PHOTOREDOX COPPER CATALYZED AMINE N-ARYLATION

By

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A capstone project submitted for Graduation with University Honors

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University Honors

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University Honors

ABSTRACT

Carbon-nitrogen (C-N) couplings have an essential role in the production of commodity chemicals. For example, 84% of drugs contain at least one nitrogen atom, with amines and amides being the most common functional groups, and 59% incorporating nitrogen-containing heterocycles. Based on previous literature, C-N cross-coupling has been extensively accomplished through palladium (Pd) and nickel (Ni) catalysis which present high costs. This research focuses on developing a new methodology for amine *N*-arylation with an inexpensive copper (Cu)-indole system as catalyst under photochemical conditions. Through multiple chemical experiments in which various laboratory techniques are utilized, a set of conditions have been tested to identify the optimal conditions for increasing product yield. Each reaction parameter like temperature, concentration, and stoichiometry was investigated in separate experiments to determine their effect on product formation. The project also explores the role and optimal structure of the indole ligand in the reaction. This optimized reaction is useful in the pharmaceutical industry utilizing a C-N bond between an aryl and an amine during medicinal drug making.

ACKNOWLEDGEMENTS

I would like to extend my deepest gratitude to my faculty-mentor, Dr. Ana Bahamonde, for her invaluable guidance and unwavering support throughout this project. Her expertise and constructive feedback were instrumental in shaping this work. I would also like to thank Lang Cheng Hung, who was the graduate student I was working on this project with, for teaching me the skills I needed to work alongside him and continuously encouraging me to be the best scientist I can be. In addition, I wish to thank Dr. Begoña Echeverria and the entire University Honors team for their continuous support and for providing the framework and resources necessary to complete this capstone.

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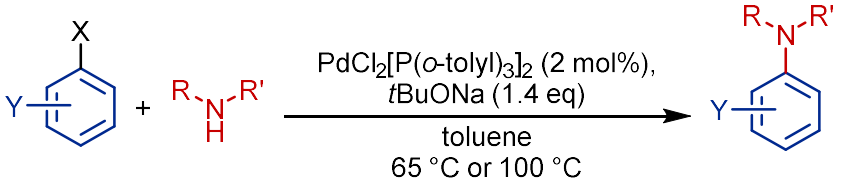
INTRODUCTION

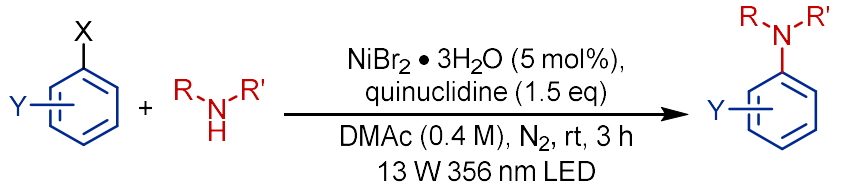
The formation of carbon-nitrogen bonds is highly significant in organic reactions and especially critical in the pharmaceutical industry. The Ullman coupling reaction is one of the most important reactions that can achieve this desired bond formation. This copper-mediated reaction allows for the coupling between aryl halides to form biaryl compounds,[1] or between aryl halides and nitrogen-containing compounds such as amines, to form carbon-nitrogen bonds.[2,3] The latter process is particularly substantial due to the difficulty in developing carbon-nitrogen bond-forming reactions, often requiring specialized methods and harsh conditions to overcome the high energy barriers required to make the C-N linkages.

Prior to the development and implementation of Ullmann-type cross-coupling, transition-metal-catalyzed cross-coupling reactions utilizing palladium (Pd) and nickel (Ni) emerged as highly efficient strategies for C-N bond formation. For palladium reactions, the Buchwald-Hartwig couplings, as depicted in **Scheme 1** below, are some of the most widely utilized methods of achieving aryl halide amination products.[4,5,6] These reactions are known for their broad substrate scope, including tolerance of a wide range of functional groups and the ability to efficiently couple aryl chlorides, bromides, and iodides under relatively mild conditions.[6] This approach also opened the door to extensive ligand developments, enabling high levels of selectivity in product formations. Unfortunately, all these benefits are offset by the disadvantages of using palladium; most notable, the high cost and limited natural abundance of palladium. Furthermore, palladium catalyzed reactions often require highly controlled conditions which can increase operational complexity and negate its practicality.



Forero-Cortés, P. A.; Haydl, A. M. *Org. Process Res. Dev.* **2019**, *23* (8), 1478–1483.
Scheme 1. Buchwald-Hartwig reaction conditions

On the other hand, nickel catalyzed C-N cross-coupling reactions, seen in **Scheme 2** below, later emerged as a promising alternative to palladium catalyzed systems. Nickel was immensely appealing due to its lower cost and greater natural abundance. In addition, when compared to palladium, which operates through a Pd(0) / Pd(II) catalytic cycle,[4,6] nickel catalysts are capable of accessing multiple oxidation states. The existence of Ni(0), Ni(I), Ni(II), and Ni(III), allow this catalyst to engage in a variety of electron pathways,[7] thus making it versatile in the activation of a wide array of substrates under milder and diverse conditions. The drawbacks to these advantages include lower reaction selectivity and susceptibility to side reactions. Moreover, nickel catalysts can be extremely sensitive to reaction conditions; the cost-effectiveness of this alternative is at the expense of the predictability of this reaction.

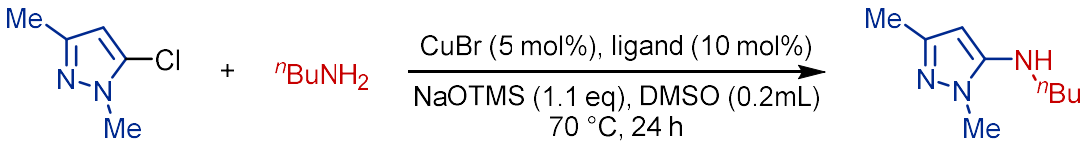


Lim, C.-H.; Kudisch, M.; Liu, B.; Miyake, G. M *J. Am. Chem. Soc.* **2018**, *140* (24), 7667–7673.
Scheme 2. Nickel-catalyzed C-N cross-coupling reaction conditions

In contrast, copper catalyzed methods, including the Ullmann coupling, offer an economical and sustainable approach while also maintaining reaction reliability. A defining limitation of the Ullmann coupling reaction is that it requires high reaction temperatures and stoichiometric amount of copper to successfully arylate amine compounds which defeats the

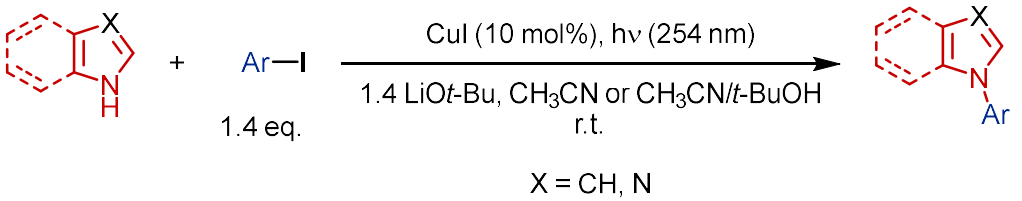
practicality of the reaction.[3] Such extreme conditions are essential when considering the relatively low reactivity of aryl halides and copper in the absence of activating substituents. This inherent characteristic of the system makes key mechanistic steps in the catalytic cycle kinetically challenging. For example, oxidative addition, which is when the aryl halide (Ar-X) bond is activated and coordinated onto the copper center. As well as reductive elimination, which forms the desired C-N cross-coupled product when releasing the Ar-NR_2 ligands from the copper metal center. The high thermal energy helps overcome these kinetic barriers by supplying the necessary energy to the reaction and enabling reactivity of the compounds. Consequently, these conditions limit the scalability of the Ullmann coupling reaction and hold it inefficient for use at an industrial scale.

An emerging strategy that can be implemented to overcome the limitations of the classical Ullmann coupling reaction, is the use of ligand design to enhance copper reactivity and eliminate the need for harsh reaction conditions.[8,9,10] Typical Ullmann coupling can be achieved without the use of added coordinating ligands that can stabilize the copper species and mediate important mechanistic steps. However, the introduction of bidentate ligands to the Ullmann coupling reaction facilitates the formation of catalytically active copper species by making it more stable.[9,10] Additionally, the complexes formed with these ligands can easily undergo key steps such as oxidative addition, which activate the aryl halide into the catalytic cycle, and reductive elimination, which generates the desired product.[8] These reactions that are utilizing ligand design, such as in **Scheme 3** below, are much more efficient due to the lowering of the activation energy typically required, and even improving selectivity, making this approach more practical.[10]



Ai, H.-J.; Mai, B. K.; Liu, C.; Liu, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2025**, *147* (42), 38275–38282.
Scheme 3. Ligand utilization for Ullmann cross-coupling reaction

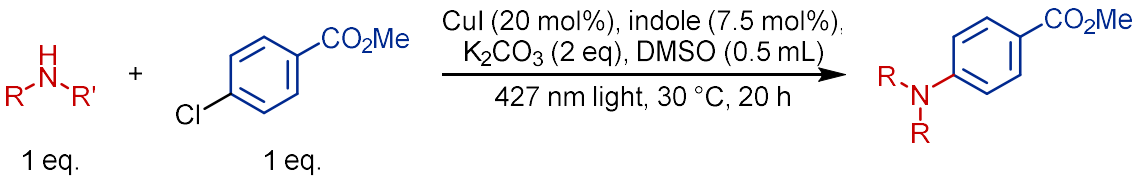
Another strategy to overcome the aforementioned limitations of the Ullmann coupling reaction is the use of high-energy light to facilitate copper-catalyzed bond formation reactions under milder conditions.[2] This has been achieved through the use of high-energy ultraviolet light to activate the copper photocatalyst to an excited state that would readily react with the aryl halide in the reaction mixture, as in the example reaction in **Scheme 4** below. Photoinduced Ullmann cross-coupling was first introduced by Peters and Fu's groups, where copper catalyzed alkylation of amines was fulfilled through the use of a 100 watt Hg lamp.[11] This approach bypasses the need for high thermal energy by providing an alternate pathway with a lower activation energy required. However, this can still be considered a limitation of the Ullmann coupling reaction as the reaction remains energy-energy light and thus expensive when scaled to an industry standard and presents a limited substrate compatibility as a lot of molecules absorb those wavelengths and are degraded under those conditions.



Ziegler, D. T.; Choi, J.; Muñoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135* (35), 13107–13112.
Scheme 4. High energy light catalyzed Ullmann cross-coupling reaction

The project discussed in this research paper takes into account the pre-existing literature on the Ullmann coupling reaction and aims to establish an optimized procedure for a carbon-

nitrogen cross-coupling reaction that does not utilize high-energy light, high temperatures, or ligand design. As shown in **Scheme 5** below, this project introduces a cross-coupling reaction between an aryl halide and an amine compound to generate a carbon-nitrogen bond with catalytic amount of copper and indole, under irradiation of 427 nm blue light and a temperature-controlled water bath.



Scheme 5. General reaction conditions

METHODOLOGY

The reaction is set-up under nitrogen gas by utilizing the Schlenk technique.[12] First, a clean and dry Schlenk tube is obtained from the drying oven kept at 135 °C. A small stir-bar is added to the flask, and the top opening is secured with a glass stopper. The air-containing Schlenk flask is attached to the Schlenk line system in the fume hood through a tube to its valve-controlled side opening. Through the connected tube, the flask is placed under vacuum to ensure an air-free internal environment. After approximately 30 seconds, the Schlenk line is utilized to fill the flask with nitrogen gas for approximately 10 seconds. This process is repeated for a total of 3 cycles to achieve an oxygen and moisture-free environment for reaction set-up. After ensuring that the flask environment is under nitrogen gas, the reaction reagents can be added. Solid reagents are weighed using weighing paper on a scale and added directly to the Schlenk flask, whereas liquid reagents are added to the flask via syringe depending on the amount needed. The first reagent added is the copper pre-catalyst (CuI, 7.6 mg, 0.04 mmol) followed by an indole scaffold reagent (2-*ortho*-toluene-indole, 6.2 mg, 0.015 mmol) and then an inorganic base (K_2CO_3, 40.6 mg, 0.3 mmol). To the solid mixture, 0.5 mL of dimethyl sulfoxide (DMSO), which is obtained from either a nitrogen-

filled glove box or solvent system to ensure it is free of O_2 and moisture, is dispensed into the Schlenk flask. The resulting mixture is left to stir at room temperature for about 10 minutes. Once the specified time has elapsed, the remaining reagents can be added; first, the aryl halide (ArCl, 40.9 mg, 0.24 mmol), and then the amine (piperdine, 23.0 μL, 0.2 mmol). The stopper of the Schlenk flask is then sealed with grease and further secured with parafilm around the neck of the flask. To ensure proper mixture of the reagents, the flask is vortexed for around 15 seconds. The reaction flask is then secured to a clamp in a 30 °C water bath directly in front of the 427 nm light lamp and left to stir at 600 rpm under the blue light for 20 hours.

Product yield analysis is done by utilizing ^{1}H Nuclear Magnetic Resonance (NMR) Spectroscopy. After the 20-hour reaction time has elapsed, the Schlenk flask is obtained from the water bath, and the neck of the flask is properly cleaned of any grease with hexanes. After that, between 3-6 mg of an internal standard (1,3,5-trimethoxybenzene) is added to the reaction mixture; and the specific amount is noted. The Schlenk flask is then vortexed and is now ready to make the NMR sample with. To make the NMR sample, a glass pipette is dipped into the reaction mixture to allow for a small sample into the pipette tip. Then, the pipette is placed inside an NMR tube and about 0.5 mL of chloroform is dispensed through the pipette and into the NMR tube. The sample is now ready to run through the NMR spectrometer. Product yield is then analyzed by comparing the integration of the product signals with the internal standard signal to calculate the amount of product using the specific amount of internal standard added to the reaction.

Further characterization of the arylated amine product can only be done after isolation and purification. The lab technique utilized to acquire an isolated yield is flash column chromatography. This is a separation and purification technique that functions on the basis of compound polarity. The column is packed with a highly polar medium, silica, and saturated with

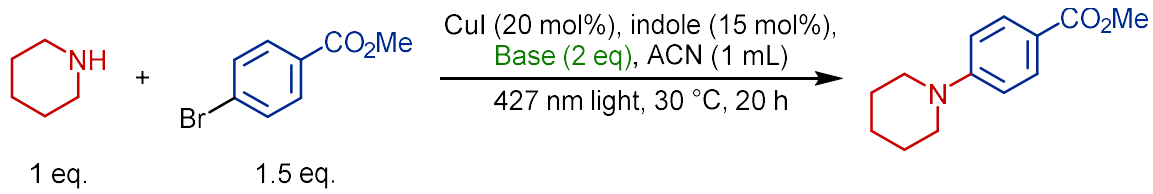
a non-polar and polar solvent mixture specific to the polarity of the compound being isolated. Then, the entire reaction mixture is loaded on top of the saturated silica. After this, the same solvent mixture is passed through the column and collected in test tubes (fractions) until all of the product has passed through the column. Thin-layer chromatography (TLC) is used to visualize what compounds are present in each fraction. All of the fractions containing the pure product are then collected in a round-bottom flask and rotovapped to evaporate all the solvent. This process results in the isolated and purified arylated amine product.

RESULTS AND DISCUSSION

Optimization of the reaction conditions:

The goal of this stage of the project is to optimize the reaction conditions to produce a relatively high yield of the arylated amine product. This consisted of a series of reactions that were run to test a single variation in the reaction conditions at a time. The results of these reactions were analyzed for patterns and to determine the best identity of each reagent as well as its most efficient equivalence.

Depicted in **Scheme 6** below are the general reaction conditions that were used the first time to test various bases. **Table 1** compiles the list of bases that were tested as well as the calculated yield of the arylated amine product. This list includes a variety of organic (entries 5 to 9) and inorganic (entries 1 to 4) bases as well as strong and weak bases. During the beginning stages of the project, the utilized aryl halide was aryl bromide (ArBr) in which this reaction worked best when using potassium phosphate (K_3PO_4) as the base, resulting in a product yield of 12% (entry 1). While screening the base with aryl bromide, there was an observed full consumption of aryl bromide. This suggested that the aryl bromide is too reactive and thus prompted the subsequent experiments with aryl chloride (ArCl).

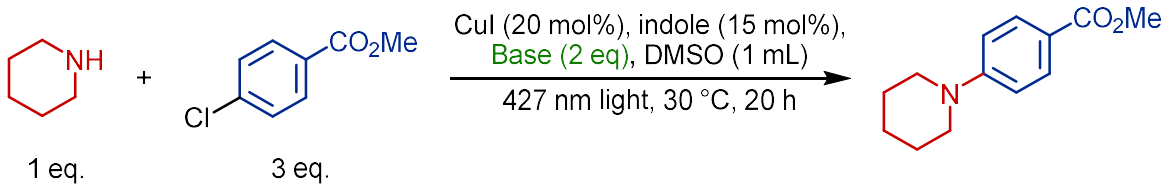


Scheme 6. Reaction conditions for the first optimization of base

Entry	Base	Product Yield
1	K_3PO_4	12%
2	$KHCO_3$	2%
3	KO*t*Bu	0%
4	Cs_2CO_3	5%
5	TBD	0%
6	Lutidine	2%
7	Pyridine	6%
8	TEA	0%
9	DIPEA	0%

Table 1. First optimization of base in the reaction

The less reactive aryl chloride was used for further optimization with the reaction conditions depicted in **Scheme 7**. Following the substrate switch to aryl chloride (ArCl), a second screening of bases was conducted. During this round of screening, as seen in **Table 2,** inorganic bases (entries 1 to 9) were tested again. Among these, we observed that potassium phosphate (K_3PO_4), potassium bicarbonate ($KHCO_3$), and potassium carbonate (K_2CO_3), yielded 24%, 32%, and 37% of the desired cross-coupled product respectively, which is significantly better than the other bases. To be specific, carbonate bases (entries 3 and 4) seemed to be favored for this developed reaction, giving the best yields. Organic bases, on the other hand, were also tested as they are soluble in the reaction mixture (entries 10 to 19); however, to our surprise, they did not work better than the less soluble inorganic bases. This result determined potassium carbonate (K_2CO_3) as the best base to use for the remainder of the project.



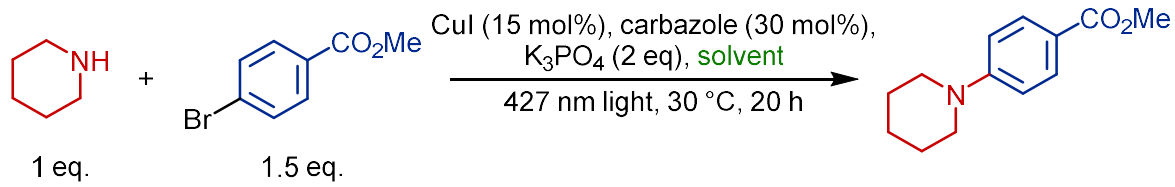
Scheme 7. Reaction conditions for the second optimization of base

Entry	Base	Product Yield
1	K_3PO_4	24%
2	Na_3PO_4	4%
3	$KHCO_3$	32%
4	K_2CO_3	37%
5	K_2HPO_4	0%
6	KH_2PO_4	0%
7	Li_2CO_3	6%
8	KOAc	0%
9	Cs_2CO_3	0%
10	TBD	0%
11	DABCO	0%
12	TMG	0%
13	DBU	0%
14	TEA	0%
15	DBU	0%
16	DIPEA	0%
17	2,6-Lutidine	0%
18	2,6-dtpy	0%
19	2,6-dtmepy	0%

Table 2. Second optimization of base in the reaction

With the optimal base in hand from the previous screening, we moved into looking at the solvent effects. The very first reaction that was run for this project, utilized acetonitrile (ACN) as the solvent. **Scheme 8** shows the general reaction conditions that were used when screening solvents of different polarities. Many of the solvents tested yielded no arylated amine product, such as toluene, dichloromethane (DCM), and tetrahydrofuran (THF) in **Table 3**. However, even better than acetonitrile (ACN), dimethoxy sulfoxide (DMSO) worked significantly well, yielding 33% of the arylated amine product. Dimethyl sulfoxide is a very strong polar aprotic solvent which

makes it efficient in stabilizing charged intermediates such as deprotonated amines and ionic copper species. These characteristics are supportive of the results obtained in this experiment and in agreement with the proposed mechanistic pathways for this reaction.

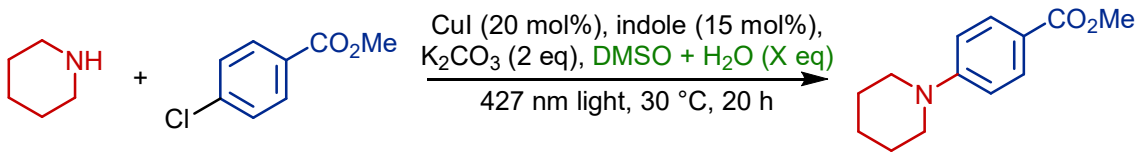


Sheme 8. Reaction conditions for the optimization of solvent

Entry	Solvent	Product Yield
1	ACN	12%
2	DMSO	33%
3	Toluene	0%
4	DMF	9%
5	DCM	0%
6	THF	0%

Table 3. Optimization of solvent in the reaction

Following these results, an additional study was conducted where specific equivalent amounts of water were incorporated into the solvent loading to test if hydration improves the product yield. The results are as detailed in **Scheme 9** below, where it can be observed that the additional water in the reaction negatively impacts the product yield. In entry 1, DMSO alone as a solvent yields 33% product, whereas adding different amounts of water provides no clear pattern of the diminished product yield, **Table 4**. This finding suggests that the addition of water has an impact on the copper catalyst or even the reactive intermediates in the reaction pathway. Water may play a role in protonating the nucleophilic amine species that is important in the formation of the necessary copper metal center yielding the product ligands. In addition, the reliance of the carbon-nitrogen bond formation on the catalytic copper means that water coordination to the copper metal center would logically decrease the product yield. Therefore, it was concluded that the reaction must proceed without the additional water in DMSO.

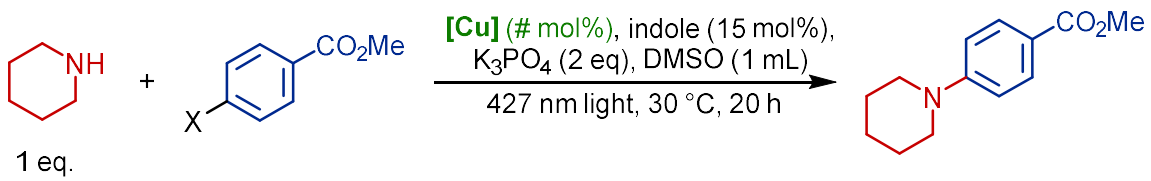


Scheme 9. Reaction conditions for the optimization of H_2O in DMSO

Entry	Solvent	Product Yield
1	DMSO + 0 eq H_2O	33%
2	DMSO + 1 eq H_2O	12%
3	DMSO + 0.5 eq H_2O	19%
4	DMSO + 0.25 eq H_2O	8%
5	DMSO + 0.125 eq H_2O	21%

Table 4. Optimization of water in DMSO in the reaction

In order to find the best copper source for this reaction, the following list of copper sources were tested with the conditions illustrated in **Scheme 10.** It is important to note that running the reaction with no copper resulted in 0% product yield, which makes copper necessary for the reaction to work. The indicated copper sources, entries 2 to 7 in **Table 5,** that were run using the aryl bromide (ArBr) substrate and at 15 mol% copper, showed no clear pattern as to which reagent was the best copper source. In later experiments (entries 8 to 15), when using aryl chloride (ArCl) and loading the copper at 20 mol%, there was a significant difference that determined copper (I) iodide as the best copper source, yielding 32% of the arylated amine product. A possible explanation for this finding includes the existence of the copper metal in its active catalytic form with an oxidation state of +1, Cu(I), in copper iodide. In addition, iodide as a ligand might also be special due to its ionic halide characteristic that might play a positive mechanistic role in the reaction pathway.

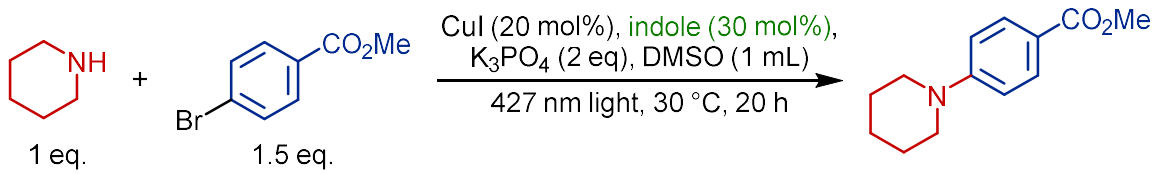


Scheme 10. Reaction conditions for the optimization of the copper source

Entry	[Cu]	ArX	Product Yield
1	None	1.5 eq ArBr	0%
2	CuI (15 mol%)	1.5 eq ArBr	12%
3	$CuCl_2$ (15 mol%)	1.5 eq ArBr	16%
4	$Cu(OAc)_2$ (15 mol%)	1.5 eq ArBr	11%
5	$CuBr_2$ (15 mol%)	1.5 eq ArBr	5%
6	$Cu(ACN)_4PF_6$ (15 mol%)	1.5 eq ArBr	10%
7	$Cu(OTf)_2$ (15 mol%)	1.5 eq ArBr	16%
8	CuI (20 mol%)	3 eq ArCl	32%
9	$CuCl_2$ (20 mol%)	3 eq ArCl	21%
10	$CuBr_2$ (20 mol%)	3 eq ArCl	19%
11	$Cu(OAc)_2$ (20 mol%)	3 eq ArCl	8%
12	CuTc (20 mol%)	3 eq ArCl	8%
13	CuOAc (20 mol%)	3 eq ArCl	1%
14	$Cu(ACN)_4PF_6$ (20 mol%)	3 eq ArCl	9%
15	$Cu(OTf)_2$ (20 mol%)	3 eq ArCl	13%

Table 5. Optimization of copper in the reaction

Different indole scaffold compounds were also tested for their effect on the yield of the arylated amine product. The role of indole in the reaction was not clear during these experiments and remained unclear due to the lack of a pattern form the results. The next experiments continued utilizing carbazole in the reaction since it yielded the highest amount of product at 33% as in **Table 6** below until 2-*ortho*-toluene-indole was tested with 3 eq aryl chloride and potassium carbonate instead of potassium phosphate. This indole yielded the same amount of product as carbazole but was done with the previously discussed better carbonate base and more difficult aryl halide. Therefore, this indole was utilized for the remainder of the experiments in the project.



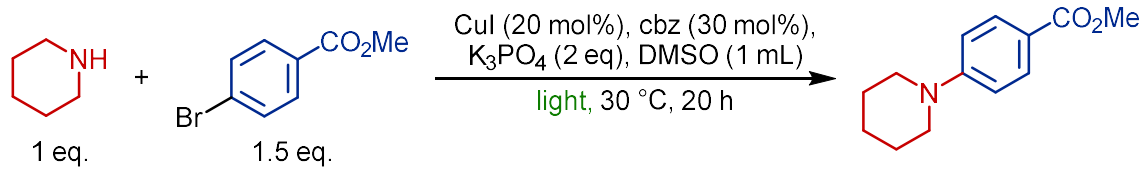
Scheme 11. Reaction conditions for the optimization of indole

Entry	Indole	Product Yield
1	Carbazole (cbz)	33%
2	Indolo[3,2-b]carbazole	13%
3	Tetrahydro carbazole	27%
4	2-Me-indole	11%
5	2-Ph-indole	14%
6	N-Me-indole	0%
7	Carbazole (60 mol%)	12%
8	Hexahydro carbazole	7%
9	2-o-tol-indole (30 mol%)*	33%
10	2-o-tol-indole (7.5 mol%)*$^{+}$	39%
11	2-o-tol-indole (5 mol%)*$^{+}$	22%
12	2-o-tol-indole (2.5 mol%)*$^{+}$	29%

*With 3 eq ArCl, and K_2CO_3 instead of K_3PO_4_
$^{+}$With 0.5 mL DMSO

Table 6. Optimization of the indole in the reaction

Considering the importance of light in the initiation of the reaction, different wavelengths of light were analyzed for their effect on product yield. Blue light, at 427 nm, was the only light source with enough energy needed to catalyze the reaction. Decreasing the intensity of the blue light lamp to 25% resulted in a decrease in yield. On the other hand, placing the blue light lamp 8 cm away from the reaction to avoid heat transfer from the lamp did not showcase a significant effect on product yield. As in **Table 7** below, other light sources, such as green light and ambient light, did not lead to any observed product formation. It is important to note that running the reaction with no light also resulted in the reaction not producing any coupled product, proving that light is necessary for reaction catalysis.



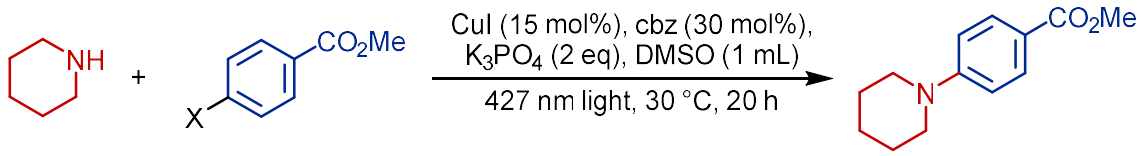
Scheme 12. Reaction conditions for the optimization of light

Entry	Light	Product Yield
1	427 nm	33%
2	25% 427 nm	20%
3	25% 427 nm (8 cm away)	19%
4	390 nm*	0%
5	Ambient light	0%
6	Green light	0%
7	None	0%

*With 3 eq ArCl, 1 eq Amine, and K_2CO_3 instead of K_3PO_4

Table 7. Optimization of the light in the reaction

Adjustments to the reaction stoichiometry, i.e. the ratios of amine and aryl halide substrates, were made throughout the duration of the project. Starting with 1.5 eq of aryl bromide, as seen in **Table 8** below, the highest product yield was achieved with 1 eq piperidine. Then, a higher product yield was achieved by using aryl chloride instead of aryl bromide, which triggered the switch of the aryl halide substrate to aryl chlorides. This represents a significant advancement in the project because aryl chlorides are known to be more difficult to activate than their aryl bromide counterparts due to the stronger C-Cl bond. Furthermore, aryl chlorides are generally more abundant and less expensive than aryl bromides, which makes them more practical and favorable for industrial use. Achieving this coupling also indicates the sufficiency of the developed copper system in overcoming these known reactivity barriers, making the reaction even more desirable for its synthetic utility. From these experiments, 1 eq amine and 1 eq aryl chloride were confirmed for usage in later parts.



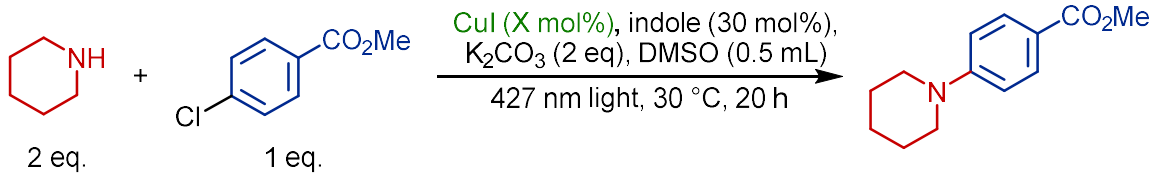
Scheme 13. Reaction conditions for the optimization of the aryl halide and amine

Entry	Aryl Halide	Amine	Product Yield
1	1.5 eq ArBr	1 eq Piperdine	33%
2	1.5 eq ArBr	3 eq Piperdine	13%
3	1.5 eq ArBr	5 eq Piperdine	12%
4	2 eq ArBr	1 eq Piperdine	34%
5	3 eq ArCl	1 eq Piperdine	38%
6	1 eq ArCl*	3 eq Piperdine	16%
7	1 eq ArCl*	2 eq Piperdine	27%
8	1 eq ArCl*	1.5 eq Piperdine	29%
9	1 eq ArCl*	1 eq Piperdine	29%

*With 2-*ortho*-tol-indole (30 mol%), K_2CO_3 instead of K_3PO_4, and 0.5 mL DMSO

Table 8. Optimization of the aryl halide and amine in the reaction

Going back to the copper source analysis, the next condition to test was the loading amount of the copper source in the reaction. It was important to find out the effective amount of copper to gain insight on the catalytic turnover of the reaction cycle and confirm sufficiency of catalytic amounts of the copper catalyst. From these experiments observing a clear pattern between product yield and copper loading, it was determined that 20 mol% of the copper source, copper (I) iodide (CuI), resulted in the highest arylated amine product yield of 41% as depicted in **Table 9** below.



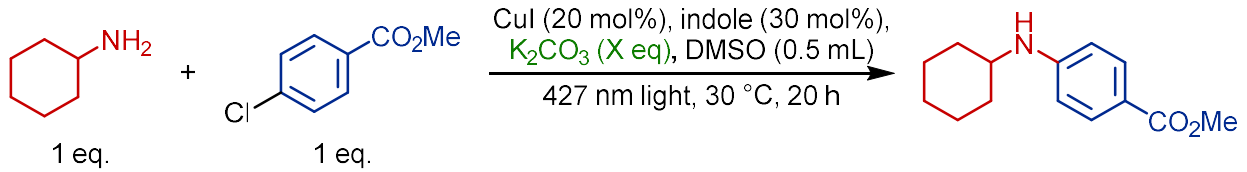
Scheme 14. Reaction conditions for the optimization of copper loading

Entry	CuI (X mol%)	Product Yield
1	20%	41%
2	15%	27%
3	10%	10%
4	7.5%	8%
5	5%	3%

Table 9. Optimization of the copper loading in the reaction

As the optimized reaction conditions became close to being finalized, fine-tuning each reagent was logical. A revisit to the analysis of the base in the reaction consisted of testing different equivalent amounts of potassium carbonate in the reaction. As in **Table 10** below, there is an

observed positive correlation between the equivalence of base and product yield. Adding 2 eq of potassium carbonate yielded the highest amount of the desired product. When testing 3 eq of potassium carbonate with the newer conditions addressed later in this work, an even higher product yield of 62% was obtained.



Scheme 15. Reaction conditions for the optimization of base equivalence

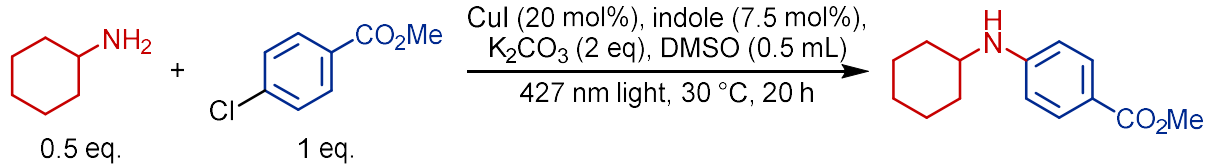
Entry	K_2CO_3 (X eq)	Product Yield
1	1 eq	30%
2	1.5 eq	36%
3	2 eq	47%
4	3 eq*	62%

*With 1.2 eq ArCl, 0.5 eq Amine, and 10 mol% indole

Table 10. Optimization of the base equivalence in the reaction

Timepoint experiment:

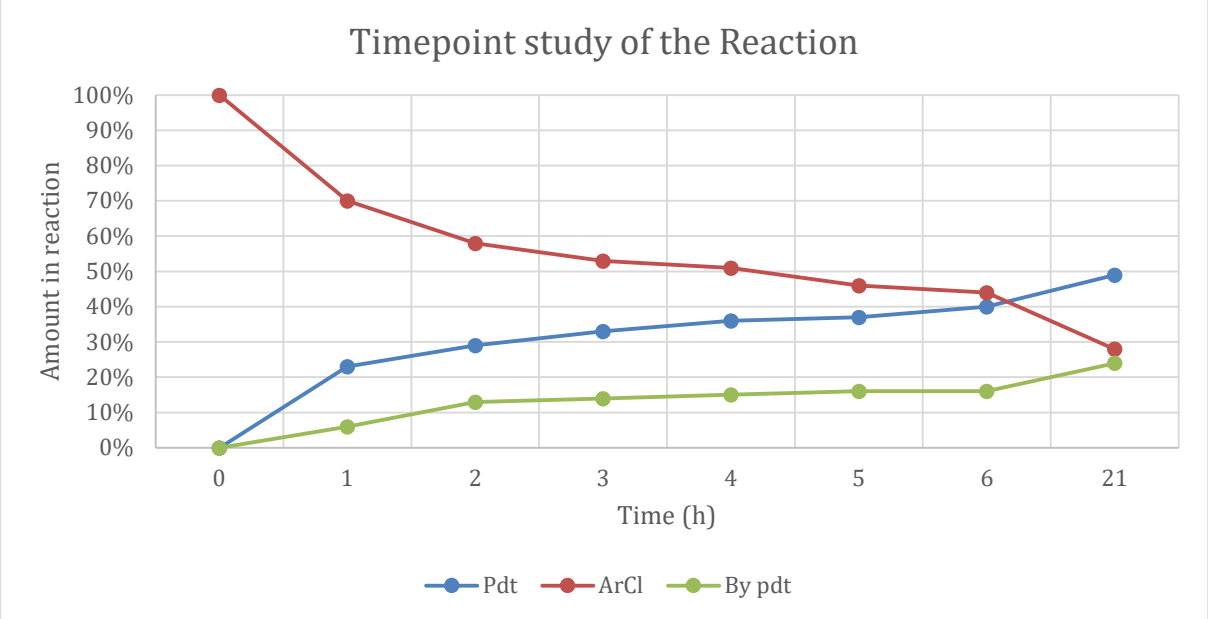
To closely analyze the consumption and formation of species in the reaction, a timepoint experiment was conducted. For this study, aliquots of the reaction were taken for NMR analysis at the timepoints listed in **Table 11** below. The formation of biaryls, aryl alcohols, and dehalogenations were collectively considered by-products for the purpose of this study. Considering the addition of only 0.5 eq of amine in this reaction, nearing 50% product indicates full consumption of the reagents needed for product formation. As can be seen in **Graph 1** below, between 2 and 6 hours of the experiment, a plateau can be observed. Hypothetically, a second addition of amine between these timepoints should continue the formation of the desired product.



Scheme 16. Reaction conditions for the timepoint study

Time(h)	Pdt	ArCl	ArOH	ArH	Ar-Ar	By pdt
0	0%	100%	0%	0%	0%	0%
1	23%	70%	2%	1%	3%	6%
2	29%	58%	5%	4%	4%	13%
3	33%	53%	6%	4%	4%	14%
4	36%	51%	6%	5%	4%	15%
5	37%	46%	7%	5%	4%	16%
6	40%	44%	7%	5%	4%	16%
21	49%	28%	10%	7%	7%	24%

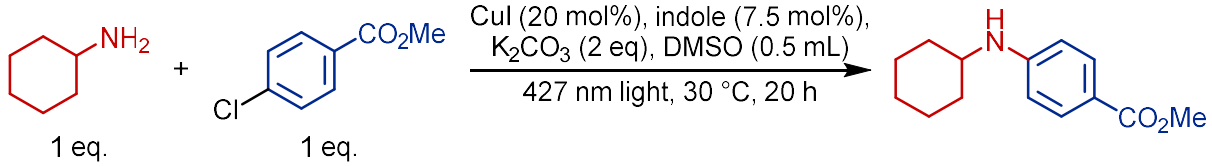
Table 11. Timepoint study



Graph 1. Timepoint study

Following the timepoint experiment, further testing on the method of addition of the amine reagent was conducted. During the time when the majority of the amine is expected to have been

consumed in the reaction, between 2 and 6 hours, a second addition of the amine was administered to the reaction to resume to formation of the desired product. Slow addition of the amine substrate at a rate of 0.2 mL/h was also tested to compare to the addition of amine in two halves.



Scheme 17. Reaction conditions for the amine addition study

Entry	Second Addition Time	Product Yield
1	2 h	19%
2	3 h*	70%
3	4 h	54%
4	6 h	48%
5	0.02 mL/h^{+}	63%

*With 1.2 eq ArCl
$^{+}$2 eq $CyNH_2$ in 0.1 mL DMSO
Table 12. Optimization of the amine addition to the reaction

Substrate scope:

Once the optimal reactions conditions were compiled, the next study focused on determining the applicability of the developed reaction to various substrates. The substrate scope of the optimized photochemical Ullmann-type coupling reaction demonstrates the versatility of the developed copper and indole catalytic system. As depicted in **Figure 1** below, both primary and secondary amines, cyclic and acyclic, are tolerated effectively through this reaction. The consistent high yields observed across the depicted scope suggest tolerance of electronically deactivating functional groups. Additionally, the incorporation of a sterically hindered aryl group further supports the potential for a wide substrate scope to be pursued in future experiments. Overall, this scope supports the functionality of the developed reaction and foreshadows its applicability towards the synthesis of structurally diverse arylated amine products.

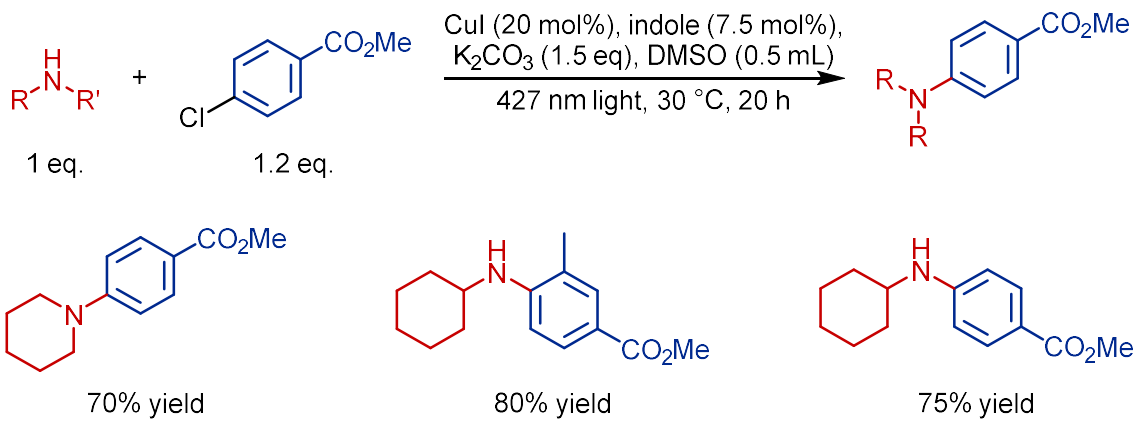


Figure 1. Scheme and substrate scope of the optimized reaction

Mechanistic proposal:

The first proposed mechanism, as illustrated in **Figure 2** below, begins with a Cu(I) species **1** that is photoexcited under blue light irradiation to generate an excited-state Cu(I)* intermediate **2**. This high-energy species is proposed to undergo oxidative addition with the aryl halide, to form a Cu(III) intermediate **3**. In the meantime, the amine substrate is deprotonated by the base to generate a nucleophilic amine, which can coordinate to the Cu(III) center **3** through ligand exchange with the halide. Formation of the Cu(III) complex **4** with both the aryl and amine ligands enables a favored reductive elimination that yields the desired carbon-nitrogen coupled product and regenerates the ground state Cu(I) catalyst **1**, and thus completing the catalytic cycle. The involvement of blue light is critical in initiating the reaction as this photoexcitation step provides an electronically excited copper state capable of overcoming the high activation barrier associated with oxidative addition. The overall transformation is consistent with milder conditions than the classic Ullman cross-coupling reaction. Notably, the role of the indole reagent remains unclear in this proposal. It could play a role as a photosensitizer that facilitates energy or electron transfer. It may also act as a ligand that further stabilizes the copper species.

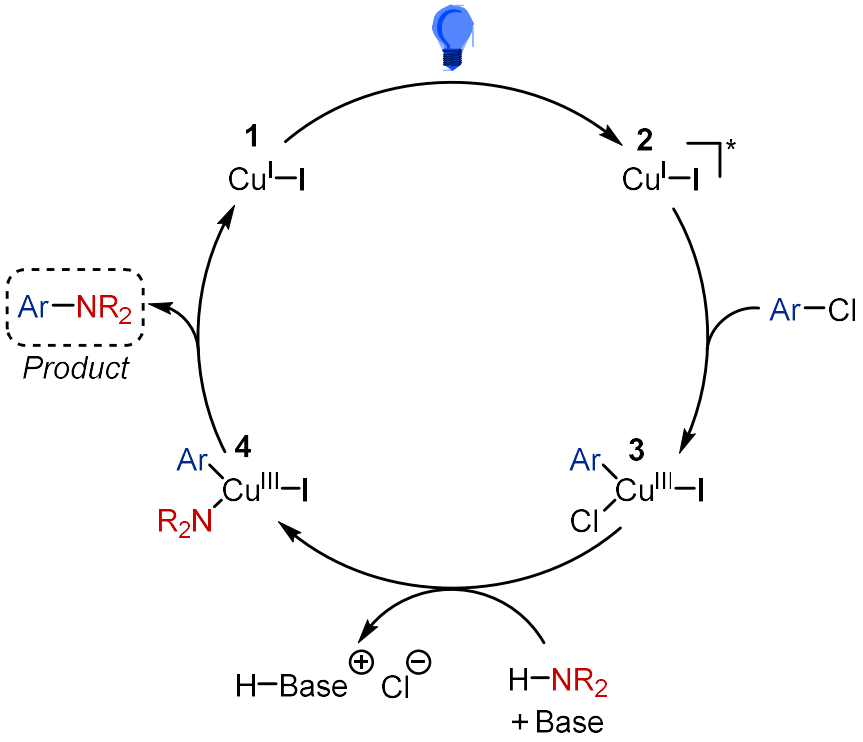


Figure 2. Proposed mechanism #1

The following alternative mechanistic pathway, **Figure 3,** incorporates the indole reagent as a key photoactive initiator of the catalytic cycle. In this proposal, blue light irradiation promotes the oxidation of indole to generate a cationic indole radical species, which induces the dehalogenation of the aryl halide, consequently forming an aryl radical intermediate. This aryl radical can then interact with the Cu(I) catalyst **1**, oxidizing it to a Cu(II) species **2**. In parallel, the amine substrate is deprotonated by the base to generate a nucleophilic amine that can coordinate to the Cu(II) center **2** via ligand exchange. The resulting Cu(II) complex **3**, bearing both the aryl and amine ligands, is further oxidized by the cationic indole radical in conjunction with a counterion present in the reaction to a more stable Cu(III) intermediate **4**. This Cu(III) species can now undergo reductive elimination, resulting in the formation of the desired C-N cross-coupled product and regenerates the Cu(I) starting catalyst **1**. This mechanism is centered around the photochemical activity of the indole reagent and its role as a radical mediator. Further mechanistic

studies, such as radical trapping studies, kinetic analysis, or UV-spectroscopy analysis are necessary to confirm this proposal.

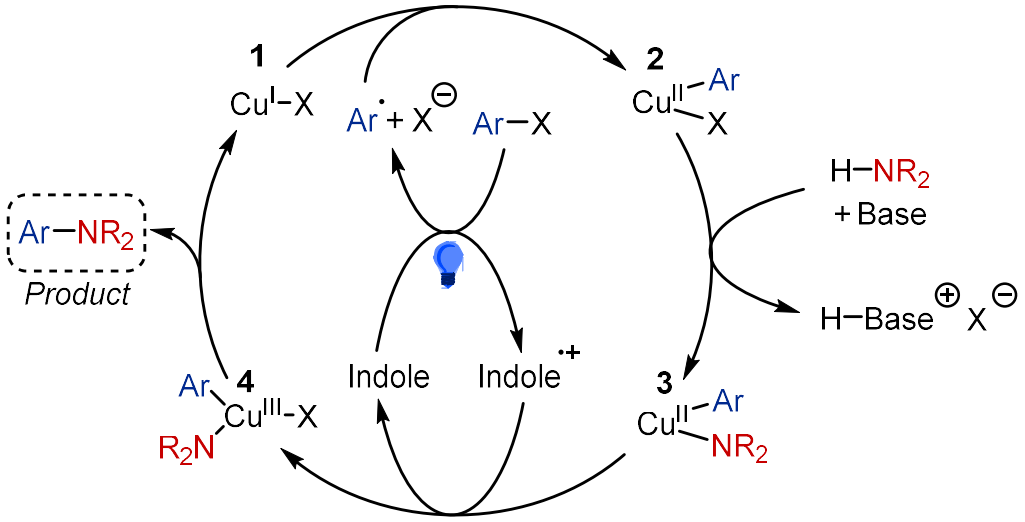


Figure 3. Proposed mechanism #2

CONCLUSION AND FUTURE DIRECTIONS

This study demonstrates the successful development of a photochemically driven copper-catalyzed methodology for C-N cross-coupling reactions between aryl halides and amines under relatively mild conditions. Through systematic optimization of the reaction parameter, such as base identity, solvent, copper source, and substrate stoichiometry, the reaction conditions were refined to achieve a maximum product yield of 80%. Compared to previous palladium and nickel catalyzed systems, this copper-based approach provides a more cost-effective and naturally abundant alternative to the catalyst in the reaction. Despite the high generality and broad substrate scope of palladium-based catalysis, and the access to a variety of reaction pathways in nickel-based catalysis, upcoming investigations of copper-based reactions are highly advantageous when considering the promising benefits copper as the alternative.

Further studies should focus on clarifying the precise mechanistic details of this transformation. Radical trapping experiments and spectroscopic techniques such as UV-Vis and

EPR spectroscopy can be utilized for insight into the involvement of radical species and elucidating the photochemical behavior of the catalytic cycle. These studies may warrant additional investigation into the specific role of the indole reagent necessary for this reaction as well. In addition, expanding the substrate scope to include a wide range of aryl halides and amines, such as those with sensitive functional groups and substituents, would further establish the generality and synthetic practicality of this reaction. Effectively, making these reaction conditions even more suitable for the scalability and efficiency needed in the pharmaceutical industry.

REFERENCES

(1) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl−Aryl Bond Formation One Century after the Discovery of the Ullmann Reaction. *Chemical Reviews* **2002**, *102* (5), 1359–1470. https://doi.org/10.1021/cr000664r.

(2) Ziegler, D. T.; Choi, J.; Muñoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. A Versatile Approach to Ullmann C–N Couplings at Room Temperature: New Families of Nucleophiles and Electrophiles for Photoinduced, Copper-Catalyzed Processes. *Journal of the American Chemical Society* **2013**, *135* (35), 13107–13112. https://doi.org/10.1021/ja4060806.

(3) Zhu, L.; Cheng, L.; Zhang, Y.; Xie, R.; You, J. Highly Efficient Copper-Catalyzed N-Arylation of Nitrogen-Containing Heterocycles with Aryl and Heteroaryl Halides. *The Journal of Organic Chemistry* **2007**, *72* (8), 2737–2743. https://doi.org/10.1021/jo062059f.

(4) Paul, F.; Patt, J.; Hartwig, J. F. Palladium-Catalyzed Formation of Carbon-Nitrogen Bonds. Reaction Intermediates and Catalyst Improvements in the Hetero Cross-Coupling of Aryl Halides and Tin Amides. *Journal of the American Chemical Society* **1994**, *116* (13), 5969–5970. https://doi.org/10.1021/ja00092a058.

(5) Guram, A. S.; Buchwald, S. L. Palladium-Catalyzed Aromatic Aminations with in Situ Generated Aminostannanes. *Journal of the American Chemical Society* **1994**, *116* (17), 7901–7902. https://doi.org/10.1021/ja00096a059.

(6) Forero-Cortés, P. A.; Haydl, A. M. The 25th Anniversary of the Buchwald–Hartwig Amination: Development, Applications, and Outlook. *Organic Process Research & Development* **2019**, *23* (8), 1478–1483. https://doi.org/10.1021/acs.oprd.9b00161.

(7) Lim, C.-H.; Kudisch, M.; Liu, B.; Miyake, G. M. C–N Cross-Coupling via Photoexcitation of Nickel–Amine Complexes. *Journal of the American Chemical Society* **2018**, *140* (24), 7667–7673. https://doi.org/10.1021/jacs.8b03744.

(8) Zhao, W.; Amberg, W. M.; Rao, G.; Xie, Y.; Pierson, C. N.; Fantasia, S. M.; Rummelt, S. M.; Püntener, K.; Britt, R. D.; Hartwig, J. F. Mechanism-Inspired Ligand Design for Efficient Copper-Catalyzed C–N Coupling of Aryl and Heteroaryl Chlorides. *Journal of the American Chemical Society* **2026**, *148* (7), 7505–7514. https://doi.org/10.1021/jacs.5c20640.

(9) Ai, H.-J.; Kim, S.-T.; Liu, C.; Buchwald, S. L. Copper-Catalyzed Amination of Aryl Chlorides under Mild Reaction Conditions. *Journal of the American Chemical Society* **2024**, *146* (38), 25949–25955. https://doi.org/10.1021/jacs.4c10237.

(10) Ai, H.-J.; Mai, B. K.; Liu, C.; Liu, P.; Buchwald, S. L. Development of a Ligand for Cu-Catalyzed Amination of Base-Sensitive (Hetero)Aryl Chlorides. *Journal of the American Chemical Society* **2025**, *147* (42), 38275–38282. https://doi.org/10.1021/jacs.5c10910.

(11) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C. Photoinduced, Copper-Catalyzed Alkylation of Amines: A Mechanistic Study of the Cross-Coupling of Carbazole with Alkyl Bromides. *Journal of the American Chemical Society* **2017**, *139* (36), 12716–12723. https://doi.org/10.1021/jacs.7b07052.

(12) Borys, A. M. An Illustrated Guide to Schlenk Line Techniques. *Organometallics* **2023**, *42* (3). https://doi.org/10.1021/acs.organomet.2c00535.