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# Copper-Catalyzed One-Pot Synthesis of *N*-Aryl Oxazolidinones from Amino Alcohol Carbamates

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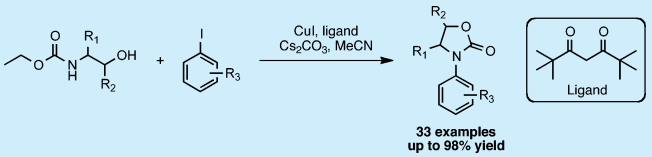
Supporting Information

**ABSTRACT:** An efficient sequential intramolecular cyclization of amino alcohol carbamates followed by Cu-catalyzed cross-coupling with aryl iodides under mild conditions has been developed. The reaction occurred in good yields and tolerated aryl iodides containing functionalities such as nitriles, ketones, ethers, and halogens. Heteroaryl iodides and substituted amino alcohol carbamates were also well tolerated.




Antimicrobial resistance is a growing area of concern in modern medicine. Newly emerging resistance mechanisms toward antibiotics is gradually reducing the latest generation of antibiotics' effectiveness toward the treatment of numerous infectious diseases. *N*-Aryl oxazolidinones have gained significant interest in the recent decade since the discovery of a new antibiotic class effective against vancomycin-resistant *enterococci* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA).[1] *N*-Aryl oxazolidinones have also shown pharmacological activity as treatments for depression and psychosis (Figure 1).[2] A number of synthetic methods have been established toward the synthesis of these compounds;[3] however, few examples were found where oxazolidinone formation and functionalization were achieved in a one-pot process.[4]

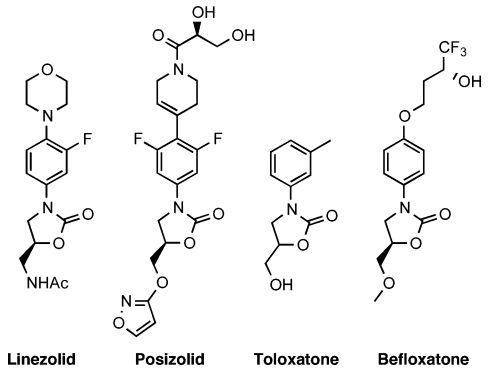



**Figure 1. Bioactive Compounds Containing an *N*-Aryl Oxazolidinone Structural Core.** Linezolid and Posizolid are applied for the treatment of bacterial infection, and Toloxatone and Befloxatone, as treatments for depression as a reversible inhibitor of MAO-A.[5]

The development of both palladium- and copper-catalyzed carbon−heteroatom bond formation has resulted in elegant examples of catalytic heterocycle synthesis.[6] It has been extensively shown that oxazolidinones can be efficiently coupled with the corresponding aryl halide under metal-catalyzed cross-coupling conditions. Copper-catalyzed Ullmann−Goldberg couplings of aryl iodides and aryl bromides with 2-oxazolidinone are well-known in the literature;[7] however, as is common with a copper cross-coupling reaction, elevated temperatures and high boiling solvents are generally required. The effectiveness of the palladium-catalyzed *N*-arylation of oxazolidinone with aryl halides and heteroaromatic tosylates has been demonstrated,[8] and work by Ghosh has developed effective systems for the reaction of aryl chlorides.[9] However, the use of palladium also requires the use of specialized and often expensive phosphine ligands.

Herein we wish to disclose a novel copper-catalyzed one-pot methodology toward the synthesis of *N*-aryl oxazolidinones derived from amino alcohols and aryl iodides. Key advantages of this developed methodology draw from the high commercial availability of starting material precursors, the potential to access a diverse and abundant chiral pool, and the application of an inexpensive catalyst/ligand system in a common, low boiling organic solvent.

To begin our study, we chose BOC-protected ethanolamine and iodobenzene as model substrates to identify suitable reaction conditions. As is common with copper-catalyzed systems, activity is largely dependent on the selection of a suitable ligand.[10]

A number of ligands commonly associated with copper-catalyzed C−N cross-couplings were used in the presence of 10 mol % of CuI as a catalyst and 1.5 equiv of $Cs_2CO_3$ as a base in toluene. The results showed that phenanthroline-based ligands gave poorer activity over ligand-free conditions. When alkyl diketone ligands were used, the desired cross-coupled *N*-aryl oxazolidinone was obtained in an improved yield.[11]

Varying the carbamate group was also shown to have a profound effect, ethylcarbamate-coupled ethanolamine being found to be the best choice. We subsequently used tetramethylheptanedione as the ligand and ethyl carbamate

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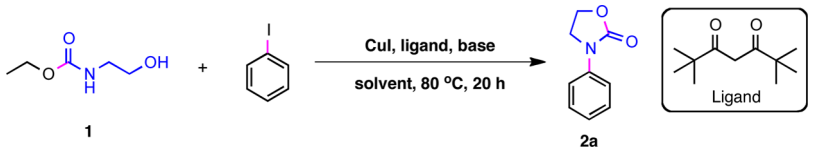
**Table 1. Optimization of Reaction Conditions**[a]




1 2a

| entry | temp (°C) | carbamate | ligand | solvent[b] | base | base (equiv) | Ar–I (equiv) | yield (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | 120 | $^t$Bu | – | PrCN | $Cs_2CO_3$ | 1.5 | 1 | 25 |
| 2 | 120 | $^t$Bu | L1 | PrCN | $Cs_2CO_3$ | 1.5 | 1 | 30[d] |
| 3 | 120 | $^t$Bu | L2 | PrCN | $Cs_2CO_3$ | 1.5 | 1 | 57 |
| 4 | 120 | $^t$Bu | L3 | PrCN | $Cs_2CO_3$ | 1.5 | 1 | 62 |
| 5 | 100 | $^t$Bu | L3 | PrCN | $Cs_2CO_3$ | 1.5 | 1 | 70 |
| 6 | 100 | Bn | L3 | PrCN | $Cs_2CO_3$ | 1.5 | 1 | 72 |
| 7 | 100 | Et | L3 | PrCN | $Cs_2CO_3$ | 1.5 | 1 | 78 |
| 8 | 100 | Me | L3 | PrCN | $Cs_2CO_3$ | 1.5 | 1 | 78 |
| 9 | 80 | Et | L3 | PrCN | $Cs_2CO_3$ | 1.5 | 1 | 30 |
| 10 | 80 | Et | L3 | THF | $Cs_2CO_3$ | 1.5 | 1 | 78 |
| 11 | 80 | Et | L3 | toluene | $Cs_2CO_3$ | 1.5 | 1 | 30 |
| 12 | 80 | Et | L3 | Me-THF | $Cs_2CO_3$ | 1.5 | 1 | 12 |
| 13 | 80 | Et | L3 | MeCN | $Cs_2CO_3$ | 1.5 | 1 | 46 |
| 14 | 80 | Et | L3 | MeCN | $Cs_2CO_3$ | 1.5 | 1 | 76 |
| 15 | 80 | Et | L3 | MeCN | $Cs_2CO_3$ | 1 | 1 | 40 |
| 16 | 80 | Et | L3 | MeCN | $Cs_2CO_3$ | 2 | 1 | 86 |
| 17 | 80 | Et | L3 | MeCN | $Cs_2CO_3$ | 3 | 1 | 72 |
| 18 | 80 | Et | L3 | MeCN | $Cs_2CO_3$ | 2 | 1.5 | 88 |
| 19 | 80 | Et | L3 | MeCN | $Cs_2CO_3$ | 2 | 2 | 92 |
| 20 | 80 | Et | L3 | MeCN | $Cs_2CO_3$ | 2 | 3 | 96 |
| 21 | 80 | Et | L3 | MeCN | $Cs_2CO_3$ | 2 | 3 | NR[e] |

[a]Unless otherwise stated, the reaction was conducted with **1** (1 mmol), CuI (0.1 mmol), ligand (0.2 mmol, solvent (2 mL) under air, 20 h. L1 = 3,4,7,8-tetramethyl-1,10-phenanthroline, L2 = 2,2,6,6-tetramethylheptane-3,5-dione, L3 = 2-isobutyrylcyclohexanone. [b]PrCN = butyronitrile, THF = tetrahydrofuran, Me-THF = 2-methyltetrahydrofuran, MeCN = acetonitrile. [c]Isolated yield. [d]Observation of competitive *O*-arylation (7%). [e]CuI (0.05 mmol).

ethanolamine as the oxazolidinone precursor to further test the solvent. A screen of solvents showed the preference for polar aprotic solvents, THF and acetonitrile proving to be the most effective (Table 1). Despite an improved yield of the desired product being achieved in THF, additional byproducts of *O*-arylated starting material were observed. Work published by Buchwald has demonstrated that copper-catalyzed *N* vs *O*-arylations can be greatly affected by the choice of solvent. Consistent with Buchwald's work, THF was conducive toward more favorable *O*-arylation, and as such acetonitrile was used in further optimizations to afford a selective reaction.[12]

Variation of the base showed that alternative inorganic and organic bases were totally ineffective for this transformation. Variation of the equivalents of base and aryl iodide showed improvement in the presence of excess base and aryl iodide. The reaction was also shown to be relatively independent of reaction concentration. Under the reaction conditions the reduction in catalytic loading of copper iodide to 5% was shown to have a significant reduction in desired product formation. Reactions performed in the absence of a catalyst yielded only the uncoupled oxazolidinone.

In order to demonstrate the generality of this one-pot methodology the substrate scope was investigated under the optimized reaction conditions (Scheme 1). We first surveyed the compatibility of substituted aryl iodides. Aryl iodides with electron-withdrawing substituents were coupled under the reaction conditions in good to excellent yields with a high tolerance of a number of functional handles (CN, $CO_2Me$, $C(O)CH_3$, F, Br). In the case of the methyl ester substituent, transesterification to the ethyl ester was observed due to the formation of the ethoxide anion generated upon cyclization. Decreased yields were also observed due to competitive transesterification with the ethanolamine-derived starting material. However, a significant yield of the desired coupled product was obtained. Electron-withdrawing substituents showed slightly lower yields than expected as the strongly withdrawing nature increased the susceptibility of the *N*-aryl oxazolidinone toward ring opening, to yield the corresponding *N*-aryl ethanolamine. In the case of 4-nitrobenzene no desired product was obtained, and the major products were a mixture of *N*-, *NN*-, and *NNO*- arylated ethanolamine. Substituents were well tolerated at the *meta* and *para* positions on the aromatic ring; however, *ortho* substituents gave little to no cross-coupled product.

A number of heteroaryl iodides were investigated and showed excellent tolerance for nitrogen- and sulfur-containing aromatics. The addition of electron-donating substituents on the ring however significantly effected the yield of the cross-coupled product. A plot of the $^1$H NMR calculated conversions of crude reaction mixtures against the calculated Hammett constant ($\sigma$) showed a reduction in conversion to the desired *N*-arylated oxazolidinone with decreasing Hammett constant.[13] This limitation is observed by a dramatic decline in conversion with even mildly electron-donating substituents. To overcome these limitations elevated temperatures were used. Increasing the temperature of the reaction to 100 °C afforded the desired *N*-aryl oxazolidinones with electron-rich aromatics in excellent yields.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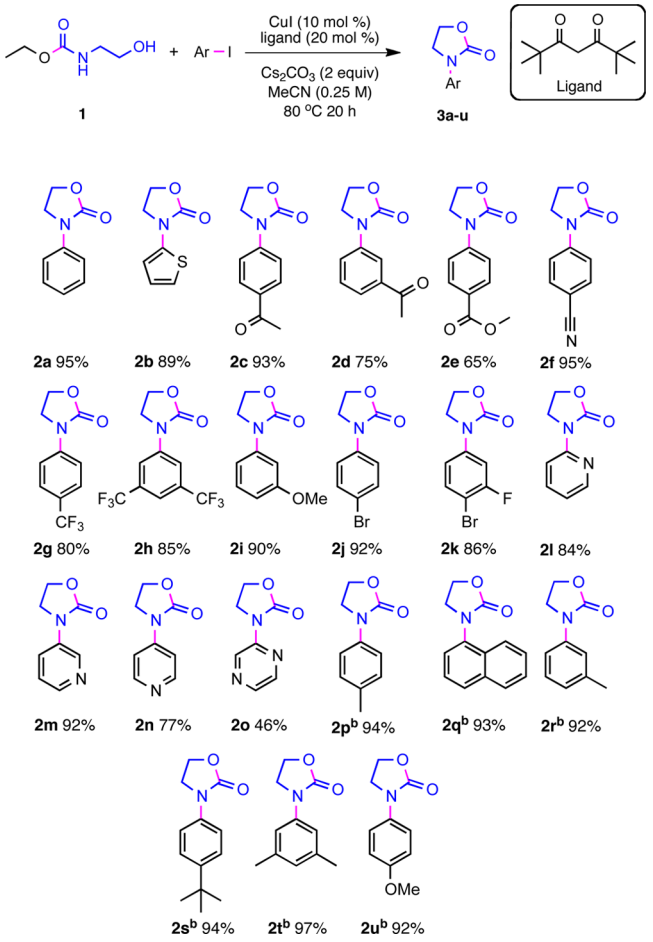
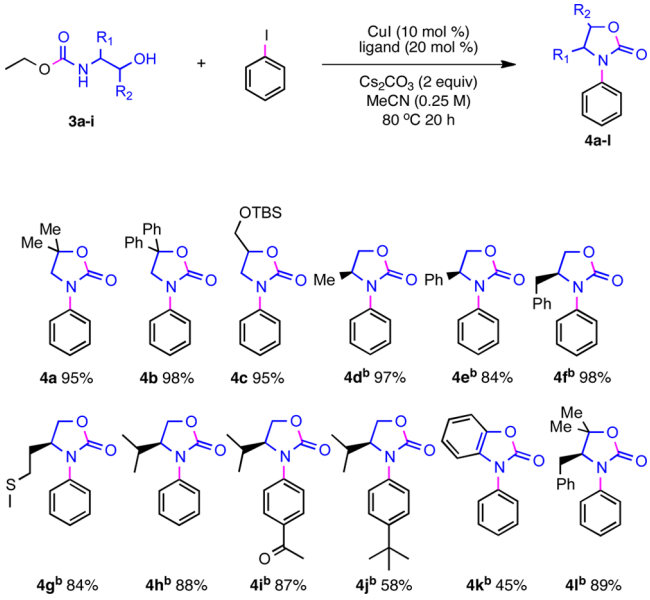
**Scheme 1. Copper-Catalyzed One-Pot Synthesis of *N*-Aryl Oxazolidinones[a]**



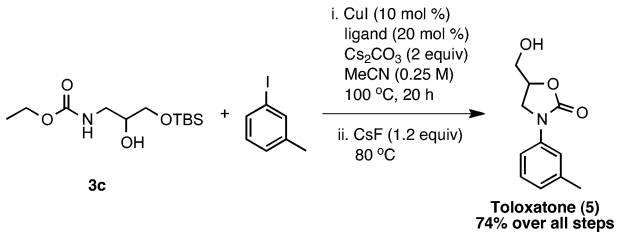

[a]Reaction conditions: **1** (1 mmol), Ar–I (2 mmol), CuI (10 mol %), ligand (20 mol %), $Cs_2CO_3$ (2 mmol), MeCN (4 mL) under air for 20 h. Isolated yields after silica gel chromatography. [b] Performed at 100 °C.

**Scheme 2. Copper-Catalyzed One-Pot Synthesis of Amino Acid Derived *N*-Aryl Oxazolidinones[a]**




[a]Reaction conditions: **3a–l** (1 mmol), Ar–I (2 mmol), CuI (10 mol %), ligand (20 mol %), $Cs_2CO_3$ (2 mmol), MeCN (4 mL) under air for 20 h. Isolated yields after silica gel chromatography. [b] Performed at 100 °C.

**Scheme 3. Synthesis of Antidepressant Toloxatone[a]**




[a]Reaction conditions: **3c** (1 mmol), Ar–I (2 mmol). Isolated yields after silica gel chromatography.

In addition, structurally diverse *N*-aryl oxazolidinones were prepared in good to excellent yields. Corresponding substituted oxazolidinones were prepared from amino alcohol derivatives and treated under the optimized reaction conditions (Scheme 2). 5-Substituted oxazolidinones proceeded well, tolerating significant steric bulk and silyl protected alcohols. 4-Substituted oxazolidinones required elevated temperatures in order to achieve satisfactory yields.[14]

The optimized reaction conditions were employed in the synthesis of Toloxatone, a reversible inhibitor of MAO-A, that is used in the treatment of depression (Scheme 3). The desired silyl ether intermediate was formed in excellent conversion. A subsequent *in situ* mild deprotection was performed to afford the corresponding unprotected product in excellent yield.

In conclusion, we have developed an efficient and mild CuI-catalyzed one-pot cyclization and arylation for the synthesis of *N*-aryl oxazolidinones. The reaction is applicable to a wide range of substrates with various substituted aryl iodides and amino alcohol derivatives in good-to-excellent yields. The ease of synthesis of the amino alcohol precursors, the performance under air using mild conditions, and the utilization of a cheap and abundant catalyst–ligand system for this two-step, one-pot synthesis make this process an attractive methodology for the preparation of important molecules.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details, procedures, compound characterization data, and copies of $^1H$, $^{13}C$, and $^{19}F$ spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

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### Notes

The authors declare no competing financial interest.

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(11) For full details of the optimization procedure, see Supporting Information.

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(14) No racemization was observed under the reaction conditions. For full details, see Supporting Information.