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# Direct Arylation of Azoles Enabled by Pd/Cu Dual Catalysis

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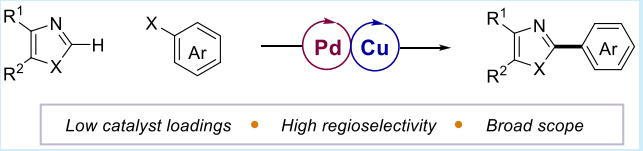
**ABSTRACT:** A practical approach toward the synthesis of 2-arylazoles via direct arylation is described. The transformation relies on a Pd/Cu cocatalyst system that operates with low catalyst loadings. The reaction conditions were found to be tolerant of a wide range of functional groups and nitrogen-containing heterocycles commonly employed in a drug discovery setting.






Direct functionalization of C−H bonds is an attractive approach for the efficient preparation and late-stage diversification of complex natural products and pharmaceutically relevant molecules.[1] Compared to traditional methods that rely on prefunctionalized starting materials, C−H bond functionalization approaches are inherently advantageous in terms of atom, redox, and step economies.[2] Despite the aforementioned advantages, the general applicability of direct C−H arylation protocols in a drug discovery setting remains challenging because of the common limitations that include site selectivity, functional group tolerance, and the need for large excesses of reagents and catalysts.[3,4]

Biaryl scaffolds, including 2-aryloxazoles, are commonly found in pharmaceutically relevant molecules, such as the ones shown in Figure 1.[5] Given their prevalence, a general, reliable,

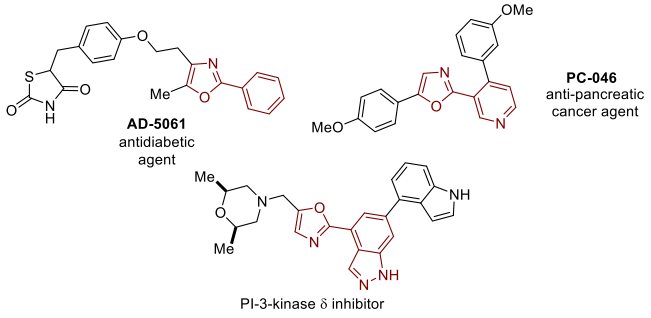



**Figure 1.** Examples of 2-aryloxazoles in biologically active molecules.

and highly efficient method for C−H functionalization of azoles would be of a significant interest (Figure 2). Furthermore, direct C−H arylation approaches take advantage of widely available aryl halide monomers, offering an attractive strategy for various classes of coupling partners.[6]

Despite numerous protocols for metal-catalyzed direct C−H arylations of azoles,[7] their applications in the pharmaceutical industry, especially in a development stage, are rare because of the high catalyst loadings (5−10 mol %) and the requirement

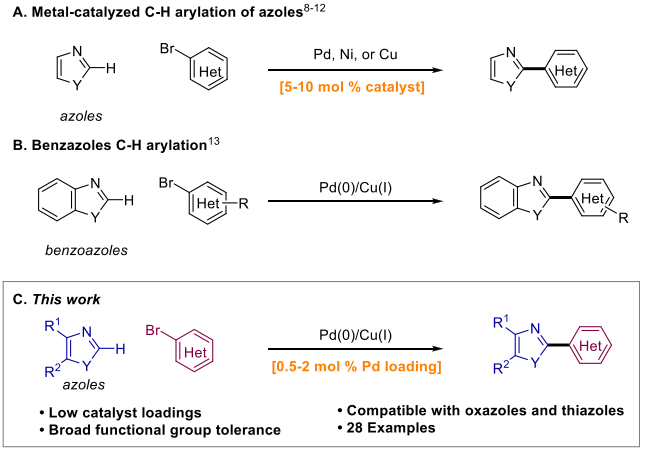



**Figure 2.** Inspiration for the development of Pd/Cu cocatalyzed C−H arylation of azoles.

for harsh conditions that significantly limit the scope of the transformations (Figure 2A).[8−11]

In 2010, Amgen disclosed the use of a novel Pd/Cu cocatalyst[12] for the direct C−H arylation of benzoazoles using just 0.25 mol % Pd loadings (Figure 2B).[13] However, to the best of our knowledge, a similar highly efficient catalytic system for C−H arylation of azoles has not been reported. The presence of an additional potentially reactive C−H bond in azoles can render couplings unselective.[14] Thus, the use of an excess of the azole partner is often required to limit the formation of the undesired bis-arylated oxazole side product. Herein, we report an efficient Pd/Cu dual-catalytic system that enables C-2 selective arylation of azoles with low catalyst

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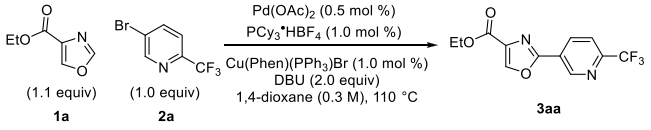
loadings, employing a mild base to ensure the tolerability of a broad range of pharmaceutically relevant heterocyclic coupling partners (Figure 2C). The salient results of our optimization study, the scope of the transformation, and preliminary mechanistic experiments are detailed below.

The results of our optimization study for the direct C−H arylation of ester oxazole **1a** with bromopyridine **2a** are summarized in Table 1. After an extensive screening

**Table 1. Optimization of C−H Arylation Conditions**




| entry | deviation from standard conditions[a] | yield (%)[b] |
|---|---|---|
| 1 | no change | 84 (87[c]) |
| 2 | CuBr instead of Cu(Phen)$PPh_3$Br | 66 |
| 3 | CuI instead of Cu(Phen)$PPh_3$Br | 74 |
| 4 | CuCl instead of Cu(Phen)$PPh_3$Br | 55 |
| 5 | $Cu(NCMe)_4PF_6$ instead of Cu(Phen)$PPh_3$Br | 73 |
| 6 | $K_2CO_3$ instead of DBU | 25 |
| 7 | DMAc instead of 1,4-dioxane | 54 |

[a]Scale: 0.70 mmol. [b]Assay yields were determined on the basis of the UPLC area percent at 210 nm with a calibrated UPLC instrument. [c]Isolated yield.

campaign,[15] we found that commercially available $Pd(OAc)_2$ (0.5 mol %), $PCy_3{\cdot}HBF_4$ (1.0 mol %), and Cu(Phen)$(PPh_3)$Br (1.0 mol %) formed a dual catalytic system to produce the desired coupling product **3aa** in 87% isolated yield. The identity of the Cu source was critical to realize the desired transformation with low catalyst loadings. Reactions that employed alternate Cu cocatalysts, such as CuI, CuBr, CuCl, or $Cu(NCMe)_4PF_6$, led to inferior levels of reactivity (entries 2−5). Couplings that utilized $K_2CO_3$ as base led to bis-arylation of the oxazole **1aa**, resulting in poor yields of the desired product **3aa** (entry 6).[14c] Notably, similar side products arising from unselective C-5 arylation were not observed with DBU.[16] Finally, 1,4-dioxane was found to be the optimal solvent, as reactions that were performed in other media, such as DMAc, resulted in lower yields of the product **3aa** (entry 7).

With an optimized set of conditions in hand, the scope of the transformation with respect to the aryl halide coupling partner was explored next (Figure 3). Substituents at the *para* or *meta* positions of the pyridine rings, irrespective of their electronic nature (−$CF_3$, −$CO_2$Et, −OMe), had no influence on the efficiency of the coupling, delivering the corresponding biaryl products **3aa**−**ac** in high yields. Unsurprisingly, using aryl iodide instead of aryl bromide afforded the product **3aa** in a similar yield. Functionalization of the oxazole **1a** with an *ortho*-substituted bromo-pyridine led to the desired product **3ad** in 88% yield. Furthermore, a strongly coordinating functional group at the *ortho* position of the aryl halide monomer, such as an unprotected amine, was tolerated, producing amino-pyridine **3ae** in 66% isolated yield. Gratifyingly, chemoselective oxidative addition of the Ar−Br bond was observed when 3-bromo-5-chloropyridine (**2f**) was used as a coupling partner, delivering chloride-containing 2-aryloxazole **3af** in excellent yield, enabling further downstream diversification of the product. The reactions that used medicinally relevant nitrogen-containing heterocycles, 2-bromopyridines

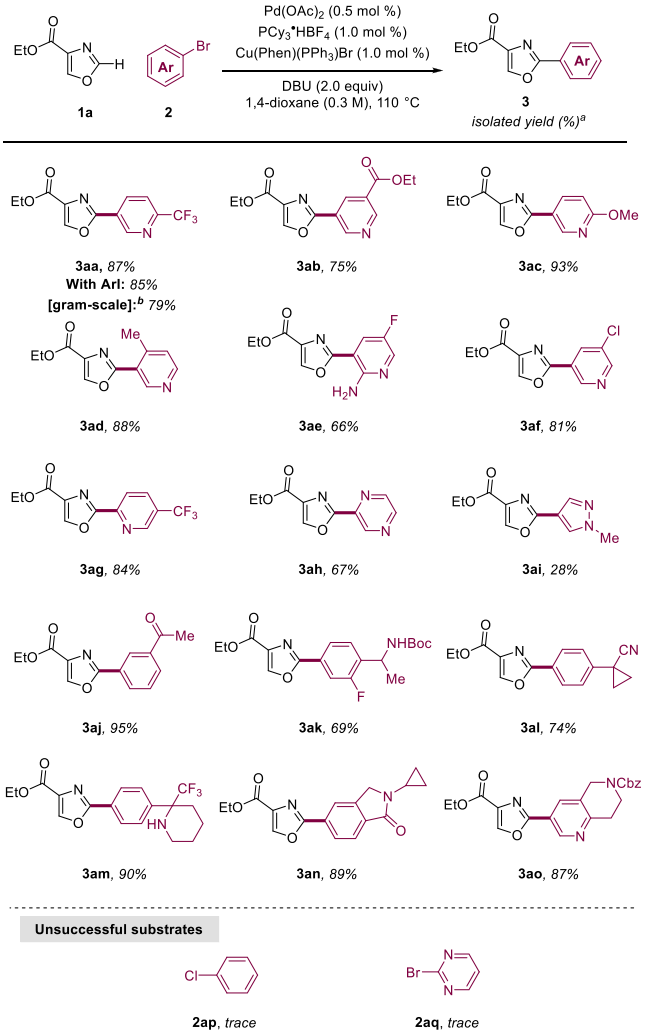



**Figure 3.** Scope studies of aryl bromides. [a]Reactions were run using standard reaction conditions: aryl bromide **2** (1.0 equiv), oxazole **1a** (1.1 equiv), $Pd(OAc)_2$ (0.5 mol %), $PCy_3{\cdot}HBF_4$ (1.0 mol %), Cu(Phen)$(PPh_3)$Br (1.0 mol %), DBU (2.0 equiv), 1,4-dioxane (0.3 M), 110 °C. Isolated yields are reported. [b]The reaction was conducted utilizing 2.0 g of **1a**. Isolated yield is reported. Boc = *tert*-butyloxycarbonyl, Cbz = benzyloxycarbonyl, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene, and Phen = phenanthroline.

and 2-bromopyrazines, furnished the corresponding products **3ag** and **3ah** in 84% and 67% yields, respectively. The couplings of oxazole **1a** with electron-rich 5-membered aryl halides were more challenging, with modest reactivity observed for bromopyrazoles, leading to products such as **3ai** in reduced yields. The ability to functionalize oxazole **1a** with 2-bromopyridines, pyrazines, and pyrazoles serves to underscore the complementarity of the C−H arylation approach to the traditional Suzuki-Miyaura coupling, as corresponding aryl boronates either are not commercially available or are significantly less stable.[17] Apart from a broad aryl substrate scope, the reaction also displayed good functional group tolerance. Couplings with substrates that contained ketone, nitrile, Boc (*tert*-butyloxycarbonyl)-protected amine, and $\alpha$-tertiary amine functional groups proceeded smoothly to afford the desired biaryl products **3aj**−**am** ranging from 74% to 95% yield. Aryl bromides containing fused nitrogen heterocycles, found in products **3an** and **3ao**, performed well under the reaction conditions, further demonstrating the utility of the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developed transformation in a drug discovery setting. Finally, the reaction was found to be readily scalable, delivering biaryl product **3aa** in 79% yield on gram scale. In general, poor reaction outcomes were observed when aryl chlorides **2ap** and 2-bromopyrimidines **2aq** were subjected to the coupling conditions, delivering only trace amounts of the expected products.[18,19]

Next, the scope of the transformation with respect to the azole coupling partner was explored (Figure 4). Conducting

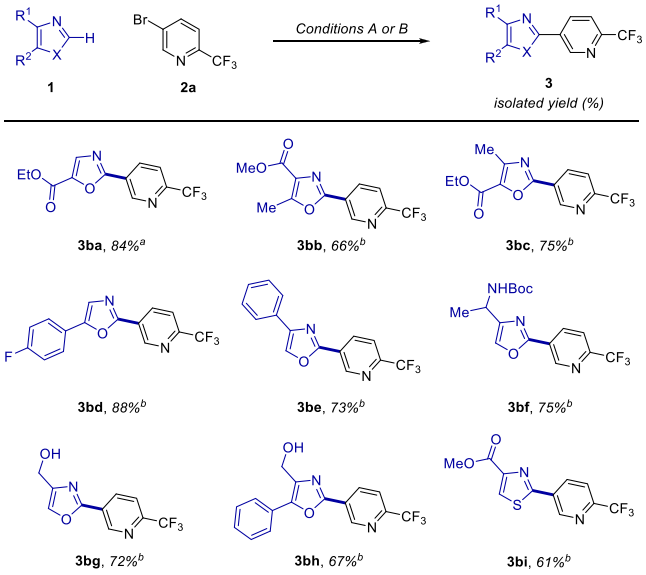


**Figure 4.** Scope studies of azoles. [a]Conditions A: aryl bromide **2a** (1.0 equiv), azole **1** (1.1 equiv), $Pd(OAc)_2$ (0.5 mol %), $PCy_3{\cdot}HBF_4$ (1.0 mol %), Cu(Phen)$(PPh_3)$Br (1.0 mol %), DBU (2.0 equiv), 1,4-dioxane (0.3 M), 110 °C. [b]Conditions B: aryl bromide **2a** (1.0 equiv), azole **1** (1.1 equiv), $Pd(OAc)_2$ (2.0 mol %), $PCy_3{\cdot}HBF_4$ (4.0 mol %), CuBr·DMS (4.0 mol %), KOPiv (2.0 equiv), toluene (0.30 M), 110 °C. DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene, DMS = dimethyl sulfide, and Phen = phenanthroline.

the reaction with the isomer of the model substrate, ethyl oxazole-5-carboxylate (**1ba**), led to the desired product **3ba** in 84% yield, similar to the 87% yield observed for **3aa** (conditions A).[20] However, when oxazoles containing a less acidic hydrogen at the C-2 position were employed, in addition to increasing Pd and Cu loadings to 2.0 mol % and 4.0 mol % to improve conversion, a carboxylate base, KOPiv, was essential to achieve high levels of reactivity (conditions B).[21] Despite the increase in catalyst loadings, near equimolar amounts of the coupling partners were retained. Utilizing this modified protocol, we were pleased to observe that both fully substituted oxazole isomers **3bb** and **3bc** were formed in 66% and 75% yields, respectively.[22] Oxazoles containing phenyl substituents, either at the 4- or the 5-position, were also found to be competent substrates under the developed reaction conditions, furnishing products **3bd** and **3be**. Furthermore, the modified reaction conditions B performed well with substantially less acidic C−H bonds found in alkyl-substituted oxazoles **3bf**−**3bh**. Strongly coordinating substituents, such as primary hydroxyl groups, were tolerated, enabling the preparation of alcohol-containing products **3bg** and **3bh** in 72% and 67% yields, respectively. Finally, the applicability of the developed method was expanded to thiazoles, delivering the biaryl product **3bi** in 61% yield.

Inspired by the broad substrate scope observed with respect to both coupling partners, we set out to further explore the applicability of the developed conditions toward late-stage functionalization of pharmaceutically relevant compounds. To this end, an "informer" set of druglike halides was used to benchmark the robustness of the reaction conditions.[23] We elected to leverage high-throughput experimentation (HTE) to evaluate reaction performance across 18 complex aryl halides using two sets of coupling conditions.[24] We were delighted to see successful late-stage functionalization of a variety of complex aryl halides with selected couplings shown in Figure 5.[25] For example, imidazole-containing aryl bromide under-

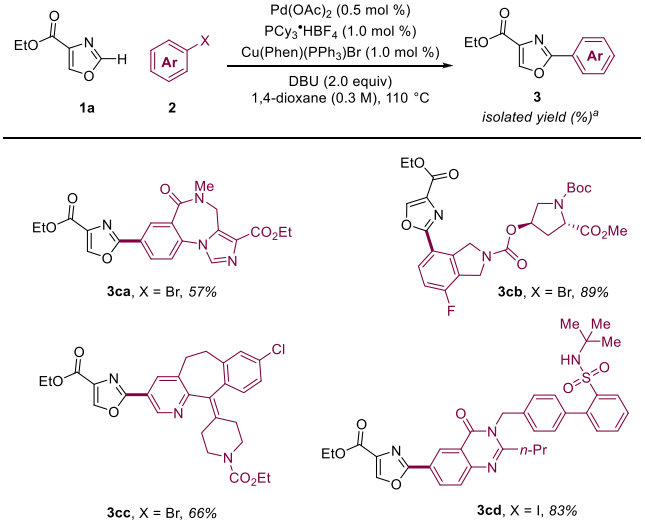


**Figure 5.** Selected examples for coupling of ethyl oxazole-4-carboxylate with informer halides. [a]Reactions were run using standard reaction conditions: aryl bromide **2** (1.0 equiv), oxazole **1a** (1.1 equiv), $Pd(OAc)_2$ (0.5 mol %), $PCy_3{\cdot}HBF_4$ (1.0 mol %), Cu(Phen)$(PPh_3)$Br (1.0 mol %), DBU (2.0 equiv), 1,4-dioxane (0.3 M), 110 °C. Boc = *tert*-butyloxycarbonyl, DBU = 1,8-diazabicyclo(5.4.0)-undec-7-ene, and Phen = phenanthroline.

went chemoselective coupling with ester oxazole **1a** to deliver the corresponding product **3ca** in 57% isolated yield.[26] Gratifyingly, the coupling of **1a** delivered the biaryl product **3cb** in excellent yield. Other complex aryl halides, bearing conjugated olefins and sulfonamide functionalities, furnished the desired products **3cc** and **3cd** in 66% and 83% yields, respectively. Noteworthy, the aforementioned transformations were carried out in the presence of just 0.5 mol % Pd and 1.0 mol % Cu, underscoring the efficiency of the discovered cocatalyst system.

To gain a better mechanistic understanding of the C−H arylation, we carried out key control experiments (Figure 6). Reactions performed in the absence of the copper complex led to low conversion with the coupling product **3aa** formed in only 34% yield (Figure 6A). No reactivity was observed with the Cu(Phen)$(PPh_3)$Br catalyst in the absence of a Pd source in the reaction. These experimental findings emphasize the crucial role of the Pd/Cu cocatalyst system to achieve high levels of reaction efficiency and indicate that both metallic species are involved in the catalytic cycle. Finally, when the reaction was conducted with $PdCl_2$ in place of $Pd(OAc)_2$, the reactivity was not affected, affording the desired product **3aa** in comparable yields. This observation suggests that the C−H


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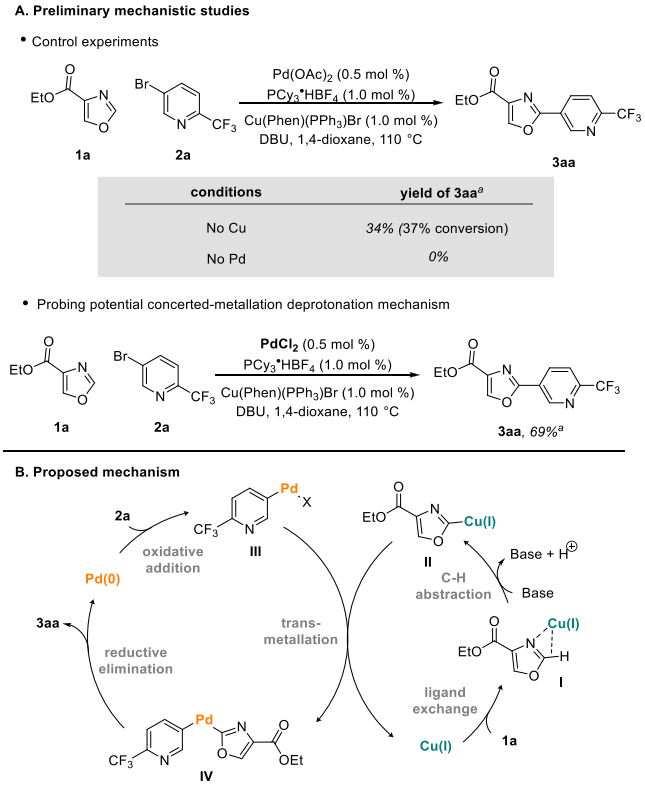


**Figure 6.** Proposed mechanism for Pd/Cu catalyzed C−H arylation of oxazoles. Ligands were omitted for the sake of clarity. [a]Assay yield.

bond cleavage is likely not going through a carboxylate mediated concerted metalation-deprotonation process.[27]

On the basis of the control experiments and previous literature reports,[28] a proposed mechanism is depicted in Figure 6B that features a bimetallic catalytic system in which Pd(0) and Cu(I) operate concomitantly.[29] First, the azaphilic Cu(I) catalyst coordinates to the nitrogen atom of the oxazole ring **I**, increasing C−H bond acidity to facilitate deprotonation and produce organocopper species **II**. The resulting Cu intermediate undergoes transmetalation with Ar−Pd(II) complex **III** (formed via oxidative addition of Pd(0) to bromopyridine **2a**) to release Cu(I) catalyst. Subsequent reductive elimination liberates product **3aa** and regenerates the Pd(0) cocatalyst. Further mechanistic studies are ongoing in our laboratory, and the results will be reported in due course.

In summary, we have identified a general and efficient set of reaction conditions utilizing Pd and Cu catalysis for the direct C−H arylation of azoles with aryl bromides. The reported dual-catalytic approach enables high catalyst turnover, requiring the use of just 0.5−2 mol % Pd. During our exploratory studies, the transformation was found to be robust, scalable, and applicable to a diverse range of aryl bromides and azoles. As a result, we believe these conditions will benefit the broader synthetic community and encourage wider implementation of direct arylation approaches overall.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00100.

Detailed experimental procedures, analytical data, and copies of spectra ($^1$H NMR and $^{13}$C NMR) of all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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(19) LCMS analyses of the crude mixtures containing 2-bromopyrimidines indicated protodehalogenation of these coupling partners in under 2 h when subjected to the reaction conditions.

(20) The coupling partner 4-bromopyridine **2a** was used to investigate the azole scope because it was employed during the reaction optimization studies. Arylation of oxazole **1ba** with 4-bromotoluene led to the formation of the corresponding product in 96% isolated yield. Please see the Supporting Information for details.

(21) The origins of the observed reactivity improvements with the inorganic bases for arylations of oxazoles bearing less acidic hydrogens at the C-2 position are not well understood at this time. Current investigations are focused on understanding the roles of each component and their contributions to the mechanistic pathway for the reported transformation. The results of the ongoing efforts will be published in due course.

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