

Oxalohydrazone Ligands for Copper-Catalyzed C–O Coupling Reactions with High Turnover Numbers

Ritwika Ray and John F. Hartwig*

Abstract: Here, we report a class of ligands based on oxalohydrazone cores and *N*-amino pyrrole and *N*-amino indole units that generates long-lived copper catalysts for couplings that form the C–O bonds in biaryl ethers. These Cu-catalyzed coupling of phenols with aryl bromides occurred with turnovers up to 8000, a value which is nearly two orders of magnitude higher than those of prior couplings to form biaryl ethers and nearly an order of magnitude higher than those of any prior copper-catalyzed coupling of aryl bromides and chlorides. This ligand also led to copper systems that catalyze the coupling of aryl chlorides with phenols and the coupling of aryl bromides and iodides with primary benzylic and aliphatic alcohols. A wide variety of functional groups including nitriles, halides, ethers, ketones, amines, esters, amides, vinylarenes, alcohols and boronic acid esters were tolerated, and reactions occurred with aryl bromides in pharmaceutically related structures.

Introduction

Biaryl ethers and alkyl aryl ethers are common structural motifs in natural products, pharmaceuticals and agrochemicals (Figure 1).^[1,2] The synthesis of biaryl ethers from the reaction of phenols with aryl bromides in the presence of KOH was first discovered by Ullmann in 1905.^[3] However, the classical Ullmann procedure for the formation of biaryl ethers and related processes required high temperatures (usually $T > 160^\circ\text{C}$) and stoichiometric amounts of copper. These requirements limited the scope of this transformation.^[4]

Pd-catalyzed reactions also form biaryl ethers and alkyl aryl ethers.^[5] However, Pd-catalyzed coupling reactions to form C–O bonds have been some of the most challenging to accomplish and usually suffer from low turnover numbers and narrow scope. Reductive elimination to form C–O bonds is slower than reductive eliminations to form other C–X bonds,^[6] and this slow rate could lead to processes that limit the lifetime of the catalyst.

In 2000, a much greater potential for Ullmann-type coupling reactions was revealed by the discovery of nitrogen- and oxygen-based ancillary ligands that enabled coupling of aryl halides with phenols and other nucleophiles with an

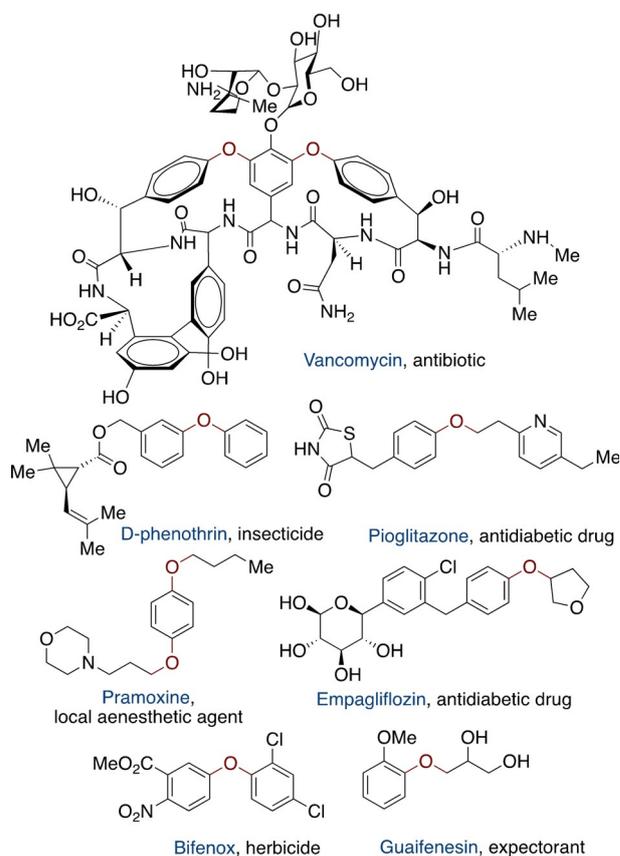


Figure 1. Selected agrochemicals and pharmaceuticals containing aryl ether and alkyl aryl ether core.

increased scope and yield under mild reaction conditions.^[7,8] Since then, Cu-catalyzed C–O coupling reactions have been developed with neutral, bidentate ancillary ligands, such as phenanthrolines,^[7] bipyridines,^[9] diamines^[10] and dipyrrolylmines,^[11] as well as anionic bidentate ancillary ligands, such as 1,3-dicarbonyl compounds,^[12] α -amino acids,^[13] 8-hydroxyquinolines^[14] and bisoxalamides.^[15,16] Yet, copper-catalyzed couplings to form biaryl ethers, like most copper-catalyzed couplings, occur with low turnover numbers, despite being one of the originally reported couplings with ligated copper and one of the more reliable copper-catalyzed coupling reactions. For example, the highest turnovers of coupling reactions to form biaryl ethers from aryl bromides with the ligands reported by Ma, which generate the most active catalysts recently developed, are less than 100.^[15b] While the cost of the copper catalyst is lower than that of palladium and the synthesis of relatively expensive materials like pharmaceuticals can tolerate high loadings of copper systems if the

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ligand is simple, the application of such reactions to the synthesis of products on larger scale, even agrochemicals, requires that the lifetime of copper catalysts be longer.

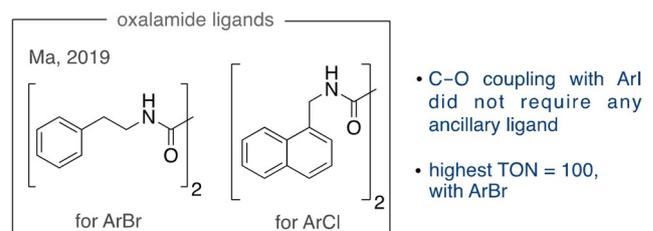
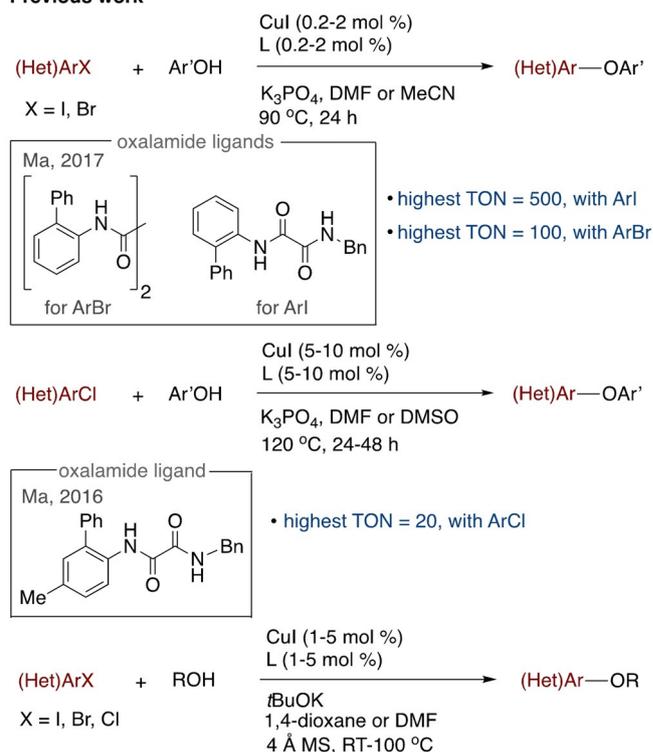
This limited activity of copper catalysts for cross coupling led us to seek a system that would enable C–O coupling reactions to occur with high TONs and tolerance for a broad range of functional groups.^[17] We report a series of oxalohydrazide ligands derived from *N*-amino pyrroles and *N*-amino indoles that generate catalysts reacting with nearly two orders of magnitude higher turnovers than those previously reported for the synthesis of biaryl ethers. Couplings of phenols with aryl bromides occur with TONs ranging from 1000 to over 7500 (Scheme 1) and approaching 2000 for a series of heteroaryl bromides. A wide variety of functional groups, including nitriles, halides, ketones, ethers, amines, esters, amides, alcohols and boronic acid esters, were tolerated, and the reaction also occurred with vinyl bromides. This system even catalyzed the coupling of phenols with aryl and heteroaryl chlorides, the coupling of benzylic and aliphatic alcohols, and coupling of pharmaceutically relevant molecules.

Results and Discussion

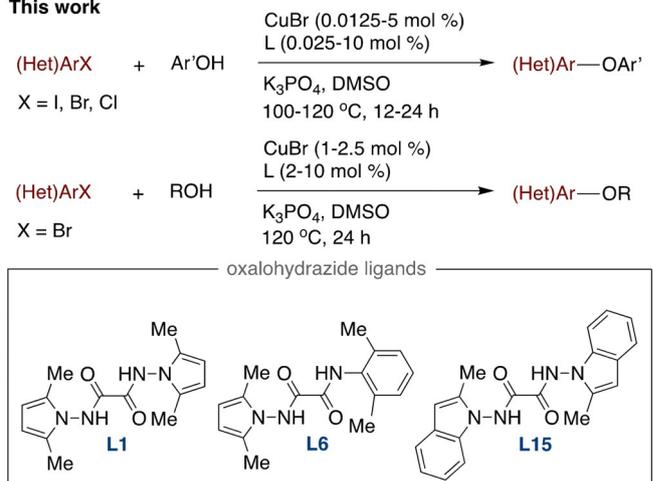
During studies to prepare agrochemical intermediates, we began to study couplings catalyzed by complexes of oxalohydrazide ligands related to the oxalamide ligands of Ma.^[15,16] Oxalohydrazide ligands, originally tested for cross coupling on the basis of the coordination chemistry of bis(cyclohexanone)oxalyldihydrazone (BCO) for sensing applications,^[18] have been reported as catalysts for C–N coupling of aryl halides in water,^[19] but these reactions required 25 mol% copper and 50 mol% ligand at 130 °C under microwave irradiation.^[19a] Milder reactions occurred by forming oxalohydrazide ligands from the parent, unsubstituted oxalohydrazide and a series of ketones, including 1,4-diketones.^[19b] The catalyst generated from isolated oxalohydrazide ligand **L1**, formed from the 1,4-diketone hexane-2,5-dione and oxalohydrazide was reported to couple hydrazine with aryl bromides in water.^[19d] We were unable to reproduce this coupling of hydrazine in water, most likely due to complications from the lack of solubility of the bromoarene and the oxalohydrazide ligand in this medium.

However, we did find that the reactions of phenols catalyzed by CuBr with oxalohydrazide ligand **L1** in DMSO solvent, in which the catalyst and reagents are more soluble, occurred in high yield at low loadings of copper. The reaction of phenol with 4-bromo chlorobenzene in the presence of 0.05 mol% of CuBr and 0.1 mol% of **L1** afforded the biaryl ether in >99% yield (Table 7 and Table S1, supporting information). Most striking, the reaction with this catalyst at just 0.0125 mol% of CuBr and 0.025 mol% of the ligand gave the coupled product in 75% yield. The same reaction after a longer period of time (36 h) afforded 85% yield of the biaryl ether, indicating that the catalyst remains active after long reaction times at 100 °C, and increasing the reaction temperature to 120 °C led to full conversion and 95% yield of the coupled product after 24 h.

Previous work



This work

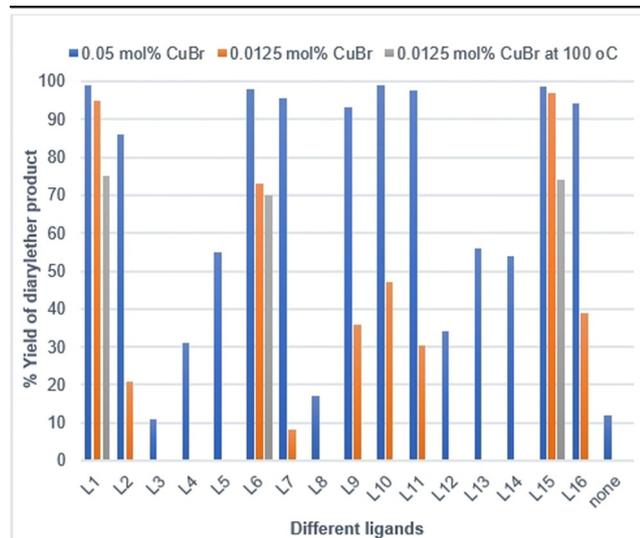
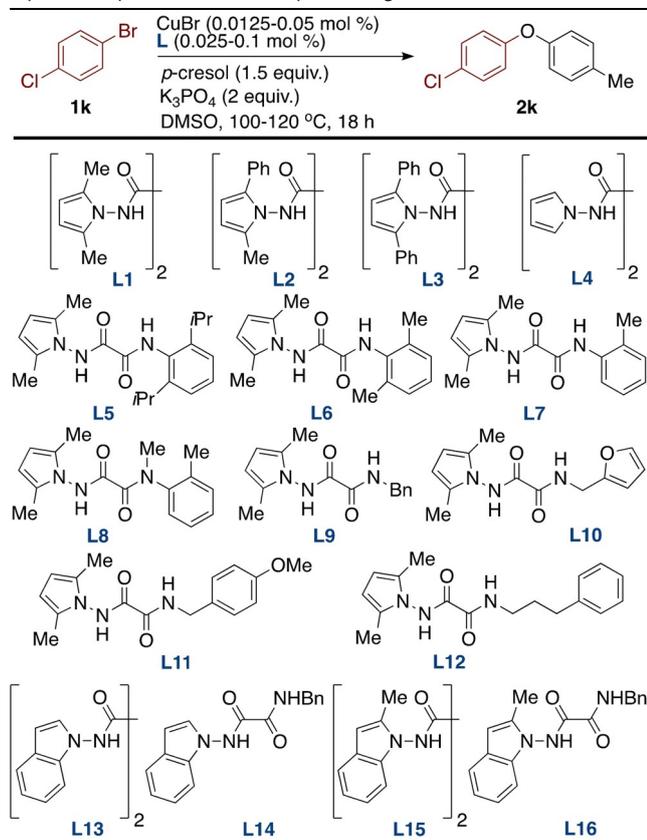


- highest TON = 8000 with ArBr
- C–O coupling with both phenols and aliphatic alcohols were achieved
- Excellent functional group tolerance; nitriles, halides, esters, amides, amines, alcohols, ketones, styrenes and boronic acid esters are well-tolerated

Scheme 1. Evolution of oxalohydrazide ligands for Cu-catalyzed C–O coupling reactions with high turnovers.

To identify relationships between the structure of oxalohydrazide ligands and catalyst activity, we synthesized a library of derivatives (**L2–L16**, Table 1) based on **L1**. The coupling of 1-bromo-4-chlorobenzene with *p*-cresol, was initially assessed in the presence of 0.05 mol% CuBr and

Table 1: Generation of new oxalohydrazide ligands for Cu-catalyzed arylation of phenols at low catalyst loading.^[a]



[a] Reaction conditions: CuBr (0.05 mol% or 0.0125 mol%) and **L1–L16** (0.1 mol% or 0.025 mol%) were mixed in the presence of K_3PO_4 (0.75 mmol) in DMSO at RT for 1 h. After this time, **1k** (0.5 mmol) and *p*-cresol (1.5 equiv) were added, and the reaction mixture was heated at 120 °C or 100 °C for 18 h. Yields were determined by NMR spectroscopy with 1,3,5-Trimethoxybenzene as the internal standard.

0.1 mol% of the corresponding oxalohydrazides, **L2–L16**. The substituents at the 2 and 5 positions of the *N*-amino pyrroles on either half of the oxalyl group were first modified (**L2–L4**). Arylation of phenols catalyzed by the complex of **L2** containing 2-methyl-5-phenyl *N*-amino pyrroles occurred in yields that were similar to those of the reaction in the presence of **L1**. However, the catalyst generated from **L3**, containing 2,5-diphenyl *N*-amino pyrroles, gave only 11% yield of the coupled product; most of the aryl bromide remained unreacted. Likewise, the reaction with the catalyst from **L4**, containing unsubstituted *N*-amino pyrroles, gave only 31% yield of the product, leaving a majority of the aryl bromide unreacted. This trend highlights the effect of the steric properties of the substituents at the 2- and 5-positions of the *N*-amino pyrroles on the course of the reaction.

Unsymmetrical oxalohydrazides containing an *N*-amino pyrrole on one side and an aniline or a primary alkylamine on the other side of the oxalyl group also were synthesized (**L5–L12**). As expected, the catalytic process was affected by the substitution pattern at the 2- and 6-positions of the anilines. The reaction in the presence of the catalyst containing **L5**, derived from 2,6-diisopropyl aniline, gave a low yield of the biaryl ether, whereas reactions in the presence of the catalyst containing **L6**, derived from 2,6-dimethyl aniline, and **L7**, derived from 2-methyl aniline, gave the biaryl ether in yields similar to those of the reaction in the presence of **L1**. In contrast, the arylation catalyzed by a combination of CuBr and **L8**, derived from 2-methyl-*N*-methyl aniline, formed the product in significantly lower yield (17%). This result suggests that the presence of an N–H bond on each half of the ligand is necessary to achieve high reactivity of the catalysts.

The catalytic reactions in the presence of unsymmetrical oxalohydrazides **L9** and **L11** afforded high yields of the product. This result shows that the reactivity of the catalyst containing the ligand with an electron neutral benzylamine (**L9**) is the same as the one with an electron rich benzylamine (**L11**). The catalyst derived from unsymmetrical oxalohydrazide **L10**, containing furfurylamine also catalyzed the arylation of phenols at low loading of the catalyst. However, the same reaction in the presence of **L12** containing 3-phenylpropylamine on one half of the ligand, gave poor yield of the product.

Finally, we also studied the effect of symmetrical and unsymmetrical bis-hydrazides derived from *N*-amino indoles (**L13–L16**) on the activity of the catalyst for the arylation of phenol. The reactivity of the catalysts containing **L13** and **L14**, derived from unsubstituted *N*-amino indoles was low; the corresponding reactions formed the coupled product in moderate yields. However, the reactions with **L15** and **L16** as ligand, both containing 2-methyl *N*-amino indoles, provided high yield of the products. Finally, consistent with these effects of the ligands on the reaction outcome, the ligand-free catalytic system gave only 12% yield of the product.

Having identified ligands (**L1**, **L2**, **L6**, **L7**, **L9–L11**, **L15** and **L16**) that enabled copper-catalyzed arylation of phenols with high TONs (≈ 2000 in each case), we further assessed the performance of these ligands in the catalytic reaction at a loading of only 0.0125 mol% CuBr and 0.025 mol% ligand.

These experiments showed that three oxalohydrazide ligands, **L1**, **L6**, and **L15**, generate catalysts for Cu-catalyzed C–O coupling reactions in high yields at this low loading of catalyst, corresponding to TONs between 5800 and 8000. For example, the coupling of 1-bromo-4-chlorobenzene with *p*-cresol occurred in the presence of CuBr and **L1** or **L15** to give the coupled product in 95% or 97% yield, corresponding to TONs of nearly 8000, a value which is almost two orders of magnitude higher than that of any previously reported copper-catalyzed cross-coupling of an aryl bromide with a phenol, and nearly an order of magnitude higher than those for any other type of copper-catalyzed coupling of an aryl bromide or chloride. Earlier, Ma reported copper-catalyzed arylation of amines at low catalyst loading, but the highest TON achieved for the reaction of an aryl bromide was below 1000.^[17c]

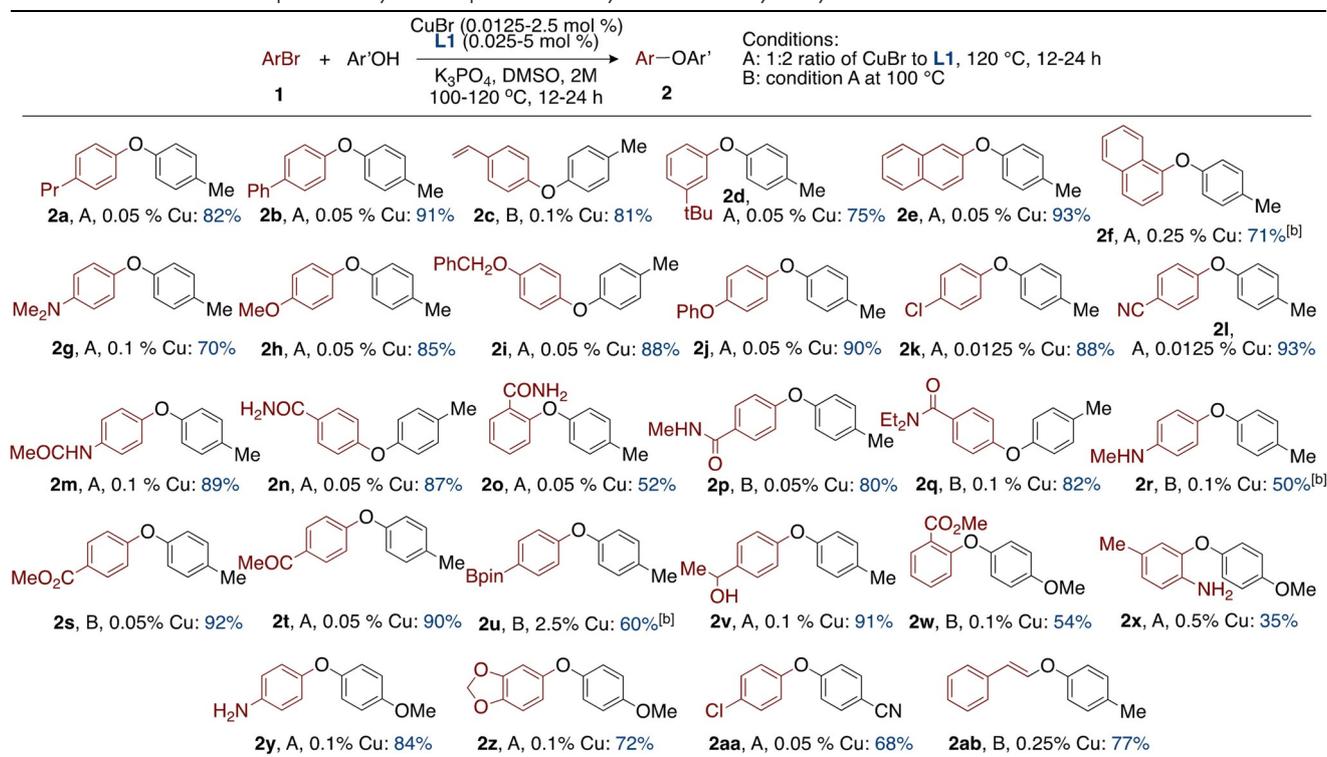
The scope of the reactions of aryl bromides with phenols conducted with copper and an oxalohydrazide ligand is shown in Table 2. These reactions were conducted with **L1** as the hydrazide ligand, due to a straightforward synthesis of **L1** and high yield of the couplings with this ligand. These reactions occurred with electron-neutral, electron-rich and electron-poor phenols. Even at the low loadings of catalyst, the tolerance of the process for functional groups remained characteristic of copper-catalyzed couplings.

The reactivity of this catalyst for electron-neutral to electron-rich bromoarenes is shown by examples **2a–2h**. The arylation of *p*-cresol with aryl bromides having moderately electron donating groups, such as -Pr, -Ph, and vinyl groups at

the *p*-position (**2a–2c**) and a -*t*Bu group at the *m*-position (**2d**) afforded excellent yields of the products. The reaction with 2-bromonaphthalene also gave high yield of the product with a similar TON of 1860 (**2e**), although the reaction with the more hindered 1-bromonaphthalene did not occur at the lowest loading (not shown), a result which is consistent with typical steric effects on copper-catalyzed couplings. The reaction of this more hindered 1-bromonaphthalene did occur with the same catalyst at a higher loading of 0.25 mol% to give 71% yield of the product (**2f**). The reactions in the presence of highly deactivated aryl bromides containing electron-donating -NMe₂ and -OMe groups at the *p*-position of the phenyl rings gave high yields of the corresponding products at loadings of the catalyst that were higher than those of the more electron-neutral or electron-poor bromoarenes, but still at loadings that correspond to turnovers that are high for any copper-catalyzed coupling of a bromoarene (**2g**, TON = 700; **2h**, TON = 1700). Other alkoxy or phenoxy groups, such as -OCH₂Ph (**2i**) and -OPh (**2j**), also were tolerated by the reaction conditions.

The tolerance of the process for a series of functional groups was initially assessed for the coupling of *p*-cresol. Electron-poor aryl bromides containing -Cl and -CN functionalities underwent clean conversion to their respective biaryl ether products with excellent yields and TONs of approximately 7000 (**2k** and **2l**). Aryl bromides containing amides, such as -NHCOMe or -CONH₂ at the *p*-position, gave high yields of the corresponding products without any by-products from intermolecular coupling between the aryl

Table 2: Evaluation of the scope of the arylation of phenols with aryl bromides catalyzed by Cu and **L1**.^[a]



[a] Reaction conditions: CuBr and **L1** were mixed in the ratio of 1:2 in the presence of K₃PO₄ (1.5 mmol) in DMSO at RT for 1 h followed by the addition of **1** (1 mmol) and the respective phenol (1.5 equiv). The reaction mixture was then heated at 120 °C or 100 °C. [b] Yields were determined by NMR spectroscopy with 1,3,5-Trimethoxybenzene as the internal standard.

bromide and the amide nitrogen (**2m** and **2n**). However, the reaction with 2-bromobenzamide was slow, afforded moderate yield of the product, and gave an appreciable amount of hydrodehalogenation product (**2o**). Aryl bromides containing secondary and tertiary amides (**2p** and **2q**) also gave high yields of the products without formation of byproducts, and the aryl bromide containing a secondary amine formed moderate yields of the corresponding ether product (**2r**). Reactions with aryl halides containing ester functionality at the *p*-position gave high yield of the ether product without any detectable hydrolysis of the ester (**2s**), and the acetyl group -COMe (**2t**) was well tolerated, despite the enolizable hydrogens, giving the product in high yield with a TON of 1800. A boronic ester (**2u**) was also tolerated without competing formation of a biaryl product. Even an aryl halide containing a secondary alcohol reacted to full conversion to afford high yield of the biaryl ether product with a TON of 910 (**2v**).

The functional-group tolerance also was evaluated for the coupling of electron-rich and electron-poor phenols. The arylation of 4-methoxyphenol with aryl halides containing an ester group at the *o*-position (**2w**) and primary amines at the *o*- and *p*-positions (**2x** and **2y**) gave good to moderate yields of the biaryl ether products without formation of side products. The yield of the products in the presence of varying functional groups at the *o*-position of the bromoarenes (**2w** and **2x**) were lower than those of other bromoarenes, due to incomplete conversion of the starting aryl bromides, again, consistent with known steric effects on copper-catalyzed coupling reactions. The electron-rich 4-methoxyphenol coupled with 5-bromobenzo-1,3-dioxole to give high yield of the corresponding biaryl ether, although a slightly higher loading of the catalyst was required to achieve complete conversion (**2z**). The coupling of a moderately electron-poor aryl bromide having a -Cl group at the *p*-position coupled with a highly deactivated phenol containing a -CN group at the *p*-position to give 68% yield of the biaryl ether product corresponding to a TON of 1360 (**2aa**). Coupling at a vinyl bromide (**2ab**) also gave high yield of the corresponding product with a TON of 308.

The scope of this method was further evaluated for a series of heteroaryl bromides (**4a–k**, Table 3). Most of the reactions in the presence of heteroaromatic substrates occurred in moderate to good yields with TONs ranging between 500 and 2000. A few noteworthy examples demonstrate the coupling of an electron-rich phenol with a sterically hindered pyridine affording high yield of the corresponding product (**4b**) and the tolerance of a primary amine and an ester group on a pyridine ring (**4c** and **4d**). One of the least reactive of the heteroaryl bromides was 8-bromo-2-methylquinoline. Reaction of this bromide required an electron-rich phenol as coupling partner and a high loading of the catalyst to afford good yield of the product (**4f** and **4i**).

Reactions with aryl and heteroaryl chlorides also occurred in the presence of the catalyst generated from **L1**. A higher loading of the catalyst (1–5 mol%) was necessary for the reactions with aryl chlorides, but high yields of the biaryl ethers were obtained (**6a–o**, Table 4). A series of electron-rich and electron-poor aryl chlorides, as well as heteroaromatic

Table 3: Evaluation of the scope for Cu/**L1**-catalyzed arylation of phenols with (hetero)aryl bromides.^[a]

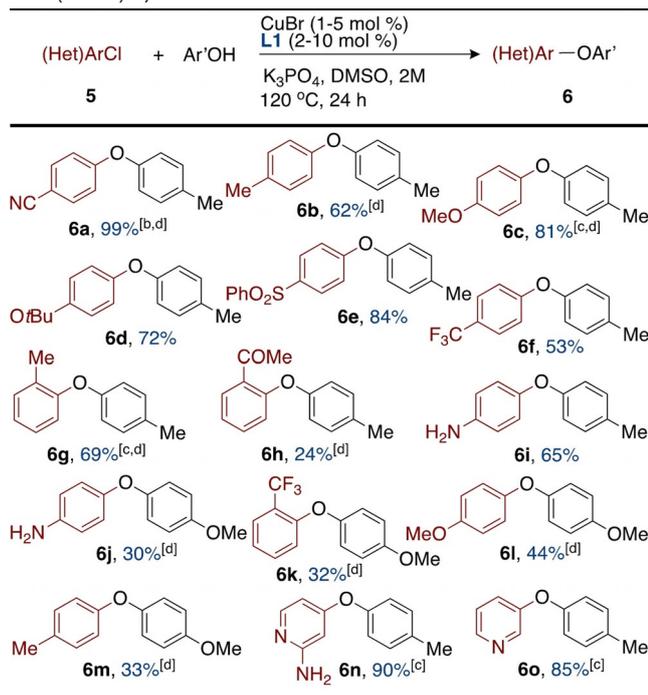
(Het)ArBr + Ar'OH	0.05–1 mol % CuBr 0.10–2 mol % L1	(Het)Ar–OAr'
3	K ₃ PO ₄ , DMSO, 2M 100–120 °C, 12–24 h	4
		4a , 81% ^[a]
		4b , 55% ^[a]
		4c , 51% ^[a]
		4d , 69% ^[c,d]
		4e , 82% ^[b]
		4f , 76% ^[e]
		4g , 91% ^[b]
		4h , 86% ^[b]
		4i , 58% ^[d,e]
		4j , 45% ^[b]
		4k , 40% ^[b]

[a] Reaction conditions: CuBr (0.1 mol%) and **L1** (0.2 mol%) were mixed in the presence of K₃PO₄ (1.5 mmol) in DMSO at RT for 1 h followed by the addition of **3** (1 mmol) and the respective phenol (1.5 equiv). The reaction mixture was then heated at 120 °C. [b] CuBr (0.05 mol%) and **L1** (0.1 mol%) were used. [c] CuBr (0.5 mol%) and **L1** (1 mol%) were used. [d] Reaction temperature was 100 °C. [e] CuBr (1 mol%) and **L1** (2 mol%) were used.

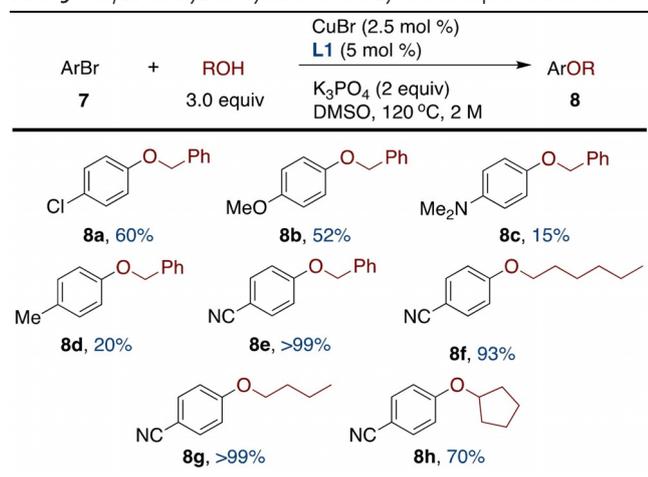
chlorides all reacted under the standard conditions. This activity is higher than that reported for reactions catalyzed by CuBr and oxalamide **L22**, which were conducted with 5–10 mol% catalyst.^[15a]

The system comprising CuBr and **L1** also catalyzed the coupling of aryl bromides with benzylic and aliphatic alcohols to form alkyl aryl ethers (Table 5). The reactions of electron-rich, electron-poor and electron-neutral aryl bromides with benzyl alcohol (**8a–e**) formed a series of aryl alkyl ethers, and reactions with primary aliphatic alcohols (**8f** and **8g**) and cyclic secondary alcohols (**8h**) also formed the corresponding ethers in high yields. Under these conditions, the reactions of aryl chlorides to generate aryl alkyl ethers (not shown) occurred to low or no conversion.

To evaluate the utility of this catalyst for coupling with more complex aryl halides, we conducted reactions of phenols with aryl bromides from Merck's informer library that evaluates the suitability of a process for reactions with pharmaceutically relevant structures (Table 6).^[20] Three of the complex aryl halides were chosen to obtain yields of isolated products, and the coupled products (**9b**, **10b** and **11b**) were obtained in good yields with relatively low catalyst loadings (CuBr: 2.5 mol%, **L1**: 5 mol%). In these cases, only the product and unreacted aryl bromide were observed as the organic materials at the end of the respective reactions. As expected, an increase in the loading of the catalyst (CuBr: 5 mol%, **L1**: 10 mol%) led to high yields of the products, and, in each case, complete conversion of the starting halides was observed without any side products. These examples highlight

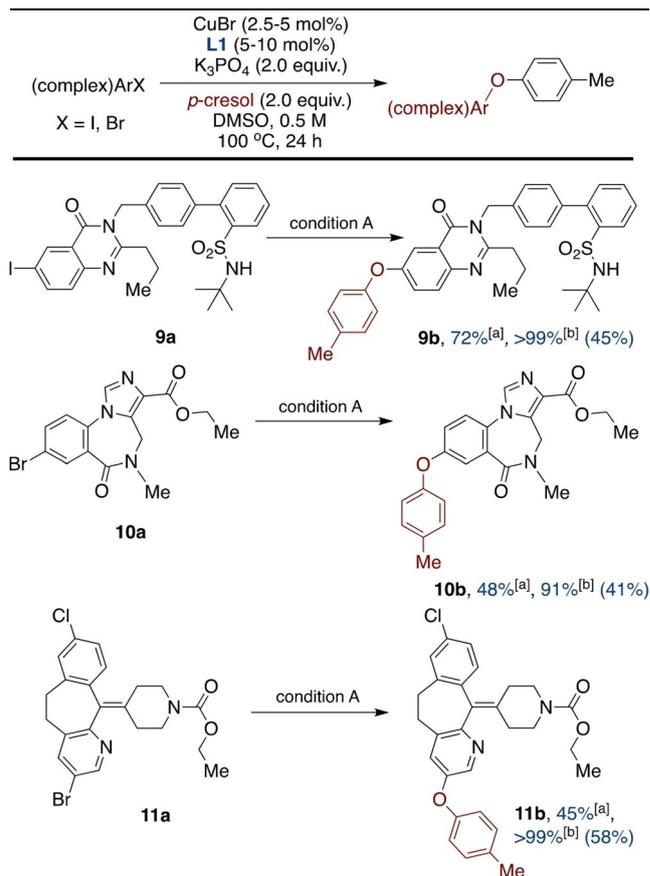
Table 4: Evaluation of the scope for Cu/L1-catalyzed arylation of phenols with (hetero)aryl chlorides.^[a]

[a] Reaction conditions: CuBr (2.5 mol %) and L1 (5 mol %) were mixed in the presence of K₃PO₄ (0.75 mmol) in DMSO at RT for 5 mins followed by the addition of **5** (0.5 mmol) and the respective phenol (1.5 equiv). The reaction mixture was then heated at 120 °C for 24 h. [b] CuBr (1 mol %) and L1 (2 mol %) were used. [c] CuBr (5 mol %) and L1 (10 mol %) were used. [d] Yields were determined by NMR spectroscopy with 1,3,5-Trimethoxybenzene as the internal standard.

Table 5: Cu/L1-catalyzed arylation of benzylic and aliphatic alcohols.^[a]

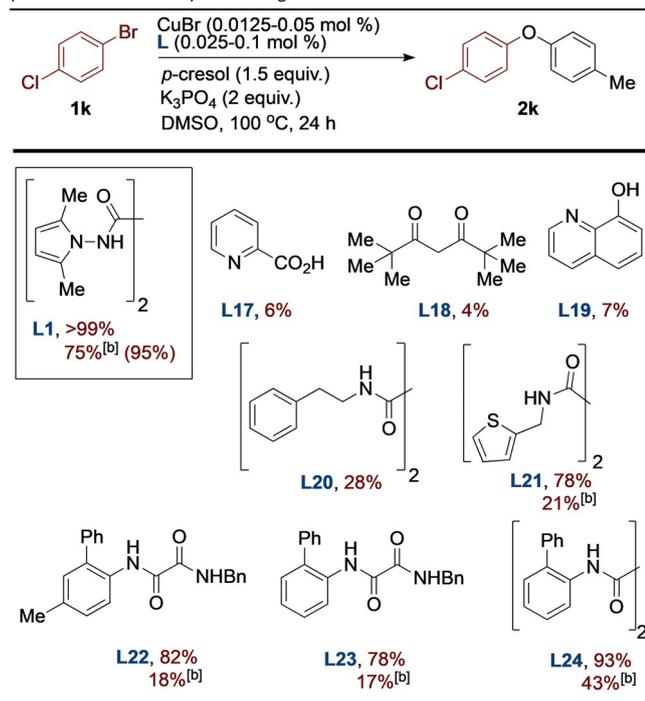
[a] Reaction conditions: CuBr (2.5 mol %) and L1 (5 mol %) were mixed in the presence of K₃PO₄ (2.0 mmol) in DMSO (300 μL) at RT for 5 mins followed by the addition of **7** (1 mmol) and alcohol (3 equiv). The reaction mixture was then heated at 120 °C. Yields were determined by NMR spectroscopy with 1,3,5-Trimethoxybenzene as the internal standard.

the potential of this catalyst for the synthesis of complex molecules.

Table 6: Cu/L1-catalyzed arylation of phenols with complex drug-like aryl halides.

[a] Reaction condition A: CuBr (2.5 mol %) and L1 (5 mol %) were mixed in the presence of K₃PO₄ (0.2 mmol) in DMSO at RT for 5 mins followed by the addition of **9a–11a** (0.1 mmol) and *p*-cresol (2.0 equiv). The reaction mixture was then heated at 100 °C. [b] CuBr (5 mol %) and L1 (10 mol %) were used. Yields were determined by NMR spectroscopy with 1,3,5-Trimethoxybenzene as the internal standard. Isolated yields are given in parentheses.

To draw comparisons to published copper catalysts with oxalamides and to determine if the known systems couple phenols with aryl halides with higher TONs than those under the conditions reported, we conducted a systematic investigation of reactions with ligands **L17–L24**^[15,16] in Table 7 under the conditions of our studies with **L1**. Initial studies with **L17–L24** were conducted in the presence of 0.05 mol % CuBr and 0.1 mol % ligand. The catalytic reactions of 1-bromo-4-chlorobenzene (**1k**) with the anionic ligands 2-picolinic acid (**L17**), 2,2,6,6-tetramethyl-3,5-heptanedione (**L18**) and 8-hydroxyquinoline (**L19**) formed the coupled product in low yield, due to low conversion of the aryl bromide. The catalytic system containing the oxalamide, **L20**, reported by Ma for the synthesis of alkyl aryl ethers,^[16] afforded low yield of the product at the catalyst loading of 0.05 mol % with K₃PO₄ base. Another catalytic system containing oxalamide ligand **L21**, which was recently reported by a team of scientists at AbbVie,^[15c] gave high yield of the product (78 %) at the higher catalyst loading but gave low yield at the lower catalyst loading of 0.0125 mol %. Likewise, the

Table 7: Evaluation of a series of ligands for Cu-catalyzed arylation of phenols at low catalyst loading.^[a]

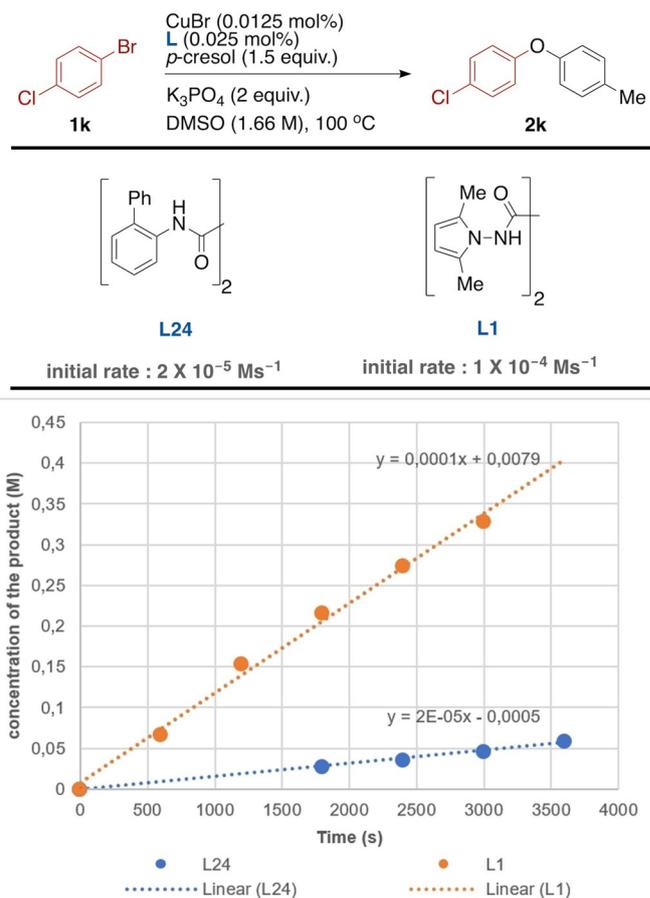
[a] Reaction conditions: CuBr (0.05 mol %) and L (0.1 mol %) were mixed in the presence of K₃PO₄ (1.0 mmol) in DMSO at RT for 1 h, followed by the addition of 1k (0.5 mmol) and *p*-cresol (1.5 equiv.). The reaction mixture was heated at 100 °C for 24 h. The reactions were quenched by addition of EtOAc, and the crude mixtures were analyzed by ¹H NMR spectroscopy. [b] CuBr (0.0125 mol %) and L (0.025 mol %) were used. Yields are measured by NMR spectroscopy with 1,3,5-Trimethoxybenzene as the internal standard. Yield in parenthesis refers to the yield of the reaction at 120 °C after 24 h.

catalysts containing oxalamides **L22–L24** formed the biaryl ether at 0.05 mol % catalyst, but did not form the biaryl ether in high yield with the lower loadings suitable for catalyst containing the ligands in this work. At the lower loading, the highest yield was observed with **L24**, and this yield was below 50%. Thus, the catalysts from some of these ligands react with higher turnovers than those reported in published literature, but the activities are lower than that of the catalyst containing oxalohydrazide **L1**.

In addition to evaluating the lifetime of the catalysts containing oxalohydrazide ligand **L1** for coupling of a series of aryl halides and phenols, we evaluated the rate of reactions conducted with this ligand on copper, relative to those of prior systems. We compared the initial rates of the coupling of 1-bromo-4-chlorobenzene with *p*-cresol catalyzed by the combination of CuBr and **L1** to that catalyzed by CuBr and **L24** because the catalyst from **L24** was the most active among those containing oxalamides for the formation of biaryl ethers. The plots showed that the initial rate of the reaction catalyzed by the combination of CuBr and **L1** ($k = 1 \times 10^{-4} \text{ Ms}^{-1}$) with potassium phosphate as base is higher than that by the combination of CuBr and **L24** ($k = 2 \times 10^{-5} \text{ Ms}^{-1}$) by approximately a factor of 5. NMR spectra of the catalytic reactions recorded at different times during the reactions

catalyzed by CuBr and **L1** or CuBr and **L24** showed no significant accumulation of side products (see supporting information for details).

In addition, the initial rates of the coupling of 1-bromo-4-chlorobenzene with *p*-cresol catalyzed by the combination of CuBr and oxalohydrazide ligands **L1** and **L6** with potassium phosphate as base were compared with the initial rates of the same coupling catalyzed by the combination of CuBr and previously reported oxalamide ligands **L22** and **L23** at a higher loading of the catalysts (Cu: 0.05 mol % and L: 0.1 mol %; Figure S2, Supporting Information). The plots showed an approximately 5-fold greater initial rate of the reaction catalyzed by the combination of CuBr and an oxalohydrazide ligand (**L1** or **L6**) than that of the reaction catalyzed by the combination of CuBr and oxalamide ligands **L22** or **L23** (see supporting information for details).

**Figure 2.** Comparison of the kinetic behavior of the oxalohydrazide (**L1**) vs. the previous oxalamide (**L24**) in Cu-catalyzed arylation of phenols at low catalyst loading.

Conclusion

In summary, we have shown that oxalohydrazides from *N*-aminoazole groups generate highly active Cu catalysts for couplings to form aryl ethers with high turnover numbers and broad scope. Experiments on reaction rates show that the lifetime of the copper catalysts ligated by **L1** is much longer

than that of the copper catalysts ligated by **L24** reported earlier by Ma for the arylation of phenols, and studies on the initial rates also show that the initial rates are measurably higher.

Based on these observations, a new library of oxalohydrazides was generated (**L2–L16**), and additional ligands were identified (**L6** and **L15**) that generated catalysts with activities similar to that generated by **L1**. With these catalysts TON approaching 8000 were achieved for the coupling of phenols with aryl bromides to form biaryl ethers **2k** and **2l**. These values are nearly two orders of magnitude higher than those previously reported for the coupling of phenols with aryl halides and almost an order of magnitude higher than those for any other type of copper-catalyzed coupling of an aryl bromide or chloride.

Aryl halides containing a wide variety of functional groups, such as nitriles, halides, ketones, ethers, amines, esters, amides, alcohols, alkenes and boronic acid esters, occurred with TONs between 1000–8000. Arylations of phenols with less reactive aryl chlorides and arylations of benzylic and aliphatic alcohols also occurred. Finally, the utility of this method for complex haloarenes was shown by the synthesis of biaryl ethers from pharmaceutically relevant aryl halides. Detailed mechanistic analysis is needed to reveal the origin of this high activity, and such studies will be the subject of future studies.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: copper catalysis · cross-coupling · high turnover numbers · oxalohydrazide ligands

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