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Reagent Design and Ligand Evolution for the Development of a Mild Copper-Catalyzed Hydroxylation Reaction

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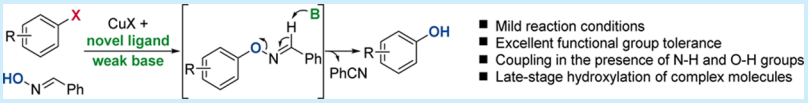
Supporting Information



ABSTRACT: Parallel synthesis and mass-directed purification of a modular ligand library, high-throughput experimentation, and rational ligand evolution have led to a novel copper catalyst for the synthesis of phenols with a traceless hydroxide surrogate. The mild reaction conditions reported here enable the late-stage synthesis of numerous complex, druglike phenols.

Cross-coupling reactions have revolutionized synthetic chemistry, with broad-reaching applications across many disciplines.[1] However, many of these reactions operate under strongly basic conditions and with reagents that are intolerant of common electrophilic and protic functionalities and cannot be applied to complex molecules. As a result, the number of protecting group manipulations in synthesis has increased significantly in recent years.[2] Therefore, the design of new catalysts and reagents that enable reactions to occur under mild conditions without protecting groups can improve efficiency in complex molecule synthesis.

The use of strongly basic conditions is particularly problematic in the conversion of aryl halides to phenols.[3−5] Phenols are versatile synthetic intermediates and components of over 200 approved drugs and 100000 natural products.[6] Thus, the forcing conditions of current methods limit which phenol targets and intermediates can be efficiently accessed in drug discovery and total synthesis. Specifically, in copper-catalyzed methods (Figure 1), hydroxide nucleophiles have been shown to result in the hydrolysis of esters and amides, hydration of nitriles, and dehydration of alcohols.[4b,e,k] Furthermore, no publications on copper-catalyzed coupling have demonstrated the synthesis of phenols in the presence of free X−H bonds of amines, unhindered amides, carbamates, sulfonamides, or aliphatic alcohols, as these groups can undergo competitive Ar−N and Ar−O bond formation with aryl halides under the reaction conditions. To address these limitations, herein we report a novel Cu-catalyzed method for the hydroxylation of complex aryl halides.

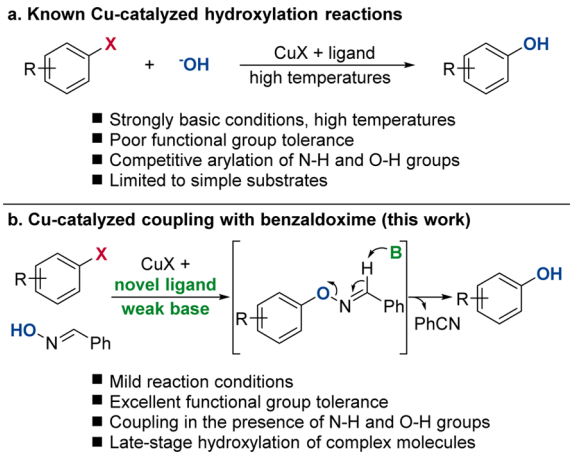


Figure 1. Copper-catalyzed synthesis of phenols from aryl halides.

We have recently developed a new paradigm to form phenols under mild conditions through the use of traceless hydroxide surrogates.[3d,5i] The hallmarks of the hydroxide surrogate reactions are (i) mildly basic conditions made possible by acidic O−H bonds, (ii) tolerance of protic and electrophilic functionality, (iii) selective coupling of the α-aza oxyanion in the presence of nucleophilic groups (NuH) prone to competitive Ar-Nu formation, (iv) the direct synthesis of phenol products without a separate deprotection step, and (v) the use of readily available, inexpensive reagents with the formation of innocuous byproducts.

Our previous work revealed that benzaldehyde oxime can act as a hydroxide surrogate in Pd/RockPhos-catalyzed cross-coupling, with the coupling and phenol-forming elimination steps occurring under mild conditions.[5i] While the Pd-catalyzed reactions occur with broad scope, the high cost of RockPhos ($545/mmol),[7] difficulty of purging Pd from complex molecules, and low yields with substrates containing primary amino groups limit the applicability of this method. A related Cu-catalyzed hydroxylation reaction could address these concerns, as Cu catalysts are typically inexpensive, Cu is readily removed from target compounds with simple aqueous workups, and Cu-catalyzed reactions can occur with complementary scope to analogous Pd-catalyzed reactions.[8]

However, the development of a Cu-catalyzed reaction with benzaldoxime faces several challenges not present with Pd. First,

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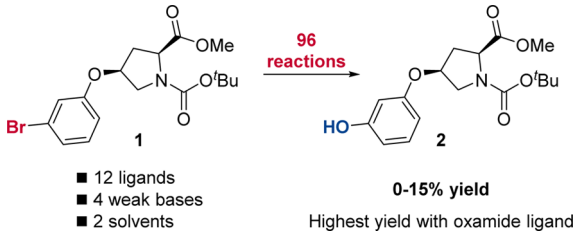
Cu-catalyzed reactions typically require higher temperatures than Pd-catalyzed reactions, a formidable challenge due the instability of benzaldoxime toward thermal dehydration.[9] Second, the nucleophilic benzaldoxime anion may lead to the displacement of auxiliary ligands and the formation of "ligandless" cuprate species, $[Cu(OR)_2]^-$, which are generally inert toward coupling with aryl halides.[10] Finally, and most significantly, is that several Cu salts are known to promote facile hydrolysis, dehydration, and/or rearrangement of benzaldoxime, which would effectively preclude the development of the proposed reaction.[11] In line with these challenges, only a single example of Cu-catalyzed coupling of oximes with aryl halides has been reported.[12] Due to the observed sensitivity of the oximes toward degradation, the C−O coupled products were formed in particularly poor yields with no functional group tolerance demonstrated.

Despite the above-mentioned challenges, Cu-catalyzed reactions with benzaldoxime were investigated with compound **1**. This substrate contains a base-sensitive methyl ester and epimerizable stereocenter and would probe the ability of copper complexes to catalyze the coupling of an unactivated aryl bromide under mild conditions. *Notably, compound 1 underwent complete ester hydrolysis and variable degrees of epimerization under the mildest conditions for the Cu-catalyzed coupling of aryl bromides with hydroxide salts.*[4] Initially, reactions with benzaldoxime as the hydroxide surrogate were screened with weak bases and with catalysts prepared in situ from CuI and 12 commonly used ligands (see the Supporting Information) (Scheme 1). Even after extensive screening, the phenol product was formed in poor yields. In all cases, incomplete conversion of **1** was observed, which could not be overcome through traditional screening efforts. Thus, it was imperative to pursue an alternative strategy that went beyond merely screening known ligands.[13]

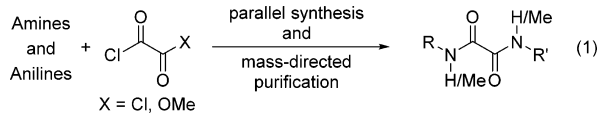
Scheme 1. Initial Screening of Cu Catalysts[a]



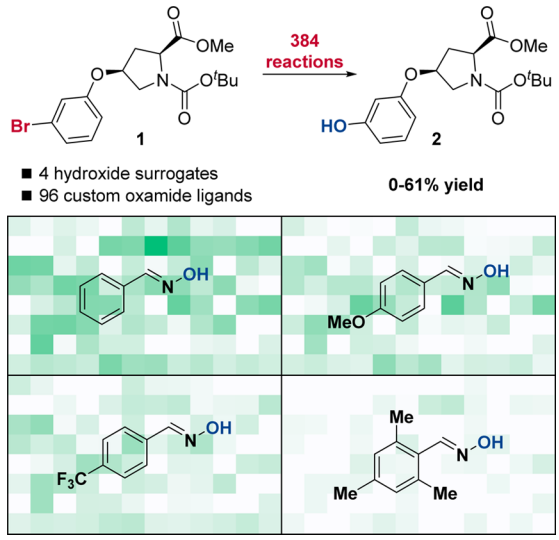
[a]Reaction conditions: 5.0 μmol of **1**, 1.2 equiv of benzaldoxime, 2.0 equiv of Cs_2CO_3, 5 mol % CuI and ligand, DMSO (1.0 M), 80 °C, 18 h. Additional details are available in the Supporting Information.

Of the 12 ligands investigated, the highest yields of **2** were observed for reactions containing an oxamide ligand.[4k,14] We proposed that varying the two ends of the oxamide ligand could lead to a series of novel ligands for the targeted hydroxylation reaction. Due to the modular nature of oxamide ligands, these ligands are ideally suited for combinatorial synthesis. A library of 96 oxamide ligands was prepared through parallel synthesis and mass-directed purification (eq 1). The 96 unique ligands were prepared from a diverse collection of primary and secondary amines and anilines and encompassed both symmetrical and unsymmetrical oxamides.

Microscale reactions of the 96 ligands were conducted with substrate **1**, CuI (5 mol %), and Cs_2CO_3 in DMSO. In Cu-catalyzed reactions, the nucleophilic coupling partner is generally bound to Cu prior to reaction with the aryl halide. As such, the identity of the oxime was predicted to have a significant impact on the outcome of the targeted hydroxylation reaction. Thus, four benzaldoxime derivatives were surveyed to expand the breadth of the screening effort beyond a single hydroxide surrogate (384 reactions in total) (Scheme 2)



Scheme 2. High-Throughput Screening of Oximes with Custom Ligand Library[a]



[a]Reaction conditions: 5.0 μmol of **1**, 2.0 equiv of oxime, 2.5 equiv of Cs_2CO_3, 5 mol % of CuI and ligand, DMSO (0.2 M), 80 °C, 18 h. Structures of all 96 ligands and yields for all 384 reactions are provided in the Supporting Information.

The 384 microscale reactions formed compound **2** in 0−61% yield and provided valuable insight into the factors that impact the targeted hydroxylation reaction. Reactions with benzaldoxime as the hydroxide surrogate provided the highest yields, followed by *p*-(trifluoromethyl)benzaldoxime and *p*-methoxybenzaldoxime. Across all reactions, no ester hydrolysis or epimerization side products were observed. Many cases were identified where minor variations in the ligand structure had profound impacts on the yields of the reaction. Reactions with previously reported oxamide ligands occurred in modest yields (0−39%), underscoring the importance of investigating an expansive ligand set for the development of new transformations.

The reaction with benzaldoxime catalyzed by CuI/**L1** (Scheme 3) provided the highest yield of **2** (61%). The related ligand where the oxazoline in **L1** is replaced by a phenyl ring formed **2** in only 18% yield with benzaldoxime. We propose that the additional coordination site (i) prevents the formation of inactive copper species formed by ligand displacement by the benzaldoxime anion and/or (ii) prevents the formation of unligated copper species that mediate benzaldoxime decomposition. The modest yield is a due to the formation of 11% of diaryl ether product and incomplete consumption of **1**. To address these issues, derivatives of **L1** were prepared, wherein the oxazoline was replaced by other coordinating groups. Reactions of **1** with the ligand bearing an oxadiazole moiety (**L2**) formed

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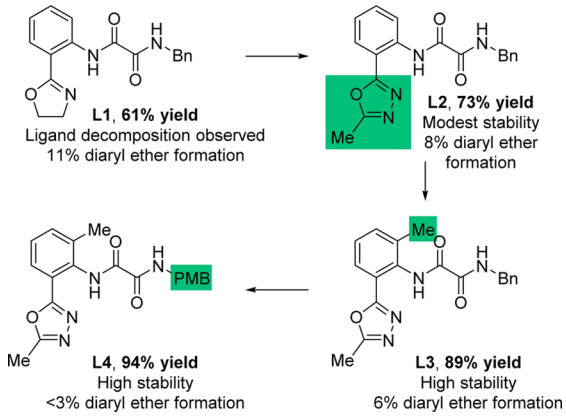
Scheme 3. Ligand Evolution from L1[a]



[a]Yields shown for the conversion of **1** to **2**. Reaction conditions: **1** (1.0 equiv), benzaldoxime (2.0 equiv), Cs_2CO_3 (2.5 equiv), CuI (5 mol %), ligand (5 mol %), DMSO (0.2 M), 80 °C, 18 h.

phenol **2** in the highest yield among the ligands prepared (73% yield).

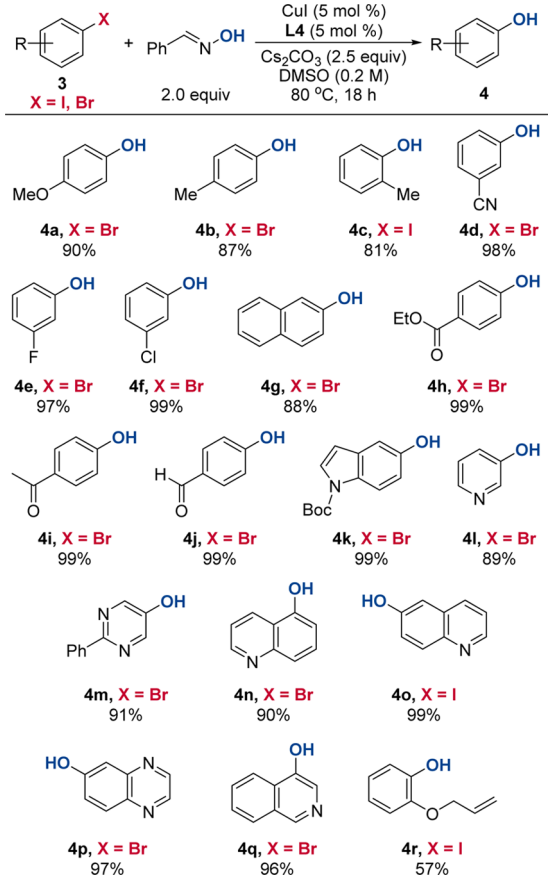
For **L1** and **L2**, amide cleavage of the anilide portion was observed during the reaction, with ligand decomposition preventing full conversion of **1**. A methyl group was installed adjacent to the C−N bond (**L3**) to slow ligand decomposition, resulting in enhanced ligand stability and an improved yield of **2**. Finally, an additional set of 11 ligands were prepared that contained groups other than benzyl. Of the ligands investigated, *p*-methoxybenzyl ligand **L4** provided the highest yield of **2** with trace diaryl ether formation.

With the novel ligand **L4** in hand, the scope of the hydroxylation reaction was investigated with a collection of aryl halides (Scheme 4). Several electron-rich, electron-poor, and *ortho*-substituted aryl halides reacted in high yields under the standard conditions. The use of a weak base enabled the hydroxylation to occur in the presence of several sensitive functional groups, including enolizable ketones, aldehydes, nitriles, and aryl halides that are susceptible to benzyne formation under strongly basic conditions (**3e** and **3f**). These results are in stark contrast to previously developed Cu-catalyzed reactions with hydroxide salts that result in ester hydrolysis and nitrile hydration. Several Lewis basic heterocycles were well tolerated.

The formation of the phenol product from substrate **3r** provides insight into the reaction mechanism.[15] The successful coupling is consistent with a mechanism proceeding via a two-electron oxidative addition/reductive elimination process, opposed to one-electron mechanisms that have been invoked for certain Cu-catalyzed reactions.

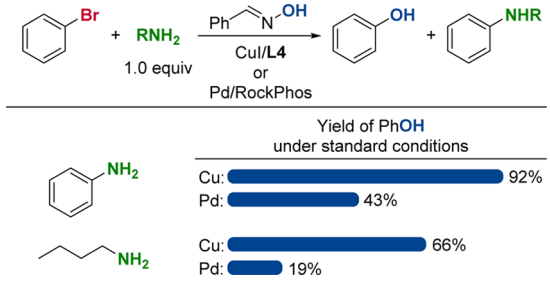
During the development of the related Pd-catalyzed method, we found that those reaction conditions are only moderately tolerant of primary amines and anilines, with significant amounts of Ar−N bond formation products being formed.[5i] A significant driver to developing this Cu-catalyzed system was to identify a catalyst system that could form phenols in the presence of primary amino groups. Indeed, spiking experiments of PhBr with 1 equiv of aniline or butylamine demonstrated that the CuI/**L4** system forms phenol in significantly higher yields, with minimal C−N coupling, compared to the same reactions with Pd/RockPhos as the catalyst (Scheme 5). This is the first example for the Cu-catalyzed synthesis of phenols from aryl halides in the presence of these functional groups and further highlights the utility of the hydroxide surrogate approach.

Scheme 4. Representative Substrate Scope[a]



[a]Assay yields shown for reactions performed on 1.0 mmol scale.

Scheme 5. Comparison of Cu- and Pd-Catalyzed Methods



Next, the hydroxylation of more challenging druglike aryl halides was investigated (Scheme 6). Significantly, the phenol products were formed with substrates containing free O−H and N−H bonds of alcohols, acids, amides, sulfonamides, and carbamates. Each of the products contained less than 10 ppm of Cu after purification, an important finding for applications of this work toward drug synthesis. Together, these results highlight the synthetic utility of the Cu-catalyzed hydroxide surrogate reaction for the late-stage synthesis of highly functionalized phenols under mild reaction conditions.

In summary, we have developed a mild Cu-catalyzed reaction to form phenols from aryl halides with a traceless hydroxide surrogate. The development of this reaction was enabled through a custom ligand library and subsequent ligand evolution. The methodology reported here is highlighted by the late-stage hydroxylation of several complex aryl halides.

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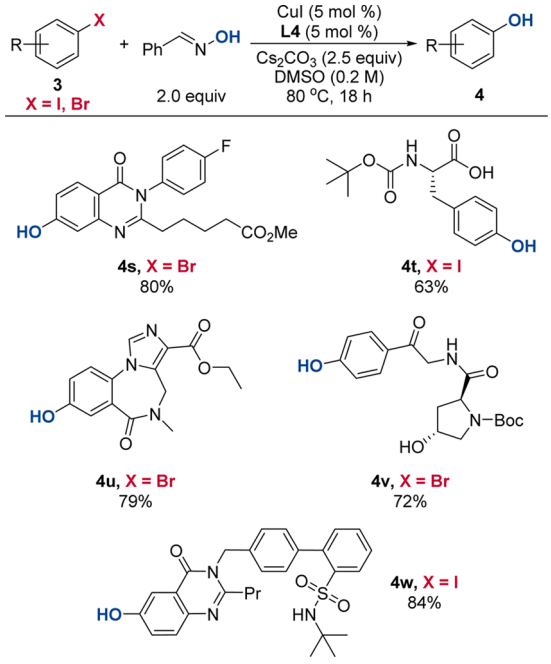
Scheme 6. Synthesis of Complex Druglike Phenols[a]



[a]Isolated yields shown for reactions conducted on 1.0 mmol scale.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01403.

Experimental details and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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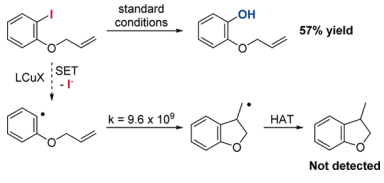

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