-m} = 6.6 Hz, $J_{n-o(cis)}$ = 10.3 Hz, $J_{n-o(trans)}$ = 17.0 Hz); 5.02 (dq, 1H, $H_{o(trans)}$, $J_{o(trans)-n}$ = 17.2 Hz, $J_{o(trans)-o(cis)}$ = $J_{o(trans)-m}$ = 1.7 Hz); 4.94-4.97 (m, 1H, $H_{o(cis)}$); 2.71-2.77 (m, 2H, H_l); 2.35-2.42 (m, 2H, H_m); 2.28 (s, 6H, H_c). **^{13}C{^{1}H}-NMR (125MHz) δ:** 157.9 (C_e); 154.7 (C_f); 139.5 (C_b); 138.4 (C_n); 133.3 (C_k); 130.5 (C_j); 127.2 (C_h); 124.3 (C_a); 123.5 (C_i); 119.4 (C_g); 115.5 (C_d); 114.8 (C_o); 34.1 (C_m); 29.8 (C_l); 21.3 (C_c). **M/z (HRMS-EI):** calcd. for $C_{18}H_{20}O$ $[M]^+$: 252.1514. Found: 252.1523.



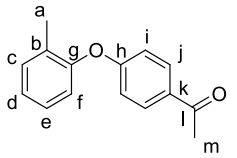
1-(4-Isopropylphenoxy)-2-methoxybenzene (26). Purified by column chromatography (Petroleum ether/Et_2O : 100/0 to 90/10); yellow oil. **^{1}H-NMR (500MHz) δ:** 7.15 (d, 2H, H_d, J_{d-e} = 8.3 Hz); 7.11 (dt, 1H, H_k, J_{k-m} = 1.9 Hz, J_{k-j} = 7.7 Hz, J_{k-l} = 7.7 Hz); 7.01 (dd, 1H, H_m, J_{m-k} = 1.3 Hz, J_{m-l} = 8.1 Hz); 6.96 (dd, 1H, H_j, J_{j-l} = 1.9 Hz, J_{j-k} = 7.9 Hz); 6.91 (dt, 1H, H_l, J_{l-j} = 1.5 Hz, J_{l-k} = 7.2 Hz, J_{l-m} = 7.2 Hz); 6.89 (d, 2H, H_e, J_{e-d} = 8.8 Hz); 3.86 (s, 3H, H_i); 2.89 (sept, 1H, H_b, J_{b-a} = 6.9 Hz); 1.25 (d, 6H, H_a, J_{a-b} = 6.8 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.7 (C_f); 151.3 (C_h); 145.7 (C_g); 143.1 (C_c); 127.3 (C_d); 124.3 (C_k); 121.1 (C_l); 120.6 (C_j); 117.3 (C_e); 112.8 (C_m); 56.0 (C_i); 33.4 (C_b); 24.1 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{19}O_2$ $[M+H]^+$: 243.1380. Found: 243.1385.



1-Methoxy-2-(*o*-tolyloxy)benzene (27).[44] Purified by chromatography (Biotage, Hexane/AcOEt : 100/0 to 98/2); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.24 (d, 1H, H_l, J_{l-k} = 7.4 Hz); 7.12 (dt, 1H, H_j, J_{j-l} = 1.4 Hz, J_{j-i} = J_{j-k} = 7.7 Hz); 7.07 (dt, 1H, H_e, J_{e-c} = 1.5 Hz, J_{e-d} = J_{e-f} = 7.7 Hz); 7.04-7.00 (m, 2H, $H_{f,k}$); 6.87 (dt, 1H, H_d, J_{d-f} = 1.6 Hz, J_{d-c} = J_{d-e} = 7.7 Hz); 6.80-6.76 (m, 2H, $H_{c,i}$); 3.89 (s, 3H, H_a); 2.31 (s, 3H, H_n). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.2 (C_h); 150.6 (C_b); 146.3 (C_g); 131.2 (C_l); 129.0 (C_m); 126.9 (C_j); 123.6 (C_e); 123.2 (C_k); 121.0 (C_d); 118.8 (C_i); 118.0 (C_c); 112.7 (C_f); 56.1 (C_a); 16.1 (C_n). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{15}O_2$ $[M+H]^+$: 215.1067. Found: 215.1069.

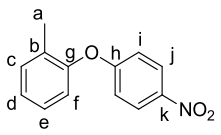


1-(4-Methoxyphenoxy)-2-methylbenzene (28).[44] Purified by column chromatography (Petroleum ether); white solid. **^{1}H-NMR (500MHz) δ:** 7.24 (d, 1H, H_c, J_{c-d} = 7.5 Hz); 7.13 (dt, 1H, H_e, J_{e-c} = 1.7 Hz, J_{e-d} = J_{e-f} = 7.7 Hz); 7.02 (dt, 1H, H_d, J_{d-f} = 1.1 Hz, J_{d-c} = J_{d-e} = 7.5 Hz); 6.91-6.86 (m, 4H, $H_{i,j}$); 6.81 (d, 1H, H_f, J_{f-e} = 8.1 Hz); 3.81 (s, 3H, H_l); 2.29 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.8 (C_g); 155.3 (C_k); 151.1 (C_h); 131.3 (C_c); 129.1 (C_b); 126.9 (C_e); 123.1 (C_d); 119.3 (C_i); 118.0 (C_f); 114.8 (C_j); 55.7 (C_l); 16.2 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{15}O_2$ $[M+H]^+$: 215.1067. Found: 215.1065.

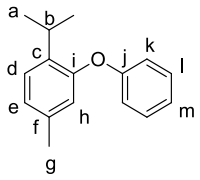


1-(4-(*o*-Tolyloxy)phenyl)ethanone (29).[45] Purified by column chromatography (Petroleum ether/Et_2O : 95/5); yellow oil. **^{1}H-NMR (500MHz) δ:** 7.93 (d, 2H, H_j, J_{j-i} = 9.0 Hz); 7.30 (d, 1H, H_c, J_{c-d} = 7.3 Hz); 7.24 (dt, 1H, H_e, J_{e-c} = 1.6 Hz, J_{e-d} = J_{e-f} = 7.6 Hz); 7.16 (dt, 1H, H_d, J_{d-f} = 1.1 Hz, J_{d-c} = J_{d-e} = 7.3 Hz); 7.00 (d, 1H, H_f, J_{f-e} = 7.9 Hz); 6.90 (d, 2H, H_i, J_{i-j} = 9.0 Hz); 2.57 (s, 3H, H_m); 2.20 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 196.7 (C_l); 162.3 (C_h); 153.0 (C_g); 131.7

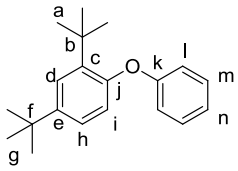
(C_c); 131.4 (C_k); 130.7 (C_j); 130.5 (C_b); 127.5 (C_e); 125.3 (C_d); 121.0 (C_f); 116.0 (C_i); 26.4 (C_m); 16.0 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{15}O_2$ $[M+H]^+$: 227.1067. Found: 227.1066.



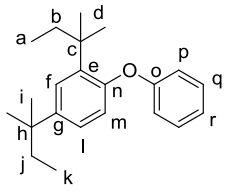
1-Methyl-2-(4-nitrophenoxy)benzene (30).[46] Purified by column chromatography (Petroleum ether/Et_2O : 95/5); yellow oil. **^{1}H-NMR (500MHz) δ:** 8.20 (d, 2H, H_j, J_{j-i} = 9.2 Hz); 7.32 (d, 1H, H_c, J_{c-d} = 7.5 Hz); 7.29-7.26 (m, 1H, H_e); 7.21 (dt, 1H, H_d, J_{d-f} = 1.2 Hz, J_{d-c} = J_{d-e} = 7.3 Hz); 7.02 (d, 1H, H_f, J_{f-e} = 7.9 Hz); 6.93 (d, 2H, H_i, J_{i-j} = 9.2 Hz); 2.19 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 163.4 (C_h); 152.4 (C_g); 142.4 (C_k); 132.0 (C_c); 130.5 (C_b); 127.7 (C_e); 126.0 (C_j); 125.9 (C_d); 121.1 (C_f); 116.0 (C_i); 16.0 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{13}H_{12}NO_3$ $[M+H]^+$: 230.0812. Found: 230.0809.



1-Isopropyl-4-methyl-2-phenoxybenzene (31). Purified by chromatography (Biotage, Hexane); yellow oil. **^{1}H-NMR (400MHz) δ:** 7.31 (t, 2H, H_l, J_{l-k} = J_{l-m} = 7.2 Hz); 7.23 (d, 1H, H_d, J_{d-e} = 7.9 Hz); 7.05 (tt, 1H, H_m, J_{m-k} = 1.1 Hz, J_{m-l} = 7.4 Hz); 6.97-6.92 (m, 3H, $H_{k,e}$); 6.72 (d, 1H, H_h, J_{h-e} = 0.9 Hz); 3.24 (sept, 1H, H_b, J_{b-a} = 6.9 Hz); 2.27 (s, 3H, H_g); 1.22 (d, 6H, H_a, J_{a-b} = 6.9 Hz). **^{13}C{^{1}H}-NMR (100MHz) δ:** 158.4 (C_j); 153.3 (C_i); 137.2 (C_c); 136.8 (C_f); 129.6 (C_l); 126.7 (C_d); 124.9 (C_e); 122.2 (C_m); 120.5 (C_h); 117.5 (C_k); 26.8 (C_b); 23.1 (C_a); 20.9 (C_g). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{19}O$ $[M+H]^+$: 227.1430. Found: 227.1429.

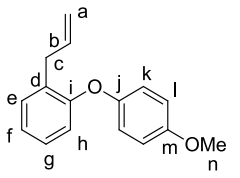


2,4-Di-*tert*-butyl-1-phenoxybenzene (32).[47] Purified by chromatography (Biotage, Hexane); yellow oil. **^{1}H-NMR (400MHz) δ:** 7.42 (d, 1H, H_d, J_{d-h} = 2.5 Hz); 7.32 (dd, 2H, H_m, J_{m-n} = 7.4 Hz, J_{m-l} = 8.6 Hz); 7.14 (dd, 1H, H_h, J_{h-d} = 2.5 Hz, J_{h-i} = 8.5 Hz); 7.06 (t, 1H, H_n, J_{n-m} = 7.4 Hz); 7.01-6.96 (m, 2H, H_l); 6.75 (d, 1H, H_i, J_{i-h} = 8.5 Hz); 1.43 (s, 9H, H_g); 1.33 (s, 9H, H_a). **^{13}C{^{1}H}-NMR (100MHz) δ:** 158.0 (C_k); 153.2 (C_j); 145.7 (C_e); 139.9 (C_c); 129.5 (C_m); 124.1 (C_d); 123.7 (C_h); 122.3 (C_n); 119.5 (C_i); 118.5 (C_l); 34.9 (C_b); 34.5 (C_f); 31.6 (C_g); 30.2 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{20}H_{27}O$ $[M+H]^+$: 283.2056. Found: 283.2053.

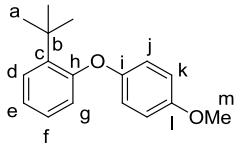


2,4-Di-*tert*-pentyl-1-phenoxybenzene (33). Purified by chromatography (Biotage, Hexane); yellow oil. **^{1}H-NMR (400MHz) δ:** 7.31 (t, 2H, H_q, J_{q-p} = J_{q-r} = 7.1 Hz); 7.28 (d, 1H, H_f, J_{f-l} = 2.5 Hz); 7.09-7.02 (m, 2H, $H_{l,r}$); 6.96 (d, 2H, H_p, J_{p-q} = 7.6 Hz); 6.75 (d, 1H, H_m, J_{m-l} = 8.5 Hz); 1.83 (q, 2H, H_b, J_{b-a} = 7.5 Hz); 1.63 (q, 2H, H_j, J_{j-k} = 7.4 Hz); 1.38 (s, 6H, H_i); 1.29 (s, 6H, H_d); 0.70 (m, 6H, $H_{a,k}$). **^{13}C{^{1}H}-NMR (100MHz) δ:** 158.0 (C_o); 153.0 (C_n); 143.8 (C_g); 138.1 (C_e); 129.5 (C_q); 126.2 (C_f); 124.3 (C_l); 122.2 (C_r); 119.5 (C_m); 118.3 (C_p); 38.5 (C_c); 37.7 (C_h);

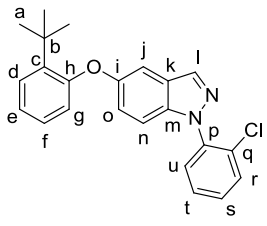
37.1 (C_j); 33.9 (C_b); 28.5 (C_d); 28.1 (C_i); 9.5 (C_a); 9.1 (C_k). **M/z (HRMS-CI):** calcd. for $C_{22}H_{31}O$ $[M+H]^+$: 311.2369. Found: 311.2379.



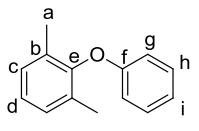
1-Allyl-2-(4-methoxyphenoxy)benzene (34). Purified by chromatography (Biotage, Hexane/AcOEt : 100/0 to 98/2); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.25 (dd, 1H, H_e, J_{e-g} = 1.5 Hz, J_{e-f} = 7.4 Hz); 7.15 (dt, 1H, H_g, J_{g-e} = 1.7 Hz, J_{g-f} = J_{g-f} = 7.7 Hz); 7.07-7.02 (m, 1H, H_f); 6.96-6.84 (m, 4H, $H_{k,l}$); 6.80 (dd, 1H, H_h, J_{h-f} = 1.0 Hz, J_{h-g} = 8.1 Hz); 6.01 (ddt, 1H, H_b, J_{b-c} = 6.7 Hz, $J_{b-a(cis)}$ = 10.2 Hz, $J_{b-a(trans)}$ = 16.9 Hz); 6.13-5.04 (m, 2H, H_a); 3.81 (s, 3H, H_n); 3.46 (d, 2H, H_c, J_{c-b} = 6.6 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.5 (C_i); 155.4 (C_m); 151.0 (C_j); 136.6 (C_b); 130.9 (C_d); 130.4 (C_g); 127.4 (C_e); 123.1 (C_f); 119.7 (C_k); 117.9 (C_a); 115.7 (C_h); 114.8 (C_l); 55.7 (C_n); 34.3 (C_c). **M/z (HRMS-ESI+):** $C_{16}H_{17}O_2$ $[M+H]^+$: 241.1223. Found: 241.1218.



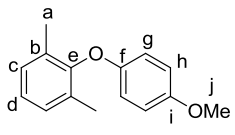
1-(*Tert*-butyl)-2-(4-methoxyphenoxy)benzene (35). Purified by column chromatography (Hexane/AcOEt : 95/5); yellow oil. **^{1}H-NMR (500MHz) δ:** 7.39 (dd, 1H, H_d, J_{d-f} = 1.6 Hz, J_{d-e} = 7.8 Hz); 7.11 (dt, 1H, H_f, J_{f-d} = 1.7 Hz, J_{f-e} = J_{f-g} = 7.7 Hz); 7.01 (m, 1H, H_e); 6.95-6.88 (m, 4H, $H_{j,k}$); 6.76 (dd, 1H, H_g, J_{g-e} = 1.3 Hz; J_{g-f} = 8.1 Hz); 3.81 (s, 3H, H_m); 1.45 (s, 9H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 156.9 (C_h); 155.4 (C_l); 151.0 (C_i); 140.2 (C_c); 127.0 (C_d); 127.0 (C_f); 122.5 (C_e); 120.3 (C_j); 118.8 (C_g); 114.8 (C_k); 55.7 (C_m); 34.8 (C_b); 30.0 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{17}H_{21}O_2$ $[M+H]^+$: 257.1536. Found: 257.1534.



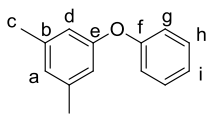
5-(2-(*Tert*-butyl)phenoxy)-1-(2-chlorophenyl)-1*H*-indazole (36). Purified by column chromatography (Hexane/AcOEt : 100/0 to 90/10); orange solid. **^{1}H-NMR (500MHz) δ:** 8.15 (s, 1H, H_l); 7.65-7.61 (m, 1H, H_u); 7.56-7.52 (m, 1H, H_r); 7.47-7.41 (m, 3H, $H_{d,s,t}$); 7.32 (d, 1H, H_j, J_{j-o} = 2.1 Hz); 7.24 (d, 1H, H_n, J_{n-o} = 9.0 Hz); 7.17 (dd, 1H, H_o, J_{o-j} = 2.1 Hz, J_{o-n} = 9.0 Hz); 7.17-7.13 (m, 1H, H_f); 7.06 (dt, 1H, H_e, J_{e-g} = 1.4 Hz, J_{e-d} = J_{e-f} = 7.6 Hz); 6.84 (d, 1H, H_g, J_{g-f} = 7.9 Hz); 1.48 (s, 9H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 156.7 (C_i); 152.4 (C_h); 140.5 (C_c); 137.2 (C_m); 137.1 (C_p); 135.3 (C_l); 131.4 (C_q); 130.8 (C_u); 129.8 (C_t); 129.4 (C_r); 127.7 (C_s); 127.2 (C_d); 127.1 (C_f); 124.9 (C_k); 122.9 (C_e); 121.0 (C_o); 119.4 (C_g); 111.7 (C_n); 108.9 (C_j); 34.8 (C_b); 30.1 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{23}H_{21}ClN_2NaO$ $[M+Na]^+$: 399.1235. Found: 399.1239.



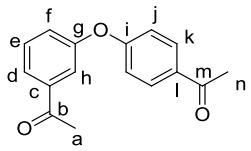
1,3-Dimethyl-2-phenoxybenzene (37).[48] Purified by chromatography (Hexane); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.26-7.23 (m, 2H, H_h); 7.09-7.03 (m, 3H, $H_{c,d}$); 6.96 (dt, 1H, H_i, J_{i-g} = 0.9 Hz, J_{i-h} = 7.3 Hz); 6.75 (dd, 2H, H_g, J_{g-i} = 0.9 Hz, J_{g-h} = 7.7 Hz); 2.12 (s, 6H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 157.9 (C_f); 151.1 (C_e); 131.5 (C_b); 129.6 (C_h); 128.9 (C_c); 125.0 (C_d); 121.2 (C_i); 114.6 (C_g); 16.3 (C_a). **M/z (HRMS-CI):** calcd. for $C_{14}H_{15}O$ $[M+H]^+$: 199.1117. Found: 199.1121.



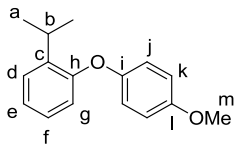
2-(4-Methoxyphenoxy)-1,3-dimethylbenzene (38). Purified by chromatography (Hexane/AcOEt : 100/0 to 98/2); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.10-7.04 (m, 3H, $H_{c,d}$); 6.80 (d, 2H, H_g, J_{g-h} = 9.2 Hz); 6.69 (d, 2H, H_h, J_{h-g} = 9.2 Hz); 3.77 (s, 3H, H_m); 2.14 (s, 6H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 154.1 (C_i); 152.0 (C_f); 151.5 (C_e); 131.6 (C_b); 128.9 (C_c); 124.8 (C_d); 115.2 (C_h); 114.7 (C_g); 55.7 (C_j); 16.3 (C_a). **M/z (HRMS-CI):** calcd. for $C_{15}H_{17}O_2$ $[M+H]^+$: 229.1223. Found: 229.1229.



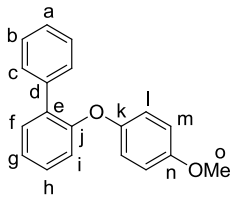
1,3-Dimethyl-5-phenoxybenzene (42).[35] Purified by column chromatography (Hexane); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.34 (t, 2H, H_h, J_{h-g} = J_{h-i} = 8.0 Hz); 7.10 (t, 1H, H_i, J_{i-h} = 7.4 Hz); 7.01 (d, 2H, H_g, J_{g-h} = 7.7 Hz); 6.76 (s, 1H, H_a); 6.65 (s, 2H, H_d); 2.30 (s, 6H, H_c). **^{13}C{^{1}H}-NMR (125MHz) δ:** 157.4 (C_f); 157.1 (C_e); 139.6 (C_b); 129.6 (C_h); 125.0 (C_a); 122.9 (C_i); 118.8 (C_g); 116.6 (C_d); 21.3 (C_c). **M/z (HRMS-APCI):** calcd. for $C_{14}H_{15}O$ $[M+H]^+$: 199.1117. Found: 199.1120.



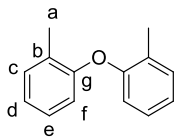
1-(3-(4-Acetylphenoxy)phenyl)ethanone (43).[49] Purified by column chromatography (Hexane/AcOEt : 100/0 to 90/10); white solid. **^{1}H-NMR (500MHz) δ:** 7.97 (d, 2H, H_k, J_{k-j} = 9.0 Hz); 7.79 (dd, 1H, H_d, J_{d-h} = 0.9 Hz, J_{d-e} = 7.7 Hz);7.67-7.64 (m, 1H, H_h); 7.50 (t, 1H, H_e, J_{e-d} = J_{e-f} = 7.9 Hz); 7.26-7.30 (m, 1H, H_f); 7.03 (d, 2H, H_j, J_{j-k} = 9.0 Hz); 2.60 (s, 3H, H_a); 2.59 (s, 3H, H_n). **^{13}C{^{1}H}-NMR (125MHz) δ:** 197.1 (C_b); 196.7 (C_m); 161.3 (C_i); 156.1 (C_g); 139.2 (C_c); 132.5 (C_l); 130.7 (C_k); 130.3 (C_e); 124.6 (C_d); 124.4 (C_f); 119.3 (C_h); 117.7 (C_j); 26.7 (C_a); 26.6 (C_n). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{14}NaO_3$ $[M+Na]^+$: 277.0835. Found: 277.0846. **M.p.:** 85-87°C.



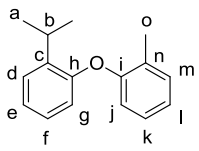
1-Isopropyl-2-(4-methoxyphenoxy)benzene (44).[37] Purified by column chromatography (Hexane/AcOEt : 100/0 to 95/5); yellow oil. **^{1}H-NMR (500MHz) δ:** 7.33 (dd, 1H, H_d, J_{d-f} = 1.6 Hz, J_{d-e} = 7.6 Hz); 7.12 (dt, 1H, H_f, J_{f-d} = 1.8 Hz, J_{f-e} = J_{f-g} = 7.8 Hz); 7.08 (dt, 1H, H_e, J_{e-g} = 1.3 Hz, J_{e-d} = J_{e-f} = 7.4 Hz); 6.91 (d, 2H, H_j, J_{j-k} = 9.4 Hz); 6.87 (d, 2H, H_k, J_{k-j} = 9.2 Hz); 6.79 (dd, 1H, H_g, J_{g-e} = 1.3 Hz, J_{g-f} = 7.9 Hz); 3.81 (s, 3H, H_m); 3.37 (sept, 1H, H_b, J_{b-a} = 6.9 Hz); 1.27 (d, 6H, H_a, J_{a-b} = 6.9 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.3 (C_l); 154.9 (C_h); 151.5 (C_i); 139.4 (C_c); 126.8 (C_d); 126.7 (C_f); 123.3 (C_e); 119.4 (C_j); 118.2 (C_g); 114.8 (C_k); 55.7 (C_m); 27.1 (C_b); 22.9 (C_a). **M/z (HRMS-APCI):** calcd. for $C_{16}H_{19}O_2$ $[M+H]^+$: 243.1380. Found: 243.1388.



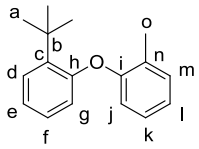
2-(4-Methoxyphenoxy)-1,1'-biphenyl (45). Purified by column chromatography (Hexane/ AcOEt : 100/0 to 95/5); yellow oil. **^{1}H-NMR (500MHz) δ:** 7.59 (d, 2H, H_c, J_{c-b} = 8.5 Hz); 7.44 (dd, 1H, H_f, J_{f-h} = 1.6 Hz, J_{f-g} = 7.6 Hz); 7.40 (t, 2H, H_b, J_{b-a} = J_{b-c} = 7.5 Hz); 7.32 (t, 1H, H_a, J_{a-b} = 7.5 Hz); 7.28-7.25 (m, 1H, H_h); 7.17 (dt, 1H, H_g, J_{g-i} = 1.1 Hz, J_{g-f} = J_{g-h} = 7.3 Hz); 6.93-6.91 (m, 3H, $H_{i,l}$); 6.84 (d, 2H, H_m, J_{m-l} = 9.2 Hz); 3.79 (s, 3H, H_o). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.5 (C_n); 154.8 (C_j); 150.9 (C_k); 137.9 (C_d); 132.8 (C_e); 131.2 (C_f); 129.3 (C_c); 128.6 (C_h); 128.1 (C_b); 127.1 (C_a); 123.2 (C_g); 120.0 (C_l); 118.6 (C_i); 114.8 (C_m); 55.6 (C_o). **M/z (HRMS-APCI):** calcd. for $C_{19}H_{17}O_2$ $[M+H]^+$: 277.1223. Found: 277.1219.



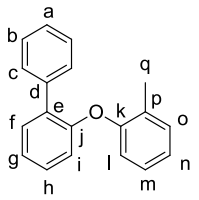
2,2'-Oxybis(methylbenzene) (46).[50] Purified by chromatography (Hexane); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.26 (d, 2H, H_c, J_{c-d} = 6.8 Hz); 7.13 (t, 2H, H_e, J_{e-d} = J_{e-f} = 7.3 Hz); 7.02 (t, 2H, H_d, J_{d-c} = J_{d-e} = 7.4 Hz); 6.73 (d, 2H, H_f, J_{f-e} = 8.1 Hz); 2.30 (s, 6H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.2 (C_g); 131.3 (C_c); 128.8 (C_b); 127.0 (C_e); 123.0 (C_d); 117.6 (C_f); 16.1 (C_a). **M/z (HRMS-APCI):** calcd. for $C_{14}H_{15}O$ $[M+H]^+$: 199.1117. Found: 119.1124.



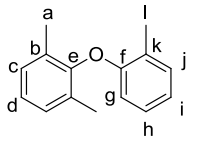
1-Isopropyl-2-(*o*-tolyloxy)benzene (47).[51] Purified by column chromatography (Hexane); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.34 (dd, 1H, H_d, J_{d-f} = 1.8 Hz, J_{d-e} = 7.3 Hz); 7.27-7.25 (m, 1H, H_m); 7.15-7.06 (m, 3H, $H_{e,f,k}$); 7.02 (t, 1H, H_l, J_{l-k} = J_{l-m} = 7.4 Hz); 6.76 (d, 1H, H_j, J_{j-k} = 8.0 Hz); 6.71 (dd, 1H, H_g, J_{g-e} = 1.6 Hz, J_{g-f} = 7.8 Hz); 3.36 (sept, 1H, H_b, J_{b-a} = 6.9 Hz); 2.32 (s, 3H, H_o); 1.29 (d, 6H, H_a, J_{a-b} = 7.1 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.5 (C_i); 154.3 (C_h); 139.0 (C_c); 131.2 (C_m); 129.0 (C_n); 127.0 (C_d); 126.8 (C_f); 126.7 (C_k); 123.1 (C_e); 123.0 (C_l); 117.8 (C_j); 117.6 (C_g); 27.2 (C_b); 22.9 (C_a); 16.2 (C_o). **M/z (HRMS-APCI):** calcd. for $C_{16}H_{19}O$ $[M+H]^+$: 227.1430. Found: 227.1436.



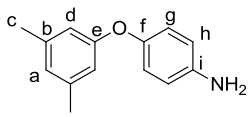
1-(*Tert*-butyl)-2-(*o*-tolyloxy)benzene (48). Purified by column chromatography (Hexane); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.41 (dd, 1H, H_d, J_{d-f} = 1.4 Hz, J_{d-e} = 7.8 Hz); 7.28-7.26 (m, 1H, H_m); 7.15 (t, 1H, H_k, $J_{k-j} = J_{k-l}$ = 7.3 Hz); 7.10 (t, 1H, H_f, $J_{f-e} = J_{f-g}$ = 7.7 Hz); 7.05-7.00 (m, 2H, $H_{e,l}$); 6.82 (d, 1H, H_j, J_{j-k} = 8.0 Hz); 6.66 (dd, 1H, H_g, J_{g-e} = 0.9 Hz, J_{g-f} = 8.0 Hz); 2.33 (s, 3H, H_o); 1.48 (s, 9H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.3 (C_h); 155.1 (C_i); 139.8 (C_c); 131.2 (C_m); 129.6 (C_n); 127.1 (C_d); 127.1 (C_k); 127.0 (C_f); 123.2 (C_l); 122.4 (C_e); 118.7 (C_j); 118.0 (C_g); 34.8 (C_b); 30.1 (C_a); 16.4 (C_o). **M/z (HRMS-APCI):** calcd. for $C_{17}H_{21}O$ $[M+H]^+$: 241.1587. Found: 241.1591.



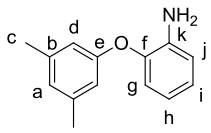
2-(*o*-Tolyloxy)-1,1'-biphenyl (49). Purified by column chromatography (Hexane); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.61 (d, 2H, H_c, J_{c-b} = 7.1 Hz); 7.46 (dd, 1H, H_f, J_{f-h} = 1.5 Hz, J_{f-g} = 7.7 Hz); 7.39 (t, 2H, H_b, J_{b-c} = 7.6 Hz); 7.32 (t, 1H, H_a, J_{a-b} = 7.3 Hz); 7.29-7.24 (m, 1H, H_h); 7.22-7.15 (m, 2H, $H_{g,o}$); 7.11 (t, 1H, H_m, $J_{m-l} = J_{m-n}$ = 7.6 Hz); 7.00 (t, 1H, H_n, $J_{n-m} = J_{n-o}$ = 7.4 Hz); 6.85 (d, 1H, H_i, J_{i-h} = 8.1 Hz); 6.82 (d, 1H, H_l, J_{l-m} = 8.1 Hz); 2.24 (s, 3H, H_q). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.1 (C_k); 154.1 (C_j); 138.0 (C_d); 132.7 (C_e); 131.2 ($C_{f,o}$); 129.3 (C_c); 129.2 (C_p); 128.5 (C_h); 128.0 (C_b); 127.1 (C_a), 127.0 (C_m); 123.2 (C_n); 123.1 (C_g); 118.3 (C_l); 118.1 (C_i); 16.3 (C_q). **M/z (HRMS-APCI):** calcd. for $C_{19}H_{17}O$ $[M+H]^+$: 261.1274. Found: 261.1272.



1,3-Dimethyl-2-(*o*-tolyloxy)benzene (50).[44] Purified by chromatography (Hexane); colourless oil. **^{1}H-NMR (500MHz) δ:** 7.24-7.21 (m, 1H, H_j); 7.12-7.04 (m, 3H, $H_{c,d}$); 6.98 (dt, 1H, H_h, J_{h-j} = 1.2 Hz, $J_{h-g} = J_{h-i}$ = 6.9 Hz); 6.88 (t, 1H, H_i, $J_{i-h} = J_{i-j}$ = 7.1 Hz); 6.27 (d, 1H, H_g, J_{g-h} = 8.1 Hz); 2.44 (s, 3H, H_l); 2.12 (s, 6H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 155.7 (C_f); 151.5 (C_e); 131.4 (C_b); 131.0 (C_j); 128.9 (C_c); 126.7 (C_h); 126.0 (C_k); 124.8 (C_d); 120.9 (C_i); 111.8 (C_g); 16.2 (C_l); 16.1 (C_a). **M/z (HRMS-APCI):** calcd. for $C_{15}H_{17}O$ $[M+H]^+$: 213.1274. Found: 213.1274.



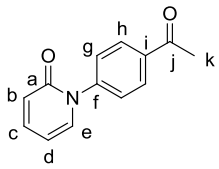
4-(3,5-Dimethylphenoxy)aniline (51).[52] Purified by column chromatography (Hexane/ AcOEt : 100/0 to 90/10); brown oil. **^{1}H-NMR (500MHz) δ:** 6.88 (d, 2H, H_g, J_{g-h} = 8.8 Hz); 6.70 (d, 2H, H_h, J_{h-g} = 8.8 Hz); 6.68 (s, 1H, H_a); 6.57 (s, 2H, H_d); 3.58 (broad s, 2H, NH_2); 2.27 (s, 6H, H_c). **^{13}C{^{1}H}-NMR (125MHz) δ:** 158.8 (C_e); 148.9 (C_f); 142.3 (C_i); 139.3 (C_b); 123.8 (C_a); 121.1 (C_g); 116.3 (C_h); 114.9 (C_d); 21.3 (C_c). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{15}NNaO$ $[M+Na]^+$: 236.1046. Found: 236.1048.



2-(3,5-Dimethylphenoxy)aniline (52). Purified by chromatography (Hexane/ AcOEt : 100/0 to 90/10); brown oil. **^{1}H-NMR (500MHz) δ:** 7.00 (dt, 1H, H_i, J_{i-g} = 1.3 Hz, J_{i-h} = J_{i-j} = 7.6 Hz); 6.89 (dd, 1H, H_g, J_{g-i} = 1.3 Hz, J_{g-h} = 7.9 Hz); 6.84 (dd, 1H, H_j, J_{j-h} = 1.3 Hz, J_{j-i} = 7.9 Hz); 6.76-6.71 (m, 2H, $H_{a,h}$); 6.61 (s, 2H, H_d); 3.73 (broad s, 2H, NH_2); 2.29 (s, 6H, H_c). **^{13}C{^{1}H}-NMR (125MHz) δ:** 157.5 (C_e); 143.3 (C_f); 139.5 (C_b); 138.5 (C_k); 124.6 (C_i); 124.4 (C_a); 120.2 (C_g); 118.8 (C_h); 116.5 (C_j); 114.8 (C_d); 21.3 (C_c). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{15}NNaO$ $[M+Na]^+$: 236.1046. Found: 236.1043.

6.2.9 – Synthesis of 1-(4-acetylphenyl)pyridin-2(1*H*)-one (41)

General procedure: The reactions were performed under nitrogen in 25 mL tubes in an Amigochem Integrity 10 Parallel Reaction Block. A dry tube was charged with 2-hydroxypyridine (114 mg, 1.2 mmol), 4-iodoacetophenone (246 mg, 1.0 mmol), caesium carbonate (652 mg, 2 mmol), CuI (19 mg, 0.1 mmol) and ligand (0.1 mmol). The reaction tube was evacuated and back-filled with nitrogen three times, then the solvent (2 mL) was added, and the tube was placed in Integrity 10 Block (preheated at a slightly higher temperature than the reflux temperature of the solvent) and the reaction was stirred for 24 h (1000 rpm). At the end of the reaction the tube was cooled to room temperature, then the crude was diluted with ≈ 2mL DCM, filtered through celite and washed thoroughly with DCM (≈ 50 mL). 1 mL of a 0.5 M solution of 1,3,5-trimethoxybenzene (internal standard) in DCM was added, and the crude solution was analysed through gas chromatography. The isolated product was purified by column chromatography (Biotage, Hexane/AcOEt : 96/4 to 60/30).



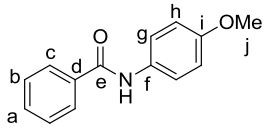
White solid. **^{1}H-NMR (500MHz) δ:** 8.10 (d, 2H, H_h, J_{h-g} = 8.7 Hz); 7.53 (d, 2H, H_g, J_{g-h} = 8.7 Hz); 7.43 (ddd, 1H, H_c, J_{c-e} = 2.1 Hz, J_{c-d} = 6.7 Hz, J_{c-b} = 9.1 Hz); 7.34 (ddd, 1H, H_e, J_{e-b} = 0.6 Hz, J_{e-c} = 2.0 Hz, J_{e-d} = 6.9 Hz); 6.68 (d, 1H, H_b, J_{b-c} = 9.3 Hz); 6.29 (dt, 1H, H_d, J_{d-b} = 1.3 Hz, J_{d-c} = J_{d-e} = 6.7 Hz); 2.65 (s, 3H, H_k). **^{13}C{^{1}H}-NMR (125MHz) δ:** 196.9 (C_j); 162.1 (C_a); 144.7 (C_f); 140.1 (C_c); 137.1 (C_e); 136.8 (C_i); 129.4 (C_h); 126.8 (C_g); 122.2 (C_b); 106.3 (C_d); 26.7 (C_k). **M/z (HRMS-ESI+):** calcd. for $C_{13}H_{12}NO_2$ $[M+h]^+$: 214.0863. Found: 214.0862.

6.2.10 – Synthesis of amides

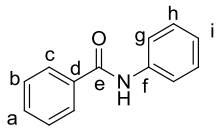
General procedure: All catalytic reactions were performed under air in 25 mL glass tubes in a Radley standard carousel. An oven dried tube was charged with the amide (1.2 mmol), the aryl iodide (1.0 mmol), potassium phosphate (424 mg, 2 mmol), CuI (19 mg, 0.1 mmol) and ligand (0.1 mmol). Isobutyl acetate (2 mL) was then added, the tube was placed in the carousel (preheated at 150°C) and the reaction was stirred for 24 h (1000 rpm). At the end of the reaction the tube was cooled to room temperature, then the crude was diluted with ≈ 2mL

DCM, filtered through celite and washed thoroughly with DCM (≈ 50 mL). 1 mL of a 0.5 M solution of 1,3,5-trimethoxybenzene (internal standard) in DCM was added, and the crude solution was analysed through ^{1}H-NMR. Isolated compounds were purified by column chromatography.

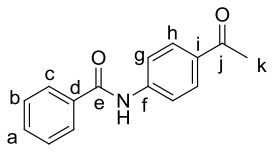
Chemicals used for screening in green solvents (Chapter 2, section 2.6): Sigma Aldrich CuI (98%); Alfa Aesar Cs_2CO_3 (99+% metal basis), Alfa Aesar K_3PO_4 (97%, anhydrous, granular); Alfa Aesar 4-iodoanisole (98+%); Sigma Aldrich benzamide (99%). **Solvents:** Sigma Aldrich MeOAc (for HPLC, ≥99.8%); VWR Prolabo EtOAc (GPR Rectapur, min 99.0%); Sigma Aldrich *n*-PrOAc (99%); Alfa Aesar *i*-PrOAc (99+%); Sigma Aldrich *n*-BuOAc (anhydrous, ≥99%); Sigma Aldrich *t*-BuOAc (≥99%); Alfa Aesar *i*-BuOAc (98%); Sigma Aldrich *n*-AmOAc (99%); Sigma Aldrich *i*-AmOAc (reagent grade, 98%); Merck Isosorbide Dimethyl ether (for synthesis, ≥98%); Sigma Aldrich Diethyl carbonate (>99%).



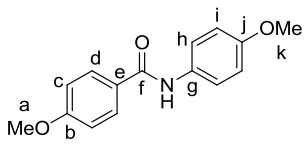
***N*-(4-Methoxyphenyl)benzamide (54).**[53] Purified by column chromatography (Hexane/EtOAc: 95/5 to 80/20). White solid, yield 83% (189 mg, 0.83 mmols). **^{1}H-NMR (300MHz) δ:** 7.87 (d, 2H, H_c, $J_{c\text{-}b}$ = 6.8 Hz); 7.78 (broad s, 1H, NH); 7.59-7.44 (m, 5H, $H_{a,b,g}$); 6.92 (d, 2H, H_h, $J_{h\text{-}g}$ = 9.1 Hz); 3.82 (s, 3H, H_j). **^{13}C{^{1}H}-NMR (75MHz) δ:** 165.6 (C_e); 156.6 (C_i); 135.0 (C_d); 131.7 (C_a); 131.0 (C_f); 128.7 (C_b); 127.0 (C_c); 122.1 (C_g); 114.2 (C_h); 55.5 (C_j). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{13}NNaO_2$ $[M+Na]^+$: 250.0838. Found: 250.0837.



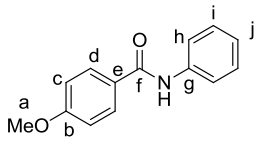
***N*-Phenylbenzamide (55).**[53] Purified by column chromatography (Hexane/EtOAc: 90/10 to 80/20). White solid, yield 85% (167 mg, 0.85 mmols). **^{1}H-NMR (500MHz) δ:** 7.89 (d, 2H, H_c, $J_{c\text{-}b}$ = 7.1 Hz); 7.81 (broad s, 1H, NH); 7.66 (d, 2H, H_g, $J_{g\text{-}h}$ = 7.7 Hz); 7.60-7.54 (m, 1H, H_a); 7.51 (t, 2H, H_b, $J_{b\text{-}a}$ = $J_{b\text{-}c}$ = 7.5 Hz); 7.39 (t, 2H, H_h, $J_{h\text{-}g}$ = $J_{h\text{-}i}$ = 7.9 Hz); 7.17 (t, 1H, H_i, $J_{i\text{-}h}$ = 7.3 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.6 (C_e); 138.1 (C_f); 135.3 (C_d); 131.8 (C_a); 129.1 (C_h); 128.8 (C_b); 127.0 (C_c); 124.6 (C_i); 120.3 (C_g). **M/z (HRMS-ESI+):** calcd. for $C_{13}H_{12}NO$ $[M+H]^+$: 198.0913. Found: 198.0918.



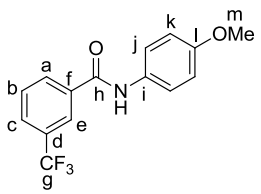
***N*-(4-Acetylphenyl)benzamide (56).**[54] Purified by column chromatography (Hexane/EtOAc: 85/15 to 65/35). Yellow solid, yield 59% (141 mg, 0.59 mmols). **^{1}H-NMR (500MHz) δ:** 8.03-7.99 [(d, 2H, H_h, $J_{h\text{-}g}$ = 8.8 Hz), and (broad s, 1H, NH)]; 7.90 (d, 2H, H_c, $J_{c\text{-}b}$ = 7.1 Hz); 7.78 (d, 2H, H_g, $J_{g\text{-}h}$ = 8.8 Hz); 7.60 (t, 1H, H_a, $J_{a\text{-}b}$ = 7.5 Hz); 7.53 (t, 2H, H_b, $J_{b\text{-}a}$ = $J_{b\text{-}c}$ = 7.6 Hz); 2.61 (s, 3H, H_k). **^{13}C{^{1}H}-NMR (125MHz) δ:** 196.6 (C_j); 165.7 (C_e); 142.3 (C_f); 134.7 (C_d); 133.5 (C_i); 132.2 (C_a); 129.8 (C_h); 129.0 (C_b); 127.1 (C_c); 119.4 (C_g); 26.3 (C_k). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{14}NO_2$ $[M+H]^+$: 240.1019. Found: 240.1020.



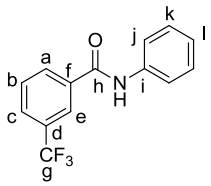
4-Methoxy-*N*-(4-methoxyphenyl)benzamide (57).[55] Purified by column chromatography (Hexane/EtOAc: 90/10 to 20/80). Yellow solid, yield 67% (173 mg, 0.67 mmols). **^{1}H-NMR (500MHz) δ:** 7.84 (d, 2H, H_d, J_{d-c} = 9.0 Hz); 7.65 (broad s, 1H, NH); 7.53 (d, 2H, H_h, J_{h-i} = 9.0 Hz); 6.98 (d, 2H, H_c, J_{c-d} = 8.8 Hz); 6.92 (d, 2H, H_i, J_{i-h} = 9.0 Hz); 3.88 (s, 3H, H_a); 3.82 (s, 3H, H_k). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.1 (C_f); 162.6 (C_b); 156.8 (C_j); 131.4 (C_g); 128.8 (C_d); 127.5 (C_e); 122.2 (C_h); 114.5 (C_c); 114.1 (C_i); 55.6 (C_a); 55.5 (C_k). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{15}NNaO_3$ $[M+Na]^+$: 280.0944. Found: 280.0948.



4-Methoxy-*N*-phenylbenzamide (58).[54] Purified by column chromatography (Hexane/EtOAc: 95/5 to 70/30). White solid, yield 88% (200 mg, 0.88 mmols). **^{1}H-NMR (500MHz) δ:** 7.85 (d, 2H, H_d, J_{d-c} = 8.8 Hz); 7.74 (broad s, 1H, NH); 7.64 (d, 2H, H_h, J_{h-i} = 8.5 Hz); 7.38 (t, 2H, H_i, J_{i-h} = J_{i-j} = 7.9 Hz); 7.15 (t, 1H, H_j, J_{j-i} = 7.4 Hz); 6.99 (d, 2H, H_c, J_{c-d} = 8.8 Hz); 3.89 (s, 3H, H_a). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.1 (C_f); 162.7 (C_b); 138.3 (C_g); 129.1 (C_i); 128.9 (C_d); 127.5 (C_e); 124.4 (C_j); 120.3 (C_h); 114.1 (C_c); 55.5 (C_a). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{13}NNaO_2$ $[M+Na]^+$: 250.0838. Found: 250.0837.

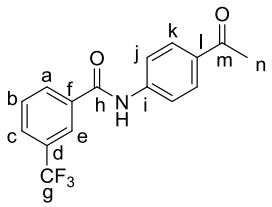


***N*-(4-Methoxyphenyl)-3-(trifluoromethyl)benzamide (59).**[56] Purified by column chromatography (Hexane/EtOAc: 90/10 to 60/40). Orange solid, yield 66% (195 mg, 0.66 mmols). **^{1}H-NMR (500MHz) δ:** 8.12 (s, 1H, H_e); 8.04 (d, 1H, H_a, J_{a-b} = 7.5 Hz); 7.90 (broad s, 1H, NH); 7.79 (d, 1H, H_c, J_{c-b} = 7.7 Hz); 7.60 (t, 1H, H_b, J_{b-a} = J_{b-c} = 7.7 Hz); 7.53 (d, 2H, H_j, J_{j-k} = 8.8 Hz); 6.91 (d, 2H, H_k, J_{k-j} = 9.0 Hz); 3.82 (s, 3H, H_m). **^{13}C{^{1}H}-NMR (125MHz) δ:** 164.3 (C_h); 157.0 (C_l); 135.9 (C_f); 131.3(C_d, q, J_{C-F} = 32 Hz); 130.5 (C_i); 130.3 (C_a); 129.4 (C_b); 128.2 (C_c, q, J_{C-F} = 3 Hz); 124.0 (C_e, q, J_{C-F} = 3 Hz); 123.7 (C_g, q, J_{C-F} = 272 Hz); 122.4 (C_j); 114.3 (C_k); 55.5 (C_m). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{12}F_3NNaO_2$ $[M+Na]^+$: 318.0712. Found: 318.0713.

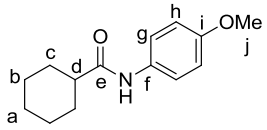


***N*-Phenyl-3-(trifluoromethyl)benzamide (60).**[57] Purified by column chromatography (Hexane/EtOAc: 95/5 to 80/20). Off-white solid, yield 81% (216 mg, 0.81 mmols). **^{1}H-NMR (500MHz) δ:** 8.12 (s, 1H, H_e); 8.07 (broad s, 1H, NH); 8.04 (d, 1H, H_a, J_{a-b} = 8.0 Hz); 7.79 (d, 1H, H_c, J_{c-b} = 7.8 Hz); 7.64 (d, 2H, H_j, J_{j-k} = 8.0 Hz); 7.60 (t, 1H, H_b, J_{b-a} = J_{b-c} = 7.8 Hz); 7.37 (t, 2H, H_k, J_{k-j} = J_{k-l} = 7.9 Hz); 7.18 (t, 1H, H_l, J_{l-k} = 7.3 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 164.4 (C_h); 137.5 (C_i); 135.8 (C_f); 131.3 (C_d, q, J_{C-F} = 33 Hz); 130.4 (C_a); 129.4 (C_b); 129.1 (C_k); 128.3 (C_c, q, J_{C-F} = 4

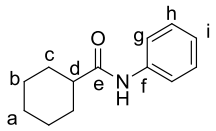
Hz); 125.0 (C_l); 124.1 (C_e, q, J_{C-F} = 4 Hz); 123.6 (C_g, q, J_{C-F} = 273 Hz); 120.5 (C_j). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{10}F_3NNaO$ $[M+Na]^+$: 288.0607. Found: 288.0604.



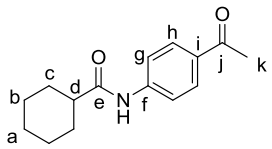
***N*-(4-Acetylphenyl)-3-(trifluoromethyl)benzamide (61).** Purified by column chromatography (Hexane/EtOAc: 85/15 to 60/40). White solid, yield 56% (173 mg, 0.56 mmols). **^{1}H-NMR (500MHz) δ:** 8.45 (broad s, 1H, NH); 8.15 (s, 1H, H_e); 8.09 (d, 1H, H_a, J_{a-b} = 7.8 Hz); 7.97 (d, 2H, H_k, J_{k-j} = 8.5 Hz); 7.83-7.77 (m, 3H, $H_{c,j}$); 7.63 (t, 1H, H_b, J_{b-a} = J_{b-c} = 7.8 Hz); 2.59 (s, 3H, H_n). **^{13}C{^{1}H}-NMR (125MHz) δ:** 197.2 (C_m); 164.5 (C_h); 142.0 (C_i); 135.3 (C_f); 133.4 (C_l); 131.4 (C_d, q, J_{C-F} = 33 Hz); 130.5 (C_a); 129.8 (C_k); 129.5 (C_b); 128.7 (C_c, q, J_{C-F} = 4 Hz); 124.1 (C_e, q, J_{C-F} = 4 Hz); 123.5 (C_g, q, J_{C-F} = 273 Hz): 119.6 (C_j); 26.4 (C_n). **M/z (HRMS-ESI+):** calcd. for $C_{16}H_{13}F_3NO_2$ $[M+H]^+$: 308.0898. Found: 308.0909.



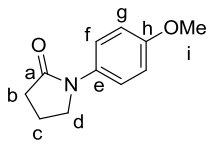
***N*-(4-Methoxyphenyl)cyclohexanecarboxamide (62).**[58] Purified by column chromatography (Hexane/EtOAc: 85/15 to 70/30). White solid, yield 71% (165 mg, 0.71 mmols). **^{1}H-NMR (500MHz) δ:** 7.43 (d, 2H, H_g, J_{g-h} = 9.0 Hz); 7.04 (broad s, 1H, NH); 6.86 (d, 2H, H_h, J_{h-g} = 9.0 Hz); 3.80 (s, 3H, H_j); 2.25-1.21 (6 multiplets, 11H, H_{a-d}). **^{13}C{^{1}H}-NMR (125MHz) δ:** 174.1 (C_e); 156.3 (C_i); 131.2 (C_f); 121.6 (C_g); 114.1 (C_h); 55.5 (C_j); 46.4 (C_d); 29.7 (C_c); 25.7 ($C_{a,b}$). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{19}NNaO_2$ $[M+Na]^+$: 256.1308. Found: 256.1305.



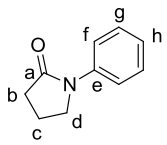
***N*-Phenylcyclohexanecarboxamide (63).**[59] Purified by column chromatography (Hexane/EtOAc: 95/5 to 70/30). White solid, yield 78% (159 mg, 0.78 mmols). **^{1}H-NMR (500MHz) δ:** 7.53 (d, 2H, H_g, J_{g-h} = 7.9 Hz); 7.32 (t, 2H, H_h, J_{h-g} = J_{h-i} = 7.9 Hz); 7.16 (broad s, 1H, NH); 7.10 (t, 1H, H_i, J_{i-h} = 7.4 Hz); 2.28-1.24 (6 multiplets, 11H, H_{a-d}). **^{13}C{^{1}H}-NMR (125MHz) δ:** 174.1 (C_e); 138.3 (C_f); 129.0 (C_h); 124.1 (C_i); 119.9 (C_g); 46.6 (C_d); 29.8 (C_c); 25.8 (C_a); 25.7 (C_b). **M/z (HRMS-ESI+):** calcd. for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1383. Found: 204.1384.



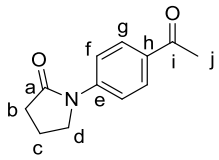
***N*-(4-Acetylphenyl)cyclohexanecarboxamide (64).** Purified by column chromatography (Hexane/EtOAc: 85/15 to 65/35). White solid, yield 72% (177 mg, 0.72 mmols). **^{1}H-NMR (500MHz) δ:** 7.94 (d, 2H, H_h, J_{h-g} = 8.8 Hz); 7.64 (d, 2H, H_g, J_{g-h} = 8.8 Hz); 7.35 (broad s, 1H, NH); 2.58 (s, 3H, H_k); 2.31-1.22 (6 multiplets, 11H, H_{a-d}). **^{13}C{^{1}H}-NMR (125MHz) δ:** 196.6 (C_j); 174.3 (C_e); 142.5 (C_f); 133.1 (C_i); 129.7 (C_h); 119.0 (C_g); 46.7 (C_d); 29.7 (C_c); 26.2 (C_k); 25.7 (C_a); 25.7 (C_b). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1489. Found: 246.1489.



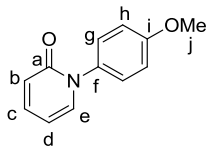
1-(4-Methoxyphenyl)pyrrolidin-2-one (65).[59] Purified by column chromatography (Hexane/EtOAc: 85/15 to 55/45). White solid, yield 97% (185 mg, 0.97 mmols). **^{1}H-NMR (500MHz) δ:** 7.50 (d, 2H, H_f, J_{f-g} = 8.9 Hz); 6.91 (d, 2H, H_g, J_{g-f} = 8.9 Hz); 3.83 (t, 2H, H_b, J_{b-c} = 7.1 Hz); 3.81 (s, 3H, H_i); 2.60 (t, 2H, H_d, J_{d-c} = 8.0 Hz); 2.16 (quint, 2H, H_c, J_{c-b} = J_{c-d} = 7.8 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 173.9 (C_a); 156.6 (C_h); 132.6 (C_e); 121.8 (C_f); 114.0 (C_g); 55.5 (C_i); 49.2 (C_b); 32.4 (C_d); 18.0 (C_c). **M/z (HRMS-ESI+):** calcd. for $C_{11}H_{13}NNaO_2$ $[M+Na]^+$: 214.0838. Found: 214.0842.



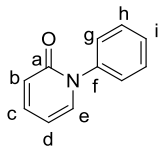
1-Phenylpyrrolidin-2-one (66).[59] Purified by column chromatography (Hexane/EtOAc: 90/10 to 60/40). White solid, yield 97% (157 mg, 0.97 mmols). **^{1}H-NMR (500MHz) δ:** 7.62 (d, 2H, H_f, J_{f-g} = 8.0 Hz); 7.38 (t, 2H, H_g, J_{g-f} = J_{g-h} = 7.8 Hz); 7.15 (t, 1H, H_h, J_{h-g} = 7.2 Hz); 3.87 (t, 2H, H_b, J_{b-c} = 7.0 Hz); 2.62 (t, 2H, H_d, J_{d-c} = 8.0 Hz); 2.17 (quint, 2H, H_c, J_{c-b} = J_{c-d} = 7.5 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 174.1 (C_a); 139.4 (C_e); 128.8 (C_g); 124.5 (C_h); 119.9 (C_f); 48.7 (C_b); 32.7 (C_d); 18.0 (C_c). **M/z (HRMS-ESI+):** calcd. for $C_{10}H_{12}NO$ $[M+H]^+$: 162.0913. Found: 162.0911.



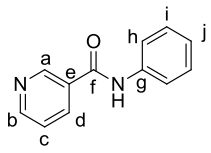
1-(4-Acetylphenyl)pyrrolidin-2-one (67).[60] Purified by column chromatography (Hexane/EtOAc: 85/15 to 50/50). White solid, yield 87% (176 mg, 0.87 mmols). **^{1}H-NMR (500MHz) δ:** 7.98 (d, 2H, H_g, J_{g-f} = 8.8 Hz); 7.76 (d, 2H, H_f, J_{f-g} = 8.8 Hz); 3.92 (t, 2H, H_b, J_{b-c} = 7.1 Hz); 2.66 (t, 2H, H_d, J_{d-c} = 8.1 Hz); 2.59 (s, 3H, H_j); 2.21 (quint, 2H, H_c, J_{c-b} = J_{c-d} = 7.6 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 196.7 (C_i); 174.5 (C_a); 143.7 (C_e); 133.1 (C_h); 129.3 (C_g); 118.8 (C_f); 48.5 (C_b); 32.8 (C_d); 26.3 (C_j); 17.9 (C_c). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_{13}NNaO_2$ $[M+Na]^+$: 226.0838. Found: 226.0842.



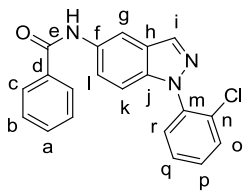
1-(4-Methoxyphenyl)pyridin-2(1*H*)-one (68).[61] Purified by column chromatography (Hexane/EtOAc: 90/10 to 40/60). Yellow solid, yield 95% (192 mg, 0.95 mmols). **^{1}H-NMR (500MHz) δ:** 7.38 (ddd, 1H, H_c, J_{c-e} = 2.1 Hz, J_{c-d} = 6.7 Hz, J_{c-b} = 9.1 Hz); 7.34-7.27 (m, 3H, $H_{e,g}$); 6.99 (d, 2H, H_h, J_{h-g} = 9.0 Hz); 6.65 (d, 1H, H_b, J_{b-c} = 9.3 Hz); 6.22 (dt, 1H, H_d, J_{d-b} = 1.4 Hz, J_{d-c} = J_{d-e} = 6.7 Hz); 3.84 (s, 1H, H_j). **^{13}C{^{1}H}-NMR (125MHz) δ:** 162.6 (C_a); 159.4 (C_i); 139.7 (C_c); 138.3 (C_e); 133.8 (C_f); 127.5 (C_g); 121.7 (C_b); 114.5 (C_h); 105.7 (C_d); 55.5 (C_j). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_{11}NNaO_2$ $[M+Na]^+$: 224.0682. Found: 224.0679.



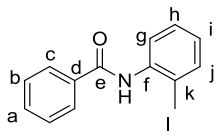
1-Phenylpyridin-2(1*H*)-one (69).[61] Purified by column chromatography (Hexane/EtOAc: 85/15 to 50/50). Off-white solid, yield 98% (167 mg, 0.98 mmols). **^{1}H-NMR (500MHz) δ:** 7.50 (t, 2H, H_h, $J_{h-g} = J_{h-i}$ = 7.6 Hz); 7.45-7.37 (m, 4H, $H_{c,g,i}$); 7.34 (dd, 1H, H_e, J_{e-c} = 2.1 Hz, J_{e-d} = 6.9 Hz); 6.68 (d, 1H, H_b, J_{b-c} = 9.2 Hz); 6.25 (t, 1H, H_d, $J_{d-c} = J_{d-e}$ = 6.5 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 162.4 (C_a); 140.9 (C_f); 139.8 (C_c); 138.0 (C_e); 129.3 (C_h); 128.5 (C_i); 126.5 (C_g); 121.9 (C_b); 105.9 (C_d). **M/z (HRMS-ESI+):** calcd. for $C_{11}H_9NNaO$ $[M+Na]^+$: 194.0576. Found: 194.0574.



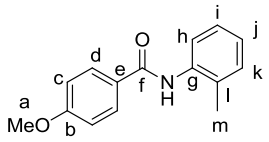
***N*-Phenylnicotinamide (70).**[62] Purified by column chromatography (Hexane/EtOAc: 85/15 to 20/80). Yellow solid, yield 61% (121 mg, 0.61 mmols). **^{1}H-NMR (500MHz) δ:** 9.08 (s, 1H, H_a); 8.72 (d, 1H, H_b, J_{b-c} = 3.9 Hz); 8.42 (broad s, 1H, NH); 8.20 (d, 1H, H_d, J_{d-c} = 7.9 Hz); 7.66 (d, 2H, H_h, J_{h-i} = 7.9 Hz); 7.43-7.33 (m, 3H, $H_{c,i}$); 7.17 (t, 1H, H_j, J_{j-i} = 7.5 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 164.0 (C_f); 152.2 (C_b); 147.9 (C_a); 137.5 (C_g); 135.5 (C_d); 130.9 (C_e); 129.1 (C_i); 125.0 (C_j); 123.7 (C_c); 120.6 (C_h). **M/z (HRMS-ESI+):** calcd. for $C_{12}H_{10}N_2NaO$ $[M+Na]^+$: 221.0685. Found: 221.0683.



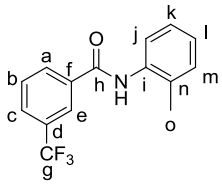
***N*-(1-(2-Chlorophenyl)-1*H*-indazol-5-yl)benzamide (71).** Purified by column chromatography (Hexane/EtOAc: 90/10 to 30/70). Yellow solid, yield 31% (109 mg, 0.31 mmols). **^{1}H-NMR (500MHz) δ:** 8.22 (d, 1H, H_g, J_{g-l} = 1.1 Hz); 8.19 (s, 1H, H_i); 8.14 (broad s, 1H, NH); 7.91 (d, 2H, H_c, J_{c-b} = 7.0 Hz); 7.62-7.58 (m, 1H, H_r); 7.58-7.53 (m, 1H, H_a); 7.53-7.50 (m, 2H, $H_{l,o}$); 7.50-7.47 (m, 2H, H_b); 7.46-7.41 (m, 2H, $H_{p,q}$); 7.22 (d, 1H, H_k, J_{k-l} = 8.9 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.9 (C_e); 138.2 (C_j); 137.2 (C_m); 135.7 (C_i); 135.1 (C_d); 132.1 (C_f); 131.8 (C_a); 131.7 (C_n); 130.8 (C_r); 129.9 (C_q); 129.5 (C_o); 128.8 (C_b); 127.7 (C_p); 127.1 (C_c); 124.7 (C_h); 122.0 (C_l); 112.5 (C_g); 110.9 (C_k). **M/z (HRMS-ESI+):** calcd. for $C_{20}H_{14}ClN_3NaO$ $[M+Na]^+$: 370.0718. Found: 370.0720.



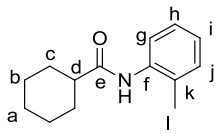
***N*-(*o*-Tolyl)benzamide (72).**[57] Purified by column chromatography (Hexane/EtOAc: 90/10 to 80/20). White solid, yield 57% (121 mg, 0.57 mmols). **^{1}H-NMR (500MHz) δ:** 7.97 (d, 1H, H_g, J_{g-h} = 7.9 Hz); 7.90 (d, 2H, H_c, H_{c-b} = 7.3 Hz); 7.69 (broad s, 1H, NH); 7.58 (t, 1H, H_a, J_{a-b} = 7.5 Hz); 7.54-7.49 (m, 2H, H_b); 7.30-7.23 (m, 2H, $H_{j,h}$); 7.14 (dt, 1H, H_i, J_{i-g} = 1.1 Hz, $J_{i-g} = J_{i-j}$ = 7.5 Hz); 2.36 (s, 3H, H_l). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.6 (C_e); 136.0 (C_f); 135.3 (C_d); 131.8 (C_a); 130.6 (C_j); 129.3 (C_k); 128.9 (C_b); 127.1 (C_c); 127.0 (C_h); 125.4 (C_i); 123.3 (C_g); 17.7 (C_l). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{13}NNaO$ $[M+Na]^+$: 234.0889. Found: 234.0893.



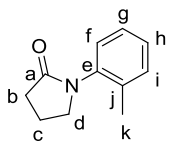
4-Methoxy-*N*-(*o*-tolyl)benzamide (73).[62] Purified by column chromatography (Hexane/EtOAc: 95/5 to 70/30). White solid, yield 55% (133 mg, 0.55 mmols). **^{1}H-NMR (500MHz) δ:** 7.96 (d, 1H, H_h, J_{h-i} = 8.0 Hz); 7.87 (d, 2H, H_d, J_{d-c} = 8.5 Hz); 7.60 (broad s, 1H, NH); 7.29-7.22 (m, 2H, $H_{i,k}$); 7.12 (t, 1H, H_j, J_{j-i} = J_{j-k} = 7.3 Hz); 7.00 (d, 2H, H_c, J_{c-d} = 8.7 Hz); 3.89 (s, 3H, H_a); 2.35 (s, 3H, H_m). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.1 (C_f); 162.5 (C_b); 136.0 (C_g); 130.5 (C_k); 129.0 (C_l); 128.9 (C_d); 127.3 (C_e); 126.9 (C_i); 125.1 (C_j); 123.0 (C_h); 114.0 (C_c); 55.5 (C_a); 17.8 (C_m). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{15}NNaO_2$ $[M+Na]^+$: 264.0995. Found: 264.0997.



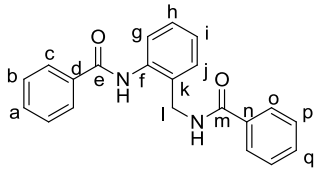
***N*-(*o*-Tolyl)-3-(trifluoromethyl)benzamide (74).** Purified by column chromatography (Hexane/EtOAc: 95/5 to 70/30). Off-white solid, yield 36% (101 mg, 0.36 mmols) **^{1}H-NMR (500MHz) δ:** 8.16 (s, 1H, H_e); 8.07 (d, 1H, H_a, J_{a-b} = 7.6 Hz); 7.87-7.81 (m, 2H, $H_{c,j}$); 7.70 (broad s, 1H, NH); 7.65 (t, 1H, H_b, J_{b-a} = J_{b-c} = 7.8 Hz); 7.30-7.22 (m, 2H, $H_{k,m}$); 7.16 (t, 1H, H_l, J_{l-k} = J_{l-m} = 7.5 Hz); 2.35 (s, 3H, H_o). **^{13}C{^{1}H}-NMR (125MHz) δ:** 164.3 (C_h); 135.8 (C_f); 135.2 (C_i); 131.4 (C_d, q, J_{C-F} = 33 Hz); 130.7 (C_m); 130.2 (C_a); 129.9 (C_n); 129.5 (C_b); 128.4 (C_c, q, J_{C-F} = 4 Hz); 126.9 (C_k); 125.9 (C_l); 124.2 (C_e, q, J_{C-F} = 4 Hz); 123.6 (C_j); 123.6 (C_g, q, J_{C-F} = 273 Hz); 17.8 (C_o). **M/z (HRMS-ESI+):** calcd. for $C_{15}H_{12}F_3NNaO$ $[M+Na]^+$: 302.0763. Found: 302.0760.



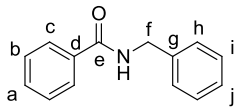
***N*-(*o*-Tolyl)cyclohexanecarboxamide (75).**[63] Purified by column chromatography (Hexane/EtOAc: 95/5 to 70/30). White solid, yield 63% (138 mg, 0.63 mmols). **^{1}H-NMR (500MHz) δ:** 7.90-7.84 (m, 1H, H_g); 7.24-7.17 (m, 2H, $H_{h,j}$); 7.09-7.05 (m, 1H, H_i); 6.98 (broad s, 1H, NH); 2.33-1.22 (6 multiplets, 14H, $H_{a-d,l}$). **^{13}C{^{1}H}-NMR (125MHz) δ:** 174.1 (C_e); 135.8 (C_f); 130.4 (C_j); 128.7 (C_k); 126.8 (C_h); 124.9 (C_i); 123.0 (C_g); 46.4 (C_d); 29.9 (C_c); 25.7 ($C_{a,b}$); 17.7 (C_l). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{19}NNaO$ $[M+Na]^+$: 240.1359. Found: 240.1357.



1-(*o*-Tolyl)pyrrolidin-2-one (76).[60] Purified by column chromatography (Hexane/EtOAc: 90/10 to 50/50). Yellow oil, yield 81% (141 mg, 0.81 mmols). **^{1}H-NMR (500MHz) δ:** 7.31-7.20 (m, 3H, $H_{f,h,i}$); 7.19-7.11 (m, 1H, H_g); 3.73 (t, 2H, H_b, J_{b-c} = 7.0 Hz); 2.59 (t, 2H, H_d, J_{d-c} = 8.0 Hz); 2.29-2.19 (m, 5H, $H_{c,k}$). **^{13}C{^{1}H}- NMR (125MHz) δ:** 174.3 (C_a); 137.4 (C_e); 135.5 (C_j); 131.1 (C_i); 127.8 (C_h); 126.8 (C_f); 126.6 (C_g); 50.7 (C_b); 31.2 (C_d); 19.1 (C_c); 17.9 (C_k). **M/z (HRMS-ESI+):** calcd. for $C_{11}H_{13}NNaO$ $[M+Na]^+$: 198.0889. Found: 198.0885.



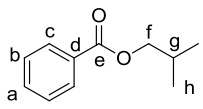
***N*-(2-Benzamidobenzyl)benzamide (77).** Purified by column chromatography (Hexane/EtOAc: 85/15 to 65/35). Off-white solid, yield 30% (59 mg, 0.18 mmols). **^{1}H-NMR (500MHz) δ:** 10.44 (broad s, 1H, NH); 8.22 (dd, 2H, H_c, J_{c-a} = 1.5 Hz, J_{c-b} = 8.1 Hz); 8.01 (d, 1H, H_g, J_{g-h} = 7.3 Hz); 7.76 (dd, 2H, H_o, J_{o-q} = 1.3 Hz, J_{o-p} = 8.3 Hz); 7.60-1.49 (m, 4H, $H_{a,b,q}$); 7.43 (t, 2H, H_p, J_{p-o} = J_{p-q} = 7.6 Hz); 7.38 (dt, 1H, H_h, J_{h-j} = 1.5 Hz, J_{h-g} = J_{h-i} = 8.1 Hz); 7.33 (dd, 1H, H_j, J_{j-h} = 1.4 Hz, J_{j-i} = 7.6 Hz); 7.17 (dt, 1H, H_i, J_{i-g} = 1.3 Hz, J_{i-h} = J_{i-j} = 7.5 Hz); 6.93 (broad s, 1H, benzyl. NH); 4.59 (d, 2H, H_l, J_{l-NH} = 6.4 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 168.3 (C_m); 166.6 (C_e); 136.8 (C_f); 134.9 (C_d); 133.7 (C_n); 131.9 (C_a); 131.7 (C_q); 130.6 (C_j); 130.1 (C_k); 128.9 (C_h); 128.7 (C_p); 128.5 (C_b); 127.9 (C_c); 127.1 (C_o); 125.5 (C_g); 125.3 (C_i); 41.1 (C_l). **M/z (HRMS-ESI+):** calcd. for $C_{21}H_{18}N_2NaO_2$ $[M+Na]^+$: 353.1260. Found: 353.1263.



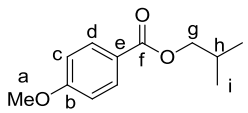
***N*-Benzylbenzamide (78).**[64] Purified by column chromatography (Hexane/EtOAc: 90/10 to 70/30). Yellow solid, different yields. **^{1}H-NMR (500MHz) δ: 7**.82-7.78 (m, 2H, H_c); 7.51 (tt, 1H, H_a, J_{a-c} = 1.2 Hz, J_{a-b} = 7.3 Hz); 7.46-7.41 (m, 2H, H_b); 7.38-7.34 (m, 4H, $H_{h,i}$); 7.34-7.28 (m, 1H, H_j); 6.46 (broad s, 1H, NH); 4.66 (d, 2H, H_f, $J_{f-f(gem)}$ = 5.6 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 167.3 (C_e); 138.4 (C_g); 134.7 (C_d); 131.5 (C_a); 128.8 (C_h); 128.6 (C_b); 127.9 (C_i); 127.6 (C_j); 127.0 (C_c); 44.3 (C_f). **M/z (HRMS-ESI+):** calcd. for $C_{14}H_{13}NNaO$ $[M+Na]^+$: 234.0889. Found: 234.0889.

6.2.10.1 – Formation of isobutanol esters as side products

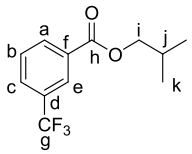
During the synthesis of amides in i-BuOAc, the corresponding isobutyl ester was formed as a side product. Below are reported the characterisation data for the isobutyl esters recovered. The different yields obtained for these compounds are reported in Chapter 2, and will not be reported here.



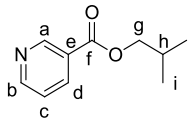
Isobutyl benzoate (79).[65] Yellow oil. **^{1}H-NMR (500MHz) δ:** 8.07 (d, 2H, H_c, J_{c-b} = 8.3 Hz); 7.57 (t, 1H, H_a, J_{a-b} = 7.5 Hz); 7.45 (t, 2H, H_b,, J_{b-a} = J_{b-c} = 7.7 Hz); 4.12 (d, 2H, H_f, J_{f-g} = 6.6 Hz); 2.10 (sept, 1H, H_g, J_{g-h} = J_{g-h} = 6.7 Hz); 1.04 (d, 6H, H_h, J_{h-g} = 6.8 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 166.6 (C_e); 132.7 (C_a); 130.8 (C_d); 129.6 (C_b); 128.3 (C_c); 71.0 (C_f); 28.0 (C_g); 19.2 (C_h).



Isobutyl 4-methoxybenzoate (80).[66] Yellow oil. **^{1}H-NMR (500MHz) δ:** 8.02 (d, 2H, H_d, J_{d-c} = 8.7 Hz); 6.93 (d, 2H, H_c, J_{c-d} = 8.9 Hz); 4.08 (d, 2H, H_g, J_{g-h} = 6.4 Hz); 3.87 (s, 3H, H_a); 2.08 (sept, 1H, H_h, J_{h-g} = J_{h-i} = 6.7 Hz); 1.03 (d, 6H, H_i, J_{i-h} = 6.6 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 166.4 (C_f); 163.3 (C_b); 131.5 (C_d); 123.0 (C_e); 113.5 (C_c); 70.7 (C_g); 55.4 (C_a); 27.9 (C_h); 19.2 (C_i).



Isobutyl 3-(trifluoromethyl)benzoate (81). Yellow oil. **^{1}H-NMR (500MHz) δ:** 8.31 (s, 1H, H_e); 8.25 (d, 1H, H_a, J_{a-b} = 7.8 Hz); 7.82 (d, 1H, H_c, J_{c-b} = 7.8 Hz); 7.60 (t, 1H, H_b, J_{b-a} = J_{b-c} = 7.8 Hz); 4.16 (d, 2H, H_i, J_{i-j} = 6.6 Hz); 2.12 (sept, 1H, H_j, J_{j-i} = J_{j-k} = 6.7 Hz); 1.04 (d, 6H, H_k, J_{k-j} = 6.6 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.3 (C_h); 132.7 (C_f); 131.4 (C_a); 131.0 (C_d, q, J_{C-F} = 33 Hz); 129.3 (C_c, q, J_{C-F} = 4 Hz); 129.0 (C_b); 126.4 (C_e, q, J_{C-F} = 4 Hz); 124.7 (C_g, q, J_{C-F} = 272 Hz); 71.5 (C_i); 27.9 (C_j); 19.1 (C_k).



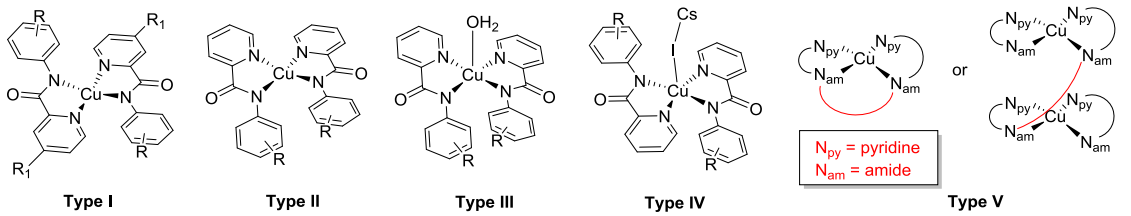
Isobutyl nicotinate (82). Orange oil. **^{1}H-NMR (500MHz) δ:** 9.25 (s, 1H, H_a); 8.78 (d, 1H, H_b, J_{b-c} = 4.1 Hz); 8.32 (dt, 1H, $H_{d,}$, J_{d-a} = J_{d-b} = 1.9 Hz, J_{d-c} = 8.0 Hz); 7.41 (dd, 1H, H_c, J_{c-b} = 4.9 Hz, J_{c-d} = 7.9 Hz); 4.15 (d, 2H, H_g, J_{g-h} = 6.6 Hz); 2.11 (sept, 1H, H_h, J_{h-g} = J_{h-i} = 6.7 Hz); 1.04 (d, 6H, H_i, J_{i-h} = 6.8 Hz). **^{13}C{^{1}H}-NMR (125MHz) δ:** 165.2 (C_f); 153.2 (C_b); 150.8 (C_a); 137.1 (C_d); 126.5 (C_e); 123.3 (C_c); 71.4 (C_g); 27.9 (C_h); 19.1 (C_i).

6.3 – Experimental for Chapter 3

6.3.1 – Synthesis of Cu complexes

General procedure: Unless otherwise specified, the synthesis of complexes was performed on 200 mg of picolinamide ligands (2 eq.), at room temperature under nitrogen, using standard Schlenk techniques. A solution of of CuI (1 eq.) in 15-20 mL of dry acetonitrile was added to a solution of ligand (2 eq.) and Cs_2CO_3 (1 eq.) in the same solvent. The solution was stirred at room temperature for 15-20 hours. At the end of the reaction the solvent was evaporated under reduced pressure, and the residual solid dissolved in DCM or MeOH. The solution was filtered, and recrystallised through vapour diffusion of Et_2O under air. Alternative recrystallisation methods are reported if used. All of the control reactions described in Chapter 3 were performed in the same way. All yields reported below refer to recrystallised products. All complexes are stable in air. The general structure of the complexes is reported below.

[N.B. HRMS data could not be obtained for all the complexes, due to dissociation of ligand in the electrospray process. Where HRMS data could be obtained, peaks corresponding to H^+ or Na^+ adducts of the expected compound are reported as $[Cu(\mathbf{L})_2+H]^+$ or $[Cu(\mathbf{L})_2+Na]^+$. In other cases, adducts of the type $[Cu(\mathbf{LH})_2]^+$ were observed (**LH** = protonated ligand). These peaks would correspond to a Cu(I) species. Redox processes in electrospray conditions are known for copper complexes.[67, 68]]



C11 (R = R_1 = H), Type I. Obtained from reaction with **L11**. Recrystallised from DCM/Et_2O. Dark green crystals, 172 mg, 75%. **Anal:** calcd. for $C_{24}H_{18}CuN_4O_2$: C, 62.94; H, 3.96; N, 12.23. Found: C, 62.90; H, 3.90; N, 12.10. **M/z (HRMS-ESI+):** calcd. for $C_{24}H_{20}CuN_4O_2$ $[Cu(\mathbf{LH})_2]^+$: 459.0882. Found: 459.0884.

C18 (R = 2,4,6-Me), Type IV. Obtained from reaction with **L18**. Recrystallised from MeOH/Et_2O. Light green powder, 210 mg, 61%. **Anal:** calcd. for $C_{30}H_{30}CuN_4O_2CsI$: C, 44.93; H, 3.77; N, 6.99; I, 15.82. Found: C, 44.70; H, 3.70; N, 6.90; I, 16.20. **M/z (HRMS-ESI+) (direct injection):** calcd for $C_{30}H_{31}CuN_4O_2$ $[Cu(\mathbf{L})_2+H]^+$: 542.1738. Found: 542.1719. **^{133}Cs-NMR (500MHz) δ (MeCN-d_3):** 39.8.

C20 (R = 2,4-OMe, R_1 = H), Type I. Obtained from reaction with **L20** (500 mg). Recrystallised from DCM/Et_2O. Dark green powder, 190 mg, 36%. **Anal:** calcd. for $C_{28}H_{26}CuN_4O_6$: C, 58.18; H, 4.53; N, 9.69. Found: C, 58.50; H, 4.50; N, 9.60.

C22 (R = 2-Cl-6-Me, R_1 = H), Type II. Obtained from reaction with **L22**. Recrystallised from DCM/Et_2O. Dark crystals, 152 mg, 67%. **Anal:** calcd. for $C_{26}H_{20}Cl_2CuN_4O_2$: C, 56.28; H, 3.63; N, 10.10. Found: C, 57.00; H, 4.00; N, 9.60. **M/z (HRMS-ESI+):** calcd. for $C_{26}H_{21}Cl_2CuN_4O_2$ $[Cu(\mathbf{L})_2+H]^+$: 554.0332. Found: 554.0334.

C23 (R = 3-NO_2, R_1 = H), Type I. Obtained from reaction with **L23** (500 mg). Recrystallised from a MeCN solution at 4°C. Considerable amounts of insoluble solid led to difficulty in the purification process. Dark green powder, 272 mg, 48%. **Anal:** calcd. for $C_{24}H_{16}CuN_6O_6{\cdot}H_2O$: C, 50.93; H, 3.21; N, 14.85. Found: C, 50.90; H, 2.90; N, 15.15. **M/z (HRMS-ESI+):** calcd. for $C_{24}H_{18}CuN_6O_6$ $[Cu(\mathbf{LH})_2]^+$: 549.0584. Found: 549.0584.

C25 (R = 4-Ac, R_1 = H), Type I. Obtained from reaction with **L25**. Recrystallised from DCM/Et_2O. Dark crystals, 185 mg, 81%. **Anal:** calcd. for $C_{28}H_{22}CuN_4O_4$: C, 62.04; H, 4.09; N, 10.34. Found: C, 61.60; H, 4.00; N, 10.15.

C26 (R = 3,5-CF_3, R_1 = H), Type III. Obtained from reaction with **L26**. Recrystallised from DCM/Et_2O. Bright blue-green crystals, 177 mg, 79%. **Anal:** calcd. for $C_{28}H_{14}F_{12}CuN_4O_2{\cdot}H_2O$:

C, 44.96; H, 2.16; N, 7.49. Found: C, 45.50; H, 1.90; N, 7.50. **M/z (HRMS-ESI+):** calcd. for $C_{28}H_{15}F_{12}CuN_4O_2$ $[Cu(\mathbf{L})_2+H]^+$: 730.0294. Found: 730.0297.

C27 (R = 2-F, R_1 = H), Type I. Obtained from reaction with **L27** (300 mg). Recrystallised from DCM/Et_2O. Dark green crystals, 287 mg, 83%. **Anal:** calcd. for $C_{24}H_{16}F_2CuN_4O_2$: C, 58.36; H, 3.27; N, 11.34. Found: C, 58.10; H, 3.25; N, 11.20. **M/z (HRMS-ESI+):** calcd. for $C_{24}H_{17}F_2CuN_4O_2$ $[Cu(\mathbf{L})_2+H]^+$: 494.0610. Found: 494.0589.

C28, Type V (mononuclear). Obtained from **L28** (R = 2-Cl) or **L29** (R = 2-Br). Recrystallised from DCM/Et_2O. Dark green crystals, 105 mg, 54%. **Anal:** calcd. for $C_{24}H_{16}CuN_4O_2 \cdot CH_2Cl_2$: C, 55.51; H, 3.35; N, 10.36; Cl, 13.11. Found: C, 55.70; H, 3.10; N, 10.70; Cl, 12.50. **M/z (HRMS-ESI+):** calcd. for $C_{24}H_{17}CuN_4O_2$ $[M+H]^+$: 456.0642. Found: 456.0643.

$C28_{Na}$ (R = 2-Cl, R_1 = H), Type I. Obtained from **L28** using Na_2CO_3 as base at 70°C. Recrystallised from MeOH/Et_2O. Dark green crystals, 112 mg, 43% (molecular formula as from elemental analysis). **Anal:** calcd. for $C_{24}H_{16}Cl_2CuN_4O_2 \cdot 0.2\ NaI_3$: C, 47.44; H, 2.65; N, 9.22. Found: C, 47.50; H, 2.70; N, 9.20.

C30, Type V (trinuclear). Obtained from reaction with **L30** (R = 2-I). Recrystallised from DCM/Et_2O. Dark green crystals, 190 mg, 98%. **Anal:** calcd. for $C_{72}H_{48}I_2Cu_3N_{12}O_6 \cdot 9\ CH_2Cl_2$: C, 40.77; H, 2.79; N, 7.04. Found: C, 40.50; H, 2.30; N, 7.30.

C31 (R = 3-F, R_1 = H), Type I. Obtained from reaction with **L31** (500 mg). Recrystallised from MeOH/Et_2O. Dark green powder, 252 mg, 44%. **Anal:** calcd. for $C_{24}H_{16}F_2CuN_4O_2 \cdot H_2O$: C, 56.30; H, 3.54; N, 10.94. Found: C, 56.05; H, 3.55; N, 10.80.

C32 (R = 3-Cl, R_1 = H), Type II. Obtained from reaction with **L32**. Recrystallised from DCM/Et_2O. Dark crystals, 136 mg, 60%. **Anal:** calcd. for $C_{24}H_{16}Cl_2CuN_4O_2$: C, 54.71; H, 3.06; N, 10.63. Found: C, 54.40; H, 3.00; N, 10.60. **M/z (HR-ESI+):** calcd. for $C_{24}H_{18}Cl_2CuN_4O_2$ $[Cu(\mathbf{LH})_2]^+$: 527.0103. Found: 527.0103.

C34 (R = 3-I, R_1 = H), Type I. Obtained from reaction with **L34**. Recrystallised from DCM/Et_2O. Dark green crystals, 75 mg, 33%; **Anal:** calcd. for $C_{24}H_{16}I_2CuN_4O_2$: C, 40.61; H, 2.27; N, 7.89. Found: C, 40.65; H, 2.20; N, 7.70.

C35 (R = 4-F, R_1 = H), Type I. Obtained from reaction with **L35**. Recrystallised from DCM/Et_2O. Green powder, 125 mg, 55%. **Anal:** calcd. for $C_{24}H_{16}F_2CuN_4O_2 \cdot 1.5\ H_2O$: C, 55.33; H, 3.68; N, 10.75. Found: C, 55.80; H, 3.20; N, 10.30.

C36 (R = 4-Cl, R_1 = H), Type I. Obtained from reaction with **L36**. Recrystallised from MeOH/Et_2O. Light green powder, 137 mg, 60%. **Anal:** calcd. for $C_{24}H_{16}Cl_2CuN_4O_2$: C, 54.71; H, 3.06; N, 10.63. Found: C, 54.95; H, 3.05; N, 10.15. **M/z (HRMS-ESI+):** calcd. for $C_{24}H_{17}Cl_2CuN_4O_2$ $[Cu(\mathbf{L})_2+H]^+$: 526.0019. Found: 526.0023.

C38 (R = 4-I, R_1 = H), Type I. Obtained from reaction with **L38**. Recrystallised from DCM/Et_2O. Light green powder, 157 mg, 71%. **Anal:** calcd. for $C_{24}H_{16}I_2CuN_4O_2$: C, 40.61; H, 2.27; N, 7.89. Found: C, 40.40; H, 2.20; N, 7.80.

C39 (R = 2,4-F, R_1 = H), Type I. Obtained from reaction with **L39**. Recrystallised from DCM/Et_2O. Green crystals, 182 mg, 80%. **Anal:** calcd. for $C_{24}H_{14}F_4CuN_4O_2$: C, 54.40; H, 2.66; N, 10.57. Found: C, 54.40; H, 2.60; N, 10.50.

C40, Type V (dinuclear). Obtained from reaction with ligand **L40** (R = 2,4-Cl). Recrystallised from DCM/Et_2O. Dark green crystals, 151 mg, 67%. **Anal:** calcd. for $C_{48}H_{28}Cl_6Cu_2N_8O_4 \cdot 0.5\ CH_2Cl_2$: C, 50.09; H, 2.51; N, 9.63; Cl, 21.34. Found: C, 50.20; H, 2.40; N, 9.60; Cl, 21.30. **M/z (HRMS-ESI+):** calcd. for $C_{48}H_{28}Cl_6Cu_2N_8O_4$ $[M+H]^+$: 1116.9029. Found: 1116.9037.

$C40_{Na}$ (R = 2,4-Cl, R_1 = H), Type II. Obtained from **L40** using Na_2CO_3 as base at 70°C. Recrystallised from MeOH/Et_2O. Dark green crystals, 165 mg, 74%. No accurate elemental analysis data could be obtained for this complex.

C41, Type V (dinuclear). Obtained from reaction with **L41** (R = 2,4-Br). Recrystallised from DCM/Et_2O. Dark green crystals, 130 mg, 49%. **Anal:** calcd. for $C_{48}H_{28}Br_6Cu_2N_8O_4 \cdot CH_2Cl_2 \cdot 2\ H_2O$: C, 39.02; H, 2.27; N, 7.43. Found: C, 39.10; H, 1.95; N, 7.40. **M/z (HRMS-ESI+):** calcd. for $C_{48}H_{29}Br_6Cu_2N_8O_4$: 1388.5929. Found: 1388.5936.

$C41_{Na}$ (R = 2,4-Br, R_1 = H), Type II. Obtained from **L41** using Na_2CO_3 as base at room temperature. Recrystallised from DCM/Et_2O. Dark green crystals, 40 mg, 39%.

C42 (R = 2,5-F, R_1 = H), Type II. Obtained from reaction with **L42**. Recrystallised from an acetonitrile solution at -25°C, 199 mg, 87%. **Anal:** calcd. for $C_{24}H_{14}F_4CuN_4O_2$: C, 54.40; H, 2.66; N, 10.57. Found: C, 53.60; H, 2.60; N, 10.40.

C43 (R = 2,5-Cl, R_1 = H), Type I. Obtained from reaction with **L43**. Recrystallised from DCM/Et_2O. Dark green crystals, 121 mg, 51%. **Anal:** calcd. for $C_{24}H_{14}Cl_4CuN_4O_2$: C, 48.39; H,

2.37; N, 9.40. Found: C, 48.50; H, 2.30; N, 9.30. **M/z (HRMS-ESI+):** calcd. for $C_{24}H_{15}Cl_4CuN_4O_2$ $[Cu(\mathbf{L})_2+H]^+$: 593.9240. Found: 593.9244.

C44 (R = 2,5-Br, R_1 = H), Type II. Obtained from reaction with **L44**. Recrystallised from DCM/Et_2O. Dark green powder, 175 mg, 81%. No accurate elemental analysis data could be obtained for this complex.

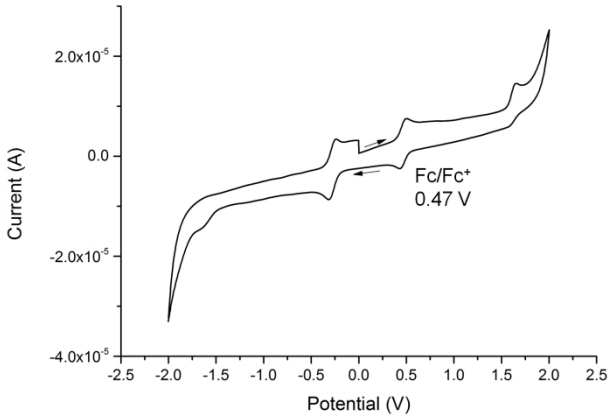
C51 (R = H, R_1 = OMe), Type I. Obtained from reaction with **L51**. Recrystallised from DCM/Et_2O. Dark green crystals, 153 mg, 67%. **Anal:** calcd. for $C_{26}H_{22}CuN_4O_4$: C, 60.28; H, 4.28; N, 10.82. Found: C, 60.00; H, 4.50; N, 10.70.

C52 (R = H, R_1 = Cl), Type I. Obtained from reaction with **L52**. Recrysatallised from DCM/Et_2O. Dark green crystals, 60 mg, 26%. **Anal:** calcd. for $C_{24}H_{16}Cl_2CuN_4O_2$: C, 54.71; H, 3.06; N, 10.63. Found: C, 55.30; H, 3.10; N, 10.90.

6.4 – Experimental for Chapter 4

6.4.1 – Electrochemical measurements

Electrochemical measurements (cyclic voltammetry experiments) were carried out using an Autolab PGSTAT20 voltammetric analyser, under an argon atmosphere in acetonitrile containing 0.1 M $[NBu_4][BF_4]$ as supporting electrolyte, prepared according to the procedure reported below. Voltammetry experiments used a Pt disk working electrode, a Pt rod counter-electrode, and an Ag/AgCl reference electrode. All potentials quoted in the thesis are referenced to the Ag/AgCl reference electrode. Ferrocene (Fc) was added to each experiment as a further reference; in these conditions the Fc/Fc^+ potential is of 0.47 V.[69] As an example, the voltammogram for **C26** with added ferrocene is reported below.



Every electrochemical measurement on complexes was preceeded by analysis of the electrolyte solution alone, used as blank to ascertain that no undesired redox active species were present in the system. The concentration of the complexes in the electrolyte/acetotrile solution

was in the order of 10^{-4} M (approx. $5x10^{-3}$ mmols in 7 mL of electrolyte solution); exact concentration for each complex is not available, due to different solubilities in the electrolyte solution. A single cycle was recorded for each complex at different scar rates, bubbling argon through the solution for a few seconds between measurements, leaving the surface to flatten before undertaking the next measurement.

Synthesis of $[NBu_4][BF_4]$ for cyclic voltammetry experiments: a solution of $[NBu_4]Br$ (28.0 g, 87 mmols) in DCM (100 mL), was added to a solution of $Na[BF_4]$ (9.9 g, 87 mmols) in distilled water (50 mL); the final mixture was stirred at room temperature for 24 hours. The organic phase was then separated, washed with water and evaporated, giving a white solid, which washed with water and Et_2O (crude yield 98%, 28.1 g, 85 mmols). The product was recrystallised from a hot water/ethanol solution (50/50) at least twice to give pure $[NBu_4][BF_4]$. **^{1}H-NMR (300MHz) δ:** 3.25-3.17 (m, 8H); 1.67-1.57 (m, 8H); 1.43 (sex, 8H, J = 7.3 Hz); 1.00 (t, 12H, J = 7.3 Hz). **^{13}C{^{1}H}-NMR (75MHz) δ:** 58.6; 23.8; 19.6; 13.5. **Anal**: calcd. for $C_{16}H_{36}BF_4N$: C, 58.36; H, 11.02; N, 4.25. Found: C, 58.40; H, 11.20; N, 4.25.

6.4.2 – Reaction profiling

Reaction profiles of the catalytic synthesis of aryl ethers were performed using a procedure similar to that described in Section 6.2.8. The reactions were performed on Radleys Standard carousel tubes, under air, charging an oven dried tube with all the chemicals (same amounts reported in Section 6.2.8), plus an internal standard (1,3,5-trimethoxybenzene, 17 mg, 0.1 mmols). 4 mL of acetonitrile were added in these reactions, instead of 2, to make the solid more dispersed and allow a more homogeneous sampling. After addition of the solvent in the tube, this was quickly placed in the heating/stirring block of the carousel; this was considered as the starting time of the reaction. Samples were taken with a syringe after each hour of reaction (1h to 8h), then at 12h and 24h, and analysed through GC after being diluted with DCM and filtered through celite. Before every sample was taken, the stirring was stopped for 5-10 seconds to allow deposition of the solids to the bottom of the tube; the stirring was resumed after the sample was taken. The profiles reported in Figures 4.4 and 4.5 in Section 4.2 were obtained using the same procedure through automated reaction sampling, using an AmigoChem Workstation and performing the reactions in an Integrity 10 Parallel Reaction Block.

6.4.3 – Dimerisation of 2,6-di-*tert*-butylphenol

General procedure: All catalytic reactions were performed under air in 25 mL glass tubes in a Radley standard carousel. An oven dried tube was charged with 2,6-di-*tert*-butylphenol (413 mg, 2.0 mmol), Cs_2CO_3 (652 mg, 2.0 mmol), CuI (19 mg, 0.1 mmol) and ligand (0.1 mmol). Acetonitrile (4 mL) was then added, the tube was placed in the carousel (preheated at 90°C) and the reaction was stirred for 24 h (1000 rpm). At the end of the reaction the tube was cooled to room temperature, then the crude was diluted with ≈ 2mL DCM, filtered

through celite and washed thoroughly with DCM (≈ 50 mL). 1 mL of a 0.5 M solution of 1,3,5-trimethoxybenzene (internal standard) in DCM was added, and the crude solution was analysed through ^{1}H-NMR. Reactions using Cu(II) complexes as catalysts were performed using half the amounts of all chemicals and solvents (1.0 mmol of phenol and base, 0.05 mmol of Cu complex and 2 mL of solvent.

6.5 – References

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Appendix:

Crystallographic data for Cu complexes

	C11 (type I)	**C18 (type IV)**	**C20 (type I)**	**C22·0.5 CH_2Cl_2 (type II)**
Empirical formula	$C_{24}H_{18}CuN_4O_2$	$C_{30}H_{30}CsCuIN_4O_2$	$C_{28}H_{26}CuN_4O_6$	$C_{26.5}H_{21}Cl_3CuN_4O_2$
Formula weight	457.96	801.93	578.07	597.36
Temperature/K	120.01(18)	150.0	120.03(10)	120.00(10)
Crystal system	monoclinic	monoclinic	triclinic	orthorhombic
Space group	$P2_1/n$	$P2_1/n$	P-1	Fdd2
a/Å	10.18128(13)	11.5083(5)	9.9233(8)	26.9124(9)
b/Å	18.9482(2)	18.2069(8)	10.8603(8)	20.0716(6)
c/Å	10.69510(15)	15.0828(7)	13.1243(7)	18.5539(5)
α/°	90	90	93.040(5)	90
β/°	104.8278(13)	105.800(2)	95.320(5)	90
γ/°	90	90	115.219(8)	90
Z	4	4	2	16
m/mm^{-1}	1.793	2.946	0.914	4.452
F(000)	940.0	1564.0	598.0	4864.0
Reflections collected	7929	7480	10603	7218
Independent reflections	3489[R(int) = 0.0338]	7480[R(int) = 0.0000]	5168[R(int) = 0.0618]	4042[R(int) = 0.0429]
Goodness-of-fit on F^2	1.077	1.017	1.058	1.121
Final R indexes [I>=2σ (I)]	R_1 = 0.0368, wR_2 = 0.1020	R_1 = 0.0383, wR_2 = 0.0764	R_1 = 0.0594, wR_2 = 0.1415	R_1 = 0.0475, wR_2 = 0.1245
Final R indexes [all data]	R_1 = 0.0380, wR_2 = 0.1031	R_1 = 0.0638, wR_2 = 0.0877	R_1 = 0.0809, wR_2 = 0.1608	R_1 = 0.0518, wR_2 = 0.1425
Largest diff. peak/hole / e $Å^{-3}$	0.34/-0.56	1.28/-0.85	0.60/-1.20	0.43/-0.31

	C23 (type I)	**C24 (type I, recovered)**	**C25 (type I)**	**C26·0.33 Me_2CO (type III, recovered)**
Empirical formula	$C_{24}H_{16}CuN_6O_6$	$C_{24}H_{16}CuN_6O_6$	$C_{28}H_{22}CuN_4O_4$	$C_{29}H_{18}CuF_{12}N_4O_{3.33}$
Formula weight	547.97	547.97	542.03	767.35
Temperature/K	100.01(10)	100.01(10)	120.2(5)	100.01(10)
Crystal system	monoclinic	triclinic	monoclinic	trigonal
Space group	I2/a	P-1	$P2_1/c$	R-3
a/Å	12.4783(19)	7.9716(14)	13.9516(8)	32.6785(8)
b/Å	7.1378(7)	11.0249(19)	20.0834(12)	32.6785(8)
c/Å	25.0688(18)	14.1235(11)	8.7777(5)	15.1563(4)
α/°	90.00	69.976(12)	90	90.00
β/°	102.313(10)	73.802(12)	102.565(6)	90.00
γ/°	90.00	88.829(14)	90	120.00
Z	4	2	4	18
m/mm^{-1}	1.925	1.036	1.651	0.813
F(000)	1116.0	558.0	1116.0	6906.0
Reflections collected	10282	18337	8958	49200
Independent reflections	1955[R(int) = 0.0695]	4556 [R(int) = 0.0779]	4290[R(int) = 0.0459]	6368 [R(int) = 0.0490]
Goodness-of-fit on F^2	1.060	1.133	1.537	1.035
Final R indexes [I>=2σ (I)]	R_1 = 0.0482, wR_2 = 0.1313	R_1 = 0.0957, wR_2 = 0.2217	R_1 = 0.1144, wR_2 = 0.3575	R_1 = 0.0505, wR_2 = 0.1304
Final R indexes [all data]	R_1 = 0.0581, wR_2 = 0.1412	R_1 = 0.1105, wR_2 = 0.2300	R_1 = 0.1264, wR_2 = 0.3682	R_1 = 0.0616, wR_2 = 0.1377
Largest diff. peak/hole / e $Å^{-3}$	0.42/-0.76	2.73/-1.51	3.64/-0.90	0.99/-0.82

	C26·CH_2Cl_2 (type III)	**C27 (type I)**	**C28·0.5 H_2O (type V)**	**C28·CH_2Cl_2 (type V)**
Empirical formula	$C_{29}H_{18}Cl_2CuF_{12}N_4O_3$	$C_{24}H_{16}CuF_2N_4O_2$	$C_{48}H_{33}Cu_2N_8O_5$	$C_{25}H_{18}Cl_2CuN_4O_2$
Formula weight	832.91	493.95	928.90	540.87
Temperature/K	99.9(4)	100.0(3)	120.00(10)	120.02(14)
Crystal system	monoclinic	monoclinic	monoclinic	orthorhombic
Space group	$P2_1/n$	$P2_1/n$	C2/c	$P2_12_12_1$
a/Å	16.62182(16)	10.2012(2)	8.8680(7)	9.5224(5)
b/Å	11.57317(12)	19.1739(4)	29.4050(17)	21.4509(14)
c/Å	16.65367(16)	10.73290(18)	15.5009(13)	21.9907(12)
α/°	90	90	90.00	90
β/°	96.2745(9)	103.6988(17)	103.449(7)	90
γ/°	90	90	90.00	90
Z	4	4	4	8
m/mm^{-1}	3.536	1.948	1.850	1.243
F(000)	1660.0	1004.0	1900.0	2200.0
Reflections collected	12066	11058	7195	23176
Independent reflections	5618[R(int) = 0.0235]	3525[R(int) = 0.0255]	3481[R(int) = 0.0617]	11975[R(int) = 0.0550]
Goodness-of-fit on F^2	1.047	1.084	1.079	1.065
Final R indexes [I>=2σ (I)]	R_1 = 0.0439, wR_2 = 0.1183	R_1 = 0.0336, wR_2 = 0.0881	R_1 = 0.0563, wR_2 = 0.1392	R_1 = 0.0569, wR_2 = 0.1254
Final R indexes [all data]	R_1 = 0.0489, wR_2 = 0.1235	R_1 = 0.0378, wR_2 = 0.0909	R_1 = 0.0742, wR_2 = 0.1530	R_1 = 0.0899, wR_2 = 0.1557
Largest diff. peak/hole / e $Å^{-3}$	0.89/-0.58	0.43/-0.38	0.89/-0.49	0.66/-0.63

	$C28_{Na}$·0.33 NaI_3 (type I)	**C30·4 H_2O (type V)**	**C31 (type I)**	**C32 (type II, recovered)**
Empirical formula	$C_{72}H_{48}Cl_6Cu_3I_3N_{12}NaO_6$	$C_{72}H_{48}Cu_3I_2N_{12}O_{10}$	$C_{24}H_{18}CuF_2N_4O_3$	$C_{24}H_{16}Cl_2CuN_4O_2$
Formula weight	1984.23	1685.64	511.96	526.85
Temperature/K	120.2(5)	99.9(3)	150	99.9(3)
Crystal system	monoclinic	orthorhombic	triclinic	trigonal
Space group	I2/a	$C222_1$	P-1	$P3_121$
a/Å	17.9088(6)	14.3846(4)	7.4412(16)	10.96221(14)
b/Å	17.5932(6)	17.2113(4)	12.402(3)	10.96221(14)
c/Å	25.0538(10)	29.3493(8)	12.731(3)	15.3971(2)
α/°	90	90	108.280(11)	90.00
β/°	107.309(4)	90	90.165(8)	90.00
γ/°	90	90	107.388(8)	120.00
Z	4	4	2	3
m/mm^{-1}	2.346	8.226	1.086	4.010
F(000)	3884.0	3348.0	522.0	801.0
Reflections collected	31649	9329	23551	13267
Independent reflections	7711[R(int) = 0.0603]	6059[R(int) = 0.0367]	6340[R(int) = 0.0385]	1881 [R(int) = 0.0413]
Goodness-of-fit on F^2	1.104	1.034	1.016	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0794, wR_2 = 0.1867	R_1 = 0.0791, wR_2 = 0.2098	R_1 = 0.0423, wR_2 = 0.0932	R_1 = 0.0214, wR_2 = 0.0555
Final R indexes [all data]	R_1 = 0.0913, wR_2 = 0.1938	R_1 = 0.0843, wR_2 = 0.2156	R_1 = 0.0727, wR_2 = 0.1051	R_1 = 0.0225, wR_2 = 0.0563
Largest diff. peak/hole / e $Å^{-3}$	3.15/-3.46	2.98/-1.48	0.95/-0.44	0.20/-0.17

	C32 (type II)	**C34 (type I)**	**C35 (type I)[a]**	**C36 (type I)[a]**
Empirical formula	$C_{24}H_{16}Cl_2CuN_4O_2$	$C_{24}H_{16}CuI_2N_4O_2$	$C_{24}H_{16}CuF_2N_4O_2$	$C_{24}H_{16}Cl_2CuN_4O_2$
Formula weight	526.85	709.75	493.95	526.85
Temperature/K	100.00(10)	119.99(14)	120(2)	150.15
Crystal system	trigonal	monoclinic	monoclinic	monoclinic
Space group	$P3_121$	$P2_1/c$	$P2_1/c$	$P2_1/c$
a/Å	10.9887(7)	11.0938(5)	13.5281(13)	14.493(3)
b/Å	10.9887(7)	8.2090(3)	20.0564(19)	20.092(3)
c/Å	15.4539(10)	25.0482(11)	8.9019(8)	8.9152(16)
α/°	90.00	90.00	90.00	90
β/°	90.00	100.507(4)	96.322(2)	95.809(7)
γ/°	120.00	90.00	90.00	90
Z	3	4	4	4
m/mm^{-1}	1.293	3.758	0.952	1.079
F(000)	801.0	1356.0	1004.0	1068.0
Reflections collected	8137	16618	14522	24688
Independent reflections	1901[R(int) = 0.0472]	5558[R(int) = 0.0464]	4164[R(int) = 0.0682]	5207[R(int) = 0.0542]
Goodness-of-fit on F^2	1.102	1.053	0.936	0.996
Final R indexes [I>=2σ (I)]	R_1 = 0.0286, wR_2 = 0.0607	R_1 = 0.0361, wR_2 = 0.0753	R_1 = 0.0569, wR_2 = 0.1166	R_1 = 0.0466, wR_2 = 0.1238
Final R indexes [all data]	R_1 = 0.0314, wR_2 = 0.0617	R_1 = 0.0494, wR_2 = 0.0828	R_1 = 0.1119, wR_2 = 0.1326	R_1 = 0.0801, wR_2 = 0.1353
Largest diff. peak/hole / e Å^{-3}	0.29/-0.26	1.05/-1.04	0.35/-0.59	0.45/-0.55

[a] Squeezed with Platon: voids account for approx. 5 molecules of DCM for **C35** and 11 molecules of MeCN for **C36** in the unit cell

	C38 (type I)[a]	**C39 (type I)**	**C40 (type V)[a]**	**$C40_{Na}$·2 H_2O (type II)**
Empirical formula	$C_{24}H_{16}CuI_2N_4O_2$	$C_{24}H_{14}CuF_4N_4O_2$	$C_{48}H_{28}Cl_6Cu_2N_8O_4$	$C_{24}H_{18}Cl_4CuN_4O_4$
Formula weight	709.75	529.93	1120.56	631.76
Temperature/K	120.02(19)	120.01(10)	99.9(5)	120.0(2)
Crystal system	orthorhombic	monoclinic	monoclinic	trigonal
Space group	Pccn	$P2_1/n$	$P2_1/c$	$P3_2$
a/Å	36.6990(15)	10.2648(2)	12.93045(16)	13.6597(8)
b/Å	19.4888(9)	19.1526(4)	21.4772(4)	13.6597(8)
c/Å	8.6607(3)	10.7778(2)	19.0602(2)	11.8142(7)
α/°	90	90	90	90
β/°	90	103.570(2)	96.1890(11)	90
γ/°	90	90	90	120
Z	8	4	4	3
m/mm^{-1}	16.833	2.122	4.204	5.423
F(000)	2712.0	1068.0	2256.0	957.0
Reflections collected	14949	9062	29307	4605
Independent reflections	5534[R(int) = 0.0520]	3563[R(int) = 0.0301]	9301[R(int) = 0.0277]	2988[R(int) = 0.0499]
Goodness-of-fit on F^2	1.061	1.073	1.051	1.184
Final R indexes [I>=2σ (I)]	R_1 = 0.0636, wR_2 = 0.1798	R_1 = 0.0347, wR_2 = 0.0853	R_1 = 0.0433, wR_2 = 0.1014	R_1 = 0.0716, wR_2 = 0.1565
Final R indexes [all data]	R_1 = 0.0828, wR_2 = 0.1938	R_1 = 0.0405, wR_2 = 0.0891	R_1 = 0.0504, wR_2 = 0.1053	R_1 = 0.0770, wR_2 = 0.1592
Largest diff. peak/hole / e $Å^{-3}$	1.00/-1.45	0.34/-0.39	1.45/-1.71	0.75/-0.57

[a] Squeezed with Platon: voids account for approx. 13 molecules of DCM for **C38** and 11 molecules of MeCN for **C40** in the unit cell

	C41·2 MeCN·H_2O (type V)	**$C41_{Na}$·0.5 H_2O (type II)**	**C42 (type II)**	**C43 (type I)**
Empirical formula	$C_{52}H_{35}Br_6Cu_2N_{10}O_{4.5}$	$C_{24}H_{14}Br_4CuN_4O_{2.375}$	$C_{24}H_{14}N_4O_2F_4Cu$	$C_{24}H_{14}Cl_4CuN_4O_2$
Formula weight	1478.44	779.57	529.94	595.73
Temperature/K	119.99(13)	120	120.1(4)	100.00(10)
Crystal system	monoclinic	orthorhombic	trigonal	monoclinic
Space group	$P2_1/c$	$C222_1$	$P3_221$	$P2_1$
a/Å	13.1510(2)	18.5507(18)	10.6503(4)	12.2634(7)
b/Å	21.8383(5)	20.006(2)	10.6503(4)	7.2514(7)
c/Å	19.3838(3)	27.895(3)	15.8613(9)	12.9072(9)
α/°	90	90.00	90	90.00
β/°	96.3550(15)	90.00	90	94.034(6)
γ/°	90	90.00	120	90.00
Z	4	16	3	2
m/mm^{-1}	6.473	8.694	2.104	1.453
F(000)	2884.0	5984.0	797.9	598.0
Reflections collected	24870	11907	3192	5983
Independent reflections	9536[R(int) = 0.0623]	7909[R(int) = 0.0481]	1832[R(int) = 0.0399]	3460[R(int) = 0.0356]
Goodness-of-fit on F^2	1.016	1.056	0.999	1.076
Final R indexes [I>=2σ (I)]	R_1 = 0.0543, wR_2 = 0.1403	R_1 = 0.0652, wR_2 = 0.1739	R_1 = 0.0354, wR_2 = 0.0804	R_1 = 0.0354, wR_2 = 0.0788
Final R indexes [all data]	R_1 = 0.0761, wR_2 = 0.1547	R_1 = 0.0797, wR_2 = 0.1866	R_1 = 0.0398, wR_2 = 0.0834	R_1 = 0.0422, wR_2 = 0.0824
Largest diff. peak/hole / e $Å^{-3}$	1.50/-0.79	2.01/-1.44	0.34/-0.33	0.50/-0.36

	C44·2 MeCN (type II)	**C51 (type I)**	**C52 (type I)**
Empirical formula	$C_{28}H_{20}Br_4CuN_6O_2$	$C_{26}H_{22}CuN_4O_4$	$C_{24}H_{16}Cl_2CuN_4O_2$
Formula weight	855.68	518.01	526.85
Temperature/K	119.99(10)	120.02(10)	120.00(13)
Crystal system	monoclinic	monoclinic	triclinic
Space group	$P2_1/c$	C2/c	P-1
a/Å	10.08715(16)	13.9182(7)	8.6377(6)
b/Å	24.1437(3)	9.7790(6)	10.6941(6)
c/Å	12.53985(19)	17.2719(9)	12.4555(5)
α/°	90	90	85.106(4)
β/°	100.3651(14)	103.425(5)	72.153(5)
γ/°	90	90	89.361(5)
Z	4	4	2
m/mm^{-1}	7.569	0.997	3.926
F(000)	1660.0	1068.0	534.0
Reflections collected	16686	5975	7466
Independent reflections	5301[R(int) = 0.0376]	2335[R(int) = 0.0820]	3767[R(int) = 0.0494]
Goodness-of-fit on F^2	0.997	1.086	1.064
Final R indexes [I>=2σ (I)]	R_1 = 0.0340, wR_2 = 0.0903	R_1 = 0.0527, wR_2 = 0.1261	R_1 = 0.0429, wR_2 = 0.1011
Final R indexes [all data]	R_1 = 0.0393, wR_2 = 0.0945	R_1 = 0.0604, wR_2 = 0.1338	R_1 = 0.0500, wR_2 = 0.1073
Largest diff. peak/hole / e Å^{-3}	1.16/-0.57	0.51/-0.49	0.63/-0.42