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A Versatile Approach to Ullmann C−N Couplings at Room Temperature: New Families of Nucleophiles and Electrophiles for Photoinduced, Copper-Catalyzed Processes

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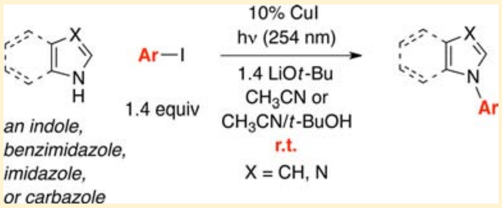
Ⓢ *Supporting Information*

ABSTRACT: The use of light to facilitate copper-catalyzed cross-couplings of nitrogen nucleophiles can enable C−N bond formation to occur under unusually mild conditions. In this study, we substantially expand the scope of such processes, establishing that this approach is not limited to reactions of carbazoles with iodobenzene and alkyl halides. Specifically, we demonstrate for the first time that other nitrogen nucleophiles (e.g., common pharmacophores such as indoles, benzimidazoles, and imidazoles) as well as other electrophiles (e.g., hindered/deactivated/heterocyclic aryl iodides, an aryl bromide, an activated aryl chloride, alkenyl halides, and an alkynyl bromide) serve as suitable partners. Photoinduced C−N bond formation can be achieved at room temperature using a common procedure with an inexpensive catalyst (CuI) that does not require a ligand coadditive and is tolerant of moisture and a variety of functional groups.



INTRODUCTION

The discovery of mild and versatile methods for the formation of C_{aryl}−N bonds can have an impact on fields ranging from biology to natural-product synthesis to materials science.[1,2] An array of powerful approaches have been developed, including Ullmann couplings[3,4] and Buchwald−Hartwig reactions.[5]

Because aromatic nitrogen heterocycles are a particularly common motif in bioactive compounds,[6] developing effective methods for their elaboration remains an important objective. Carbon−nitrogen bond-forming processes between nucleophilic nitrogen heterocycles and aryl electrophiles provide an attractive, convergent strategy for synthesizing derivatives, and such reactions can be accomplished with good efficiency with the aid of catalysts based on copper, palladium, and other metals.[1,4,5,7] The use of copper can be advantageous from the standpoints of cost[8] and/or toxicity,[9] although an elevated temperature is almost always required[10] and a plethora of catalyst/ligand combinations have been described that are often specific to certain families of nucleophiles.

Building on our previous studies of the photophysics of a copper−carbazolide complex,[11] we recently reported that *photoinduced*, copper-catalyzed C−N bond formation between carbazole and iodobenzene[12] and several carbazoles and alkyl halides[13] can be achieved. We postulated that these photoinduced couplings may proceed through initial photoexcitation of a copper−carbazolide complex (Figure 1).[14]

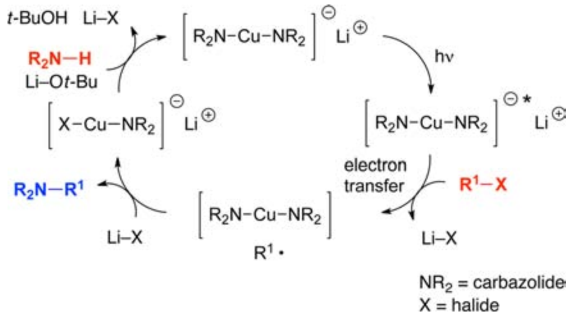


Figure 1. Outline of a possible pathway for photoinduced, copper-catalyzed C−N coupling reactions.

If this hypothesis is correct, then the structure of the nucleophile would be expected to have a significant impact on photoexcitation/electron transfer of the copper−nucleophile complex (as well as subsequent steps); indeed, a change in the identity of NAr_2 (e.g., NPh_2 vs carbazolide) or even simply in the para substituents of a copper−diarylamido complex, $(Ph_3P)_2Cu(NAr_2)$, results in a substantial change in photoluminescence properties.[11] It was therefore unclear if effective C−N bond formation would be possible with nitrogen nucleophiles other than carbazoles.[15] In this paper, we describe the development of a unified set of reaction conditions for the N-arylation of a variety of aromatic nitrogen nucleophiles, thereby achieving C−N bond construction at an unusually mild temperature (room temperature)[10] with a simple and inexpensive method (10% CuI, without a ligand coadditive, eq 1).

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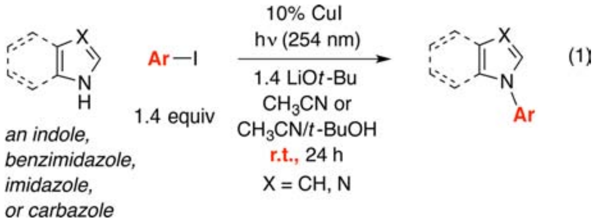
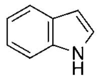
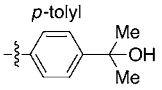
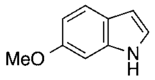
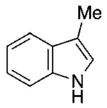
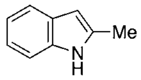
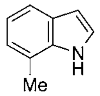


(1)

RESULTS AND DISCUSSION

Because indoles bear a structural resemblance to carbazoles and are a privileged scaffold in natural products and medicines,[6,16] they were a natural starting point for our efforts to expand the scope of photoinduced Ullmann C−N couplings.[17,18] In an initial study, we determined that the method that we had developed for the N-arylation of carbazole[12] was not useful for the arylation of indole with iodobenzene (<20% yield). As might be anticipated, the wavelength of light that is employed has proved to be important, and by irradiating at 254 nm, rather than at 350 nm, we were able to achieve the desired C−N bond formation in good yield at room temperature (entry 1 of Table 1).[10,19]

Table 1. N-Arylation of Indoles at Room Temperature[a]

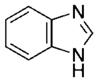
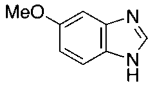
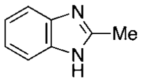
entry	indole	Ar	yield (%)[b]
1		Ph	75
2		*p*-tolyl	68
3			57
4		Ph	66
5		*o*-tolyl	68
6		Ph	72
7		*p*-anisyl	58
8		Ph	60
9		Ph	66

[a] For the reaction conditions, see eq 1. [b] Yield of purified product (average of two experiments).

These conditions can be applied to room-temperature couplings of an array of indoles with iodobenzene (entries 1, 4, 6, 8, and 9 of Table 1). An ortho-substituted (entry 5) and a deactivated (entry 7) aryl iodide serve as suitable coupling partners. This method for Ullmann coupling is not highly water-sensitive: the addition of 10 mol% H_2O leads to only a small loss in yield (for the reaction of indole with iodobenzene, −7%).

This method for photoinduced, copper-catalyzed Ullmann coupling reactions can also be applied to a second family of nitrogen heterocycles, benzimidazoles, which are a common subunit in bioactive compounds (Table 2).[6,20−22] Thus, at room temperature, benzimidazole cross-couples with iodobenzene, as well as with an activated and a deactivated aryl iodide, in good yield (entries 1−3).[10] Not surprisingly, the two nitrogens of a 5-substituted benzimidazole are arylated at similar rates (entry 4).[23] A hindered 2-substituted benzimidazole is a suitable coupling partner, even with an ortho-substituted aryl iodide and with 3-iodopyridine (entries 5−7).[24]

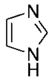
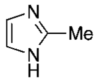
Table 2. N-Arylation of Benzimidazoles at Room Temperature[a]

entry	benzimidazole	Ar	yield (%)[b]
1		Ph	83
2		4-CN-C_6H_4	83
3		*p*-anisyl	76
4		Ph	83[c]
5		Ph	82
6		*o*-tolyl	76
7		3-pyridyl	66

[a] For the reaction conditions, see eq 1. [b] Yield of purified product (average of two experiments). [c] A 1.1:1 mixture of isomers.

Furthermore, the standard conditions for photoinduced C−N coupling can be employed for room-temperature N-arylations of imidazoles (Table 3).[6,10,21,22] Whereas the Ullmann reaction of a hindered electrophile proceeds in acceptable yield (entry 2), a sterically demanding nucleophile cross-couples with modest efficiency (entry 3).

Table 3. N-Arylation of Imidazoles at Room Temperature[a]

entry	imidazole	Ar	yield (%)[b]
1		Ph	68
2		*o*-tolyl	66
3		Ph	46

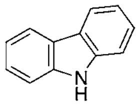
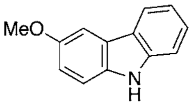
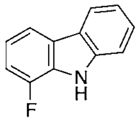
[a] For the reaction conditions, see eq 1. [b] Yield of purified product (average of two experiments).

The fourth and final family of aromatic nitrogen heterocycles that we have examined as coupling partners are carbazoles.[6,25,26] In our original paper, we had described the photoinduced, copper-catalyzed arylation of carbazole itself with iodobenzene.[12] The method that we have developed herein for Ullmann reactions of indoles, benzimidazoles, and imidazoles is also effective for cross-coupling an array of carbazoles and aryl iodides at room temperature (Table 4), including deactivated (entry 3), hindered (entries 4, 6, and 7), and heteroaryl (entry 5) electrophiles.[10]

In our initial study of photoinduced Ullmann reactions, only an aryl iodide was employed as an electrophile in the copper-catalyzed process, although an aryl bromide and an aryl chloride served as partners in stoichiometric couplings with a preformed copper−carbazolide complex.[12] We have now determined that copper-*catalyzed* arylations of a range of nitrogen heterocycles can be achieved at room temperature with an unactivated aryl bromide as well as an activated aryl chloride (Table 5).[10]

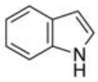
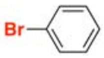
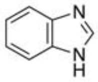
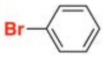
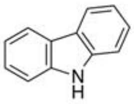
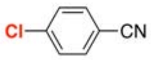
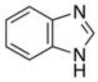
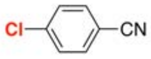
We were interested in exploring the selectivity of photoinduced Ullmann reactions with respect to both the nucleophilic and electrophilic coupling partners. With regard to the nucleophile, we have observed in competition experiments that, in the presence of 1.0 equiv of base (relative to one of the nucleophiles), good-to-excellent selectivity can be

Table 4. N-Arylation of Carbazoles at Room Temperature[a]

entry	carbazole	Ar	yield (%)[b]
1		Ph	86
2		4-CN-C_6H_4	77
3		*p*-anisyl	76
4		*o*-tolyl	81
5		3-pyridyl	66
6		*o*-tolyl	76
7		*o*-tolyl	74

[a] For the reaction conditions, see eq 1. [b] Yield of purified product (average of two experiments).

Table 5. An Unactivated Aryl Bromide and an Activated Aryl Chloride as Electrophiles

entry	nucleophile	electrophile	yield (%)[a]
1			62
2			62
3			72
4			61

[a] Yield of purified product (average of two experiments).

obtained (Table 6). The propensity of a heterocycle to be arylated parallels its acidity.[27]

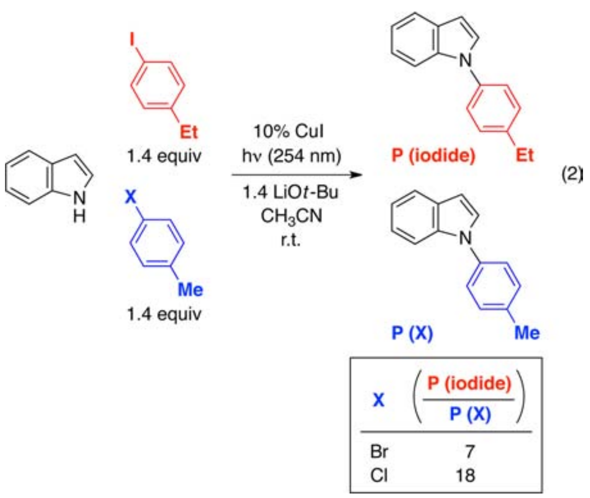
With regard to the electrophile, competition experiments reveal that an aryl bromide and an aryl chloride are substantially less reactive toward indole than is an aryl iodide (eq 2). This observation correlates with the susceptibility of the aryl halide to one-electron reduction (Figure 1)[28] (as well as the weakness of the C–X bond and the proclivity toward concerted oxidative addition).

Table 6. Relative Reactivity of Nucleophilic Coupling Partners[a]

$$\begin{matrix}\text{Nu}^1\text{–H}\\ \text{1.0 equiv}\\ \text{Nu}^2\text{–H}\\ \text{1.0 equiv}\end{matrix} \quad \begin{matrix}\text{Ph–I}\\ \text{1.4 equiv}\end{matrix} \quad \xrightarrow[\text{1.0 LiO}t\text{-Bu, CH}_3\text{CN}/t\text{-BuOH, r.t.}]{\text{10\% CuI, h}\nu\text{ (254 nm)}} \quad \begin{matrix}\text{Nu}^1\text{–Ph}\\ \text{Nu}^2\text{–Ph}\end{matrix}$$

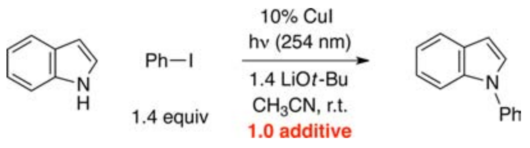
Nu¹–H	Nu²–H	$\left(\frac{\text{Nu}^1\text{–Ph}}{\text{Nu}^2\text{–Ph}}\right)$
imidazole (14.4)	carbazole (19.9)	13
imidazole (14.4)	indole (21.0)	>50
benzimidazole (16.4)	carbazole (19.9)	>50
benzimidazole (16.4)	indole (21.0)	>50
carbazole (19.9)	indole (21.0)	6

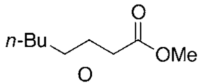
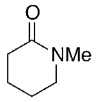
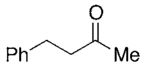
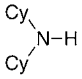
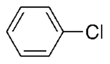
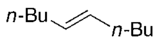
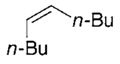
[a] All ratios are the average of two experiments. pKa values (DMSO) are provided in parentheses.



We have examined the functional-group compatibility of the photoinduced Ullmann coupling method. As illustrated in Tables 1–4, cross-coupling proceeds in the presence of an ether, a nitrile, a pyridine, and an aryl fluoride, as well as a relatively weak C–H bond (e.g., benzylic or α to oxygen) that could be susceptible to reaction with an intermediate aryl radical (Figure 1). We have further determined that photoinduced Ullmann couplings occur in the presence of an array of stoichiometric additives (Table 7). Thus, an ester, amide, ketone, secondary amine, primary amine, aryl chloride, *trans*-

Table 7. Functional-Group Tolerance[a]

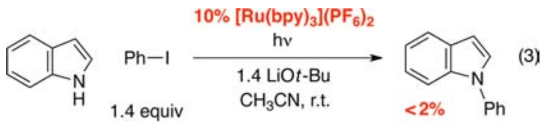


additive	yield (%)	recovery of additive (%)
no additive	79	–
	69	>95
	72	>95
	62	85
	73	>95
Cy–NH_2	58	82
	72	90
	66	>95
	73	>95
n-Bu–≡–*n*-Bu	74	>95

[a] All data are the average of two experiments.

alkene (<2% isomerization), *cis*-alkene (<2% isomerization), and alkyne can be recovered largely intact at the end of a cross-coupling, with at most a modest impact on the efficiency of the desired C−N bond-forming process. The small inhibitory effect of an additive on N-arylation can be partly offset by running the reaction for a longer period of time; for example, in the case of benzylacetone and $CyNH_2$, the yield increases from 62% to 68% and from 58% to 66%, respectively, upon further irradiation.

For each family of photoinduced coupling processes described herein, we have conducted control reactions that establish that, in the absence of light, CuI, or light and CuI, essentially no C−N bond formation is observed (<2%). Photoredox catalysis, wherein metal complexes such as $[Ru(bpy)_3]X_2$ shuttle electrons but are not directly involved in inner-sphere bond-forming processes, has emerged as an increasingly powerful tool in synthetic organic chemistry;[29] in control experiments, we have determined that $[Ru(bpy)_3](PF_6)_2$ does not function as a replacement for CuI under our standard, or under related, conditions (eq 3).



(3)

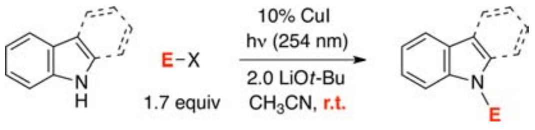
Conditions
254 nm
compact fluorescent light bulb
compact fluorescent light bulb; 10% CuI

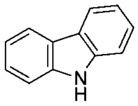
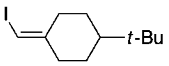
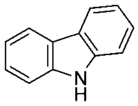
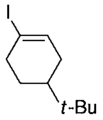
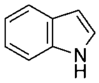
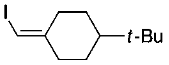
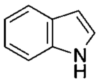
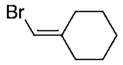
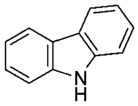
Finally, we have begun to explore the possibility of expanding these photoinduced C−N bond-forming reactions beyond arylation and alkylation processes. Because enamines and ynamines are important targets in organic synthesis,[30] we have pursued couplings of nitrogen heterocycles with both alkenyl and alkynyl halides. For example, we have established that photoinduced alkenylations can be achieved at room temperature with both an iodide and a bromide as electrophiles (entries 1−4 of Table 8).[31−33] Furthermore, we have determined that coupling a nitrogen heterocycle with an alkynyl halide is possible under the same conditions (entry 5).[34] Collectively, these observations provide an indication of the potential versatility of photoinduced, copper-catalyzed coupling processes.

CONCLUSIONS

The scope of photoinduced, copper-catalyzed C−N couplings has been expanded substantially with respect to both the nucleophile and the electrophile. Whereas our initial reports were limited to reactions of carbazoles with iodobenzene and alkyl halides, we have now determined that nitrogen nucleophiles other than carbazoles (e.g., common pharmacophores such as indoles, benzimidazoles, and imidazoles) and electrophiles other than iodobenzene and alkyl halides (e.g., hindered/deactivated/heterocyclic aryl iodides, an aryl bromide, an activated aryl chloride, alkenyl halides, and an alkynyl bromide) also serve as useful coupling partners. Photoinduced C−N bond formation can be accomplished using a common procedure with a simple and inexpensive catalyst (CuI, without a ligand coadditive) under unusually mild conditions (room temperature) with tolerance of moisture and a range of functional groups. Current investigations are focused on further expanding the scope and on exploring the mechanism of these and related photoinduced processes.

Table 8. New Families of Electrophiles: Alkenyl and Alkynyl Halides



entry	nucleophile	electrophile	yield (%)[a]
1			85
2			75
3			74
4			56
5		Br—≡—TIPS	63

[a]Yield of purified product (average of two experiments).

EXPERIMENTAL SECTION

General Procedure (Arylation). The nitrogen heterocycle (1.00 mmol), LiO*t*-Bu (112 mg, 1.40 mmol), and CuI (19.0 mg, 0.10 mmol) were added to an oven-dried 10 mL quartz test tube that contained a stir bar. The test tube was fitted with a rubber septum, the joint was wrapped with electrical tape, and the test tube was evacuated and backfilled with nitrogen (three cycles). Then, CH_3CN (4.0 mL) and the aryl iodide (1.40 mmol) were added in turn via syringe. The test tube was detached from the nitrogen manifold, and the puncture holes in the septum were covered with vacuum grease. The resulting mixture was stirred for 5 min, and then the test tube was transferred to a Luzchem LZC-4V photoreactor (a Honeywell ultraviolet air treatment system (model RUVLAMP1), available for ~$110 from retail outlets such as Amazon or The Home Depot, furnishes a comparable yield), where it was irradiated at 254 nm for 24 h. Next, the mixture was passed through a long plug of silica gel (monitored by TLC), the solvent was removed, and the residue was purified by column chromatography.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) For example, see: (a) Figure 8 in ref 2b. (b) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347−361. (c) *The Alkaloids: Chemistry and Biology*; Knölker, H.-J., Ed.; Elsevier: San Diego, CA, 2012; Vol. *71*. (d) Zirngibl, L. *Antifungal Azoles*; Wiley-VCH: Weinheim, Germany, 1998. (e) *Imidazole Receptors and Their Endogenous Ligands*; Gothert, M., Molderings, G. J., Reis, D. J., Eds.; New York Academy of Sciences: New York, 1999.

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(9) The limits for metal impurities set by the United States Pharmacopeial Convention and by the European Medicines Agency are $\geq$10 times greater for Cu than for Pd: Cu, 1000−2500 μg/day; Pd, 100 μg /day: (a) *Chemical Tests and Assays: Section (232) Elemental Impurities—Limits*, second supplement to USP 35-NF 30; U.S. Pharmacopeial Convention: Rockville, MD, 2012. (b) *Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents*; Doc. Ref. EMEA/CHMP/SWP/4446/2000; Committee for Medicinal Products for Human Use, European Medicines Agency: London, Feb 21, 2008.

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