



**Copper catalysed Ullmann type chemistry: from mechanistic aspects to modern development**

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ARTICLE TYPE

# Copper catalysed Ullmann type chemistry: from mechanistic aspects to modern development

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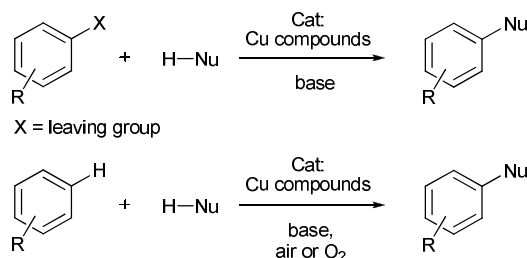
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Cu-catalysed arylation reactions devoted to the formation of C-C and C-heteroatom bonds (Ullmann-type couplings) have acquired great importance in the last decade. This review discusses the history and developments of coupling reactions between aryl halides and various classes of nucleophiles, focusing mostly on the different mechanism proposed through the years. Selected mechanistic investigations are treated more in depth than others. For example, evidence in favour or against radical mechanisms is discussed. Cu(I) and Cu(III) complexes involved in the Ullmann reaction and *N/O* selectivity in aminoalcohol arylation are discussed. Finally, recent developments in green chemistry for these reactions, such as reactions in aqueous media and heterogeneous catalysis, have also been reviewed.

## 1 Introduction

Since the advent of palladium as a promising catalyst for many cross-coupling reactions, insertions and other interesting transformations, its use has steadily increased, and today palladium-based catalysis is used not only in research and development, but also on industrial scale.<sup>1</sup> Cu has been known for its ability to bind to alkynes, famous applications of which being its use in the bimetallic-catalysed Sonogashira coupling and the cycloaddition reaction with azides (click chemistry). Although these are still among its most common applications, together with oxidation processes, such as Water Gas Shift processes<sup>2</sup> and oxidation of methane to methanol,<sup>3</sup> Cu is also able to catalyse arylation reactions of many nucleophilic species. The most common aryl donors in these reactions are aryl halides (especially iodides) 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.<sup>4</sup> Other than these, following the recent developments in transition metal catalysed C-H activation,<sup>5-13</sup> Cu catalysis has been extended to the functionalisation of unsubstituted arenes, which are cheaper and have (green) advantages such as the avoidance of halogen side-products and the use of air or oxygen as oxidants (Scheme 1).<sup>14-25</sup>



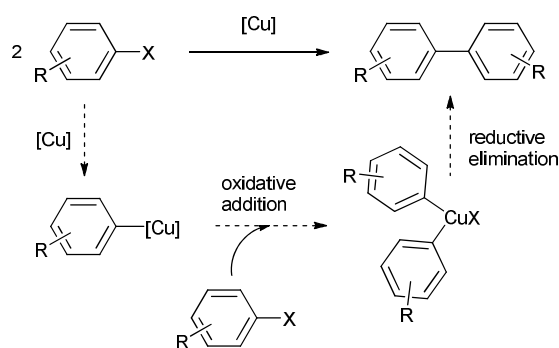
Scheme 1

This review will focus on Ullmann-type reactions (namely those Cu-catalysed arylations in which aryl halides are involved). Compared to other catalytic methodologies, Cu-catalysed couplings are still affected by some drawbacks: despite all the efforts put into the research so far, these Cu-mediated processes have not reached yet the high levels which characterise Pd chemistry, 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, however, Cu catalysis shows some interesting advantages over Pd or other metals. First of all, Cu is cheaper than the many other metals used in catalysis, and has attracted recently high interest from the industry, which is now the most consistent driving force for the research in this field. The range of nucleophiles suitable for Ullmann arylations has become wider with time, and nowadays N-, O-, S-, P- and C-aryl bonds formation are easily accessible through these processes. Such bonds can be found in many bioactive organic compounds,<sup>26, 27</sup> as well as in material chemistry.<sup>28, 29</sup> Also, the scope of Cu-catalysed cross coupling reactions is increasing, and it seems to be somewhat complementary to that of Pd-based methodologies.<sup>30-32</sup> 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 are often complex, expensive and air-sensitive).

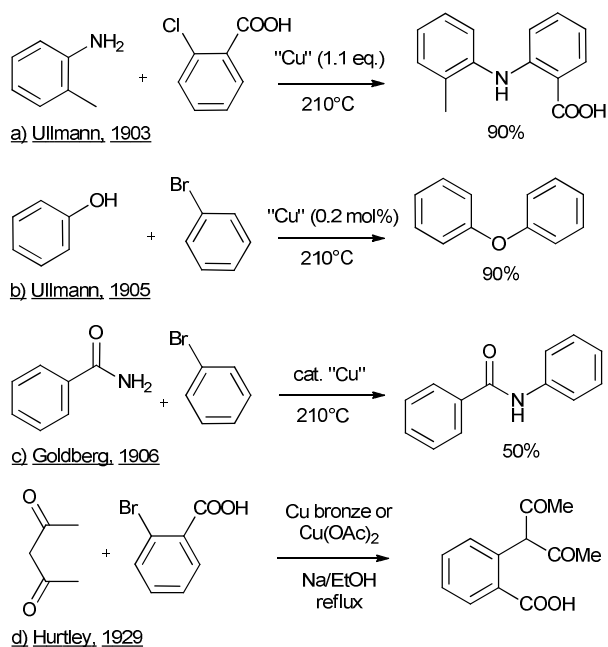
## 2 Historical overview

In 1901 Fritz Ullmann observed that Cu compounds were able to catalyse the formation of biaryl moieties through coupling of two molecules of aryl halides.<sup>33</sup> This reaction became what is now called the “classical Ullmann reaction”. The mechanism generally accepted for this reaction involves the formation of an organocuprate intermediate from a molecule of aryl halide, which then reacts with a second molecule through oxidative addition, furnishing the final product after reductive elimination (Scheme 2).<sup>34,35</sup>



Scheme 2

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, in 1903 and 1905 respectively,<sup>36, 37</sup> and in 1906 the first Cu-catalysed synthesis of aryl amides was reported by Irma Goldberg<sup>38</sup> (Scheme 3a-c). Goldberg also reported the first catalytic arylation of amines in the same year.<sup>38</sup> Almost 30 years later, in 1929, William Hurtley reported the coupling between *o*-bromobenzoic acid and  $\beta$ -dicarbonyls mediated by Cu bronze or Cu(OAc)<sub>2</sub> (Scheme 3d).<sup>39</sup>

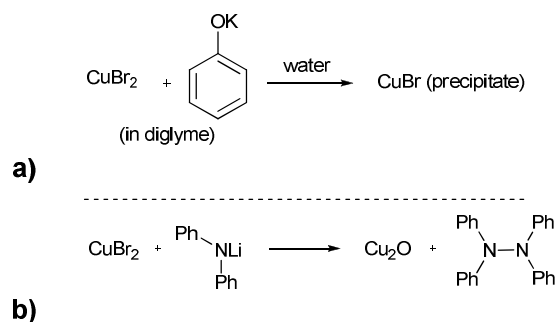


Scheme 3

Despite these early impressive examples, these Cu-mediated reactions required harsh conditions (high temperature, strong bases, long reaction time and stoichiometric amounts of copper reagent), 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.<sup>40</sup>

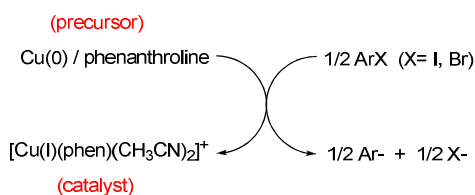
### 2.1 Copper precursors

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.<sup>40</sup> This suggested that a common Cu species could be formed during the reaction from the different sources. Much work has therefore been carried out since the early 1960s in this direction, investigating the particular electrochemical behaviour of Cu sources.<sup>41-43</sup> Since Cu(I) seemed to lead to slightly higher reaction rates, it was proposed by Weingarten in 1964 that Cu(I) species could have been the common intermediate.<sup>41</sup> It was demonstrated, indeed, 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 get oxidised as the redox counterpart (Scheme 4).<sup>41,42</sup>



Scheme 4

Moreover, in 1987, Paine found, by means of electron microscopy and X-ray powder diffraction studies, that Cu(0) particles used as catalyst were actually covered in a layer of Cu<sub>2</sub>O, and he reasoned that this oxide, if leached into the solution, would provide the Cu(I) species required for the catalysis. The solid catalyst, recovered after the reaction, was covered with crystallites of Cu<sub>2</sub>O which were not present in the original catalyst.<sup>42</sup> This was explained by suggesting that the cuprous ion leached into solution and crystallised after the reaction upon the original Cu particles (*i.e.* the recrystallisation of the Cu oxide would not be possible if it had not leached into solution).<sup>42</sup> The oxidation of Cu(0) to Cu(I) in a coordinating environment (this time in the presence of an exogenous ligand), was recently confirmed by Taillefer *et al.* through *in-situ* cyclic voltammetry studies (Scheme 5).<sup>44</sup> 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 source to Cu(I) by the atmospheric oxygen in the reaction, on the basis of colour change and catalytic results in different conditions.<sup>45</sup>



Scheme 5

These investigations seemed to demonstrate the active catalyst to be a Cu(I) species, but it has been implied that the initial copper source remained 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.<sup>43, 46</sup>

## 2.2 Mechanisms

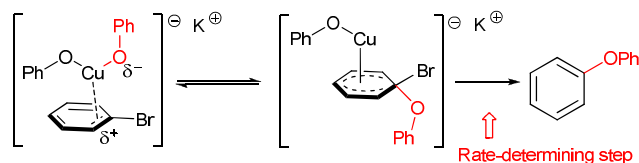
Together with the identification of the catalytic species in the reaction, the first mechanistic hypotheses began to appear in the literature, and between 1960 and 1990 several mechanisms were proposed.<sup>41, 43, 47-50</sup> Whereas it was generally agreed that at a certain point of the reaction the coordination of the nucleophile to the Cu atom was involved, the activation of the aryl halide was the most troublesome aspect of the process. Indeed, the reactivity of the halide observed for the coupling reaction followed the

order I>Br>Cl, which is the opposite of that observed for common aromatic nucleophilic substitution. It was therefore obvious that the metal was in some way involved in the activation of the aryl halide, and its interaction was not only limited to the nucleophile.

The mechanisms proposed until the 1990s can be conveniently divided into four main classes:

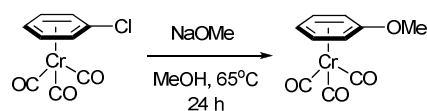
- Aromatic nucleophilic substitution, with Cu(I)  $\pi$ -coordinating to the aromatic ring of the aryl halide to render the aromatic position more electrophilic and susceptible to substitution;
- Mechanisms *via* Single Electron Transfer (SET) or Halogen Atom Transfer (HAT), involving the redox couple Cu(I)/Cu(II) and radical intermediates;
- 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;
- 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).

In 1964 Weingarten suggested that the rate determining step of the Cu-catalysed arylation was the cleavage of the aryl-halogen bond.<sup>41</sup> On the basis of kinetic studies upon the coupling between potassium phenoxide and bromobenzene, the existence of a cuprate species [Cu(OPh)<sub>2</sub>]<sup>-</sup> was hypothesised which would coordinate to the aryl halide during the reaction. The suggested interaction was a  $\pi$ -coordination to the aromatic ring, the metal acting essentially as an activating group, making the aryl halide more susceptible to nucleophilic substitution (Scheme 6).<sup>41</sup>



Scheme 6

This mechanism, somewhat like a simple aromatic nucleophilic substitution, was judged attractive for several reasons: a)  $\eta^2$ -Cu(I)-benzene complexes had been synthesised the year before,<sup>51</sup> and b)  $\eta^6$ -haloarenes Cr(0) complexes had been demonstrated to be very effective substrates for halogen nucleophilic substitution (Scheme 7).<sup>52</sup>

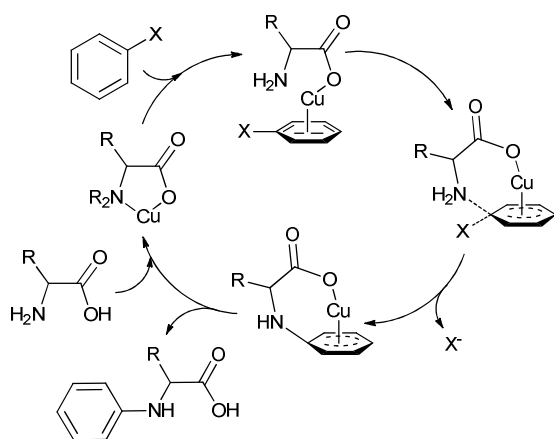


Scheme 7

However, as Paine pointed out later,<sup>42</sup> 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 (see Section 3). Also the analogy with the chromium  $\pi$ -complexes was not valid, because the order of halide reactivity in

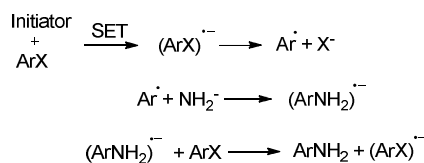
the latter was  $\text{Cl} > \text{Br} > \text{I}$ , the opposite of that observed for copper catalysed reactions.<sup>53</sup> Moreover, very weak  $\eta^6$ -Cu-benzene interactions have been observed only rarely in particular structures,<sup>54, 55</sup> whereas  $\eta^2$ -complexes are more common for Cu with aromatic ligands<sup>51, 56, 57</sup> (note however, that  $\eta^2$ -complexes would still reduce the electron density around the substitution site, although to a much lesser extent).

Weingarten's mechanism was reconsidered by Ma in 1998 to explain the coupling between aminoacids and aryl halides (Scheme 8). However, no explanation for the two problems above was supplied.<sup>58</sup>



Scheme 8

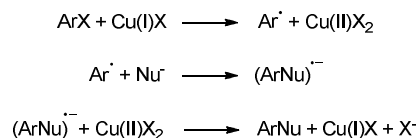
Some years after Weingarten's proposal, a radical type of aromatic nucleophilic substitution, called  $\text{S}_{\text{RN}}1$ , was postulated by Bunnett when studying the reaction of iodoarenes with potassium amide.<sup>47</sup> The author proposed a radical chain mechanism for this reaction, involving single electron transfer (SET) as the initiation step (Scheme 9). 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 9

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. Cu species are known to act as single electron oxidants in many reactions, thus leading to radical cations,<sup>59-61</sup> whereas Cu acting as a single electron reductant, thus leading to a reduced organic substrate, is found in Atom Transfer Radical Polymerisation (ATRP) processes.<sup>62</sup> Bunnett's sequence was invoked as a possible mechanism for Ullmann-type coupling reactions some years later (see below).<sup>63</sup> In the meantime, another radical mechanism had been proposed for the Ullmann coupling,

based on Kochi's studies on radical reactions (Scheme 10).<sup>48, 64</sup> 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 and an halide ion). This mechanism is called "halogen atom transfer" (HAT) or "inner sphere" electron transfer.



Scheme 10

A combination of a radical mechanism and a substitution reaction was proposed by Litvak in 1974,<sup>49</sup> 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,<sup>50</sup> and was also suggested for amides in the 1970s.<sup>65</sup> These mechanisms are often referred to in the literature as metathesis, and their transition states are depicted as four-centred structures (Figure 1).

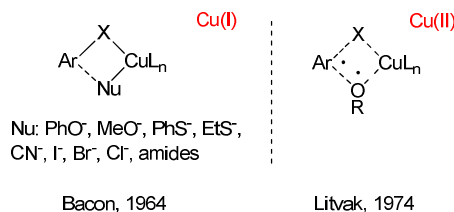
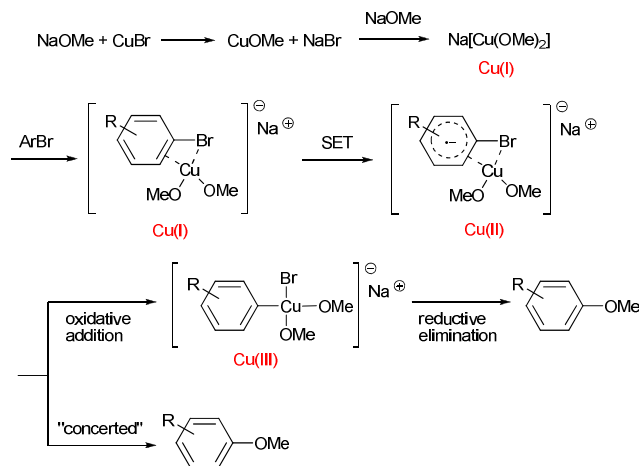


Figure 1

The transition states shown in Figure 1 involve the binding between Cu and one molecule of nucleophile, whereas in 1964 Weingarten had proposed a Cu species bound to two molecules of phenoxide (Scheme 6), basing his proposal on kinetic considerations.<sup>41</sup> Indeed, in 1989, an enhancement of the reaction rate at high concentration of alkoxide was again observed by van Koten and co-workers.<sup>43</sup> This and other evidence seemed to confirm the hypothesis that two equivalents of alkoxide had to be bound to the Cu atom for the species to be effective, and that a cuprate species like  $\text{Na}[\text{Cu}(\text{OR})_2]$  was formed. The mechanism proposed by van Koten was thus similar to Weingarten's in this respect, but an oxidative addition initiated by a SET process was considered (Scheme 11).<sup>43</sup>

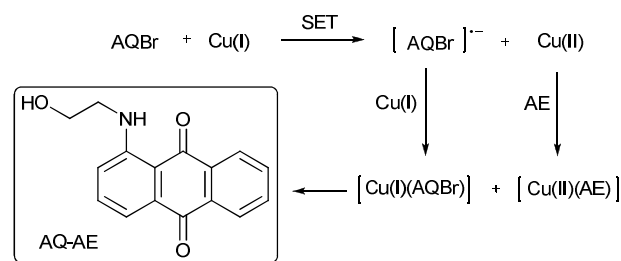


Scheme 11

5 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 already been proposed,<sup>66</sup> the authors  
 10 thought a Cu(III) intermediate would still be improbable, especially in an environment where even Cu(II) was reduced to Cu(I) (Scheme 4). Therefore, they suggested a concerted mechanism for the coupling.<sup>43</sup>

Previously, other authors had proposed oxidative addition mechanisms for the Cu-catalysed substitution reaction. Bowman had proposed a mechanism similar to van Koten's, suggesting Cu(II) transition states also for the reductive elimination,<sup>67</sup> while Cohen<sup>66</sup> and Bethell<sup>68</sup> had proposed a direct Cu(I)/Cu(III) oxidation (see below).

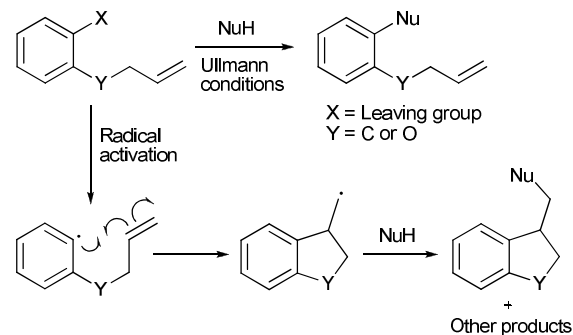
20 The oxidative addition/reductive elimination and the radical mechanisms are still under debate. The only evidence of a Cu(III) intermediate in these reactions derive from a particularly stable macrocyclic system (see Section 5), so not extendable to typical reaction systems. Experimental evidence and theoretical  
 25 discussion was provided both for and against the existence of radical intermediates. Van Koten reported that a radical mechanism would easily explain the formation of de-halogenated products, which are often observed as side-products during the reaction.<sup>43</sup> Studying the reaction between haloanthraquinones and aminoethanol (AQBr and AE in Scheme 12) in the 1970s, Hida and co-workers observed, through EPR experiments, the formation of an organic radical species and Cu(II) species.<sup>63, 69</sup> Hypothesising the radical species as derived from the AQBr,  
 30 Arai's results fitted well with the SET process depicted in Scheme 9. The Cu(II) formed in the reaction was suggested to coordinate to the nucleophilic AE and react with the Cu(I)(AQBr) complex in an intermolecular reaction (Scheme 12).<sup>63</sup>



Scheme 12

For the same reaction, in 1985 Bethell suggested an oxidative addition/reductive elimination cycle, although reactions performed in air were completely inhibited by atmospheric  
 45 oxygen.<sup>68</sup> Radical mechanisms were invoked recently for copper-catalysed couplings on several occasions: a notable recent example comes from Buchwald (see Section 3.1).<sup>70</sup> A radical mechanism has also been suggested for the Cu-catalysed coupling between phenols/thiols and hydrofluorocarbons (HCFCs)  
 50 by Chen and co-workers.<sup>71</sup>

Evidence was also reported against the formation of radicals during the reaction. In a comparative study between different S<sub>RN</sub>1 procedures available for the synthesis of heterocycles (Scheme 31), Bowman found the Cu-catalysed coupling the most  
 55 efficient, but at the same time, this strategy appeared to be particularly different from other radical processes.<sup>67, 72</sup> For example, the lack of inhibition by radical scavengers or oxygen (compare with Bethell's results above) in the reaction mixture, made the authors think that this coupling did not occur through  
 60 radical aromatic substitution.<sup>67, 72</sup> Radical clock experiments (Scheme 13) have been performed many times on thermal reactions<sup>67, 73-79</sup> to investigate the existence of aryl radical intermediates in the reaction medium, and negative results have been obtained so far. A small amount of radical-derived product  
 65 was detected only once from these experiments, showing that radical mechanisms can actually occur in the reaction, although to a minimal extent.<sup>79</sup>



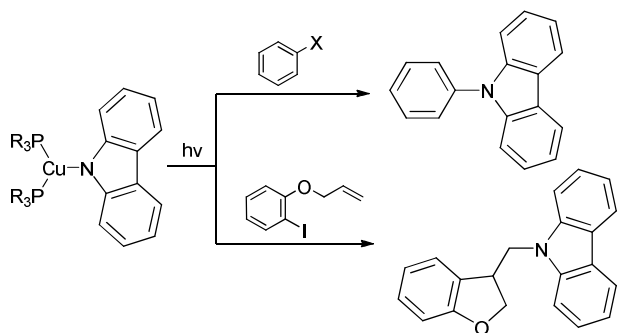
Scheme 13

Radical clock experiments are based upon the fact that, in radical conditions, the formation of a methylcyclopentane moiety through 5-*exo-trig* closure is the most kinetically favoured  
 75 transformation.<sup>80, 81</sup> 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. This possibility has been in fact suggested several times,<sup>70, 82, 83</sup> but has not been demonstrated yet.

Another series of experiments were reported in 2008 by Hartwig and co-workers using aryl chlorides and bromides with higher reduction potentials than the relative aryl iodide.<sup>75</sup> If a radical mechanism was involved, the reaction rate should be faster along with the 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.<sup>75</sup> 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.<sup>70</sup> 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.<sup>70</sup>

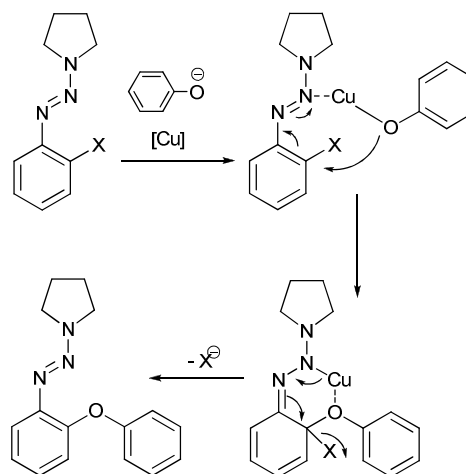
These types of experiments, plus EPR observation of Cu(II) intermediates in the reaction, gave instead positive results for a photoinduced Ullmann-type coupling, reported by Fu and Peters in 2012, using a ligated Cu(I)-carbazolide complex as coupling partner (Scheme 14).<sup>83</sup> The same authors later reported the use of an anionic  $[\text{Cu}(\text{carbazolide})_2]^-$  complex as a substrate for the coupling with cycloalkyl halides, and the coupling of aryl halides and thiols in the same photochemical conditions<sup>84, 85</sup> (for a discussion on other Cu(I) complexes, see Section 4). Although photochemical conditions are known to favour radical mechanisms, the reaction did not occur in the absence of Cu, thus demonstrating its catalytic role in these conditions.<sup>83</sup>



Scheme 14

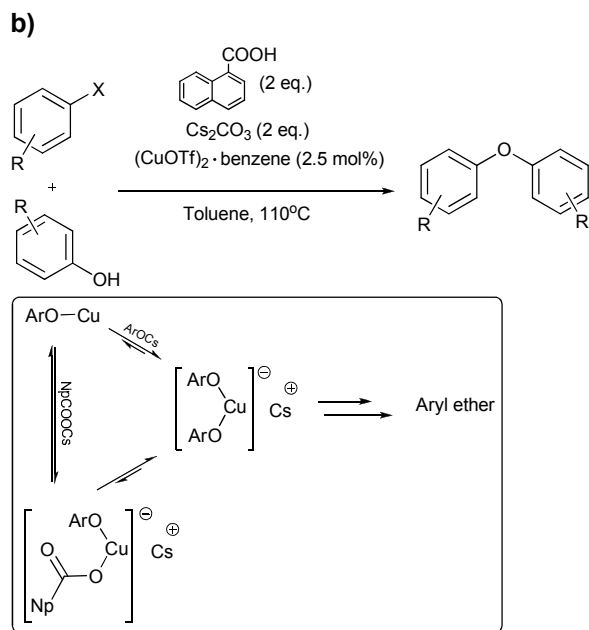
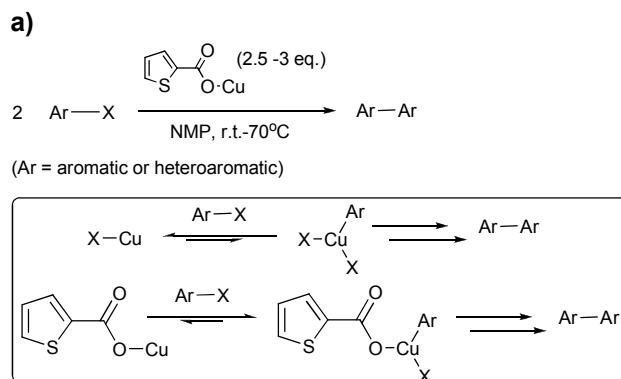
### 3 The introduction of ligands

The idea that some esters or ketones could accelerate the reaction was suggested in 1964,<sup>41</sup> but their role was mostly linked to the increased solubility of the Cu catalyst, rather than to other effects. In 1997, the use of CuBr for the reaction of phenols with *o*-triazene-substituted haloarenes was reported by Nicolaou and co-workers.<sup>86</sup> The triazene unit was proposed to act as a coordinating agent (an internal ligand) for the copper atom, thus facilitating the aromatic substitution (Scheme 15):



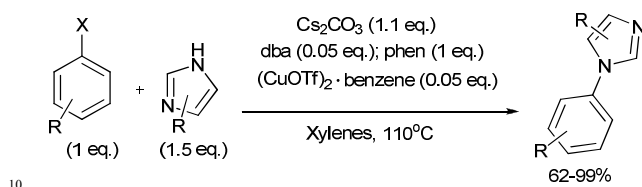
Scheme 15

However, no exogenous ligands had been used intentionally in the reaction. A step forward in this direction came from Liebeskind and Buchwald in 1997, respectively for the Cu-catalysed synthesis of biaryls<sup>87</sup> and aryl ethers.<sup>88</sup> Two different roles were at the time attributed to the used (overstoichiometric) additives. While Liebeskind suggested that copper thiophenecarboxylate would facilitate an oxidative addition of the aryl halide to the Cu atom, thus accelerating the coupling (Scheme 16a), Buchwald proposed that the combined effect of naphtic acid and caesium carbonate would enhance the solubility of an intermediate cuprate species (Scheme 16b), similar to those reported by Weingarten<sup>41</sup> and van Koten.<sup>43</sup>



Scheme 16

A few years later, investigating the coupling of aryl halides with imidazoles, Buchwald used a stoichiometric amount of phenanthroline as ligand and dibenzylideneacetone (dba) as a catalytic additive (Scheme 17).<sup>89</sup>



Scheme 17

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.<sup>89</sup>

In the following years, the first studies on different types of bidentate ligands, which appeared to be much more efficient than

monodentate ones,<sup>90</sup> were published. It was proposed that bidentate ligands would facilitate the reaction by blocking two adjacent coordination sites, so that the aryl donor and the nucleophile could be close enough to couple easily.<sup>90</sup> 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.<sup>91</sup> Some of the first successful ligands are reported in Figure 2.<sup>89, 90, 92-101</sup>

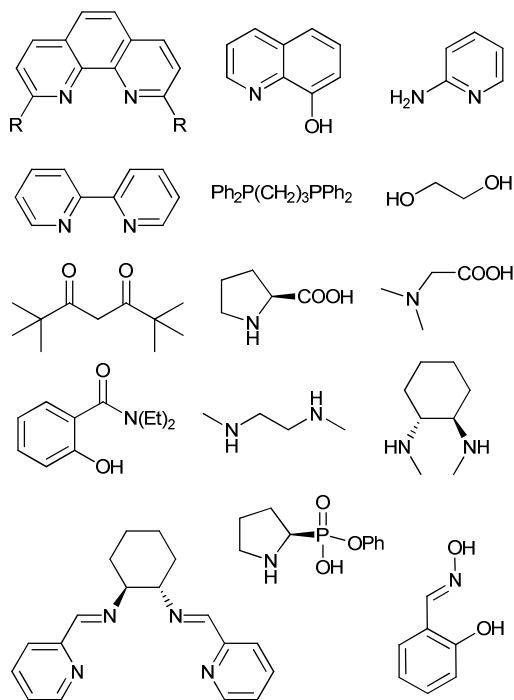


Figure 2

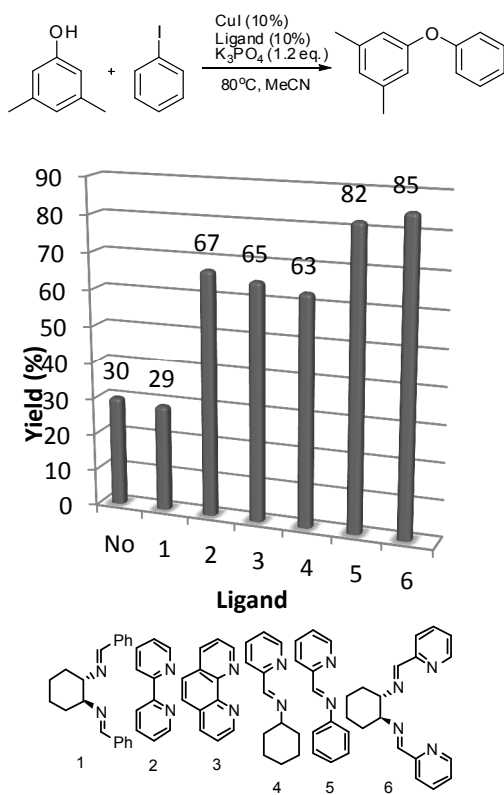
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The introduction of ligands in Ullmann type reactions made the use of much milder reaction conditions possible, and temperatures <100°C (usually 80-100°C) could be used achieving good results, and amount of Cu source and ligand in the range 5-20% relative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

Since 2004 much effort was put into the discovery of the role of the ligand in these couplings, and in particular to find out whether the increase of solubility of the Cu species was the only effect. 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 investigation of new classes of imine-based ligands and their Cu complexes for Ullmann *N*- and *O*-arylations.<sup>100, 102-106</sup> Moreover, interesting mechanistic investigations were performed through cyclic voltammetry experiments.<sup>44, 106-108</sup> In 2007 Taillefer *et al.* reported one of the first structure-activity relationship studies in the literature of Ullmann couplings: a comparison between their bifunctional imino-pyridine ligands with phenanthrolines and bipyridines showed them to be useful to make the first hypothesis on the effect of the ligand structure in the catalytic reactions (Scheme 18).<sup>105</sup>

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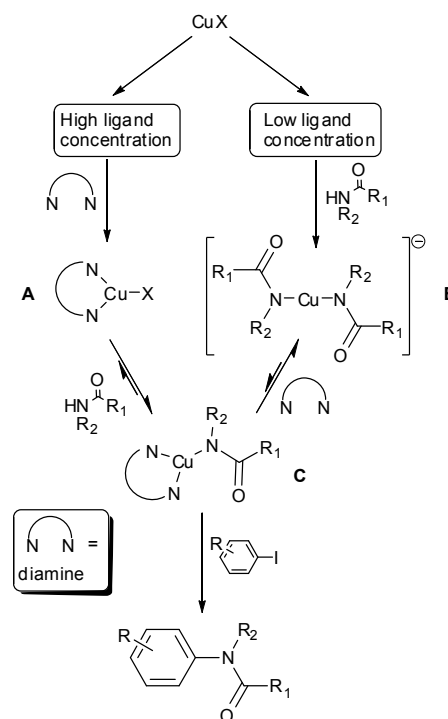


Scheme 18

5

Imine ligands alone were found ineffective in enhancing the reaction yield (ligand 1 in Scheme 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, considered among the best ligands. When a tetradentate ligand was used instead (ligand 6), the yield was only slightly higher than with the bidentate ligand.<sup>105</sup> The authors also observed that an electron-withdrawing substituent on the imine moiety and an electron-donating substituent on the pyridine nucleus led to higher yields. Based on these data, they proposed that the two different ligand moieties (pyridine and imine) could intervene in two different steps of the catalytic cycle. The electron-rich pyridine, transferring electrons to the Cu atom, could increase its tendency to oxidative addition, while the electron-poor imine would make the Cu atom more electrophilic, hence more susceptible to reductive elimination.<sup>105</sup>

A different point of view was put forward by Buchwald and co-workers.<sup>109, 110</sup> On the basis of kinetic investigations, they proposed that a series of equilibria between different Cu species was involved in the arylation reaction.<sup>109</sup> Since the concentration of CuI used was only 0.02M, and the reaction reached the maximum rate at a ligand concentration of *ca.* 0.2 M, the solubilising effect initially assumed for the ligand was ruled out or, at least, it was clear that it was not the only effect. They 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 19).<sup>109</sup>



35

Scheme 19

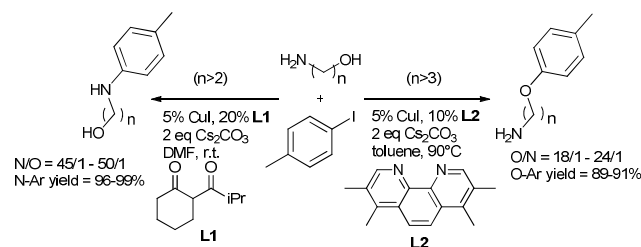
Their hypothesis was that, at high ligand concentration, the Cu source is initially coordinated by the diamine ligand (A, Scheme 19) and then the halogen atom undergoes substitution with the amide anion, furnishing the intermediate amidate complex C. The latter then reacts with the aryl donor to give the coupled product. Alternatively, at low ligand concentration, the Cu atom is coordinated to two molecules of amide (B, a bis-amidate complex, inactive), which can 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).<sup>109</sup> 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.<sup>109</sup>

### 5.1 *N/O*-arylation selectivity

Because of the importance of the functionalised amino-alcohol motif in medicinal chemistry (examples are epinephrine and  $\beta$ -blockers), the advances in Cu-catalysed arylation methods prompted the research toward the application of this catalysis on these substrates. Arylation of amino-alcohols is a challenging subject, and faces the problem of selectivity between *O*- and *N*-arylation, which strongly depend on the added ligand and the coordinating ability of the aminoalcohols itself.

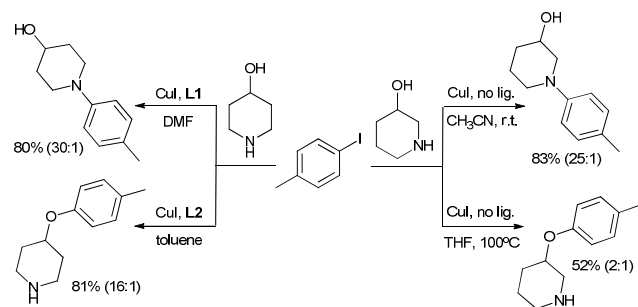
Although some reports had already been published before 2000,<sup>58, 69</sup> it was only later that some better understanding of the selectivity of the reaction was achieved. In 2002, Buchwald *et al.* performed the arylation of  $\beta$ -amino-alcohols of the ephedrine family using the amino-alcohols as ligands.<sup>111</sup> 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<sub>2</sub>O (or isopropanol) as solvent, the *N*-arylation was highly favoured (*N*/*O* arylation ratio > 50), whereas performing the reaction with milder bases (K<sub>3</sub>PO<sub>4</sub> or Cs<sub>2</sub>CO<sub>3</sub>) in the presence of ethylene glycol led to decreased *N*/*O* selectivity. The *O*-arylation was favoured using Cs<sub>2</sub>CO<sub>3</sub> in butyronitrile as solvent, even though the yields were modest. Finally, using less reactive amino-alcohols bearing secondary amino groups, competition between *N*- and *O*-arylation was observed, as a result of the increased steric requirements around the more nucleophilic amino group.<sup>111</sup> 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 20) as a ligand in toluene, *O*-arylation was favoured, while the use of isopropylcarbonylcyclohexanone (**L1**) in DMF favoured the *N*-arylation (Scheme 20).<sup>112</sup> In general, acceptable selectivities were observed for longer chain amino-alcohols, while C<sub>2</sub> and C<sub>3</sub> 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.<sup>112</sup>



Scheme 20

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.<sup>113</sup> 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 20 for conditions), whereas 3-piperidinol performed better without any additional ligand using different solvents/conditions (Scheme 21).<sup>112</sup>



Scheme 21

To explain the role of the ligand in the selectivity, it was proposed that the anionic ligand **L1** (Scheme 20) 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 3).<sup>112</sup>

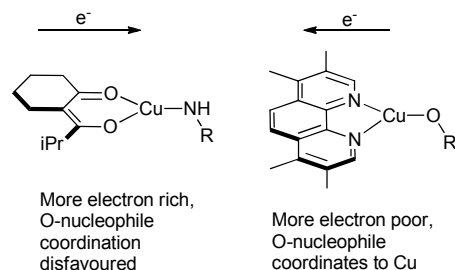
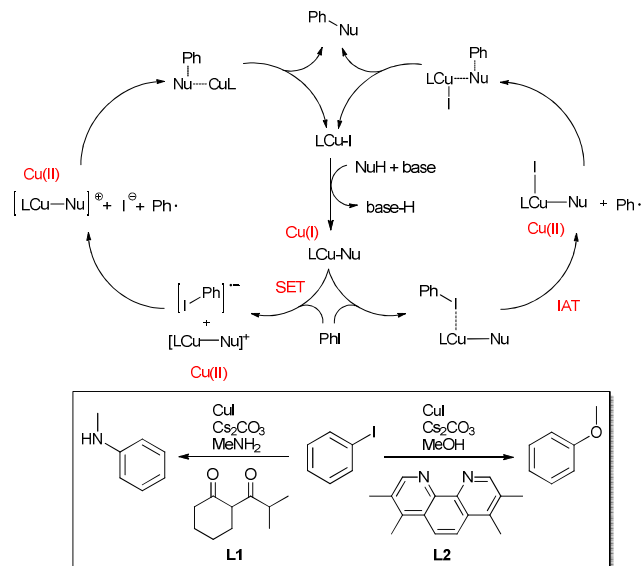


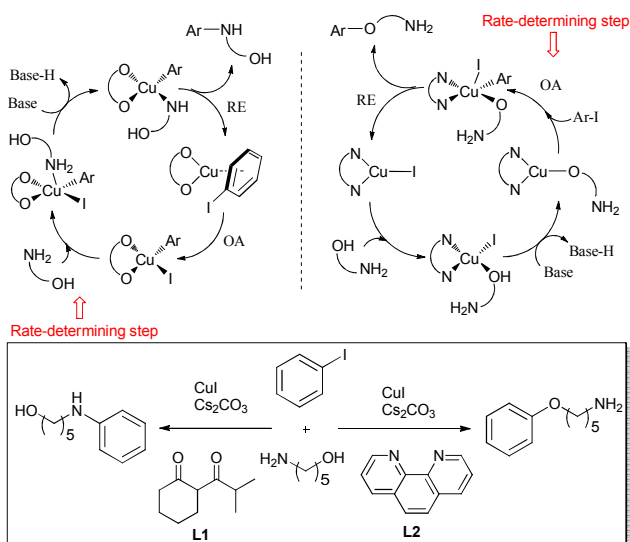
Figure 3

A few years later, Buchwald and co-workers reported a computational study to explain the selectivity they observed with the two ligands (see Scheme 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.<sup>70</sup> 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.<sup>70</sup> Using the diketone ligand **L1**, the *N*-arylation was always favoured over *O*-arylation, and the lower energy pathway resulted to be 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 22).<sup>70</sup> From the analysis of the energies of the species involved, the authors suggested that the radical intermediates originated in these reactions have a very short life-time and exist in the form of caged radical pairs (Section 2.2).<sup>70</sup>



Scheme 22

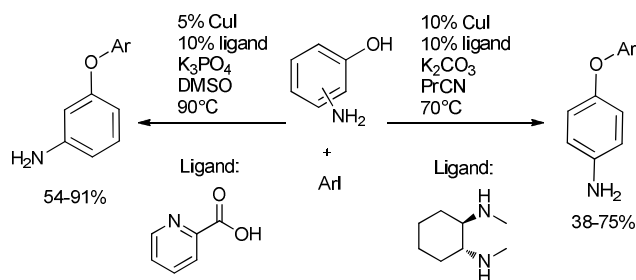
Another computational investigation was reported by Fu to explain the selectivity observed in amino-alcohols. In this case, the calculations were undertaken using an amino-alcohol as model, which was considered a more realistic system (Scheme 23, notice however that the neocuproine was substituted with the less electron rich phenanthroline).<sup>114</sup> 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 term of a different order of nucleophile coordination and oxidative addition.<sup>114</sup>



Scheme 23

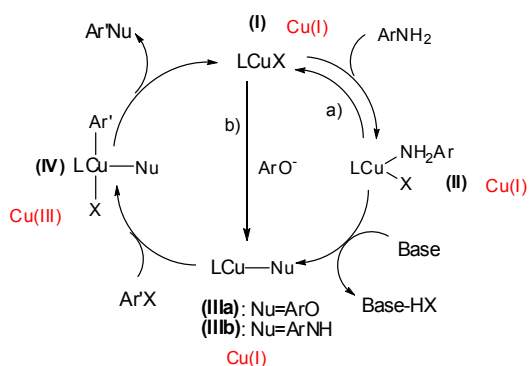
Because **L1** (Scheme 23) is an anionic ligand, its Cu(I) ligated species is neutral, and therefore more prone to oxidative addition with the aryl halide than the **L2**-ligated complex, which would need to bind to the nucleophile first (note that the deprotonation occurs after coordination in both cases, due to the weakness of

the base used).<sup>114</sup> 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 23).<sup>114</sup> 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.<sup>115</sup> 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 24).<sup>115</sup>



Scheme 24

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.<sup>115</sup> 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.<sup>115</sup> 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.<sup>115</sup> On the basis of these results they discussed the possibility of a catalytic cycle where the deprotonation step plays a very important role (Scheme 25):

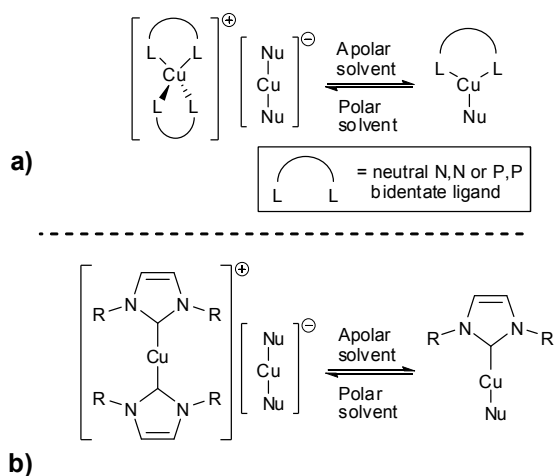


Scheme 25

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, they can be deprotonated before coordination and proceed through the path b, thus being more competitive in the reaction.<sup>115</sup>

#### 4 Well-defined Cu(I) complexes as catalysts

The idea of using well defined complexes as catalysts for these arylation reactions was not new,<sup>90-92, 100, 102, 106, 116-118</sup> but complexes Cu(I)/ligand/nucleophile in a 1/1/1 ratio such as those proposed by Buchwald (Scheme 19),<sup>109</sup> had not been thoroughly 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 coupled product.<sup>119</sup> 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.<sup>75</sup> Through NMR and conductivity studies they 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 26a).<sup>75</sup> The same behaviour was observed for phenoxides,<sup>76</sup> when used as nucleophiles. In the same year, the same behaviour was also observed, by Vici and co-workers, during their studies of Cu-catalysed trifluoromethylation of aryl halides, using carbenes as ligands (Scheme 26b),<sup>120, 121</sup> that in the meantime had started to be investigated in Ullmann reactions.<sup>122-124</sup> Some of the stable complexes isolated by Hartwig (Figure 4a and 4b) and Vici (Figure 4c and 4d) are reported below.



Scheme 26

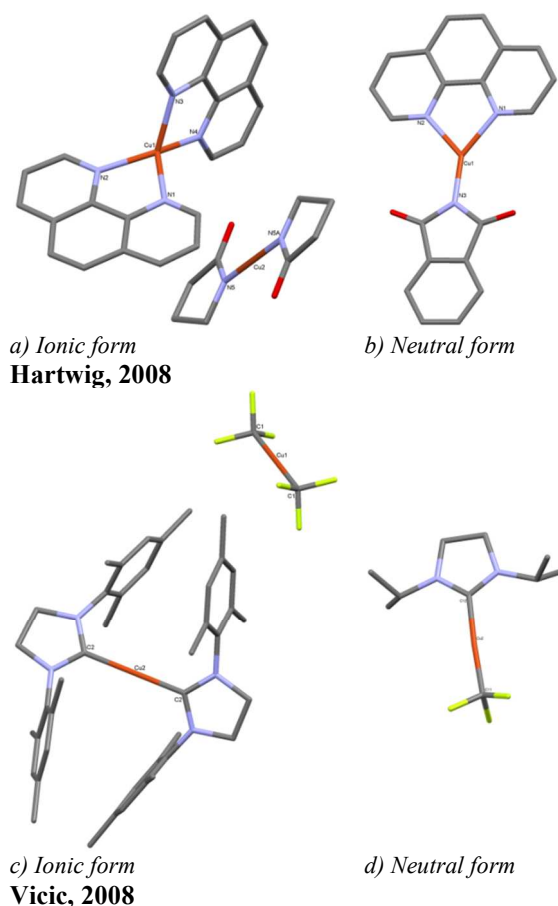


Figure 4

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.<sup>74</sup> 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-amidate Cu(I) anion, and a ligated K or Li cation (Figure 5). Whereas these

complexes were active in catalytic arylation reactions, similar complexes without added ligands were reported to be much less effective.<sup>74</sup> A very similar complex with a ligated sodium cation was obtained in Shyu's group in 2011.<sup>125</sup>

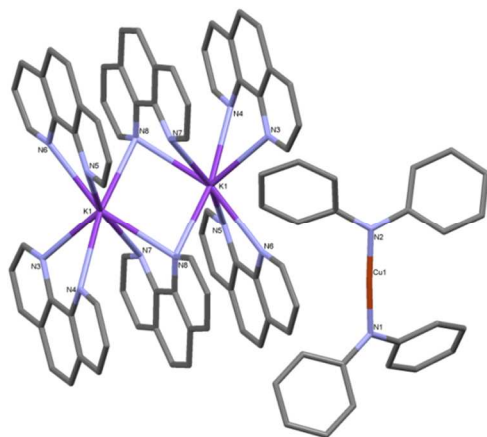


Figure 5

Attempts to synthesise analogous complexes using sulphur nucleophiles led to the formation of neutral dimeric structures (Figure 6a), and conductivity measurements did not account for ionic forms in polar solvents.<sup>77</sup> Despite the difference with the complexes reported in Figure 4, this complex was nonetheless very reactive in the coupling with aryl donors.

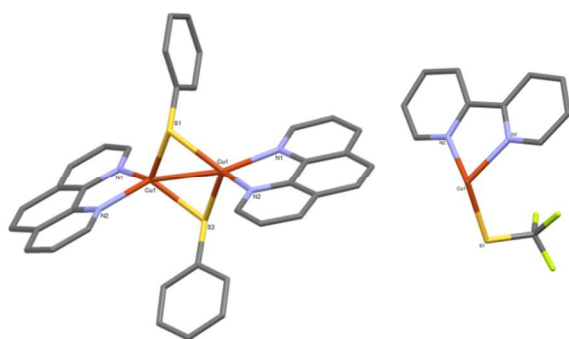
a) Dimeric form  
Hartwig, 2012b) Monomeric form  
Weng, 2013

Figure 6

A mononuclear complex with sulphur nucleophiles was obtained by Weng and co-workers using bipyridyl as a ligand (Figure 6b), although no neutral-ionic equilibrium was reported.<sup>126</sup>

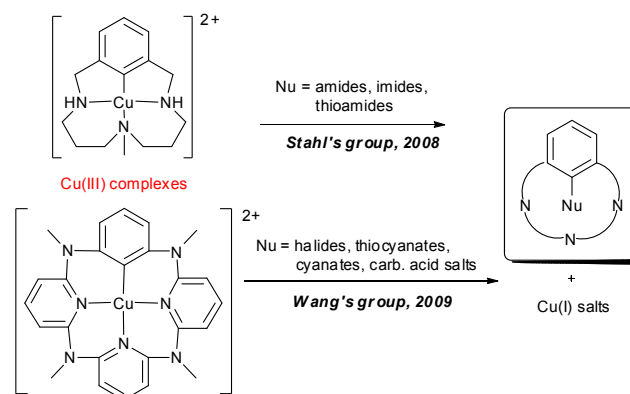
The existence of an ionic complex for thiophenols, analogous to that reported in Figure 4a, has been proposed, on the basis of *in-situ* ESI-MS studies, by Shyu in 2011.<sup>127</sup> Through ESI-MS, Shyu's group also confirmed the existence in solution of potassium/sodium-phenanthroline complexes analogous to that reported in Figure 5, which were observed during the arylation of thiols and anilines.<sup>125, 127</sup> Based on the species observed during the reaction, Shyu proposed that cuprate species such as [Cu(SAr)<sub>2</sub>]<sup>-</sup> or [Cu(NHAr)<sub>2</sub>]<sup>-</sup> 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<sup>+</sup> as counter cation in the stabilisation of Cu(I) intermediates (Scheme 16b).<sup>88</sup>

On the other hand, this is in contrast with what is showed in Scheme 19, where the diamidate complex is actually considered an inactive species.<sup>109</sup> Through the use of *in-situ* ESI-MS, complexes in which the Cu is coordinated to the aromatic ring of the aryl halide have also been identified.<sup>128</sup> For the use of Cu(I) complexes in photochemical Ullmann-type reactions see Section 2.2.

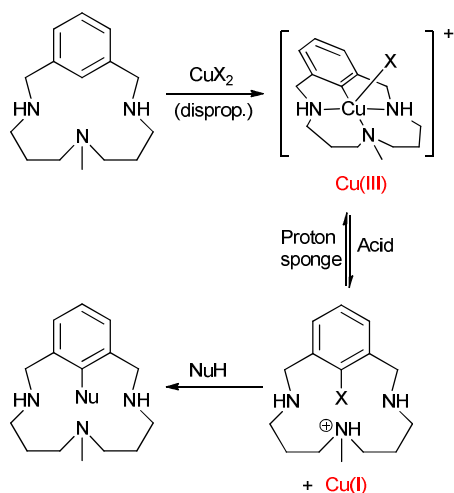
## 5 Cu(III) in Ullmann chemistry

In 2002 Ribas' group reported the synthesis and properties of a new family of Cu(III) organo-macrocyclic complexes, obtained initially by disproportionation of Cu(II) precursors in the presence of the ligands.<sup>129-131</sup> These complexes were, some years later, applied to Ullmann type couplings in Stahl's group, in particular to the arylation of amides.<sup>132</sup> This work represents the first example of well defined Cu(III) complexes used in Ullmann couplings. Similar complexes were used in the same period by Wang, for the coupling of different nucleophiles (Scheme 27).<sup>133</sup>



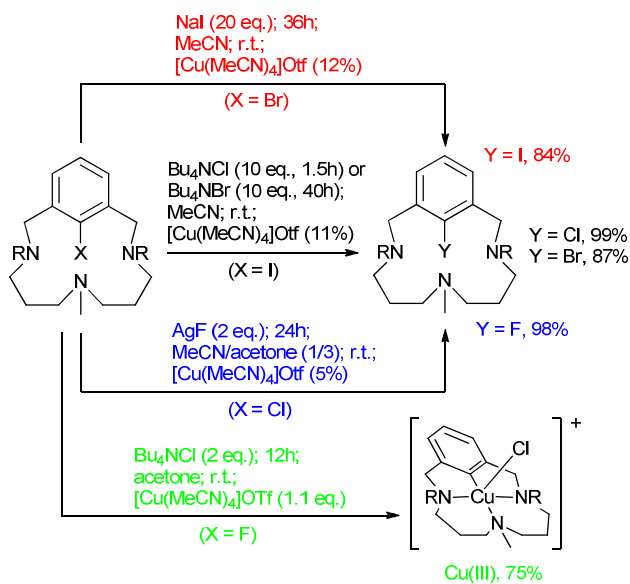
Scheme 27

In their study with different types of amides, Stahl and co-workers observed an increase in the reaction rate with lowering the pK<sub>a</sub> of the nucleophiles, which led them to hypothesise the involvement of the deprotonation process in the rate determining step.<sup>132</sup> They reported that two different mechanisms were possible that could correlate with the experimental kinetic data: direct nucleophilic substitution or reductive elimination from a Cu(III) intermediate.<sup>132</sup> Following investigation demonstrated the feasibility (under acidic conditions) of a reductive elimination from penta-coordinated Cu(III) complexes to furnish the coupled product. This reaction was reversed with the addition of a base to the solution, thus demonstrating the occurrence of an oxidative addition of Ar-X compound to Cu(I) (Scheme 28).<sup>134, 135</sup>



Scheme 28

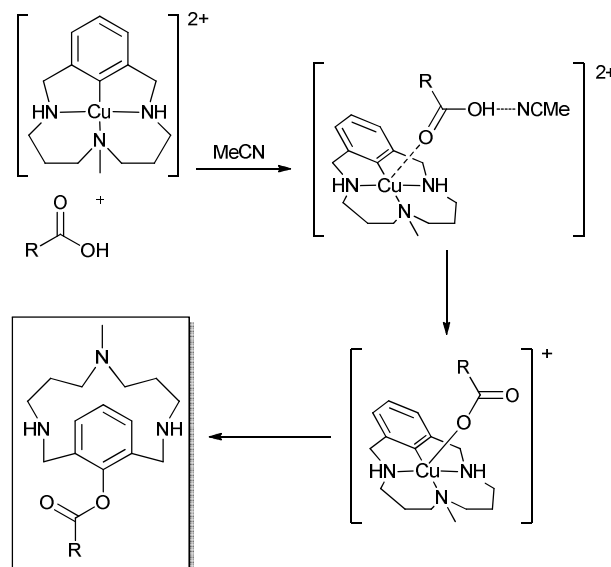
After the reductive elimination step, the addition of a nucleophile was found to lead to the formation of the substituted macrocyclic ligand (Scheme 28). The use of Ribas' macrocyclic ligand was applied some time later to halide exchange reactions on the halogenated macrocyclic ligand, simply adding a Cu(I) source and a salt of the desired halide (Scheme 29).<sup>136</sup> In these reactions, the formation of a specific halide could be controlled by precipitation of the inorganic side-products, and the reactivity followed the order  $I > Br > Cl$  for substitution by lighter halides, as expected for Ullmann-type reactions. The investigation of AgF as a nucleophile showed that substitution by fluoride was also possible. Interestingly, also oxidative addition of the Aryl-F product to Cu(I) and successive halide exchange on the corresponding Cu(III) complex was proved to be easy, opening the way to fluorine substitution reaction (Scheme 29).<sup>136</sup>



Scheme 29

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.<sup>137</sup> 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 30).<sup>137</sup>



Scheme 30

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).<sup>137</sup> It is noteworthy that, contrary to this system, in typical Ullmann couplings phenols with electron-donating substituents, less acidic, are more reactive. A similar mechanism was proposed for the same system for the coupling with S, Se and P nucleophiles, reported by Ribas and co-workers in a recent publication.<sup>138</sup>

## 6 Computational investigations

Recently, several publications dealing with computational studies about the Ullmann reaction have appeared.<sup>70, 75, 114, 139-141</sup> Ciofini and co-workers reported DFT calculations for the arylation of amines with  $\beta$ -diketones as anionic ligands, through aryl-halogen bond activation by an unusual N-halogen bond.<sup>139</sup> The theory of halogen-bonding (XB) is based upon the fact that halogens can behave as Lewis acids, and this makes halogen atoms potential acceptors for negative charges.<sup>142, 143</sup> In Ullmann-type couplings this interaction is in theory possible between the halogen atom of the aryl donor and the Cu/ligand/nucleophile negative complex,

in which, according to the authors' calculations, the negative charge is mostly localised on the nucleophilic nitrogen atom (Figure 7, I).<sup>139</sup>

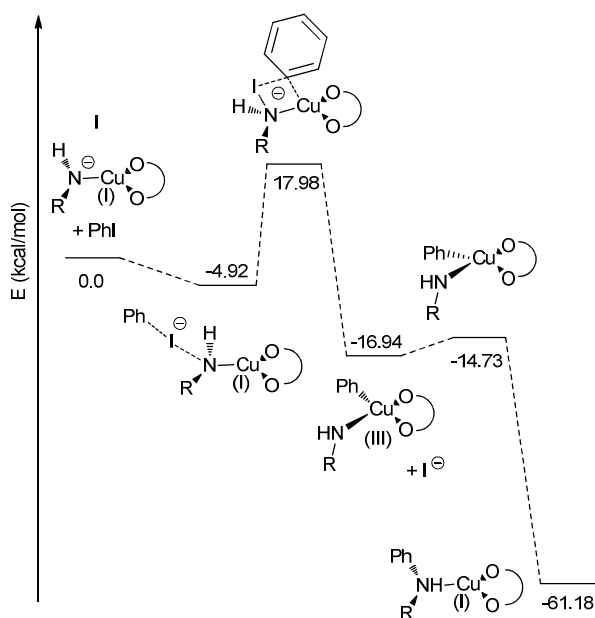


Figure 7

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 8).<sup>140</sup> Calculations on the Cu-catalysed hydroxylation of aryl halides (see Section 8.1.1) performed by the same authors led to the suggestion of a similar mechanism.<sup>107</sup>

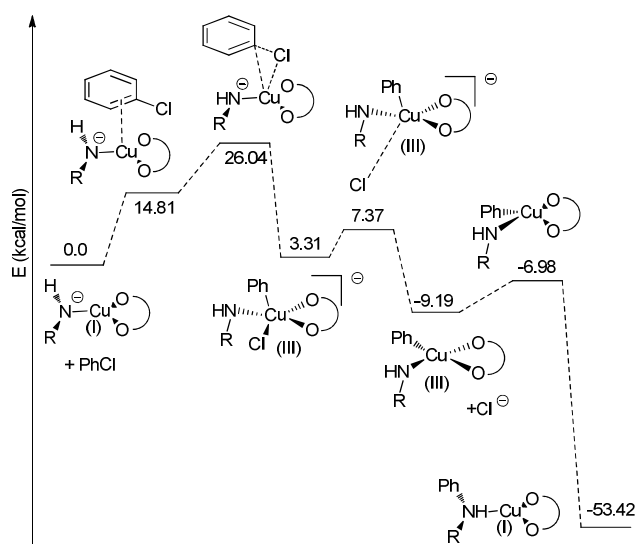


Figure 8

Apart from this, relatively few mechanistic investigations upon anionic ligands has been reported so far. Electrochemical and spectroscopic studies using  $\beta$ -diketones as ligands have been reported by Taillefer and Jutand,<sup>108</sup> and Lei and co-workers respectively.<sup>144</sup>

## 7 Scope and applications

Ullmann-type chemistry until the mid 1990s was characterised by many limitations in the scope of the reaction. In spite of this, however, many couplings on a variety of substrates and nucleophiles could still be performed.

The classical Ullmann reaction, leading to the formation of biaryls, was extensively investigated, and exhaustive lists of the involved moieties until the mid 70s were reported by Fanta.<sup>34, 145,</sup>

<sup>146</sup> For the synthesis of non-symmetric biaryls, the use of an activated (with electron-withdrawing substituents) aryl halide and a non-activated one was generally necessary to achieve good yields. On the other hand, the use of two activated or two non-activated aryl halides as substrates for the coupling usually led to the formation of mixtures, with very low selectivity. These and other interesting aspects of the reaction were extensively explained in a series of reports by Forrest in 1960.<sup>147-152</sup> Later, during the first half of the 1990s, another series, now specifically on asymmetric (atropisomeric) biaryl synthesis, was published by

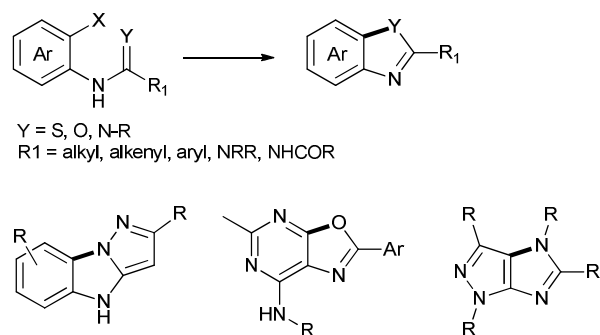
<sup>153-155</sup> Meyer and Nelson. Successive results have been recently extensively reviewed.<sup>156</sup>

The substitution reaction for a variety of other nucleophiles was extensively studied as well, and before the mid 1980s the first reactions with N, O, S, P, C and Se nucleophiles had already been performed; many references to that pioneering work can be found in Lindley's review.<sup>40</sup> Since the early 2000s the use of ligands has increased the scope of Ullmann-type couplings, and Cu source/ligand systems were applied to the synthesis of di- and triaryl amines,<sup>29, 90</sup> *N*-arylation of heterocyclic compounds<sup>99, 102,</sup> <sup>157, 158</sup> and hydrazides,<sup>159</sup> *O*-arylation of aromatic<sup>96, 100</sup> and aliphatic alcohols,<sup>160</sup> synthesis of arylamides<sup>157, 161</sup> and arylation and vinylation of phosphorus nucleophiles.<sup>162-164</sup> The first couplings with sulphur nucleophiles were reported in this period, and have been reviewed by Stambuli.<sup>165</sup> Also some applications in total synthesis can be found in the literature.<sup>58, 166-168</sup>

Interesting applications of Ullmann-type couplings are the syntheses of heterocyclic scaffolds. Either intermolecular, intramolecular, and tandem/domino/multicomponent processes involving Ullmann couplings have been applied to the synthesis of such compounds,<sup>26, 169-173</sup> but intramolecular reactions are of particular chemical interest, due to the many synthetic possibilities that they offer. We will review here some of the most interesting synthetic strategies encountered in Ullmann chemistry, and will highlight some aspects regarding regioselectivity, chemoselectivity, and interesting disconnections available for Ullmann coupling employment.

Among the earliest heterocyclic nucleuses encountered in Ullmann-type chemistry are benzothiazoles, benzoxazoles and benzimidazoles. The first use of copper catalysis in the synthesis of benzothiazoles from *o*-iodo thioanilides was reported by Bowman in 1982.<sup>72</sup> After this first publication, many examples of benzothiazoles, benzoxazoles and benzimidazoles synthesis through analogous processes were reported.<sup>174-181</sup> The same

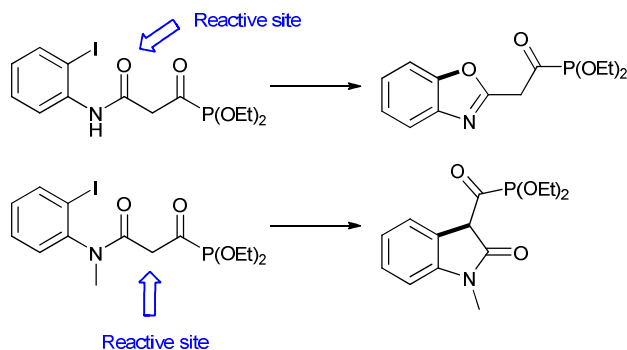
procedure was also used for the synthesis of more complex structures, such as those reported below (Scheme 31, the bond formed is highlighted):<sup>182-184</sup>



Scheme 31

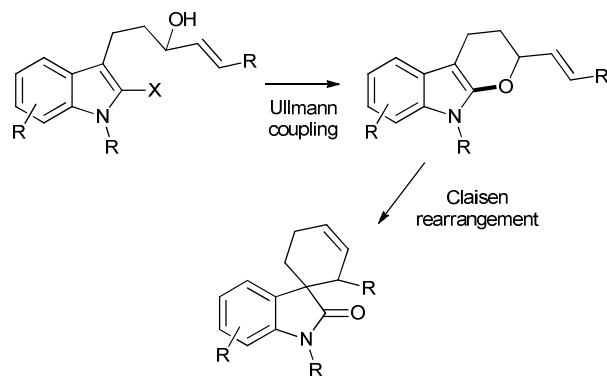
Alternatively, the synthesis of these compounds can be accomplished through cascade, tandem or domino reactions, where the anilide or thioanilide is formed *in situ*.<sup>185-188</sup>

In 1993, investigating arylation reaction of phosphonate-based carbanions including a 1,3-diketone moiety, Minami observed that the intramolecular version using iodoanilides derivatives led to benzoxazoles, but *N*-methyl iodoanilides were instead reacted to give oxindole derivatives, due to the coupling between the halogenated ring and the acidic methylene group (Hurtley reaction), since the formation of the amidic enol was made unavailable (Scheme 32).<sup>174</sup>



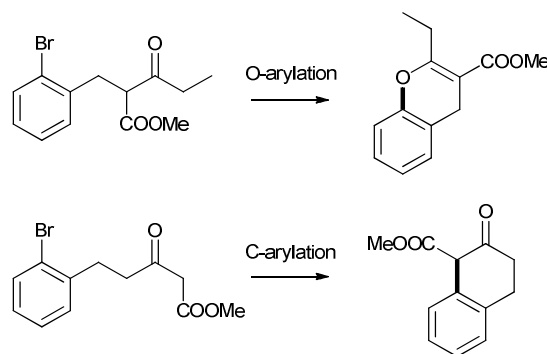
Scheme 32

*N*-protected or unprotected oxindoles can also be obtained by intramolecular copper catalysed amidation reaction, either directly or through domino processes.<sup>189-191</sup> Another interesting strategy was developed by Kobayashi and co-workers for the synthesis of spirocyclic oxindoles, in which an intramolecular copper catalysed formation of a dihydropirane ring was followed by a Claisen rearrangement, giving the final oxindole (Scheme 33).<sup>192-194</sup>



Scheme 33

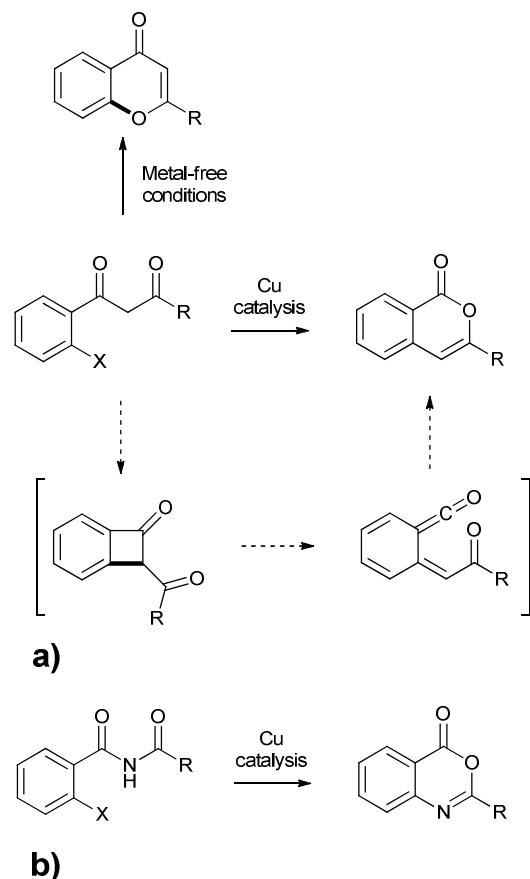
The synthesis of oxazoles is an example of the use of enols as intramolecular nucleophiles. Minami's example<sup>174</sup> shows how 1,3-diketone moiety can act as an oxygen or carbon nucleophile, depending on the structural features of the starting material. Another notable example of this kind was reported by Li in 2006.<sup>195</sup> Li and co-workers observed that the position of the diketone residue in the substrate could also determine the selectivity between C and O arylation, thus allowing the synthesis of benzopyranes and dihydronaphthalenones (Scheme 34).



Scheme 34

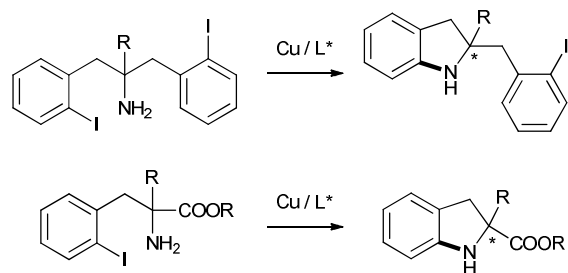
In 2011 Fu reported the synthesis of chromone derivatives through intramolecular O-arylation of 1,3 diketone compounds in copper-free conditions (Scheme 35a).<sup>196</sup> One year later Shen reported that the use of copper catalysts for the same reaction led to completely different results: isocoumarin derivatives were in fact obtained after the reaction.<sup>197</sup> Their formation was proposed to derive from an intramolecular C-arylation of the methylene carbon, followed by a rearrangement to release the strain of the four-member ring formed (Scheme 35a). The same transformation was demonstrated for *N*-acyl-2-halobenzamides, leading to the formation of benzoxazinones (Scheme 35b).<sup>198</sup>





Scheme 35

Recently, Cai reported the first examples of enantioselective intramolecular C-N coupling, used for desymmetrisation of an achiral compound, and in kinetic resolution (Scheme 36).<sup>199, 200</sup> Chiral BINOL ligands were used in these processes.



Scheme 36

Also the synthesis of medium-size rings was explored through Cu-catalysed strategies. Important differences exist between the intermolecular reaction (or intramolecular formation of small size rings), and the intramolecular formation of medium and large size rings, which need to be considered. Whereas, normally, intermolecular reactions benefit from high concentration, intramolecular formation of medium-large rings can be severely affected by high concentrations, which can favour intermolecular transformations, leading to an array of undesired products. Also, structural and conformational features can assume important roles

in determining proximal vicinity and, therefore, reactivity. Moreover, in metal mediated transformations, the presence of coordinating groups in the acyclic precursor is also to be considered. All these aspects are evident in Cu-catalysed intramolecular reactions, and some of them will be highlighted here. The first examples were reported by Ma and Fukuyama in early 2000s, who performed the synthesis of seven-member rings through an intramolecular amination reaction.<sup>166, 201</sup> Zhu and Spring investigated this process more in depth, reporting several examples of, respectively, intramolecular amidation and amination.<sup>202, 203</sup> Fu reported an intramolecular arylation of phosphoramidates and carbamates, leading to up to 16-member nitrogen containing rings,<sup>204</sup> while Argade reported investigations on the synthesis of more complex fused structures through intramolecular arylation of heterocycles<sup>205</sup> (Figure 9).

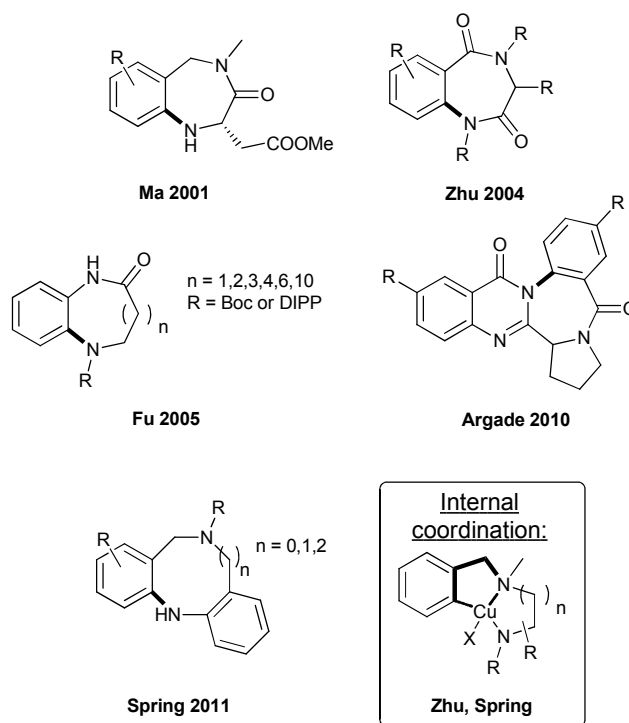
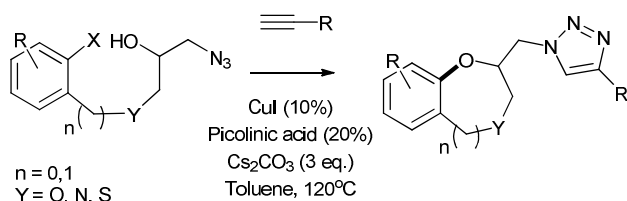


Figure 9

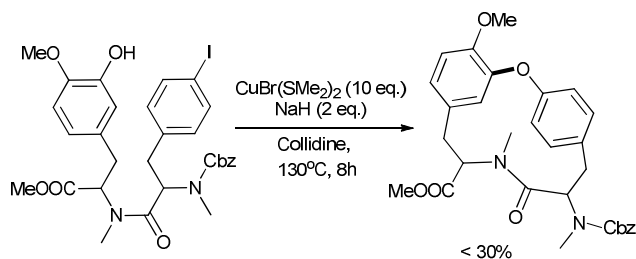
Interestingly, both Zhu and Spring reported that the reaction did not succeed when no additional nitrogen atom was present in the initial starting material, and suggested that this atom would coordinate to the copper atom, thus favouring the intramolecular coupling (Figure 9).<sup>202, 203</sup> Fu's procedure<sup>204</sup> showed instead to be dependent on the presence of the protecting group on the amine. The reaction failure in the absence of this group was related to conformational effects.<sup>204</sup> Fewer reports can be found in the literature regarding medium size ring synthesis through C-O bond formation. A recent example was furnished by Swamy, who reported the synthesis of a series of triazole-tethered heterocycles through one-pot Ullmann coupling and click reaction (Scheme 37).<sup>206</sup>



Scheme 37

Interesting comparisons were made between Cu and Pd catalysis in these reactions have been made by Zhu, Argade and Piersanti.<sup>202, 205, 207</sup>

Although not yet particularly exploited for the synthesis of medium size rings, copper catalysed C-O bond formation has found wide application in the synthesis of larger rings, which are of great biological interest. Before the 1990s, syntheses of macrocyclic (>15 member ring) peptides containing the diaryl ether moiety were approached by intermolecular formation of aryl ethers through Ullmann reaction, followed by macrolactamisation or other macrocyclisation reactions.<sup>208</sup> In 1991-1993, the pioneering work of Boger and co-workers led to the development of an intramolecular diaryl ether formation as the key macrocyclisation step, although for smaller rings (14 member), applied to the synthesis of the natural macrocycles bouvardin and deoxybouvardin (Scheme 38).<sup>209-213</sup> Despite the use of ten equivalents of a Cu source and the relatively low yields obtained for the cyclisation step, the method revealed to be much more effective than other previously reported procedures.



Scheme 38

In 1999 Nicolaou improved Boger's procedure and applied Ullmann macrocyclisation to the total synthesis of vancomycin (2.5 equivalents of copper source were used).<sup>214</sup> Since then, several authors have reported about syntheses of natural macrocycles through Ullmann macrocyclisations. In general the conditions used are harsher than those required for intermolecular or other intramolecular reactions, for example higher temperatures and larger amounts of catalyst are often necessary, but several catalytic mild conditions were sometimes successful. Diaryl heptanoids (15 member ring) are one of the most common target molecules for Ullmann type chemistry, and are obtained through intramolecular aryl ether formation.<sup>215-218</sup> The coupling of an aryl halide and an aliphatic alcohol was used by Uchiro as a key step for the synthesis of the strained 13 member ring of hirsutellone B (conditions: CuI 6 eq., phen 12 eq., Cs<sub>2</sub>CO<sub>3</sub> 120 eq., in toluene at 160°C).<sup>219</sup> Intramolecular amidation reactions were instead used by Panek and co-workers for the synthesis of

reblastatin, geldanamycin and autolytimycin (conditions: CuI 0.5 eq., DMEDA 1 eq., K<sub>2</sub>CO<sub>3</sub> 3 eq., in toluene at 100°C).<sup>220-222</sup>

## 8 Applications in green chemistry

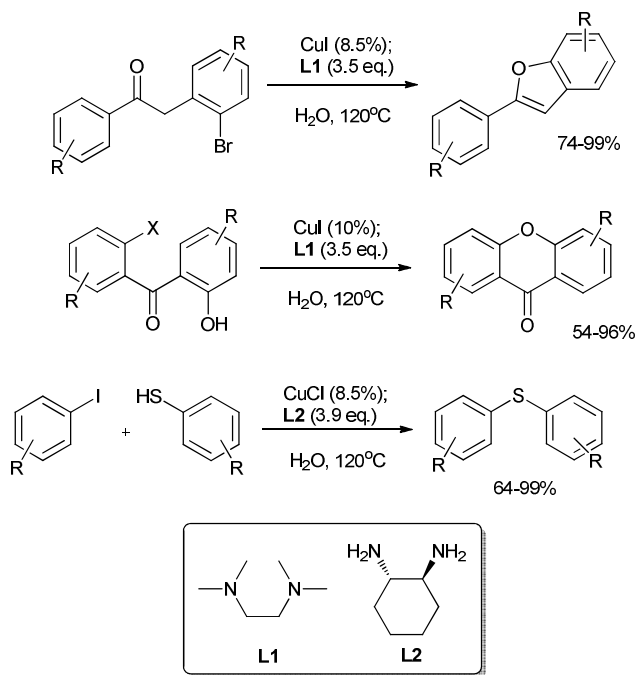
An interesting aspect of Ullmann-type chemistry, which has been emphasised only few times in the literature,<sup>223</sup> is its application in green methodologies and procedures. Green chemistry is acquiring an increasingly important role in modern research, and many metal-catalysed reactions have been subjected to investigation regarding the use of water or other eco-friendly solvents,<sup>224</sup> and heterogeneous systems.<sup>225</sup> Cu-catalysed carbon-heteroatom coupling reactions have also been addressed for this type of chemistry in recent years. Here we will present the current research in these two, most investigated fields.

### 8.1 Reactions in water

Early reports concerning Ullmann reactions in water or aqueous media appeared in the early 2000s,<sup>226, 227</sup> but it was only around the years 2006-2009 that this field saw an expansion. A discussion on previous work can be found in another review.<sup>228</sup>

It is possible to identify two different procedures in the literature: the use of phase transfer catalysts (PTCs) to favour the reaction is the most common procedure, but a few notable examples of reactions performed in the absence of this aid have also been reported. A recent publication also reported the use of surfactants to favour the formation of coupling products in water.<sup>229</sup> In general, these procedures require typical amounts of copper source and ligand, between 5 and 20 mol%, high reaction temperature (typically 100-130°C) and strong bases such as KOH or NaOH (amount: 2 eq. relative to substrate), which are not effective in the reactions in organic solvents. When a PTC is used, typical Cu amounts are 10-20%.

In 2006-2009, investigations in Dominguez's group showed that intramolecular C-O and intermolecular C-S bonds could be formed in water in the presence of Cu(I) sources and an excess of diamines, which were used as ligands and base at the same time (Scheme 39).<sup>230-232</sup> At the end of the reaction, the product was collected by extraction with an organic solvent, and the aqueous solution containing the catalyst could be reused as medium for other reactions.<sup>231</sup> An interesting article was published by Wei and co-workers, who reported the arylation of small chain aliphatic amines in water using Cu powder as a catalyst without any ligand or base (the amine itself acted as ligand and base, and was used in excess).<sup>45</sup>

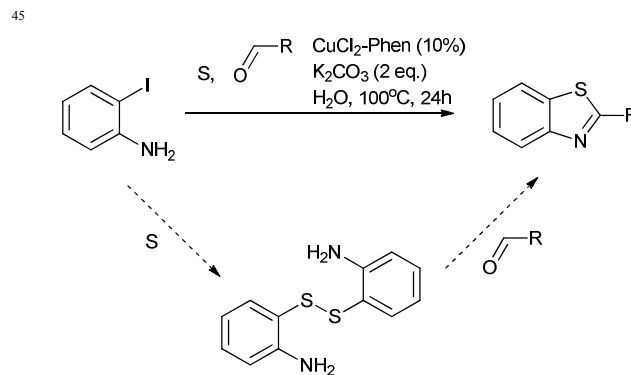


Scheme 39

In 2007-2008 Chan's group reported the use of potassium phosphate or sodium hydroxide in combination with the phase transfer catalyst TBAB (tetrabutylammonium bromide) for the arylation of *N*-heterocycles, phenols and thiols in organic solvents, without addition of any ligands. It was observed that excessively dry bases were detrimental for the reaction outcome, suggesting that small amounts of moisture were beneficial for the reaction. Reactions in the absence of any phase transfer catalyst were observed to furnish no coupling products.<sup>113, 233, 234</sup> In the same period many reports also appeared on the use of TBAB in combination with organic ligands in water, for the arylation of *N*-nucleophiles. An interesting example is given in Wan's work, who studied the use of microwave for these systems, leading to high yields in few minutes for the arylation of aromatic and aliphatic amines and *N*-heterocycles by aryl bromides.<sup>235-237</sup> Wang reported the use of TBAB in water using low amounts of Cu source for arylations of azoles with aryl iodides and bromides (0.1 mol% and 1.0 mol% of CuI respectively).<sup>238</sup> In 2009 Zhou reported the use of TBAB in small amounts (5%) in combination with a Cu(II)-salen complex (2%) in water, reporting the re-use of the aqueous medium up to three times without yield changes.<sup>239</sup> The use of aryl chlorides in these systems was reported by Fu and co-workers, using *ortho* substituted chlorides (see Section 3) or the addition of KI to initiate the reaction.<sup>240</sup> Recently the synthesis of symmetrical disulfides and diselenides through coupling of elemental chalcogens with aryl iodides was reported by Ke and Zhou, using TBAF (tetrabutylammonium fluoride) as PTC. Interestingly, caesium carbonate was used as a base (this base is usually ineffective in water), and electron rich aromatic iodides reacted better in the coupling, in contradicition to what was generally observed.<sup>241</sup> The use of PTCs such as TBAB or TPAB (tetraphenylammonium bromide) in aqueous coupling in the absence of ligands was also reported for thiophenols<sup>242</sup> and

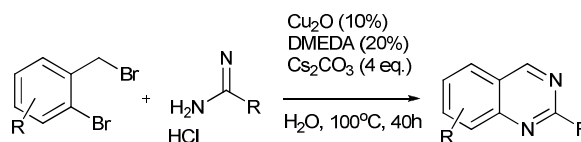
amides.<sup>243</sup> Apart from TBAB or similar PTCs, other compounds were reported to be effective in facilitating coupling reactions in water, such as PEG-400.<sup>244</sup>

40 Interesting examples of multicomponent and domino reaction processes catalysed by Cu in water have also been reported. Zhou's group reported a multicomponent reaction between *o*-iodoanilines, aldehydes and elemental sulphur in water catalysed by cupric chloride (Scheme 40).<sup>245</sup>



Scheme 40

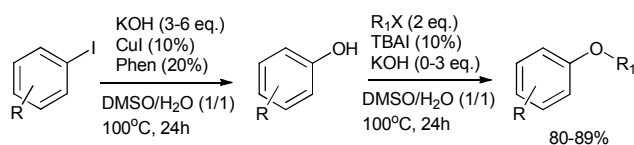
Another example is the synthesis of quinazolines through a 50 domino process from *o*-halobenzyl halides and amidines reported by Beifuss and co-workers (Scheme 41).<sup>246</sup>



Scheme 41

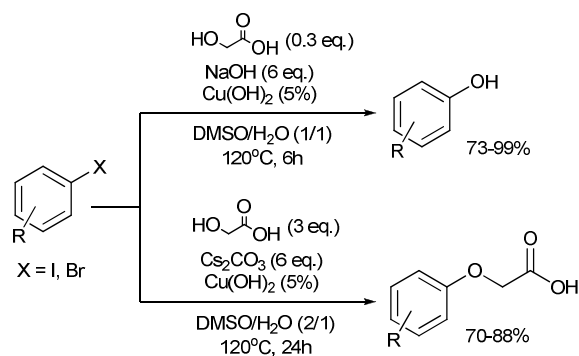
### 8.1.1 Hydroxylation reactions

In recent years, with the increased level of the research in Ullmann type couplings, new nucleophiles have started to be investigated, and classes of compounds such as *N*-unsubstituted 60 anilines, phenols and thiols can now be obtained by Cu catalysis. An obvious problem with these products is that they can further react with the initial aryl halide to form diarylamines, ethers or thioethers, and the formation of one or the other product strongly depends on the conditions and solvent employed.<sup>247, 248</sup> In particular, phenols have been mostly investigated in this field, and are interesting for the purpose of this section because of their easy formation in aqueous media. Hydroxylation reactions were observed already by Hurltley and Bethell,<sup>39, 68</sup> but it was not until the 2000s that focused research was undertaken. In 2009 Taillefer and You independently reported the use of CuI as a catalyst for such a reaction in a mixture DMSO/H<sub>2</sub>O : 1/1, using CsOH or KOH as coupling partner/base and  $\beta$ -diketones and phenanthroline as ligands respectively.<sup>247, 249</sup> You *et al.* reported the results obtained from a one-pot process to obtain aryl alkyl 75 ethers, with the aid of a PTC (TBAI, tetrabutylammonium iodide) (Scheme 42).<sup>249</sup> The same methodology was demonstrated again some years later, using similar conditions.<sup>250</sup>



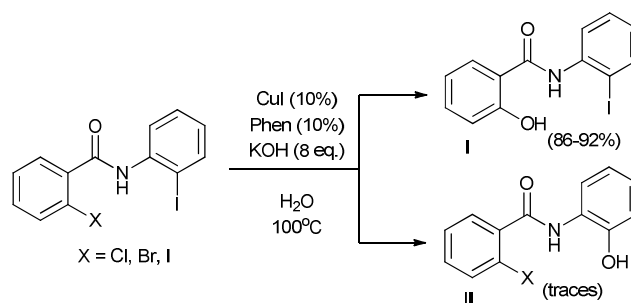
Scheme 42

5 Ma and Chae reported later some limitation of the hydroxylation reaction, such as hydrolysis of cyano and ester substituents,<sup>251, 252</sup> while competition investigations were performed by Sekar.<sup>253</sup> their system (glucose was used as a ligand) proved to be selective for phenol formation in the presence of different *O*- and *N*-nucleophiles. Chae reported in 2013 the use of glycolic acid as ligand/additive for the hydroxylation of aryl halides in DMSO/water mixtures catalysed by Cu(OH)<sub>2</sub>.<sup>252</sup> Changing the conditions they were able to promote the coupling with the acid over the hydroxylation reaction (Scheme 43). Interestingly, the authors were also able to scale the reaction up to 100 mmol of aryl halide, achieving high yields.



Scheme 43

20 Fewer reports were published concerning the use of water as the sole solvent: these reactions were only few times performed with the aid of a PTC, although without particular benefits to the reaction conditions.<sup>248, 254</sup> From this point of view an improvement was achieved by Xu and Feng, who reported the use of CuI nanoparticles as heterogeneous and recyclable catalyst for the synthesis of phenols, anilines and thiols in water (the last two with the addition of concentrated liquid ammonia and sulphur respectively).<sup>255</sup> Without the addition of any ligands, and using tetrabutylammonium hydroxide (TBAH) as PTC/base they were able to obtain several phenols from aryl iodides and bromides at 60°C and 80°C respectively. Low temperatures were also made possible for the reactions with ammonia (r.t.) and sulphur (40°C). An interesting report by Kumar *et al.* showed the formation of 2-hydroxybenzamides in one-pot from 2-chlorobenzoic acid in water without any PTC with Ph as ligand.<sup>256</sup> The authors observed that the hydroxylation at the *ortho* position to the amidic group was preferred even in the presence of an accessible iodide in the same substrate (Scheme 44), which they proposed as the coordinating effect of the amido group<sup>256</sup> (see Section 3).



Scheme 44

## 8.2 Heterogeneous Ullmann couplings

The potential use of heterogeneous Ullmann-type couplings in the pharmaceutical industry, and the increasing attention to recycling and reuse of metal-based catalysts led recently to many reactions being heterogenised in different ways.<sup>225, 257</sup> The use of heterogeneous catalytic systems is of importance for the quality of the final product and from the economical point of view. In fact, the ease of separation and recovery of the catalyst leads to a lower amount of metal leached in the desired products, and makes the reuse of the catalyst for many cycles of production possible. Moreover, the improved technologies in material chemistry have furnished the availability of nanostructures and nanoporous solids with very large surface areas, which lead to increased yields when compared to homogeneous catalysts. Several reports have appeared since the years 2006-2007 on cross coupling reactions catalysed by silica-<sup>258-262</sup> and polymer-supported<sup>263</sup> Cu species, dendrimeric ligand systems<sup>264</sup> and other heterogeneous copper sources,<sup>265-267</sup> and a discussion on some of these developments can be found in a recent review by Taillefer.<sup>223</sup>

### 8.2.1 Copper nanoparticles

Nowadays, metal nanoparticles have assumed an important role in catalysis, and many investigations have been reported on their catalytic performance.<sup>268, 269</sup> Of course, chemical and physical properties of nanoparticles, such as chemical composition, surface reactivity, size, surface area, tendency of aggregation, strongly depend on the preparation method and the starting materials used. In the case of nanoparticles supported on porous solids, or coated with polymers many other properties are also to be considered when studying their performances in catalysis.<sup>270, 271</sup> Because of this, it is often difficult to compare the results reported in the literature. In this section the general features of non-supported Cu nanoparticles will be discussed, while polymer-stabilised,<sup>272</sup> silica-supported,<sup>273, 274</sup> graphene oxide-supported,<sup>275</sup> nitrogen-doped carbon-supported nanoparticles<sup>276</sup> and nanoalloys<sup>277</sup> will not be discussed. In 1998, Gedanken reported a comparison of different Cu nanoparticles for the catalytic conversion of iodobenzene to biaryl (classical Ullmann reaction), pointing out that different particle size led to very different catalytic activity.<sup>278</sup> This fact was later confirmed for the coupling of iodobenzene and phenol.<sup>279</sup> The different efficiency of different particle size could be due to the different surface areas, which decreases with increasing the particle size. However, the formation of aggregates

(which could occur during the reaction or even before) is also to be considered: despite many authors having reported that particle size and shape for CuO or CuI nanoparticles remained the same even after several reuse cycles,<sup>280-283</sup> formation of aggregates was observed several times.<sup>279, 284</sup> The recovery and reuse of the Cu nanoparticles was generally reported to lead to very small loss of catalytic activity after several cycles of reaction, even at temperature higher than 100°C.<sup>280, 281, 285-287</sup> Leaching studies were undertaken by several authors and, after filtration/centrifugation of CuO/CuI nanoparticles from the reaction solution, no trace of copper was detected by ICP analysis of the remaining solution,<sup>283</sup> and no coupling reaction occurred if the remaining solution was used to catalyse the coupling.<sup>281, 282</sup> These experiments demonstrate that leaching of Cu species in the solution using this kind of particles is at least improbable, (thus rejecting Paine's theory of leaching of active form of Cu species in solution<sup>42</sup>) and demonstrating the heterogeneity of the reaction. An important advantage of the use of Cu nanoparticles is the possibility to use small amount of catalyst, about 1-2 mol%,<sup>282, 285, 288, 289</sup> whereas the typical amount used in other conditions is around 5-10 mol%. However, the use of high boiling solvent and high temperature are often required to obtain good yields from several substrates.<sup>280, 282, 283, 285, 288</sup> The use of room temperature for the arylation of phenols and thiophenols was reported recently by Karvembu and co-workers, using KOH as base and 3 mol% of CuO nanoparticles.<sup>290</sup>

The scope of the reaction using copper nanoparticles showed to be broad, and couplings with nitrogen nucleophiles,<sup>281-283, 285, 287</sup> phenols,<sup>279-281, 286, 288</sup> thiols<sup>281, 284, 289</sup> and xanthogenates,<sup>291</sup> selenium and tellurium nucleophiles<sup>284, 292, 293</sup> were performed in the range of conditions reported. Interestingly, in several of these reports, also usually unreactive aryl chlorides were found to lead to coupling products in good to excellent yields.<sup>282, 286, 294</sup> Braga and Rodrigues also reported an interesting series of papers on the use of Cu nanoparticles in ionic liquids.<sup>295-297</sup>

## 9 Conclusions

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 (depending on the reaction, better results are achieved under air or inert atmosphere; also, Cu is known to form many complexes with molecular oxygen, thus broadening the variability of complexes in solution)<sup>298, 299</sup>, since Cu compounds are able to promote both radical and non-radical transformations. The generally accepted mechanism is now that involving an oxidative addition/reductive elimination cycle after coordination of the nucleophile. 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. It is noteworthy that the charge of the tri-coordinated intermediate depends on the identity of the ligand and the "deprotonation timing", which in turn would depend on

the acidity of the nucleophiles, leading to neutral or ionic complexes. These complexes (and their counter-ions, if ionic) 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 been identified yet. Below are listed the factors influencing the reaction.

- **Copper source:** either metallic Cu, Cu(I) and Cu(II) salts and oxides have been successfully used; Cu(I) salts give generally the best results;
- **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;
- **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; phosphine 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 cesium carbonate are the most effective. The latter is the most common, and is generally used in 2 equivalents relative to the substrate;
- **Solvent:** depending on the reaction, polar or non-polar solvents produce the best results; DMF, DMSO, and toluene are among the most used; NMP is a commonly used solvent for microwave reactions;
- **Temperature:** it is now usually in the range 80-110°C, but there are also examples of r.t. reactions; higher temperatures usually lead to higher yields;
- **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<sup>-</sup> in the reaction (ion exchange reactions are catalysed by Cu);
- **Nucleophile:** the better the nucleophile, the better the results, e.g. amines and thiols are more reactive than phenols and amides are more reactive than imides;
- **Steric hindrance:** a noticeable sensitivity is usually observed, both on the aryl halide and the nucleophile (e.g. a methyl group *ortho* to the nucleophilic site can dramatically reduce the yield);
- **Atmosphere:** usually a nitrogen or argon atmosphere lead to better results in Cu-catalysed couplings.

Although many experimental variables are nowadays well-known for Ullmann-type couplings, and some generalisations can be made to predict the general outcome of these reactions, there is still much uncertainty about the actual intermediates involved and the oxidation state of the metal during the reaction. This is, in our opinion, 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.

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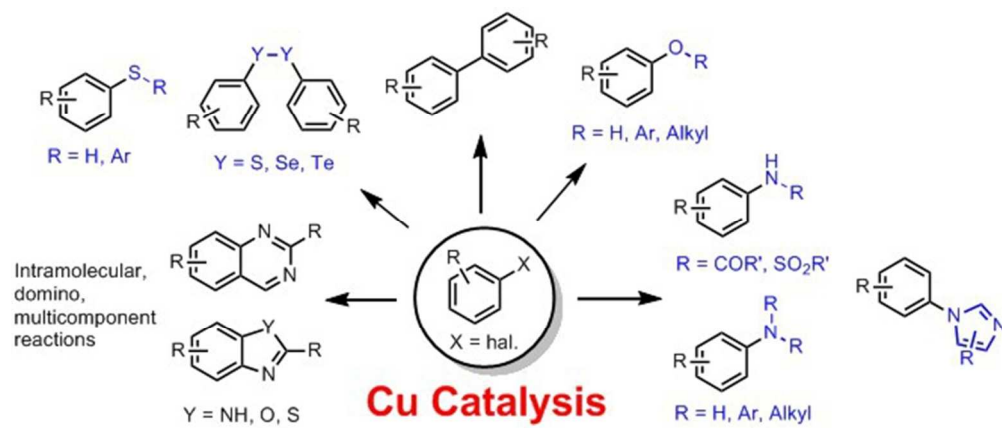


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Graphical abstract text:

Copper-catalysed arylations represent a valid and complementary alternative to Pd catalysis. This review discusses the different mechanism suggested for these reactions, and summarises some of the latest applications in synthesis.

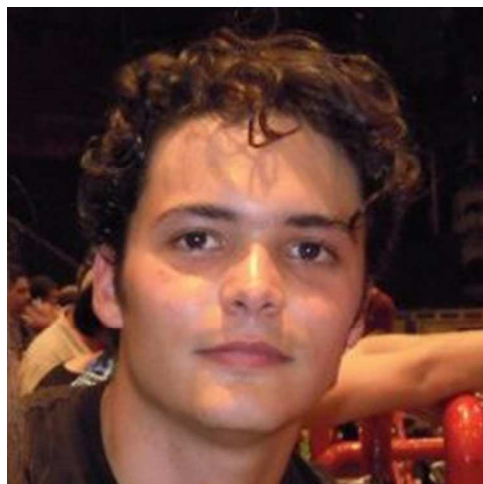
### Biographies:

Carlo Sambigioglio studied chemistry at the Università di Cagliari, Italy, receiving his Laurea Triennale in 2009 and Laurea Magistrale in 2011. In 2011 he spent 6 months as an Erasmus student at the Université Paris-Sud XI, working on the synthesis and photochemistry of dihydropyridinones with Dr. J. Ollivier, at the ICMMO/LSOM laboratory. In 2012 he started his PhD at the University of Leeds / iPRD (Institute of Process Research and Development) under the supervision of Dr. Patrick McGowan. His research project focuses on copper-catalysed arylation reactions.

Steve Marsden is Professor of Organic Chemistry at Leeds and a founding member of iPRD. He received his PhD (1993) from Imperial College London working with Professor Steve Ley FRS. Following a year as a NATO Postdoctoral Fellow at Columbia University with Professor Samuel Danishefsky, he commenced his independent career at Imperial College in 1994, moving to Leeds in 2001. His research interests are in the development of new catalytic processes (both metal and organic-based) and stereoselective synthesis. He received the Meldola Medal of the Royal Society of Chemistry in 1998 and was a Royal Society Industry Fellow 2008-2010.

John Blacker is Chair of Process Chemistry (jointly between Schools of Chemistry and Process, Environmental and Materials Engineering) and Technical Director of the (iPRD). He received his PhD (1988) at Université Louis Pasteur, Strasbourg working with Nobel Laureate Prof. J.-M. Lehn, then Postdoctoral Fellow with Prof. Sir Alan Fersht at University of Cambridge, before joining ICI and subsequent owners Zeneca, Avecia and Piramal Healthcare for 18 years. Blacker has interests in process chemistry, (bio)catalysis, reaction engineering and sustainable chemicals. In 2007 Blacker was awarded the RSC Industrial Award for Process Chemistry, and in 2002 the RSC Innovation Award for Teamwork.

Patrick McGowan completed his DPhil at the University of Oxford in 1992 with Prof. M. L. H. Green FRS. McGowan completed Postdoctoral stints at Stanford University and the University of Florida USA with Prof. Lisa McElwee-White and with Prof. Bruno Chaudret at the Laboratoire de la Chimie de Coordination du C.N.R.S., Toulouse, France. McGowan took up an Academic position at Leeds in 1996. His research interests lie broadly in the areas of catalysis and polymers and metals in medicine.



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