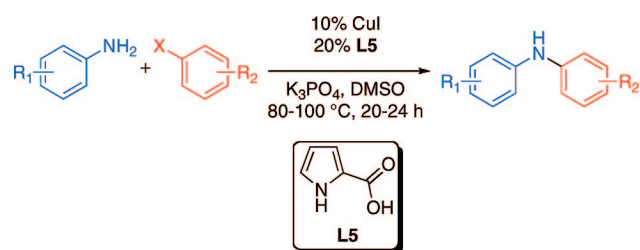# Pyrrole-2-carboxylic Acid as a Ligand for the Cu-Catalyzed Reactions of Primary Anilines with Aryl Halides

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Pyrrole 2-carboxylic acid (**L5**) was found to be an effective ligand for the Cu-catalyzed monoarylation of anilines with aryl iodides and bromides. Under the reported conditions (10% CuI/20% **L5**/DMSO/K₃PO₄/80−100 °C/20−24 h), a variety of useful functional groups were tolerated, and moderate to good yields of the diaryl amine products were obtained.

The diaryl amine moiety can be found in a variety of biologically active pharmaceuticals, natural products, and materials. Metal-catalyzed cross-coupling reactions of anilines with aryl halides are among the foremost methods for assembling this substructure.[1,2] For reactions of poorly nucleophilic primary anilines with aryl halides, Pd-based catalyst systems are highly efficient.[1] This is due, in great part, to the rapid transmetalation of anilines to Pd(II), a phenomenon that arises from the large increase in acidity of the nucleophile when coordinated to Pd(II).[3] The complementary nature of Pd- and Cu-catalyzed C−N bond-forming processes, and the issues involving removal of the trace Pd from the products encourage the development of Cu-based catalyst systems for the preparation of diaryl amines.

In recent years, Cu-catalyzed C−N bond-forming reactions have evolved as reliable alternatives to Pd-catalyzed reactions.[2] However, Cu-based catalyst systems for the synthesis of diaryl amines are less general and useful than the Pd-based protocols.[4] The Cu-catalyzed reactions of anilines with aryl halides are slow enough that a wide variety of N−H and O−H nucleophiles, including amides, nitrogen heterocycles, aliphatic, benzylic and allylic amines, as well as aliphatic and benzylic alcohols are selectively arylated in the presence of an anilino-NH₂ group.[5] In the absence of a competing reactant, the poor nucleophilicity of the aniline, when employing Cu-based catalysts, further manifests itself in the need to use high catalyst loadings (>20% Cu),[4a,f] long reaction times (>30 h),[4b,c,e] strong bases that preclude the presence of many common functional groups,[4g] and/or anilines with strong electron-withdrawing groups in the para-position.[4b] Further, the few examples of Cu-catalyzed reactions of anilines with ortho-substituted aryl halides require even higher catalyst loadings (35−50% Cu).[4f] Finally, when employing Cu-based catalysts, the propensity of the diaryl amine product to undergo further N-arylation to form a triarylamine provides an added level of complexity to developing a suitable catalyst system.[6]
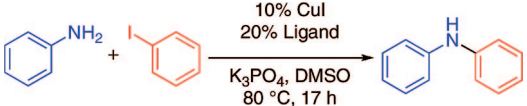
We began our investigation into the Cu-catalyzed reactions of aromatic amines with aryl iodides by evaluating previously reported catalysts for this transformation.[4] Since the more successful systems employed proline-type ligands,[4b–e] we sought to evaluate the use of new ligands that would provide a more active and generally applicable catalyst for the reaction of aniline with an aryl iodide (Table 1). While several heterocyclic-2-carboxylic acids, including some previously reported as ligands for Cu-catalyzed and -mediated nucleophilic substitution reactions of aryl halides,[7] provided poor results for this transformation (entries 1−4), pyrrole-2-carboxylic acid, **L5** (Figure 1), manifested good catalytic activity (entry 5). Both the N−H and carboxylate functional groups of this ligand are important to the activity of the catalysts derived from it. This can be seen as modification of these groups provided less-active catalysts (entries 6−8). Benzannulated analogues **L9** and **L10** also provided less-active catalysts (entries 9 and 10), presumably because they are too hindered. Finally, **L5** provided a more active catalyst system than those derived from commercially

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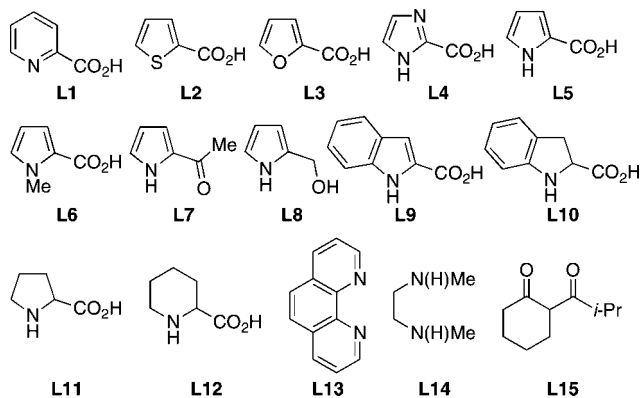
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**TABLE 1. Cu-Catalyzed Reaction of Aniline with Iodobenzene[a]**



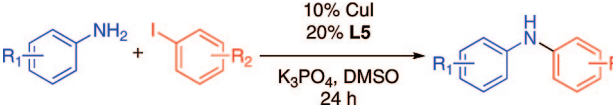| entry | ligand | GC conversion (%) | GC yield (%) |
|-------|--------|-------------------|--------------|
| 1 | **L1** | 58 | 35 |
| 2 | **L2** | 46 | 27 |
| 3 | **L3** | 47 | 27 |
| 4 | **L4** | 0 | 0 |
| 5 | **L5** | 94 | 68 |
| 6 | **L6** | 57 | 37 |
| 7 | **L7** | 55 | 22 |
| 8 | **L8** | 66 | 0 |
| 9 | **L9** | 62 | 26 |
| 10 | **L10** | 60 | 22 |
| 11 | **L11** | 64 | 34 |
| 12 | **L12** | 64 | 29 |
| 13 | **L13** | 48 | 15 |
| 14 | **L14** | 64 | 19 |
| 15 | **L15** | 51 | 30 |

[a] Reaction conditions: 1.0 mmol of $ArNH_2$, 0.5 mmol of ArI, 1.0 mmol of $K_3PO_4$, 0.050 mmol of CuI, 0.10 mmol of ligand, 0.25 mL of DMSO, at 80 °C in a sealed tube under an $N_2$ atmosphere for 17 h.
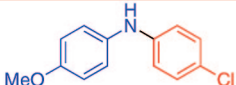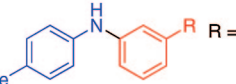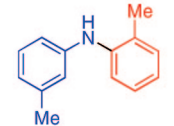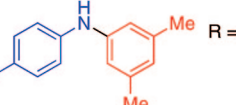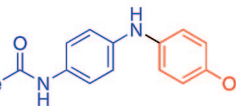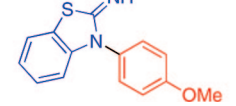


**FIGURE 1.** Ligands examined for *N*-arylation reactions of aniline.

**TABLE 2. Cu-Catalyzed Reactions of Anilines with Aryl Iodides[a]**



| entry | product | temperature (°C) | yield (%)[b] |
|-------|---------|------------------|--------------|
| 1 | | 70 | 82[c] |
| 2 | R = $CO_2Et$ | 80 | 78 |
| 3 | CN | 80 | 73 |
| 4 | | 80 | 71 |
| 5 | R = Ac | 90 | 60 |
| 6 | $CO_2Et$ | 90 | 50 |
| 7 | CN | 90 | 52 |
| 8 | | 80 | 82 |
| 9 | | 90 | 68 |

[a] Reaction conditions: 2.0 mmol of $ArNH_2$, 1.0 mmol of ArI, 2.0 mmol of $K_3PO_4$, 0.10 mmol of CuI, 0.20 mmol of **L5**, 0.5 mL of DMSO, in a sealed tube under an $N_2$ atmosphere for 24 h. [b] Yields reported are the average of at least two runs determined to be >95% pure by elemental analysis or $^1H$ NMR. [c] 5% of CuI, 10% of **L5**, 1.5 mmol of $ArNH_2$.

available ligands previously reported for this transformation (entries 11−14).[4a,b,d,f]

Further optimization of the reaction conditions with **L5** revealed that the base/solvent combination of $K_3PO_4$/DMSO typically provided a superior system than combinations involving $K_2CO_3$, $Cs_2CO_3$, KOH, and NaO*t*-Bu in DMF, 1,4-dioxane, toluene, and acetonitrile. Since diaryl ether and phenolic products (up to 20% of ArX consumption) were frequently produced under the reaction conditions and observed by GC/MS,[8] the base was flame-dried under reduced pressure then cooled under a positive pressure of $N_2$ prior to use.

The reaction conditions we developed (1.0 equiv of ArX/2.0 equiv of $ArNH_2$/10% CuI/20% **L5**/$K_3PO_4$/DMSO/80−90 °C) could be used to couple aryl iodides with anilines in moderate to good yields (Table 2). For the reaction of *p*-anisidine with 4-chloroiodobenzene, the catalyst loading and reaction temperature could be reduced to 5% CuI and 70 °C, respectively (entry 1). Attempts to reduce the catalyst loading down to 2 mol %, however, were unsuccessful. For this example, the lower catalyst loading employed can be attributed to the increased nucleophilicity of *p*-anisidine relative to anilines that lack a strong

electron-donating substituent at the para position. Substrates containing base-sensitive functional groups such as benzoic esters and benzonitriles, which do not tolerate heating in the presence of hydroxide,[5c] were transformed to the desired product in respectable yields (entries 2 and 3). In addition, the presence of an ortho substituent on the aryl halide was tolerated (entry 4). Using the standard conditions, reactions of anilines containing strongly electron-withdrawing substituents at the 4-position provided the diaryl amine product in lower yields (entries 5−7). In these reactions, significant quantities of triarylamine byproducts were observed.[4d] The reaction of 4-nitroaniline with an aryl iodide provided the undesired triarylamine as the major product. However, an aryl halide could be coupled with *N*-(4-aminophenyl)acetamide to provide a product with a similar substitution pattern (entry 8). As previously noted, the Cu-catalyzed coupling of an anilino-$NH_2$ group in the presence of an amide is unusual for a Cu-catalyzed reaction of this type.[6a,b] In this case, the observed chemoselectivity is likely due to the slow reaction of secondary amides.[9] In contrast to this result, the reaction of 4-aminobenzamide with 4-iodoanisole provided a complex mixture of products. Last, the Cu/**L5**-catalyzed reaction of

(8) Cristau, H. J.; Cellier, P. P.; Hamada, S.; Spindler, J. F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913.

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**TABLE 3. Cu-Catalyzed Reactions of Anilines with Aryl Bromides**[a]



| entry | product | | yield (%)[b] |
|---|---|---|---|
| 1 | | X = Cl | 76 |
| 2 | | F | 72 |
| 3 | | | 55 |
| 4 | | | 71 |
| 5 | | R = 2,5-Me$_2$ | 75[c] |
| 6 | | 2-OMe | 70 |
| 7 | | R = Me | 74[d] |
| 8 | | OMe | 67[d] |
| 9 | | | 51 |

[a] Reaction conditions: 2.0 mmol of ArNH$_2$, 1.0 mmol of ArBr, 2.0 mmol of K$_3$PO$_4$, 0.10 mmol of CuI, 0.20 mmol of **L5**, 0.5 mL of DMSO, in a sealed tube under an N$_2$ atm for 24 h. [b] Yields reported are the average of at least two runs determined to be >95% pure by elemental analysis or $^1$H NMR. [c] 20% of **L15** employed as a ligand in DMF at 110 °C. [d] 30 h.

2-aminobenzothiazole with 4-iodoanisole arylated the heterocyclic nitrogen as opposed to the anilino-NH$_2$ (entry 9).[10] This result is noteworthy, since the Pd-catalyzed reactions of this nucleophile with aryl bromides selectively react at the anilino-NH$_2$ position.[11]

Aryl bromides were also successfully coupled by using the CuI/L catalyst system (Table 3), although higher temperatures were required (100 °C). Increasing the reaction temperature to 110 °C provided significant quantities of *N*-arylated and decarboxylated pyrrole, and low yields of the diarylamine

(10) Authentic *N*-(4-methoxyphenyl)benzo[*d*]thiazol-2-amine was independently prepared from the reaction of 2-chlorobenzothiazole and *p*-anisidine according to the procedure in: Cossey, H. D.; Judd, J.; Stephens, F. F. *J. Chem. Soc.* **1965**, 954. The product of this uncatalyzed reaction was found to be different than the product obtained from the reaction described in Table 2, entry 9.
(11) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481.

products. Electron-donating and -withdrawing substituents were tolerated on both the nucleophile and electrophile (entries 1−4). In addition, anilines and aryl bromides containing ortho substituents were effectively combined (entries 5−8). When employing 3-bromoquinoline as a substrate, a significant quantity of reduced heteroarene was observed (entry 9). The formation of this byproduct is common for Cu-catalyzed reactions of heteroaryl halides with amines.[5c]

In conclusion, pyrrole 2-carboxylic acid was employed as a suitable ligand for the Cu-catalyzed monoarylation of anilines with aryl iodides and bromides. Anilines and aryl halides possessing diverse electronic properties and useful functional groups were all tolerated. In many cases, the relatively low catalyst loading (10% Cu), the breadth of functional groups tolerated by the catalyst system, and the cost and commercial availability of the metal and ligand might offset the required use of 2 equiv of amine and the moderate yields obtained. We are continuing our investigations to develop newer and more active Cu-based catalyst systems for this transformation.

## Experimental Section

**General Procedure for the Cu-Catalyzed Cross-Coupling of Anilines with Aryl Halides.** An oven-dried screw-cap test tube was charged with K$_3$PO$_4$ (424 mg, 2.0 mmol). The tube was sealed and the base was flame-dried under vacuum and cooled under a purge of N$_2$. CuI (19 mg, 0.10 mmol), pyrrole 2-carboxylic acid (22 mg, 0.20 mmol), aryl halide (1.0 mmol, if solid), amine (2.0 mmol, if solid) and a magnetic stir bar were added to the cooled vessel. The tube was then evacuated and back-filled with nitrogen. The evacuation/backfill sequence was repeated two additional times. Aryl halide (1.0 mmol, if liquid), amine (2.0 mmol, if liquid), and DMSO (0.50 mL) were then added by syringe. The vessel was immersed in a preheated oil bath and the reaction mixture was stirred vigorously until TLC and/or GC analysis of the crude reaction mixture indicated that the aryl halide had been completely consumed. The reaction mixture was cooled to room temperature. Ethyl acetate (15 mL), NH$_4$Cl$_{(aq)}$ (2 mL), and H$_2$O (1 mL) were added and the mixture was stirred. The organic layer was separated and filtered through a plug of silica. The aqueous layer was extracted twice more with ethyl acetate (10 mL), and each extract was sequentially filtered through the pad of silica gel. The filtrate was concentrated and the resulting residue was purified by flash chromatography (hexanes/ethyl acetate, gradient elution) to provide the desired product.

**Supporting Information Available:** Experimental procedures and characterization data for all new and known compounds and kinetic and computational data for complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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