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Biaryl cross-coupling enabled by photo-induced electron transfer

Hirohito Hayashi,^a Bin Wang,^a Xiangyang Wu,^a Shi Jie Teo,^a Atsushi Kaga,^a Kohei Watanabe,^b Ryo Takita,^b Edwin K. L. Yeow,^{a*} and Shunsuke Chiba^{a*}

^a Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.

[shunsuke@ntu.edu.sg (for S.C.); edwinyeow@ntu.edu.sg (for E. K. L. Y.)]

^b Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

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Abstract. We report a protocol for aryl cross-coupling of electron-deficient aryl halides with electron-rich (hetero)arenes that is driven solely by violet light. This process takes advantage of formation of photo-excited state of electron-deficient aryl halides, that are reduced by electron-rich (hetero)arenes to form a pair of aryl anion and cation radicals.

The resulting aryl anion radicals of aryl halides undergo mesolysis of the carbon-halogen bond to generate aryl radicals, that are coupled most likely with aryl cation radicals to afford functionalized biaryls.

Keywords: Aryl radicals; Anion radicals; Visible light; Cross-coupling; Single-electron-transfer

Introduction

The cross-coupling reaction is a central subject in synthetic chemistry and catalysis, enabling carbon-carbon and carbon-heteroatom bonds from various sets of feedstock chemicals. Conventional methods for the aryl cross-coupling to incorporate aromatic motifs into the products use transition-metal catalysts to mediate coupling of aryl (pseudo)halides as an electrophile with organometallic or heteroatom nucleophiles (Scheme 1A).^[1] Alternatively, aryl cross-coupling can be mediated with open-shell aryl radicals, which are typically generated from aryl (pseudo)halides by a classical tin radical-mediated method, single-electron-reduction (via anion radicals), or photo-excitation (typically by irradiation of UV light) (Scheme 1B).

Recently, photo-induced radical chemistry has proven complementary for aryl cross-coupling reactions.^[2] For example, it was demonstrated that photo-excited highly reducing *fac*-Ir(ppy)₃ can undergo reduction of aryl halides^[3] to form aryl radicals, that can mediate base-promoted homolytic aromatic substitution (BHAS)-type radical chain biaryl coupling with unactivated arenes.^[4,5] Generation of highly reducing photo-excited anion radicals of several π -conjugate organic dyes has also been utilized in reductive formation of aryl radicals from aryl (pseudo)halides and subsequent biaryl cross-coupling.^[6] Very recently, Lambert/Lin and

Wickens independently disclosed an elegant combination of electricity and visible light to generate highly reducing excited radical anions of dicyanoanthracene (DCA) and naphthalene monoimide (NpMI) derivatives, that can mediate single-electron-reduction of aryl halides to afford aryl radicals for the subsequent cross-coupling.^[7] Electron-donors activated by photo-irradiation or generated by photo-induced electron-transfer are found capable in inducing single-electron-reduction of aryl halides to initiate biaryl-coupling under BHAS radical chain mechanism.^[8] The electron-donor-acceptor (EDA) interaction, which induces electron transfer within the resulting charge-transfer complexes by photo-irradiation,^[9] could also facilitate generation of aryl radicals and their cross coupling reactions.^[10-13]

On the other hand, leveraging of photo-induced electron transfer to photo-excited aryl (pseudo)halides would be an attractive alternative to facilitate aryl cross-coupling (Scheme 2). In this regard, Li has recently developed a protocol for photo-induced generation of aryl radicals from aryl (pseudo)halides through single-electron-reduction of their photo-excited state by an iodide ion.^[14] The resulting aryl radicals undergo coupling reactions with molecular iodine (I₂) (Scheme 2A) or bis(pinacolato)diborane (B₂pin₂) (Scheme 2B), and 5-exo cyclization with a pendant alkene followed by iodination of the resulting alkyl radicals. The same

A. Transition-metal catalyzed aryl cross coupling

B. Generation of aryl radicals for aryl cross coupling

Scheme 1. Aryl cross-coupling

A. Photo-induced iodination of aryl bromides and triflates

B. Photo-induced borylation of aryl triflates

C. Photo-induced radical based aryl cross coupling

Scheme 2. Photo-induced aryl cross-coupling.

group also reported photo-induced synthesis of aryl phosphonates from aryl halides and H-phosphonates in the presence of NaOt-Bu, in which single-electron-reduction of photo-excited aryl halides by *in-situ* generated sodium phosphite/phosphinite may operate to initiate the ensuing radical coupling process (Scheme 2C).^[15] These methods commonly require irradiation of energy intensive UV light to excite aryl halides except for more reactive aryl iodides. We reasoned that electron-rich arenes having a lower ionization potential are capable in transferring an

electron to photo-excited aryl halides, promoting subsequent C-C bond formation for construction of biaryl motifs. Herein, we report a protocol for biaryl-cross coupling between electron-deficient aryl halides and electron-rich (hetero)arenes, that is enabled solely by irradiation of violet light. The reaction design, reaction optimization, and substrate scope as well as mechanistic investigation are described.

Results and Discussion

To realize photo-induced biaryl cross-coupling reactions via the photo-induced electron-transfer, we first became interested in a pair of aryl halides having an electron-withdrawing group such as 4'-bromoacetophenone (**1-Br**) as the electron-acceptor and *N*-methylpyrrole (**2**) as an electron donor, possessing a lower ionization potential ($I_p = 7.94$ eV)^[16] compared with other 5-membered ring heteroaromatics such as furan ($I_p = 8.88$ eV) and thiophene ($I_p = 8.87$ eV). Their cross-coupling was recently demonstrated by highly reducing photo-excited anion radicals generated under photoredox^[6] or electrophoto-catalytic^[7] reaction conditions as depicted in Scheme 3.^[17]

Scheme 3. Biaryl cross-coupling catalyzed by highly reducing photo-excited anion radicals.

Figure 1. Transient absorption spectra. (A) ns-TA spectra of **1-Br** (0.1 M) and (B) the corresponding transient kinetic profile probed at 360 nm. (C) The reaction pathway by photo-excitation of **1-Br**. (D) ns-TA spectra of a mixture of **1-Br** (0.1 M) and **2** (2 M). (E) The corresponding transient kinetic profile probed at 370 nm. (F) The reaction pathway by photo-irradiation of **1-Br** in the presence of **2**. The mono-exponential decay/rise fits are also given in red. All samples were prepared in DMSO under an Ar atmosphere. The pump wavelength is 355 nm. OD = optical density; ISC = intersystem crossing; Ac = acetyl.

Photochemistry of substituted acetophenone derivatives was studied previously and the absorption profiles of the corresponding triplet states^[18,19] and anion radicals^[20] were well characterized under transient absorption spectroscopy. We recorded the nanosecond-transient absorption (ns-TA) spectra of **1-Br** in degassed DMSO using 355 nm pulsed excitation at different delay times t (Figure 1A). At short delay times (e.g., $t = 44$ ns), a broad band centred at 430 nm is observed. This is attributed to the triplet state $[1\text{-Br}]^{\text{T1}}$ formed *via* rapid intersystem crossing (ISC) from the excited $S_1(n,\pi^*)$ singlet state

$[1\text{-Br}]^{\text{S1}}$ (Figure 1C).^[18] It was also reported that the absorption of triplet *para*-substituted acetophenones containing electron-withdrawing groups falls in a similar wavelength range.^[19] At later times (e.g., $t = 984$ ns), a new peak at 360 nm and a featureless broad band at wavelengths > 400 nm are seen, which is likely due to the absorption of aryl radical $[1]^{\bullet}$ formed after C-Br bond cleavage of the triplet state $[1\text{-Br}]^{\text{T1}}$.^[18a, 21] At delay time $t \sim 3$ μs , the absorption peak at 360 nm begins to decay mono-exponentially with a rate constant $k_{\text{rd}} = 7.2 \times 10^4 \text{ s}^{-1}$ (Figure 1B).

We next examined the ns-TA spectra of a mixture of **1-Br** and *N*-methylpyrrole (**2**) in DMSO at different delay times (Figure 1D). A band centred at 470 nm was observed at early delay times (e.g., $t = 48$ ns), which was assigned to the absorption of the anion radical $[\mathbf{1-Br}]^{\cdot-}$.^[20] The anion radical $[\mathbf{1-Br}]^{\cdot-}$ decays (e.g., $t = 978$ ns) as it undergoes back-electron-transfer to $[\mathbf{2}]^{+\cdot}$ or C-Br bond mesolysis to form aryl radical $[\mathbf{1}]^{\cdot}$. The lifetime of $[\mathbf{1-Br}]^{\cdot-}$ is 0.6 μ s, obtained from the transient kinetic profile probed at 470 nm (Figure S1). After $t \sim 1$ μ s, a new peak at 370 nm and a broad featureless band appearing at > 400 nm are observed (e.g., $t = 2.518$ and 3.018 μ s). In this case, the ΔOD bands are attributed to aryl radical $[\mathbf{1}]^{\cdot}$ formed after C-Br bond mesolysis of $[\mathbf{1-Br}]^{\cdot-}$. The bathochromic shift of the peak when compared to aryl radical $[\mathbf{1}]^{\cdot}$ generated from **1-Br** itself (Figure 1A) is plausibly due to an environmental effect on the absorption of aryl radical $[\mathbf{1}]^{\cdot}$ in the presence of *N*-methylpyrrole (**2**). The rate of formation of $[\mathbf{1}]^{\cdot}$ ($k_{rf} = 6.8 \times 10^5$ s⁻¹), obtained from the rise of the 370 nm peak (Figure 1E), is slower than the rate of $[\mathbf{1-Br}]^{\cdot-}$ decay ($k_{ad} = 1.7 \times 10^6$ s⁻¹); indicating that back-electron-transfer is more efficient than the C-Br bond mesolysis as the decay pathway of $[\mathbf{1-Br}]^{\cdot-}$. The aryl radical $[\mathbf{1}]^{\cdot}$ decays mono-exponentially after $t \sim 3$ μ s with a rate constant $k_{rd} = 1.3 \times 10^6$ s⁻¹ (Figure 1E). This implicates that the radical coupling between $[\mathbf{1}]^{\cdot}$ and $[\mathbf{2}]^{+\cdot}$ within the solvent cage to produce biaryl **3** (Figure 1F) could contribute to the faster decay of $[\mathbf{1}]^{\cdot}$ as compared to the solution of sole $[\mathbf{1}]^{\cdot}$ (Figure 1B).

UV-vis absorption spectrum on **1-Br** in DMSO showed strong absorbance at 260 nm derived from the π - π^* transition (Figure 2A) and much weaker one around at 352 nm from the n - π^* transition (Figure 2B). However, addition of pyrrole **2** to **1-Br** did not show clear enhancement and red-shifted tailing of the absorbance, indicating that the EDA interaction between **1-Br** and **2** in their ground state is less likely present.^[22] Therefore, we assumed that photo-induced electron-transfer to the photo-excited triplet state $[\mathbf{1-Br}]^{\text{T1}}$ from *N*-methylpyrrole **2** is most likely responsible for the formation of the anion radical $[\mathbf{1-Br}]^{\cdot-}$.^[23]

Figure 2. (A) UV-vis absorption spectra of **1-Br** (0.1 mM in DMSO). (B) UV-vis absorption spectra of **1-Br** (100 mM in DMSO) with 0 to 20 equiv of **2**.

Based on the above observations and mechanistic hypothesis for biaryl-coupling between **1-Br** and **2**, optimization of the reaction conditions was implemented (Table 1). We observed that irradiation of violet light ($\lambda_{\text{max}} = 390$ nm) in DMSO as a solvent promotes the expected cross-coupling to provide biaryl **3** in 67% yield after stirring for 20 h (run 1). The reaction could be accelerated by adding inorganic carbonate bases (M_2CO_3 ; $\text{M} = \text{K}, \text{Na}, \text{or Cs}$), completing the process within 6-7 h to give **3** in good yields (runs 2-4).^[24] However, use of other inorganic salts such as KOAc (run 5) and KF (run 6) as well as organic amines such as *N,N*-diisopropylethylamine (*i*-Pr₂NEt) (run 7) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (run 8) did not improve the process efficiency. We next examined the effect of the wavelength of the light sources. The cross-coupling under shorter wavelength of the light ($\lambda_{\text{max}} = 370$ nm) proceeded to give **3** in 83% yield, while the reaction progress became slower (run 9). In this case, we speculated that the absorption of the light by the coupling product **3** rendered the reaction progress sluggish. On the other hand, light of longer wavelength ($\lambda_{\text{max}} = 427$ or 440 nm) was unable to promote this process (runs 10 and 11). Under irradiation of violet light ($\lambda_{\text{max}} = 390$ nm), the reaction in acetonitrile gave a comparable yield of **3**, while longer reaction time was required (run 12). Use of other solvents such as methanol and

dichloroethane was found detrimental (runs 13 and 14).

Table 1. Optimization of the reaction conditions^{a)}

Run	$\lambda_{\max}$ (nm) ^{b)}	Solvent	Base	Time (h)	Yield (%) ^{c)}
1	390	DMSO	—	20	67 (6) ^{d)}
2	390	DMSO	K ₂ CO ₃	6	73 (76) ^{e)}
3	390	DMSO	Na ₂ CO ₃	6.5	68
4	390	DMSO	CS ₂ CO ₃	7	72
5	390	DMSO	KOAc	16	62
6	390	DMSO	KF	16	73
7	390	DMSO	<i>i</i> Pr ₂ NEt	20	43 (5) ^{d)}
8	390	DMSO	DABCO	20	64 (6) ^{d)}
9	370	DMSO	K ₂ CO ₃	14	83
10	427	DMSO	K ₂ CO ₃	14	8 (88) ^{d)}
11	440	DMSO	K ₂ CO ₃	14	0 (90) ^{d)}
12	390	CH ₃ CN	K ₂ CO ₃	25	72
13	390	MeOH	K ₂ CO ₃	14	36 (47) ^{d)}
14	390	DCE	K ₂ CO ₃	14	9 (91) ^{d)}

^{a)} All the reactions were conducted using 0.5 mmol of **1** in degassed DMSO (5 mL) under an Ar atmosphere. ^{b)} The Kessil PR160 series (at $\lambda_{\max}$ = 440, 427, 390, and 370 nm) were used as the LED light source for the reactions (<https://www.kessil.com/photoredox/Products.php>). The radiated energies of the light per area measured at a distance of 3.5 cm are 41.3 mW/cm² (440 nm), 49.4 mW/cm² (427 nm), 50.4 mW/cm² (390 nm), and 42.5 mW/cm² (370 nm). See the Supporting Information for the detailed reaction settings. ^{c)} ¹H NMR yields based on the internal standard. ^{d)} Recovery yield of **1-Br**. ^{e)} Isolated yield.

The coupling reaction of **1-Br** with 10 equiv of *N*-methylpyrrole (**2**) afforded coupling product **3** in comparable yield (69%), while longer reaction time (11 h) was required (Scheme 4A). Further reduction of the amount of **2** to 5 equiv lowered the yield of coupling product **3** (57%). This protocol could be implemented in a gram scale of **1-Br** (6 mmol) without loss of the process efficiency (Scheme 4B). The coupling reaction of 4'-chloroacetophenone (**1-Cl**) also proceeded to give **3** in 70% yield, but required three times the reaction time presumably due to the higher of bond dissociation energies of an aryl-chloride bond (C₆H₅-Br, 80 kcal/mol; C₆H₅-Cl, 95 kcal/mol) (Scheme 4C).^[25]

A Effect of the amounts of *N*-methylpyrrole (**2**)

1-Br (0.5 mmol)	K ₂ CO ₃ (1.5 equiv)	3	2 (equiv)	time (h)	yield of 3 (%)
+	DMSO (0.1 M)		20	6	76%
2	<i>hν</i> ($\lambda_{\max}$ = 390 nm)		10	11	69%
	25 °C, time		5	11	57%

B The reaction in gram scale

C The reaction with 4'-chloroacetophenone (**1-Cl**)

Scheme 4. The reactions of **1-Br** and **1-Cl**.

We found that this protocol is applicable to aryl bromides having π -polar electron-withdrawing groups such as acyl, formyl, cyano, and methoxy carbonyl regardless of their position (i.e. *para*, *meta*, or *ortho* to the dissociative C-Br bond) (**4-7**, **10-16**), whereas those with 4-bromoanisole and 4-bromotrifluorotoluene were detrimental under the reaction conditions (**8** and **9**) (Scheme 5A). It should be noted that the coupling reactions of 4-bromobenzophenone (for **4**) and 2-acetyl-6-bromonaphthalene (for **15**) occur even under irradiation of light of longer wavelength ($\lambda_{\max}$ = 427 nm) with similar performance probably because their π -extended structures lend red-shifted absorption to the corresponding aryl bromides. Chemoselective coupling with bromide over fluoride or chloride was observed in the reaction of 4-bromo-2-fluorobenzonitrile, 2-bromo-3-fluorobenzaldehyde, and 2-bromo-4-chlorobenzaldehyde to afford the corresponding coupling products (**17**, **18**, and **19**, respectively) in good yields as a sole product. Polysubstituted biaryls **20** and **21** could be accessed efficiently by the current protocol. Furthermore, the present cross-coupling method is amenable to various heteroaromatic bromides, allowing for a rapid access to a series of unique heterobiaryls of medicinal interests (**22-31**) (Scheme 5B). Of worthy to note is the late stage functionalization of a drug compound, nicergoline (for **31**), demonstrating wide functional group compatibility of the present protocol (Scheme 5B).

Scheme 5. Substrate scope. ^a) All the reactions were conducted using 0.5 mmol of aryl bromides (or chlorides) in degassed DMSO (5 mL) under an Ar atmosphere. ^b) The yields from the reactions under 427 nm (λ_{max}). ^c) The yields from the reactions using the corresponding aryl chlorides. ^d) ¹H NMR yield based on the internal standard. ^e) Recovery yields of the aryl bromides. ^f) Due to instability of the coupling product **10**, the formyl group was subsequently reduced by NaBH₄ to convert it to the corresponding alcohol. The isolated yield of the alcohol was noted.

To capture transient aryl radical species, we prepared radical clock substrate **32** having an alkoxy tether *ortho* to the C-Br bond. The reaction of **32** in the presence of *N*-methylpyrrole (**2**) under the present optimized reaction conditions resulted in full conversion within 21 h, affording three different dihydrobenzofurans **33**, **34**, and **35** in 19%, 10%, and

14%, respectively (Scheme 6A). This outcome indicated that aryl radical **A** is formed and subsequently undergoes rapid 5-exo cyclization^[26] to form alkyl radical **B**. Hydrogen atom abstraction of alkyl radical **B** affords **33**, whereas it also reacts with pyrrole **2** and substrate **32** to form **34** and **35** (through homolytic allylic substitution), respectively. The reaction in the presence of 1,4-cyclohexadiene as a hydrogen atom donor rendered the process more selective and efficient, affording **33** in 80% yield as a sole product (Scheme 6B). The cyclization of **36** with a 3,3-dimethylallyloxy tether similarly worked well to afford dihydrobenzofuran **37** in 92% yield (Scheme 6C).

Scheme 6. Radical clock experiments.

We next investigated other arenes as an alternative coupling partner to *N*-methylpyrrole (**2**) (Scheme 7). As for electron-rich arenes, we found that *N*-H pyrrole ($I_p = 8.2 \text{ eV}$) and 1,4-dimethoxybenzene ($I_p = 7.9 \text{ eV}$) promote the cross-coupling to afford **38** and **39**, respectively, in good yields.^[27] On the other hand, the reaction with benzene ($I_p = 9.24 \text{ eV}$) was sluggish, resulting in formation of biaryl **40** only in 31% yield with incomplete conversion even by using larger excess amounts (56 equiv) of benzene. Interestingly, the reactions with 6-membered ring nitrogen-heteroaromatic compounds, pyridine ($I_p = 9.32 \text{ eV}$) and pyrazine ($I_p = 9.29 \text{ eV}$) proceeded slowly but reached to the full conversion to afford **41** (as a mixture of C2-, C3-, and C4 coupling adducts) and **42** in 77% and 54% yields, respectively.^[28]

Scheme 7. Screening of arene coupling partners. ^a) All the reactions were conducted using 0.5 mmol of **1-Br** with 20 equiv of arenes (H-Ar) in degassed DMSO (5 mL) under an Ar atmosphere. Isolated yields of the products were noted unless otherwise stated. ^b) The reaction was conducted in DMSO (2.5 mL) and benzene (2.5 mL). The yield of **40** was measured by ¹H NMR based on the internal standard.

Finally, the reactivity of 3,5-dibromobenzonitrile (**43**) toward photo-induced double arylation was investigated (Scheme 8). The reaction of **43** in the presence of *N*-methylpyrrole (**2**) could be controlled by the reaction time: photo-irradiation of the mixtures for 3 h provided mono-coupling product **44** in 63% yield along with di-coupling adduct **45** in 10% yield, whereas the reaction for 20 h allowed for formation of di-coupling product **45** as a sole product in 63% yield (Scheme 8A). Iterative coupling of **43** was also achieved under the current protocol (Scheme 8B).^[29] Namely, treatment of **43** with 1,4-dimethoxybenzene afforded mono-coupling adduct **46** in 40% yield.^[30] Subsequent photo-irradiation to the mixture of **46** and *N*-methylpyrrole (**2**) gave **47** in 83% yield.

A Controlled mono- or di-coupling of **43** with **2**.

B Iterative coupling of **43**.

Scheme 8. Arylation of 3,5-dibromobenzonitrile (**43**).

Conclusion

This work demonstrated an operationally simple protocol for aryl cross-coupling of electron-deficient aryl bromides or chlorides with electron-rich (hetero)arenes such as pyrroles and 1,4-dimethoxybenzene, which is driven solely by violet light. Photo-induced electron transfer to the transient photo-excited aryl halides from electron-rich (hetero)arenes is the key to enable the process, that was supported by the nanosecond-transient absorption spectroscopy.^[31] It is our strong belief that the leveraging of photo-induced electron-transfer to drive light-induced bond-forming processes continues to be exploited further in various synthetic endeavours.

Experimental Section

A typical procedure (Table 1, entry 2): To a 25 mL sealed tube was added 4'-bromoacetophenone (**1-Br**) (0.498 mmol, 99.1 mg), K₂CO₃ (0.747 mmol, 103 mg) and *N*-methyl pyrrole (**2**) (9.96 mmol, 0.88 mL). Degassed anhydrous DMSO (5 mL) was added and the reaction was sparged with Ar. The tube was sealed and irradiated by LED lamp (λ_{max} = 390 nm) for 6 h. The reaction mixture was then diluted with Et₂O and water. The aqueous layer was separated and

extracted thrice with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. ¹H NMR yield of **3** was recorded based on **1-Br** using 1,1,2,2-tetrachloroethane (0.19 mmol, 20 μL) as an internal standard. The resulting crude material was purified by flash column chromatography (silica gel; Hexane/EtOAc 95:5–90:10) to give **3** (0.378 mmol, 75.4 mg) in 76% yield as a white solid.

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- [22] The slight enhancement of absorbance in the presence of 5 and 20 equiv of **2** observed in Figure 2C is derived simply from absorbance of **2**.
- [23] The emission spectra of the mixture of **1a** and **2** showed formation of a new peak around at 467 nm and its intensity is enhanced with increase of the concentration of **2** (see Figure S14). Since the ground state absorption spectra of **1a** do not shift in the presence of **2** (Figure 2), we ascribe the newly formed peak at 467 nm to the emission from an exciplex formed between triplet state [**1a**]^{T1} and **2**. Then, rapid electron-transfer process might occur to form anion radical [**1a**]^{•-} as observed in Figure 1D, while direct electron-transfer from **2** to [**1a**]^{T1} cannot be ruled out. For details, see the Supporting Information. Further investigation is underway to fully characterize the dynamics of electron-transfer occurring after formation of the exciplex.
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- [29] Acetonitrile was better solvent than DMSO for this iterative coupling (see the SI for details).
- [30] Double coupling product was formed in 17% yield. See the SI for details.
- [31] During the revision of this manuscript, it was reported by Zheng that the coupling reactions of aryl halides and *N*-methylpyrrole (and their derivatives) are mediated by irradiation of blue LED light (455 nm) even under aerobic conditions. The process is likely triggered by photo-induced disproportionation of polypyrroles to form a highly reducing anion radical of *N*-methylpyrrole, which reduces aryl halides to generate aryl radicals for ensuing biaryl coupling, see: Z.-J. Li, S. Li, E. Hofman, A. H. Davis, G. Leem, W. Zheng, *Green. Chem.* DOI: 10.1039/c9gc04248b.

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Hirohito Hayashi, Bin Wang, Xiangyang Wu, Shi Jie Teo, Atsushi Kaga, Kohei Watanabe, Ryo Takita, Edwin K. L. Yeow,* and Shunsuke Chiba*