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Copper Catalysis

Picolinamides as Effective Ligands for Copper-Catalysed Aryl Ether Formation: Structure–Activity Relationships, Substrate Scope and Mechanistic Investigations

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Abstract: The use of picolinic acid amide derivatives as an effective family of bidentate ligands for copper-catalysed aryl ether synthesis is reported. A fluorine-substituted ligand gave good results in the synthesis of a wide range of aryl ethers. Even bulky phenols, known to be very challenging substrates, were shown to react with aryl iodides with excellent yields using these ligands. At the end of the reaction, the first examples of end-of-life Cu species were isolated and identified as Cu^{II} complexes with several of the anionic ligands tested. A preliminary mechanistic investigation is reported that suggests that the substituents on the ligands might have a crucial role in determining the redox properties of the metal centre and, consequently, its efficacy in the coupling process. An understanding of these effects is important for the development of new efficient and tunable ligands for copper-based chemistry.

Introduction

The discovery of copper-catalysed couplings between aryl halides and anilines, phenols and amides by Fritz Ullmann and Irma Goldberg during the early 1900s[1–4] represents the starting point of a significant amount of research in the field. Ullmann–Goldberg couplings could, until the late 1990s–early 2000s, be performed only on electron-poor aryl halides and under harsh conditions, such as high temperatures (>200 °C), the use of high-boiling polar solvents and stoichiometric or over-stoichiometric amounts of copper source.[5] At the end of the 20th century, pioneering research by, among others, Nicolaou,[6] Liebeskind,[7] Goodbrand,[8] Ma[9] and Buchwald,[10,11] led to investigations on the use of ligands in copper-catalysed cross-coupling reactions, allowing for much milder conditions to be used in these transformations, as well as increased substrate scope and functional group tolerance.[12–16] Ligands most frequently used nowadays for this type of chemistry are mostly bidentate ligands, such as phenanthrolines, bipyridines, β-diketones, β-diamines, and amino acids. Despite much investigation, the role of the structural features of the ligand in the reaction has not been yet completely understood, and very few structure–activity relationship studies have been reported for specific families of ligands.[17]

To establish the effect of the ligand structure on the reaction, and to develop new effective ligands for this process, we sought to perform a screening of commonly used, structurally diversified ligands in a model aryl ether synthesis reaction. Among other ligands, the use of picolinamide derivatives was of interest to us for several reasons. Firstly, their precursor picolinic acid was shown to be an effective ligand in several cases.[18,19] Moreover, while a great deal of mechanistic investigation has been performed on neutral ligands such as phenanthrolines,[20–22] diamines[20,23,24] and iminopyridines,[25] comparatively less information is available regarding anionic ligands in the reaction,[26,27] which can potentially influence the copper species involved. Furthermore, picolinamide derivatives contain several coordination sites, and different coordination modes with a metal centre are therefore available,[28] making them flexible and useful ligands in catalytic reactions. These ligands have been used in different transition metal-catalysed reactions.[29–35] Also, picolinamide-derived substrates are nowadays widely used as coordinating substrates in group-directed C–H bond activation, due to their favourable coordination to the metal centre.[36–38] Reports recently appeared on the use of picolinamides as ligands in Cu-catalysed synthesis of biphenyls,[39] and as chiral ligands in asymmetric Mannich-type reactions.[40] To our knowledge, however, no reports have appeared in the literature on the use of such ligands for Cu-catalysed C–O bond formation. Herein we report the use of *N*-arylpicolinamide ligands for the synthesis of aryl ethers. A structure–activity relationship study has led to the discovery of a very effective ligand, even under aerobic conditions. Bulky phenols, normally very challenging substrates for Cu-catalysed couplings, proved

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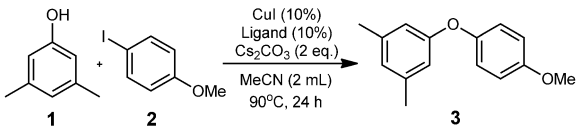
to be effective coupling partners, allowing for the synthesis of *ortho*-substituted aryl ethers, which have several applications in medicinal chemistry[41–43] and can be found in naturally occurring compounds.[44] The recovery of end-of-life Cu^{II} species and preliminary mechanistic investigation revealed the crucial role of the ligand in altering the redox behaviour of the metal centre, thus considerably influencing the reaction outcome.

Results and Discussion

Ligand screening, effect of conditions, and structure–activity relationships

The model reaction between 3,5-dimethylphenol (**1**) and 4-iodoanisole (**2**), leading to aryl ether **3**, was carried out in acetonitrile using CuI and Cs_2CO_3 as base (Scheme 1). In order to build a comparison of ligand structures for this reaction, we tested a diverse range of bidentate ligands (Figure 1, **L1**–**L11**). Typically, Ullmann-type reactions are performed under nitrogen or argon atmosphere, but several reactions under air have also been reported.[45,46] Moreover, the hygroscopicity of the chemicals used can influence considerably the outcome of the reaction. An example of this effect for caesium carbonate in Pd catalysis was reported by Denmark and co-workers.[47] In their studies, non-anhydrous base led to considerably better results than the corresponding dry one for the coupling between aryl halides and aryl silanols.[47] On the basis of these observations, we investigated the use of three different reaction conditions for each ligand in a preliminary screening (Methods A–C; Figure 1). Method A refers to reactions performed in air, using shelf chemicals and non-treated solvent (aerobic, non-anhydrous); method B involved reactions in air using dry reaction components (aerobic, anhydrous); finally, method C involved reactions under a nitrogen atmosphere, using anhydrous degassed solvent and dry chemicals (anaerobic, anhydrous). The results of the preliminary ligand screening are shown in Figure 1. Control experiments without ligand and with neither ligand nor copper were also performed, leading to maximum yields of **3** of 25% and 0%, respectively (see the Supporting Information, Table S1).



Scheme 1. Model reaction between phenol **1** and iodoanisole **2**.

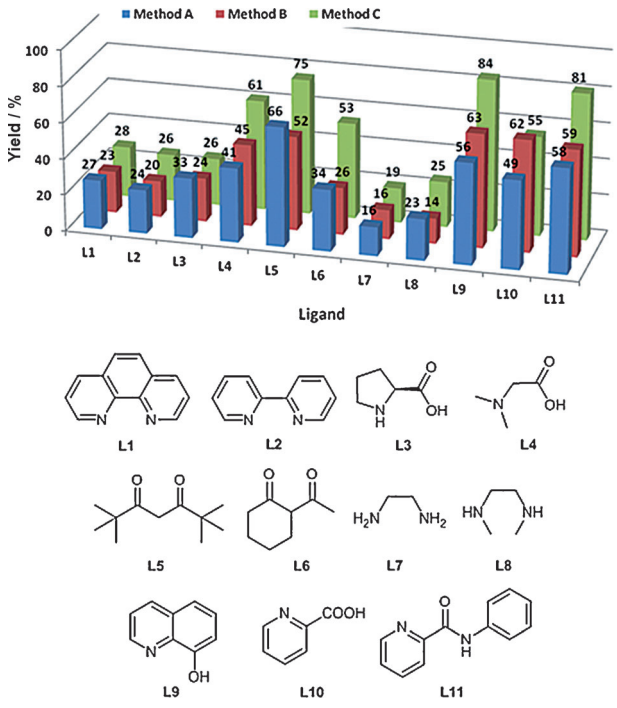


Figure 1. Effect of reaction conditions for several common ligands (GC yields).

From the results, it is clear that the effect of the reaction conditions strongly depends on the ligand used. The use of anhydrous chemicals (method B) did not generally influence the reaction outcome, with respect to method A, and only in some cases was a significant (>10%) increase (**L10**) or decrease (**L5**) in yield observed. The improvement obtained under nitrogen atmosphere (method C) is more remarkable, although only a few ligands (**L4**–**L6**, **L9**, **L11**) were positively affected. All of the other ligands seem to be relatively insensitive to the different conditions. Under air-free conditions a slightly higher amount of anisole, obtained as a side product from reductive dehalogenation of **2**, was generally formed (see the Supporting Information, Tables S2 and S4).

Among those tested, the picolinamide ligand **L11** proved one of the most effective ligands. The yield of **3** obtained in air (method A) is comparable with those observed with ligands **L5**, **L9**, and **L10**, while in anaerobic conditions (method C), only with ligands **L5** and **L9**. Encouraged by these results, we sought to modify the parent ligand **L11** to assess a structure–activity relationship. To investigate the role of the heteroaromatic group we compared picolinic acid **L10** and picolinamide **L11** with a series of other heterocyclic carboxylic acids (Figure 2, **L12**, **L14**, **L16**, with heterocycles furan, thiophene, and quinoline, respectively) and the corresponding *N*-phenylamides (**L13**, **L15**, **L17**) with method A. The use of ligands **L12**–**L17**, however, resulted in much lower yields than with **L10** and **L11** (Figure 2), thus confirming the primarily important role of the pyridine ring in the ligand.

Next, we synthesised a series of *N*-phenylpicolinamide ligands with electron-donating and electron-withdrawing substituents on the phenyl ring (Figure 3a, **L18**–**L26**), and tested them in the catalytic reaction in air (method A). The trends reported in Figure 3a show the remarkable effect of the substituent on the ligand. The addition of electron donating groups on picolinamide ligands (**L18**–**L20**) led to lower yields of **3** than the unsubstituted **L11**, while the presence of electron withdrawing groups (**L21**–**L26**) generally increased the activity of the ligand (Figure 3a). The importance of electronic effects on the ligand can be clearly observed by comparing ligands **L20** and **L21**; the substitution of the second methoxy group in

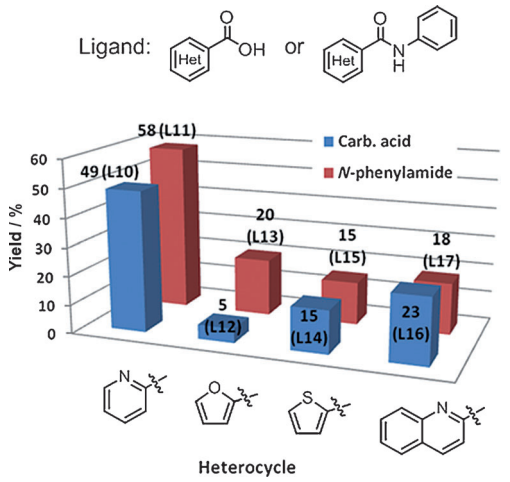


Figure 2. Effect of the heterocycle in carboxylic acid and amide ligands (method A, GC yields).

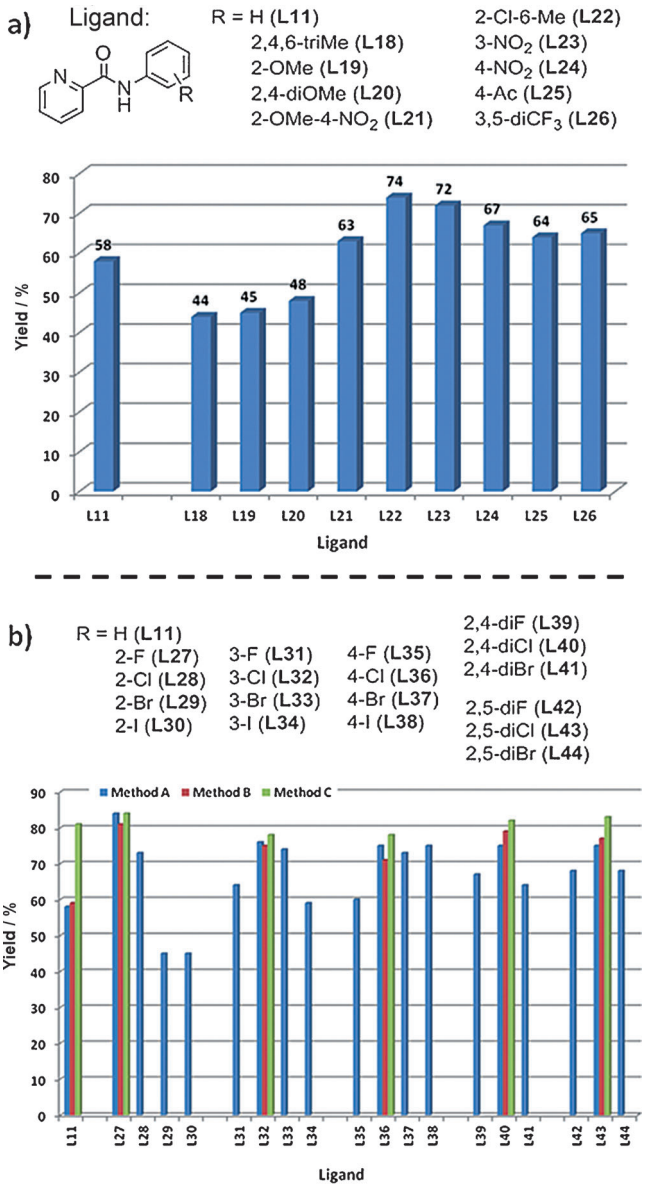


Figure 3. Screening of substituted picolinamide ligands (GC yields).

L20 with a nitro group in **L21** led to a 15% increase in the yield of aryl ether **3** (Figure 3a).

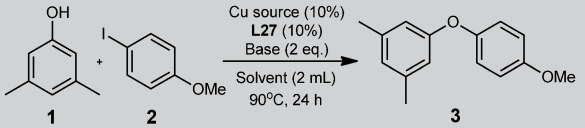
Ligand **L22**, functionalised with a chlorine atom (2-Cl-6-Me), led to the best yield among the ligands tested (74% of ether **3**). This prompted us to investigate halogen substituents on the ring, and a series of ligands substituted with F, Cl, Br and I in different positions (Figure 3b, **L27**–**L44**) were prepared and tested in the reaction with method A. Some of the halogenated ligands were more effective than the other electron-poor ligands (Figure 3b), in particular *N*-(2-fluorophenyl)picolinamide **L27** led to an excellent yield of **3** (84%) 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 expected, the use of method B did not particularly influence the reaction outcome; interestingly, even anaerobic conditions (method C) furnished little or no improvement, showing a much lower sensitivity to atmospheric oxygen than the parent **L11**. It is interesting to note that a trend is recognisable in the activity of differently substituted ligands. For ligands substituted in the *ortho* position (**L27**–**L30**), the activity decreased from fluorine to iodine; this trend may be due to the possibility of intramolecular coupling within the ligand, which has been previously observed.[48,49] The decrease in yield when using *ortho*-brominated ligands **L41** and **L44**, in comparison with **L33** and **L37** (*meta*- and *para*-substituted), may be due to the same reason. The yield decreases 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. A complete list of yields with these ligands is reported in Table S4 (see the Supporting Information).

Optimization and substrate scope for ligand L27 in air

After the identification of the 2-fluoro-substituted picolinamide **L27** as the best ligand for the model reaction in air, we sought to investigate the effect of other parameters. A screening of solvents, bases and copper sources was performed, and the results are reported in Table 1. The use of other polar solvents led to moderate yields (43–61%; Table 1, entries 2–5), whereas the use of toluene led to 17% yield (entry 6). DMSO, being a very common solvent for Ullmann arylations, was also used with ligands **L1**–**L11**, but no better results were obtained (see the Supporting Information, Table S5). The use of potassium and sodium carbonate as bases gave respectively 32% and 8% yield (Table 1, entries 7 and 8). The use of potassium phosphate led to 70% yield (entry 9), whereas potassium *tert*-butoxide only furnished **3** in 22% yield (entry 10). Different Cu sources, either metallic copper, Cu^{I} or Cu^{II} (Table 1, entries 11–14), all led to yields above 70%, showing the relative unimportance of the copper source in the reaction.

We then investigated the remaining parameters in the catalysis, such as amount of base, copper source and ligand, time and temperature (Table 2). An increase in the amount of caesi-

Table 1. Screening of solvent, base and Cu source.[a]

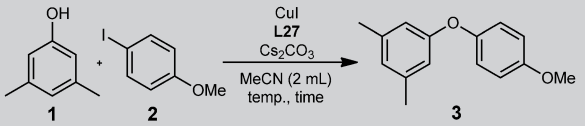


1 2 3

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	K_3PO_4	CuI	70
10	MeCN	*t*BuOK	CuI	22
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.

Table 2. Optimisation of the reaction for ligand **L27**.[a]



1 2 3

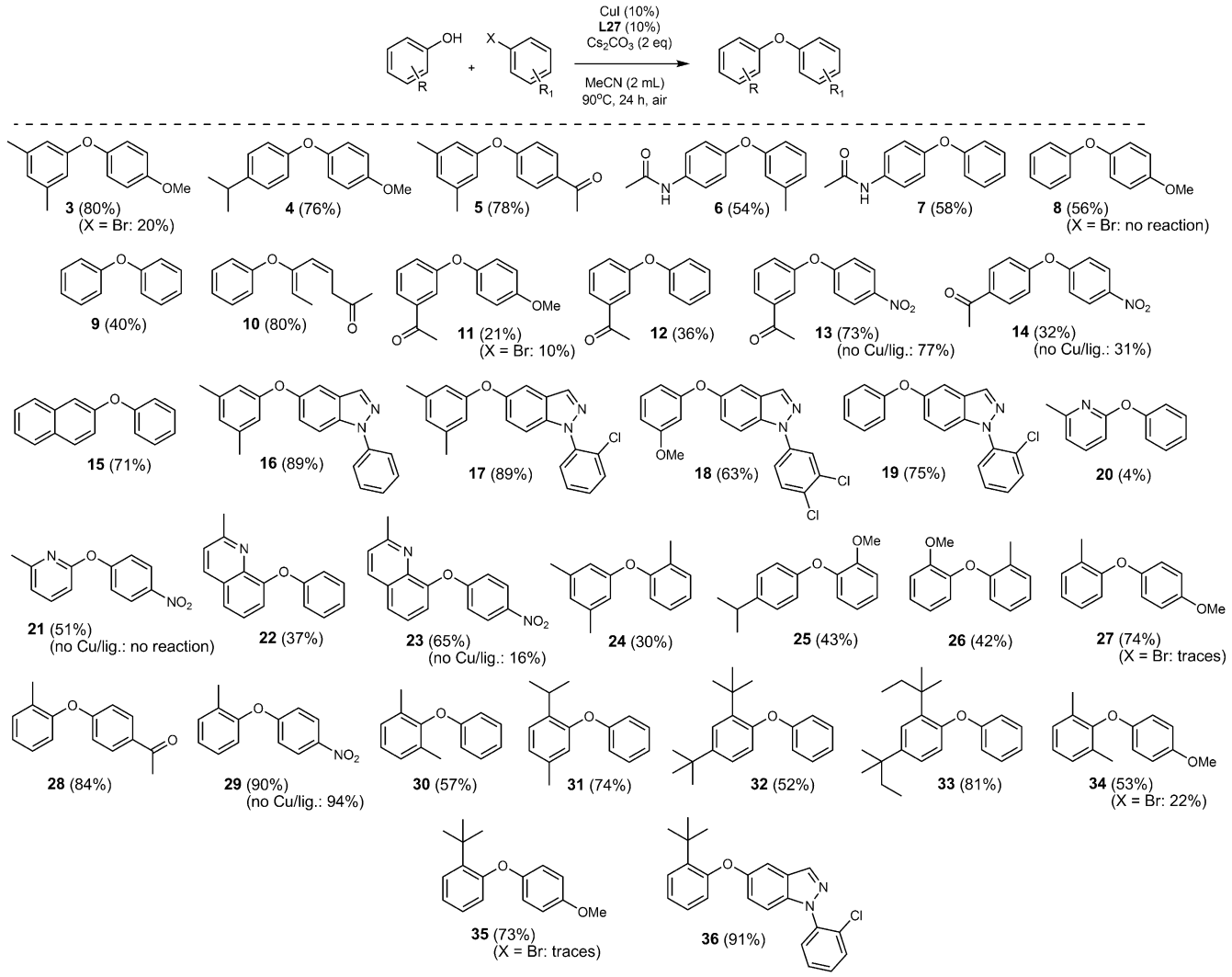
Entry	Equiv Cs_2CO_3	CuI/**L27** [mol%]	*t* [h]	*T* [°C]	Yield [%][b]
1	3.0	10/10	24	90	77
2	1.5	10/10	24	90	73
3	1.0	10/10	24	90	52
4	2.0	5/5	24	90	66
5	2.0	5/10	24	90	71
6	2.0	10/20	24	90	78
7	2.0	10/10	18	90	77
8	2.0	10/10	12	90	62
9	2.0	10/10	24	80	68

[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.

um carbonate did not lead to any improvement, but decreasing the amount of base led to a decrease in yield (Table 2, entries 1–3). The use of 5 mol% of copper iodide also led to decreased yields (Table 2, entries 4 and 5), and higher amounts of ligand did not have any beneficial effect (entry 6), so the initial ratio 1:1 (10 mol% each) was considered optimal. Finally, either reducing the reaction time or lowering the temperature resulted in lower yields (Table 2, entries 7–9).

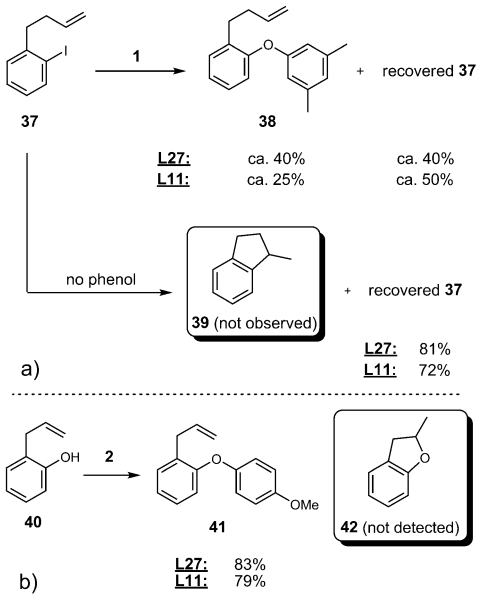
With the optimised conditions in hand, the scope of the reaction was investigated. The results are reported in Scheme 2. The reaction between activated phenols and deactivated (electron-rich) aryl iodides led to very good isolated yields (compounds **3** and **4**, 80%, 76% yield). Similar results were obtained with more reactive electron-poor aryl iodides (**5**, yield 78%). The same effect was observed for compounds **6** and **7**, obtained with comparable yields (54–58%). The sensitivity to the electronics on the aryl halide increases when more electron-poor phenols are used. A comparison between **3**–**5**, **8**–**10**, **11**, and **12** highlights this effect.[50] A similar trend can be observed for the phenol. When electron-withdrawing aryl halides are used, the reaction is relatively insensitive to the electronics on this moiety (compounds **5**, **10**), but using electron-rich halides the reaction becomes considerably dependent on the substituent (compounds **3**, **4**, **8**, **11**). β-Naphthol reacted with iodobenzene giving **15** in 71% yield, whereas electron-rich or unsubstituted phenols coupled with novel *N*-phenylindazole substrates to furnish products **16**–**19** in good yields (63–89%); no coupling with the chlorinated ring was observed for compounds **17**–**19**. This type of indazolic nucleus is of importance because of their applications in medicinal chemistry, for example in glucocorticoid receptor modulators.[51–54] Reactions using 2-hydroxypyridine and 8-hydroxyquinoline as nucleophiles were also investigated. Unfortunately, no reaction was observed under the optimised conditions. However, the use of 6-methyl-2-pyridone resulted in selective arylation of the hydroxy group, with moderate to low yields (compounds **20** and **21**). 8-Hydroxyquinaldine was more reactive, leading to compounds **22** and **23** with 37 and 65% yields, respectively. *O*-arylation of 2-pyridones is known to be a challenging process, with most of the literature data showing a strong preference for the *N*-arylation.[55–58] However, substitution at the 6-position proved to inhibit *N*-arylation,[56,58] facilitating *O*-arylation instead,[59] as observed in our case. The latter selectivity can also be favoured by hindered aryl halides, as demonstrated by Buchwald.[56] In the case of 8-hydroxyquinoline, taking into account the stabilisation of its Cu^{II} complexes (see below), the failure of the coupling is not entirely surprising,[56] although this substrate can react at higher temperature or by using microwave techniques.[56,60,61] In 8-hydroxyquinaldine, the methyl group might act as a destabilising agent for its copper complex, thus making the substrate more available for the coupling. Due to their ligating ability, these substrates would probably require different reaction conditions to react properly.

Ortho-substituted, hindered aryl ethers are found in many natural products and biologically active molecules. For example, polyhalogenated (thyroid hormone thyroxin, antibacterial triclosan) or polyphenol derivatives (vancomycin and related macrocyclic compounds) are common naturally-occurring compounds and have different biological effects.[44] Aryl ethers bearing carbonaceous side chains in the *ortho* position have also shown biological activity, for example triclosan derivatives showing antimalarial effects[62,63] and thyroid receptor antagonists derived from thyroxin.[64] Other examples can be found of various medicinal applications of substituted aryl ethers.[41–43] The formation of such hindered aryl ethers in Ullmann chemistry is rare, especially in intermolecular reactions, and only a few examples have been reported.[10,19,65–69] Interesting results



Scheme 2. Substrate scope, isolated yields (X = I if not specified otherwise).

were obtained with bulky substrates in our system (Scheme 2). A comparison of the yields for compounds **3** and **4** with those of **24** and **25** shows how just the presence of the substituent on the electron-rich aryl halide in the *ortho* position, instead of the *para*, reduces the yields by 40–50%, although the yields remain remarkable for such substrates. Compound **26**, bearing steric hindrance on both substrates, was obtained in 42% yield, comparable with **24** and **25**. The similar results suggest insensitivity to the steric hindrance on the phenol. When the reaction was performed using *o*-cresol as a nucleophile (compounds **27** and **28**), high yields were obtained, comparable with those obtained for non-hindered compounds **3**–**5**. This effect was further demonstrated by the synthesis of compounds **30**–**33**, bearing increasingly bulky *ortho* substituents, obtained in 52–81% yields. Strong sensitivity to the steric hindrance on the aryl iodide (see also compound **38**, Scheme 3a), but not (or to a much lesser extent) to that on the phenol, was also observed by Hsieh and Ma using different systems.[67,69] Couplings with hindered phenols and deactivated iodoanisole, or with indazole precursors, were also accomplished in very



Scheme 3. Radical clock experiments.

good yields (**34**–**36**; see also compound **41**, Scheme 3b). Interestingly, the use of 2,6-dimethylphenol in the reaction led to considerably lower yields than other phenols (compounds **30**, 57% and **34**, 53%). Even lower yields for the use of 2,6-dimethylphenol were reported by Buchwald, Wu and Qian.[10,66,68] Better results with this substrate were later reported by Buchwald using a different ligand.[19] Very hindered groups, such as *tert*-butyl and *tert*-amyl are rarely found in Ullmann ether synthesis, and, to our knowledge, only a single example of the use of *o*-*tert*-butylphenol in the coupling with iodobenzene was reported by Hsieh.[67]

Despite their lower reactivity toward S_NAr reactions than bromides and chlorides, strongly electron-poor aryl iodides have been reported to react even in the absence of copper catalyst.[70] To verify this, we performed the synthesis of compounds **13**, **14**, **21**, **23** and **29** without Cu or ligand. Products **13**, **14** and **29** were obtained with similar yields, thus demonstrating a non-catalytic S_NAr process in these cases. However, compound **21** was not obtained under these experimental conditions, and compound **23** was obtained only in 16% yield (Scheme 2).

The use of aryl bromides in the reaction, in particular the electron-rich bromoanisole, for the synthesis of **3**, **8**, **11**, **27**, **34** and **35** did not furnish high yields under our catalytic conditions. However, reaction was still observed even with electron-poor phenols (**11**, 10%) and 2,6-dimethylphenol (**34**, 22%), which suggests that improvements are possible.

Radical trap experiments

The mechanism of Cu-catalysed couplings is still not certain, and several authors have reported different possible mechanisms for these reactions. In particular, oxidative addition/reductive elimination cycles involving $Cu^{I/III}$ species and single electron transfer (SET) mechanisms involving $Cu^{I/II}$ species are the mechanisms on which much debate has arisen.[71–74] The large difference in catalytic activity of ligands **L11** and **L27** in air, although being quite similar under anaerobic conditions (Figure 3b), prompted us to perform some mechanistic investigations, aiming to gain an explanation for such a difference and an understanding of the role of the substituents on the ligand.

Having observed the formation of blue/green compounds in the reaction tubes,[75] we suspected the formation of Cu^{II} species during the reaction. Because Cu^{II} intermediates were suggested to be formed from Cu^{I} during SET radical-chain mechanisms,[76,77] we performed radical clock experiments, with both ligands **L11** and **L27**, to investigate the presence of radical intermediates in the reaction (Scheme 3a). Using ligand **L27**, the coupling between 2-(3-butenyl)iodobenzene (**37**) and 3,5-dimethylphenol (**1**) led to the formation of the aryl ether **38** in 40% yield, and a further 40% of unreacted starting material was recovered. The same reaction with **L11** led, as expected, to a lower yield of **38** (ca. 25%), while approximately 50% of the starting aryl iodide was recovered. The radical cyclisation product **39** was not recovered or detected after the reactions. Although the intramolecular radical cyclisation is known to be a very fast reaction,[78,79] some authors have argued that the coupling with the nucleophile might be faster than the radical closure, thus invalidating the test.[72,80] To rule out this possibility, we performed the same reaction in the absence of phenol **1**, but 81% (**L27**) and 72% (**L11**) of unreacted iodide **37** was isolated at the end of the reaction (Scheme 3a). No other compounds were detected in the reaction mixture.

Early research demonstrated that Cu^{II} species could be reduced during the reaction, thus leading to the active Cu^{I}.[81,82] This reduction process in the presence of phenols would lead to the formation of phenoxy radicals, as occurs in copper-based oxidase enzymes.[83] The high yields obtained with hindered phenols, together with their ability to stabilise phenoxy radicals,[84] prompted us to investigate this possibility. Although phenoxy radicals typically isomerise to carbon-centred radicals, leading to the formation of C–C or C–O dimers,[84] which were not observed during the reaction, we reasoned that, if the *O*-centred radical was stabilised through copper coordination, the use of a cyclisation radical clock experiment may be envisaged, as a similar process occurs for corresponding aliphatic alkoxy radicals.[85] Thus, we used 2-allylphenol (**40**) in coupling reactions with 4-iodoanisole (**2**). However, the reaction with either **L11** or **L27** led to the coupling product **41** with high isolated yields, without trace of the cyclisation product **42** or other side products (Scheme 3b). To be sure of the non-involvement of a radical intermediate, we also carried out the reaction of 4-iodoanisole (**2**) without phenol using both ligands, with and without TEMPO (1 equiv). In all cases, $>99\%$ of **2** was unreacted after 24 h. Leaving either phenol **1** or **40** under the reaction conditions in the absence of aryl iodide, resulted in about 30% (**40**) or 50–60% (**1**) of phenol left in the crude reaction, with both ligands.[86] Similar results were obtained with 1 equivalent of TEMPO added to the reaction. Again, no side products or TEMPO-trapped compounds were detected in solution.

Recovery of end-of-life Cu^{II} species: the role of the ligand

Although no evidence was obtained for a radical mechanism (furnishing or derived from Cu^{II} species), the presence of Cu^{II} species was proven by the isolation of Cu^{II} complexes of the type $[Cu(ligand)_2]$ at the end of the reaction, with several of the anionic ligands tested. Single crystals suitable for X-ray diffraction were obtained with ligands **L5** and **L9** directly by slow evaporation of the crude filtrate and successive washing with water and diethyl ether. Cu^{II} complexes with picolinamide ligands were obtained as powders and, following recrystallisation, led to single crystals of $[Cu(\mathbf{L24})_2]$ (vapour diffusion, DCM/Et_2O), $[Cu(\mathbf{L26})_2(H_2O)]$ (evaporation of acetone solution) and $[Cu(\mathbf{L32})_2]$ (vapour diffusion, DCM/Et_2O). X-ray crystal structures for these complexes are depicted in Figure 4; a discussion on the crystal structures and selected bond lengths and angles for Cu-picolinamide complexes are reported in the Supporting Information. It is worth noting that the recovered complexes are formed with ligands that performed well in the catalysis. To our knowledge, this is the first example of end-of-life copper species recovered from Ullmann-type reactions.

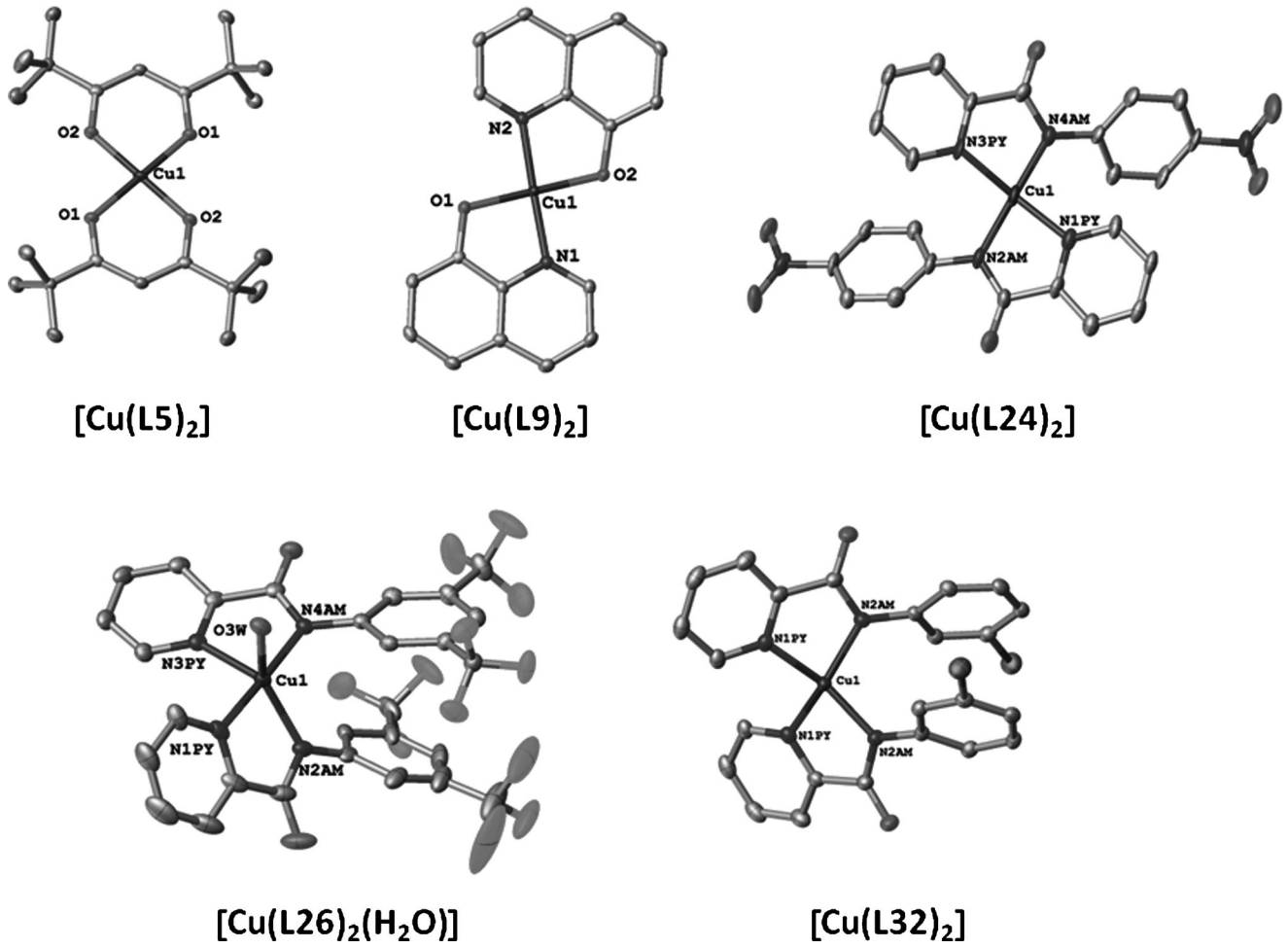
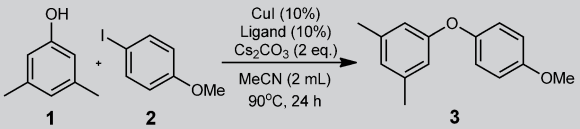


Figure 4. End of life Cu^{II} species (50% probability ellipsoids, hydrogen atoms omitted for clarity).

The formation of these complexes from reactions into which CuI and ligand were introduced in a 1:1 ratio indicates that a maximum of 50% of the copper can be present in this form. A related phenomenon was recently reported by Lei, who proposed the disproportionation of Cu^{I} to explain the formation of Cu^{II} species.[27] The same process may thus be suggested for our system. However, Lei suggested the formation of the Cu^{II} species to be a detrimental off-cycle side reaction, making the active Cu^{I} species labile and low in concentration during the whole reaction, whereas Cu^{II} was considered as a spectator species not involved in the catalysis.[27] Because of the negative results of the radical clock experiments, the involvement of the Cu^{II} species may be external to the actual mechanism of the reaction, but the equilibrium between Cu^{I} and Cu^{II} species might also be reversible, in which case the Cu^{II} species may play an important role in the reaction, instead of being merely a spectator species. With this idea in mind, we performed further experiments to try to assess the effect of the ligand on the electronic properties of the copper atom in the reaction. The synthesis of compound **3** was performed in the presence of TEMPO, L-ascorbic acid and DDQ, with 10 mol% or 1 equivalent of each, with ligands **L11** and **L27** (Table 3). Although the addition of 1 equivalent of TEMPO to the reaction did not result in any significant difference from the standard conditions (Table 3, entry 3),[87] the addition of only 10 mol% of TEMPO resulted in the formation of **3** in about half the yield

Table 3. Control experiments with TEMPO, L-ascorbic acid and DDQ.[a]



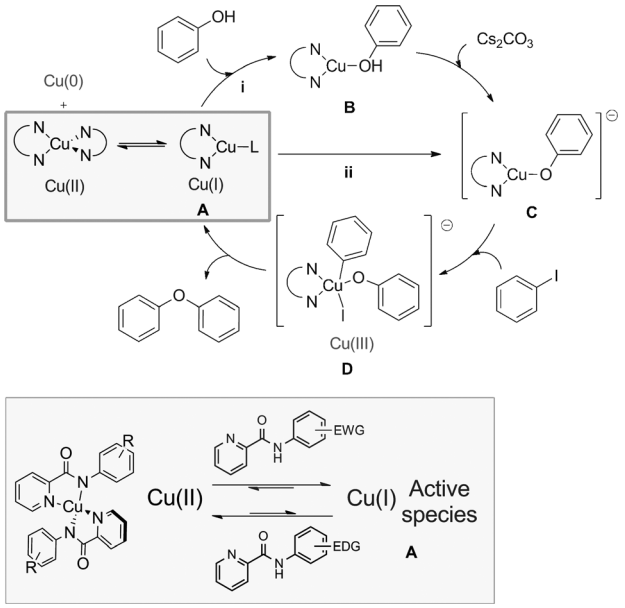
1 2 3

Entry		Yields [%] L27[b]	L11[b]
1	Standard conditions	87	40
2	TEMPO (10 mol%)	51	21
3	TEMPO (1 equiv)	76	41
4	L-ascorbic acid (10 mol%)	77	77
5	L-ascorbic acid (1 equiv)	85	68
6	DDQ (10 mol%)	48	39
7	DDQ (1 equiv)	9	2

[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 1,3,5-trimethoxybenzene as internal standard.

with each ligand (entry 2), which is in agreement with the possibility that an electron transfer occurs during the reaction. The addition of L-ascorbic acid, a common agent for the reduction of Cu^{II} to Cu^{I}, resulted in a significant increase in the reaction yield with ligand **L11**, whereas it did not particularly affect the reaction with ligand **L27** (Table 3, entries 4 and 5). In contrast, the addition of 10 mol% of DDQ, an oxidant species, notably reduced the yield when using ligand **L27**, leaving unaltered the result with **L11** (Table 3, entry 6). The use of 1 equivalent of DDQ resulted in almost complete inhibition with both ligands.

Based on these results, and in the absence of evidence for radical mechanisms, we suggest the tentative mechanism depicted in Scheme 4, whereby an initial Cu^{I} species **A** formed



Scheme 4. Suggested reaction mechanism.

from CuI undergoes coordination with the nucleophile, followed by oxidative addition and reductive elimination to form the aryl ether. The identity of the active Cu^{I} species **A** is uncertain, and it might be a neutral (L = MeCN) or an anionic species (L = I). The coordination of the nucleophile may occur before (**B**, path i) or after deprotonation (**C**, path ii), depending on its electronic properties. This step is followed by an oxidative addition (**D**) and a reductive elimination to release the product and reform **A**.

Cu^{II} species such as those reported above might be in equilibrium with the active species **A**; the substituent on the ligand affects the redox properties of the copper atom, altering the equilibrium and stabilising the Cu^{II} or Cu^{I} state to different extents (Scheme 4). The low yields obtained with the addition of TEMPO may be due to the inhibition of this redox process, in one direction or the other. The different effect that air plays on the two ligands (Figure 3b) can be explained in that ligand **L11** requires a more reductive environment to be efficient (addition of ascorbic acid), which favours the formation of the active copper species from Cu^{II}, whereas **L27**, already facilitating the formation of the active Cu^{I} species, is not particularly sensitive to the presence of air, although a more oxidative environment becomes deleterious (addition of DDQ).

Due to the small amounts of Cu^{II} complexes recovered from the reactions, these could not be used in the catalysis without changing drastically the reaction conditions, but ongoing investigation shows that preformed complexes of this type are effective in the catalytic reaction in the same conditions, and different reduction potentials (Cu^{II} to Cu^{I}) are actually observed for these complexes, thus supporting the theory that these compounds are not just spectator or decomposition species.[88]

Conclusion

During a comparative study of a model coupling reaction, *N*-phenylpicolinamide ligands were discovered to be an effective ligand family for Cu-catalysed aryl ether formation. Electron-withdrawing substitutents on the phenyl ring of the ligand proved to lead to the most active catalysts. In particular, ligand **L27** (*N*-(2-fluorophenyl)picolinamide), was effective in catalysing the coupling between a broad range of substrates in air and under relatively mild conditions. Excellent results were obtained with sterically hindered phenols, and even *tert*-butyl and *tert*-amyl substituents in the *ortho* position were well tolerated. *Ortho*-substituted phenols are known to be challenging coupling partners in Cu-catalysed reactions, and only few examples have previously been reported. Aryl bromides are not very reactive under these conditions, although some product is still formed even with *ortho*-substituted phenols. Further modification of the ligand and the conditions might be necessary to increase their reactivity. The first examples of end-of-life Cu^{II} complexes were isolated with several effective ligands, which we consider fundamental in understanding the mechanism of the reaction. Results from radical trapping experiments strongly suggest that the reaction does not proceed through free-radical mechanisms, thus the Cu^{II} species observed may be involved as off-cycle species, which can, nonetheless, be in equilibrium with an active Cu^{I} species. Control reactions using two different ligands showed that the reaction outcome can be altered by the addition of an oxidant or reductant species, with different results for the two ligands. This suggests that the ligand plays an important part in altering the redox properties of the metal centre, thus inhibiting or favouring the reaction, and explaining the different results obtained in aerobic or anaerobic conditions.

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Keywords: aryl ethers · copper · cross-coupling · N ligands · structure–activity relationships

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tered brown/green (aerobic)or light blue (anaerobic)solid residue remains on the celite plug. These products are not due to the presence of complexes of the type [CuL_2], because these are soluble in DCM, with which the plug is washed. The colours depend on the starting materials used (in aerobic conditions), especially on the phenol. Very dark blue/purple (ex. **32** and **33**) or dark green (**41**) solid was observed from the reaction with bulky phenols, and pink/red solid from the reactions with unsubstituted phenol (**8**–**10**). Metal (Cs or Cu) phenoxide species may thus constitute at least part of this solid.

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[86] Considering the presence of the base, it is likely that part of the phenol would be deprotonated under the reaction conditions, thus formation of insoluble metal phenoxides species may account for such small amount of protonated phenol in the crude solution.
[87] The results for the standard conditions in Table 3 are slightly different from those reported in Figure 3b, due to the different commercial source of chemicals used for these data.
[88] C. Sambiagio, R. H. Munday, S. P. Marsden, A. J. Blacker, P. C. McGowan, unpublished results.

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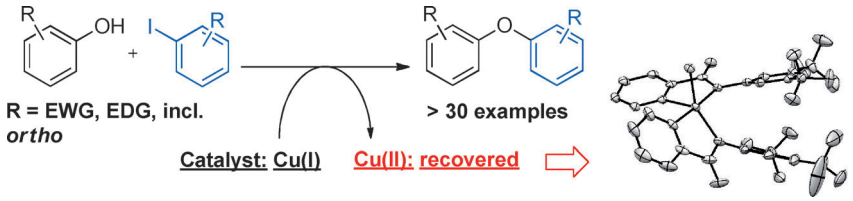
FULL PAPER



Picolinamides for Ullmann coupling: A structure–activity relationship study using picolinamide ligands for Cu-catalysed aryl ether synthesis is reported. Electron-withdrawing substituents on the ligand allow the coupling of a broad range of substrates in air, including sterically hindered compounds, normally challenging substrates. Preliminary mechanistic investigation shows how the substituents on the ligand might influence the redox properties of the metal centre.

Copper Catalysis

*C. Sambiagio, R. H. Munday, S. P. Marsden, A. J. Blacker, P. C. McGowan**

■■ – ■■

Picolinamides as Effective Ligands for Copper-Catalysed Aryl Ether Formation: Structure–Activity Relationships, Substrate Scope and Mechanistic Investigations