Organic LETTERS
Letter
pubs.acs.org/OrgLett

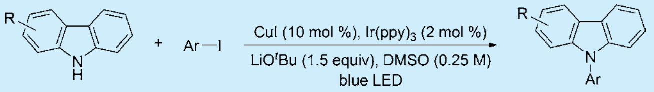
Visible Light-Mediated Ullmann-Type C–N Coupling Reactions of Carbazole Derivatives and Aryl Iodides

Woo-Jin Yoo, Tatsuhiro Tsukamoto, and Shū Kobayashi*

Department of Chemistry, School of Science, The University of Tokyo, Bunkyo-ku, Tokyo 113-0033, Japan

Ⓢ *Supporting Information*

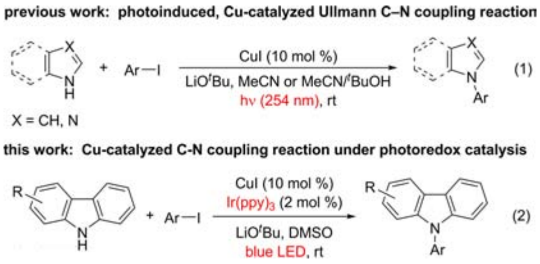
ABSTRACT: The combined use of an iridium-based photocatalyst and a copper salt under blue light emitting diode irradiation enables the Ullmann-type C–N cross-coupling reaction between carbazole derivatives and aryl iodides to proceed under mild conditions.



Visible light-driven photoredox catalysis has emerged as a powerful means to promote efficient organic transformations under mild conditions.[1] This is, in part, due to the realization that photoredox active transition metals can mediate single electron transfer (SET) processes of various organic functional groups to generate reactive charged radical intermediates. Moreover, it has been demonstrated that the inclusion of photoredox catalysis into other types of catalytic cycles can lead to new synthetic methodologies and improve the reaction conditions of established organic transformations.[2−4]

Owing to the numerous examples of functionally important nitrogen-containing organic compounds found in the pharmaceutical, agrochemical, and material sciences, the development of efficient methods to construct carbon–nitrogen (C–N) bonds is of paramount importance. As such, the palladium-catalyzed Buchwald–Hartwig[5] and the copper-catalyzed Ullmann-type[6] coupling reaction between aryl halides and nitrogen-based nucleophiles have been extensively studied. Although the original report by Ullmann required the use of a stoichiometric amount of copper under extremely harsh reaction conditions to effectively form the C–N bond, the use of copper as a catalyst is advantageous due to its lower cost and toxicity when compared to palladium. Thus, considerable efforts have been made to improve the Ullmann-type C–N coupling reaction and catalytic protocols that permits the cross-coupling reaction to occur under mild conditions have been developed. Recently, Fu and Peters disclosed a series of copper-catalyzed protocols for the cross-coupling reactions of various heteroatom nucleophiles with aryl and alkyl halides under ultraviolet (UV) light irradiation (Scheme 1, eq 1).[7] Interestingly, they reported that the copper-catalyzed cross-coupling reaction of indole and iodobenzene did not occur under visible light irradiation, even in the presence of Ru(bpy)$_3$2PF$_6$ as a photoredox catalyst.[7c] However, the combined use of visible light photoredox catalysis and transition metal catalysis in cross-coupling reactions has recently appeared. For instance, Doyle and MacMillan demonstrated a productive merger between a nickel catalyst and a heteroleptic iridium photocatalyst to effectively induce the decarboxylative cross-coupling reaction of aryl and vinyl halides with alkyl carboxylic acids.[4e,k] Similarly, Molander reported that alkyltrifluoroborates could undergo efficient transmetalation via photoredox catalyst-mediated SET for the nickel-catalyzed cross-coupling reaction with aryl halides.[4c,d,j] In addition, Lu and Xiao found that a dual catalyst system comprising a nickel catalyst and a ruthenium-based photoredox catalyst allowed for an efficient carbon–phosphorus cross-coupling reaction.[4a] Related to these redox-neutral cross-coupling reactions, we recently reported a copper-catalyzed Chan–Lam coupling reaction of aniline derivatives and aryl boronic acids under visible light irradiation in air.[4b] Based on these examples, we believed that it was possible to achieve the copper-catalyzed Ullmann-type C–N coupling reaction under visible light irradiation. Herein, we describe the productive merger between copper catalysis and photoredox catalysis that enables the cross-coupling reaction of aryl iodides and carbazole derivatives under visible light irradiation (Scheme 1, eq 2).

Scheme 1. Light-Mediated, Copper-Catalyzed C–N Ullmann-Type Coupling Reactions



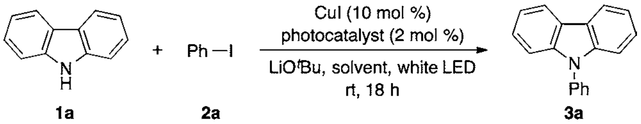
The starting point of our optimization studies was based on Fu and Peters's previous conditions for the photoinduced C–N Ullmann-type coupling reaction[7c] using carbazole (**1a**) and iodobenzene (**2a**) as model substrates with Ir(ppy)$_3$ as a photoredox catalyst under white light emitting diode (LED) irradiation (Table 1).

We initially screened various solvents (entries 1–3) and found that DMSO provided 9-phenylcarbazole (**3a**) in a moderate yield. Since oxygen gas can diminish the performance of a photoredox catalyst,[8] we carefully degassed the reaction mixture

Received: June 5, 2015
Published: July 7, 2015

DOI: 10.1021/acs.orglett.5b01645
Org. Lett. 2015, 17, 3640–3642

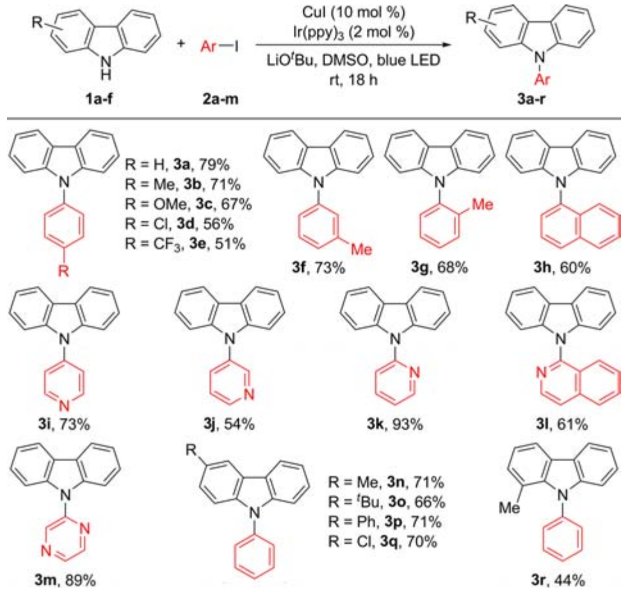
Table 1. Screening of Reaction Conditions[a]



entry	photocatalyst	solvent	yield (%)[b]
1	$Ir(ppy)_3$	MeCN	8
2	$Ir(ppy)_3$	DMF	41
3	$Ir(ppy)_3$	DMSO	67
4[c]	$Ir(ppy)_3$	DMSO	72
5[c]	$Ir(dFppy)_3$	DMSO	41
6[c]	$Ir(ppy)_2(dtbbpy)PF_6$	DMSO	N.D.
7[c]	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	DMSO	14
8[c]	$Ru(dtbbpy)_32PF_6$	DMSO	22
9[c]	$Ru(bpz)_32PF_6$	DMSO	N.D.
10[c,d]	$Ir(ppy)_3$	DMSO	80
11[c,d,e]	$Ir(ppy)_3$	DMSO	79
12[c,d,e]		DMSO	39
13[c,e,f]		DMSO	N.D.

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.38 mmol), CuI (0.025 mmol, 10 mol %), photocatalyst (0.005 mmol, 2 mol %), LiO^{t}Bu (0.38 mmol), solvent (1.0 mL) for 18 h under an atmosphere of Ar and white LED irradiation. [b] Yield based on **1a** and determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Reaction mixture was degassed via freeze−pump−thaw method. [d] Irradiation with blue LED. [e] Using 1.1 equiv of **2a** (0.28 mmol). [f] In the absence of light.

Scheme 2. Substrate Scope[a]



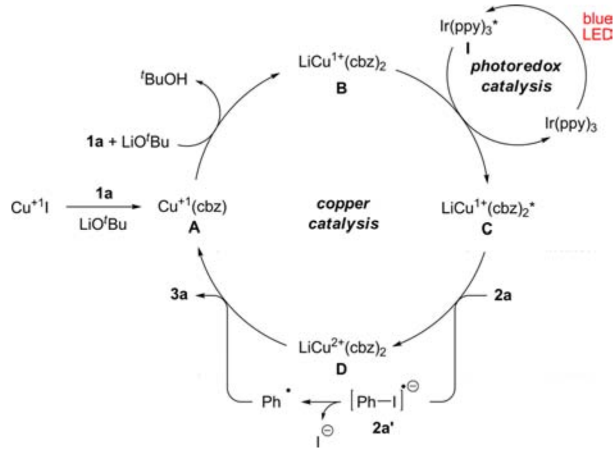
[a] Reaction conditions: **1a−f** (0.50 mmol), **2a−m** (0.55 mmol), CuI (0.050 mmol, 10 mol %), Ir(ppy)$_3$ (0.01 mmol, 2 mol %), LiO^{t}Bu (0.75 mmol), DMSO (2.0 mL degassed via freeze−pump−thaw method) for 18 h under an atmosphere of Ar and blue LED irradiation. Yield based on **1a−f** and determined by weight of **3a−r**.

by the freeze−pump−thaw method and found that **3a** could be obtained in a good yield (entry 4). Next, we screened various well-established polypyridyl metal complexes as photoredox catalysts and could not find a suitable replacement for Ir(ppy)$_3$ (entries 5−9). In addition, no improvement was observed when factors, such as the copper source, ligands, and bases, were examined.[9] However, when the reaction mixture was subjected to blue LED irradiation, a slight improvement in the yield of **3a** was observed (entry 10). In addition, we found that the amount of iodobenzene (**2a**) could be reduced to 1.1 equiv without affecting the yield (entry 11). Finally, control studies were performed, and it was found that some of the expected C−N cross-coupled product **3a** was observed with blue LED irradiation in the absence of Ir(ppy)$_3$ (entry 12), while the absence of blue LED irradiation prevented the copper-catalyzed cross-coupling reaction from occurring (entry 13).

Next, we investigated the substrate scope of the photoinduced, copper-catalyzed C−N Ullmann-type coupling reactions with various carbazole derivatives (**1a−f**) and aryl iodides (**2a−m**) (Scheme 2). When various 4-substituted aryl iodides **2b−e** were examined, it was found that the yields of the desired carbazole derivatives **3b−e** were generally lower than that of the model reaction. In particular, aryl iodides bearing sensitive functional groups, such as carbonyl, nitrile, and hydroxyl moieties failed to provide the desired products in synthetically useful yields.[9] The substitution pattern of the aryl moiety was examined using 3- and 2-iodotoluenes **2f−g** as substrates, and it was found that no significant difference in the yields of the corresponding carbazole products **3f−g** was observed. Furthermore, various nitrogen-containing heteroaromatic iodides **2i−m** were examined and modest to excellent yields of carbazoles bearing heteroaromatic moieties **3i−m** were obtained. Finally, various 3- and 1-substituted carbazoles **1b−f** were tested as nucleophiles for the photoinduced, copper-catalyzed C−N Ullmann-type cross-coupling reaction, but in all cases, the yields of the desired products **3n−r** were lower than the model reaction.

A plausible reaction mechanism to account for the dual catalytic system needed to facilitate the room temperature C−N Ullmann-type reaction of carbazole derivatives and aryl iodides under visible light irradiation is described in Scheme 3. Initially, we assume that copper iodide could form copper(I) amide complex **B** in the presence of carbazole (**1a**) under strong basic conditions. Concurrently, a blue LED-induced metal-to-ligand charge transfer (MLCT) of Ir(ppy)$_3$ would lead to the formation of photoexcited complex **I**, and this transient iridium polypyridyl complex **I** could be quenched by **B** to afford excited copper carbazolide **C** and the ground state Ir(ppy)$_3$. Next, iodobenzene (**2a**) could experience a SET from the excited copper complex **C** to generate its corresponding radical anion **2a′**. Disproportionation of **2a′** would result in the formation of an aryl radical, which

Scheme 3. Proposed Mechanism



could react with copper(II) amide **D** to produce 9-phenylcarbazole (**3a**) and close the copper catalysis cycle.[10] An alternative mechanistic proposal based on a single-electron oxidation of **A** or reduction of **2a** by photoexcited Ir(ppy)$_3$* could be used to rationalize the effect of Ir(ppy)$_3$ for the photoinduced, copper-catalyzed C−N Ullmann-type coupling reaction. However, Ir(ppy)$_3$* may not be a sufficiently strong enough oxidant ($E_{1/2}{}^{*\mathrm{III/II}} = -0.3$ V vs Fc/Fc$^+$)[11] to oxidize the copper amide complexes, and emission quenching experiments revealed that **2a** does not quench Ir(ppy)$_3$*.[12]

In summary, we have demonstrated that copper catalysis and visible light photoredox catalysis can work in concert to facilitate the C−N Ullmann-type cross-coupling reactions between carbazole derivatives and aryl iodides under mild reaction conditions. Further investigations into expanding the scope and understanding the mechanism are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01645.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shu_kobayashi@chem.s.u-tokyo.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), the Global COE Program (Chemistry Innovation through Cooperation of Science and Engineering), the University of Tokyo, the Japan Science and Technology Agency (JST), and the Ministry of Education, Culture, Sports, Science and Technology (MEXT, Japan).

■ REFERENCES

(1) For reviews on visible light photocatalysis, please see: (a) Hopkinson, M. N.; Sahoo, B.; Li, J.-L.; Glorius, F. *Chem. - Eur. J.* **2014**, *20*, 3874. (b) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176. (c) Yoon, T. P. *ACS Catal.* **2013**, *3*, 895. (d) Xi, Y.; Yi, H.; Lei, A. *Org. Biomol. Chem.* **2013**, *11*, 2387. (e) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (f) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (g) Ischay, M. A.; Yoon, T. P. *Eur. J. Org. Chem.* **2012**, *2012*, 3359. (h) Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687. (i) Hoffmann, N. *ChemSusChem* **2012**, *5*, 352. (j) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (k) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (l) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527.

(2) For representative examples of photoredox catalysis combined with organocatalysis, please see: (a) Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 6858. (b) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593. (c) Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 10022. (d) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094. (e) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77.

(3) For representative examples of photoredox catalysis merged with Lewis acid catalysis, please see: (a) Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 2452. (b) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392. (c) Yoo, W.-J.; Tanoue, A.; Kobayashi, S. *Chem. - Asian J.* **2012**, *7*, 2764.

(4) For examples of photoredox catalysis merged with transition metal catalysis, please see: (a) Xuan, J.; Zeng, T.-T.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem. - Eur. J.* **2015**, *21*, 4962. (b) Yoo, W.-J.; Tsukamoto, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 6587. (c) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 4896. (d) Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2015**, *137*, 2195. (e) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624. (f) Xuan, J.; Zeng, T.-T.; Feng, Z.-J.; Deng, Q.-H.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J.; Alper, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 1625. (g) He, Y.; Wu, H.; Toste, F. D. *Chem. Sci.* **2015**, *6*, 1194. (h) Perepichka, I.; Kundu, S.; Hearne, Z.; Li, C.-J. *Org. Biomol. Chem.* **2015**, *13*, 447. (i) Lang, S. B.; O'Nele, K. M.; Tunge, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 13606. (j) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science* **2014**, *345*, 433. (k) Zuo, Z.; Ahneman, D.; Chu, L.; Terrett, J.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. (l) Zoller, J.; Fabry, D. C.; Ronge, M. A.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13264. (m) Fabry, D. C.; Zoller, J.; Raja, S.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10228. (n) Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 2794. (o) Shu, X.-Z.; Zhang, M.; He, Y.; Frei, H.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5844. (p) Sahoo, B.; Hopkinson, M. N.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 5505. (q) Ye, Y.; Sanford, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 9034. (r) Neufeldt, S. R.; Sanford, M. S. *Adv. Synth. Catal.* **2012**, *354*, 3517. (s) Rueping, M.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem. - Eur. J.* **2012**, *18*, 5170. (t) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566. (u) Osawa, M.; Nagai, H.; Akita, M. *Dalton Trans.* **2007**, 827.

(5) For representative reviews, please see: (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (d) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

(6) For representative reviews, please see: (a) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014**, *43*, 3525. (b) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283. (c) Beletskaya, I. P.; Cheprakov, A. V. *Organometallics* **2012**, *31*, 7753. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (e) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (f) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(7) (a) Tan, Y.; Muñoz-Molina, J. M.; Fu, G. C.; Peters, J. C. *Chem. Sci.* **2014**, *5*, 2831. (b) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 2162. (c) Ziegler, D. T.; Choi, J.; Muñoz-Molina, J. M.; Bissember, A. C.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 13107. (d) Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 9548. (e) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 5129. (f) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647.

(8) Oxygen gas can quench photoexcited Ir(ppy)$_3$*, please see: (a) Sun, J.; Zhao, J.; Guo, H.; Wu, W. *Chem. Commun.* **2012**, *48*, 4169. (b) Takizawa, S.-Y.; Aboshi, R.; Murata, S. *Photochem. Photobiol. Sci.* **2011**, *10*, 895.

(9) Additional data for the optimization and substrate scope of the visible light-induced, copper-catalyzed C−N Ullmann-type coupling can be found in the Supporting Information.

(10) There is limited precedent for the energy transfer mechanism in photoredox/transition metal catalysis. However, energy transfer has served as the mechanistic basis for the [2 + 2] cycloaddition reaction of electron-neutral styrenes and aliphatic olefins: Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10329. We thank a reviewer for this suggestion.

(11) Doeven, E. H.; Zammit, E. M.; Barbante, G. J.; Francis, P. S.; Barnett, N. W.; Hogan, C. F. *Chem. Sci.* **2013**, *4*, 977.

(12) The proposed mechanism based on a SET manifold and subsequent discussion can be found in the Supporting Information.