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A transition metal- and photosensitizer-free approach for site-selective (hetero)arylation of polychlorinated heteroarenes†

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We have developed an effective photochemical method for site-selective (hetero)arylation of polychlorinated heteroarenes. This approach eliminates the need for transition metal catalysts and photosensitizers by relying on *in situ* formation of unconventional electron donor–acceptor (EDA) complexes between two substrates and a basic additive. Our protocol yields chlorine-containing biaryl heterocyclic compounds with high levels of site-selectivity, which are of significant importance in both synthetic and medicinal chemistry.

Polyhalogenated aromatic compounds are valuable starting materials in organic synthesis, serving as prevalent scaffolds in various natural products, biological probes, functional materials, and drug candidates.^{1–3} Site-selective functionalization of (hetero)arenes with identical halogen substitution is a versatile method that offers abundant opportunities not only to advance this field but also chemical synthesis as a whole. However, accurately distinguishing C–X bonds with slight differences in polarity and other characteristics remains a challenge in these transformations.^{4,5} To address this issue, several sophisticated strategies have been developed, including electronic and steric control,⁶ directing group control,⁷ and ligand control in transition metal catalysis (Scheme 1a).⁸ For instance, Gundersen *et al.* demonstrated that substituent alteration at the C3 position of 2,4-dichloropyridine substrates could switch C2- and C4-selectivity in Pd-catalyzed Stille coupling reactions.⁶ Phipps *et al.* found that noncovalent interactions between sulfonated phosphine ligands and substrates could enable site-selective Suzuki–Miyaura coupling and Buchwald–Hartwig coupling across a range of dichlorinated and trichlorinated arenes.⁸

Visible light photoreactions have demonstrated immense potential in cleaving and converting relatively unreactive chemical bonds, such as unactivated C–H, C–C, and aryl C–Cl bonds, through mechanistic pathways that differ from conventional thermal processes.⁹ However, achieving useful reactivity and selectivity in the direct functionalization of polychlorinated arenes and heteroarenes *via* photochemical strategies, which do not follow the traditional cross-coupling catalytic cycle, is typically more challenging. This difficulty may be attributed to the electronic feedback of aryl radical species, and the lack of effective methods, such as metal-coordination induction, to distinguish highly similar, inert C(sp²)–Cl bonds.¹⁰ In this regard, Weaver *et al.* reported a photocatalytic cross-coupling reaction of perfluoroarenes with other arenes using an iridium-based photosensitizer, providing a convenient route to obtain multifluorinated biaryls (Scheme 1b).¹¹ Glorius *et al.* developed a site-selective thiolation of dihalogenated heteroarenes with thiols, where C–S bond coupling occurred at the most electron-enriched position of the (multi)halogenated substrates.¹² Additionally, our group discovered that an arylamine-based organophotocatalyst with an appropriate window of reductive potentials at the excited states could effectively catalyze selective deuterodehalogenation of aryl and alkyl chlorides.¹³ Despite these promising achievements, practical systems are still needed to facilitate site-selective conversions of polychlorinated (hetero)arenes into valuable products, such as multi-substituted biaryl indole derivatives.^{14–22}

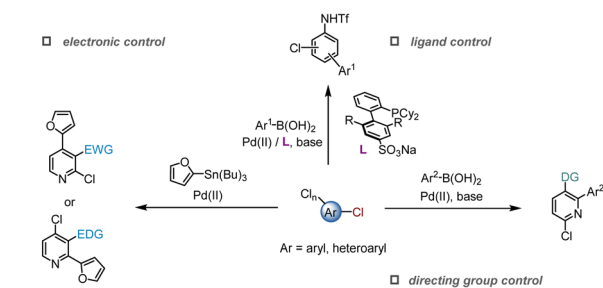
Herein, we present our findings of a novel photochemical method for the selective C(sp²)–X/C(sp²)–H cross-coupling of polychlorinated heteroarenes with indole derivatives or electron-rich arenes. Our approach relies on *in situ* generation of unconventional electron donor–acceptor (EDA) complexes^{23,24} originating from two substrates and a basic additive, namely heteroarene-indole anion-cesium cation complexes (Scheme 1c). The controlled single electron transfer (SET) process occurring in these EDA complexes, followed by the combination of resulting radical species, permits high reaction efficiency and site-selectivity in the formation of biaryl heterocyclic compounds

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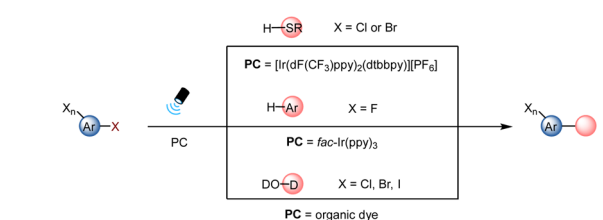
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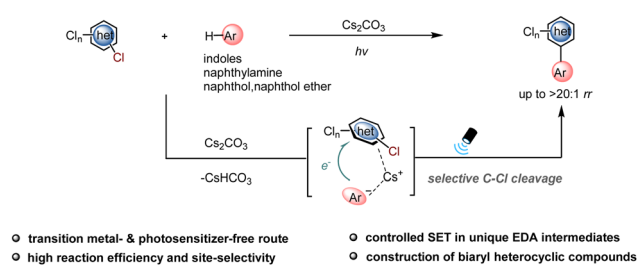
(a) Conventional methods for the selective functionalization of polyhalogenated (hetero)arenes



(b) Photochemical methods for the selective functionalization of polyhalogenated (hetero)arenes



(c) This work



Scheme 1 Overview of this work. EWG = electron-withdrawing group, EDG = electron-donating group, DG = directing group, PC = photocatalyst, rr = regioisomeric ratio.

without the need for transition metal catalysts or external photosensitizers.

We investigated the photochemical (hetero)arylation reaction of polychlorinated heteroarenes using 1,3-dichloroisoquinoline (**1a**) and 2-phenylindole (**2a**) as model substrates (Table 1). After being irradiated with a 20 W LED lamp ($\lambda_{\text{max}} = 427$ nm) for 15 h, only trace amounts of the desired product (**3aa**) were detected (entry 1). However, adding 2.0 equivalent of K₂CO₃ as the basic additive significantly improved the reaction, resulting in a yield of 59% and a regioselectivity of > 20:1 rr for the product (**3aa**) (entry 2). Subsequent solvent screening experiments determined that acetonitrile was the optimal choice (entries 2–5). Other inorganic basic additives such as KOAc, K₃PO₄, and Na₂CO₃ were found to be less efficient (entries 7–9). When switching from a 20 W to a 40 W LED lamp, Cs₂CO₃ showed an improved yield of 61% within 6 h compared to K₂CO₃ (entries 11 and 12). The use of a mixed solvent (MeCN: H₂O = 7:3) led to completion of the reaction in 6 h, affording **3aa** in a 72% yield and with a > 20:1 rr (entry 13). Control experiments confirmed that both light irradiation and an inert atmosphere were necessary for the transformation. The reaction did not produce the product (**3aa**) when conducted without light irradiation or in air (entries 14, 15).

We next evaluated the generality of this photochemical reaction of polychlorinated heteroarenes with indole derivatives or

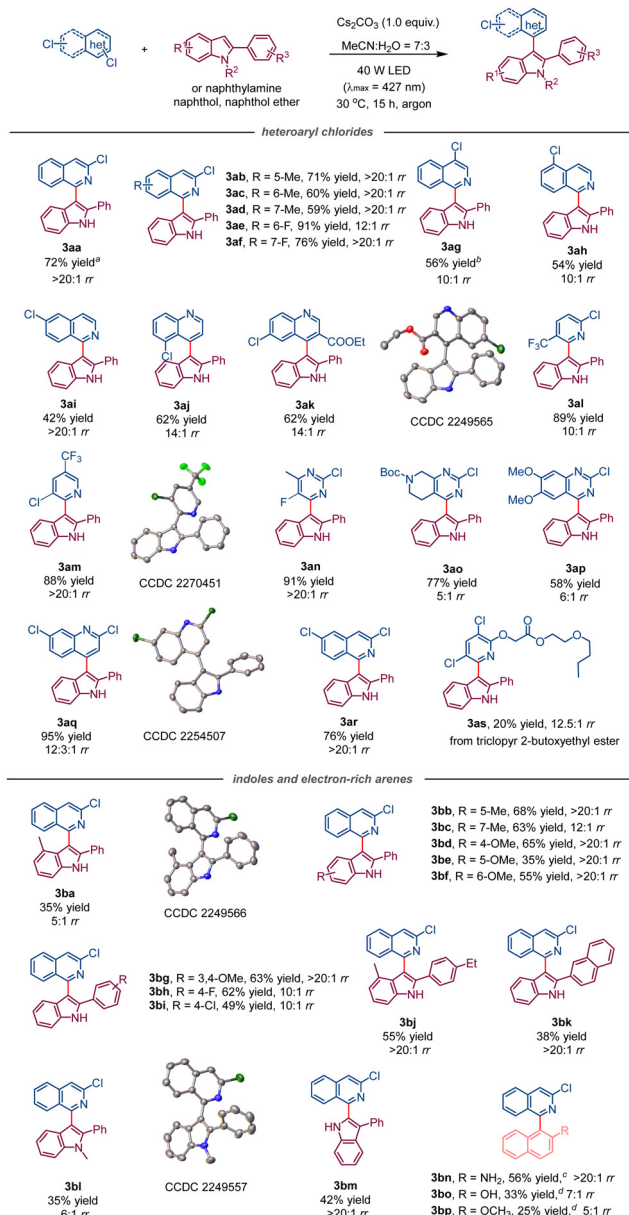
Table 1 Optimization of reaction conditions^a

Entry	427 nm LED (power)	Basic additive	Solvent	T (h)	Yield ^b
1	20 W	None	MeCN	15	Trace
2	20 W	K ₂ CO ₃ ^c	MeCN	15	59%
3	20 W	K ₂ CO ₃ ^c	CH ₂ Cl ₂	15	N.d.
4	20 W	K ₂ CO ₃ ^c	toluene	15	N.d.
5	20 W	K ₂ CO ₃ ^c	CH ₃ OH	15	31%
6	20 W	K ₂ CO ₃ ^d	MeCN	15	59%
7	20 W	KOAc ^d	MeCN	15	37%
8	20 W	K ₃ PO ₄ ^d	MeCN	15	48%
9	20 W	Na ₂ CO ₃ ^d	MeCN	15	42%
10	20 W	Cs ₂ CO ₃ ^d	MeCN	15	49%
11	40 W	K ₂ CO ₃ ^d	MeCN	6	17%
12	40 W	Cs ₂ CO ₃ ^d	MeCN	6	61%
13	40 W	Cs ₂ CO ₃ ^d	MeCN:H ₂ O = 7:3	6	72%
14	In dark	Cs ₂ CO ₃ ^d	MeCN:H ₂ O = 7:3	6	N.d.
15 ^e	40 W	Cs ₂ CO ₃ ^d	MeCN:H ₂ O = 7:3	6	N.d.

^a Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), basic additive (0.10 or 0.20 mmol), indicated solvent (1.0 mL), under argon, upon irradiation with a LED lamp ($\lambda_{\text{max}} = 427$ nm), at 30 °C. ^b Isolated yield. ^c 2.0 equiv. ^d 1.0 equiv. ^e Reaction in air. n.d. = not detected.

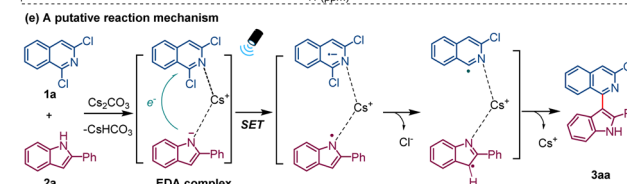
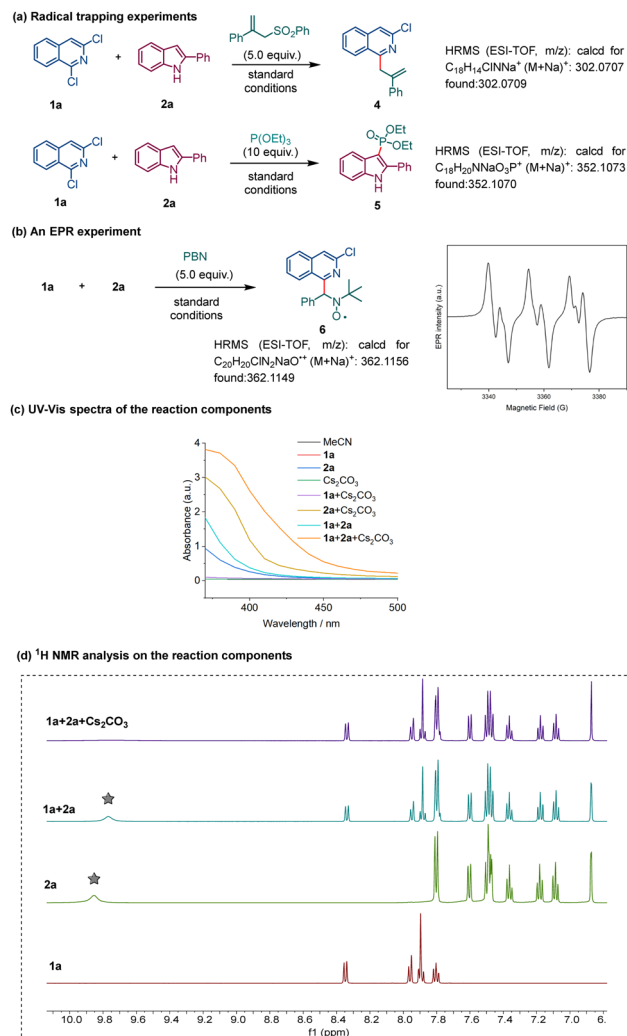
electron-rich arenes (Scheme 2). In terms of polychlorinated heteroarenes, 1,3-dichloroisoquinoline derivatives bearing a 5-methyl, 6-methyl, 7-methyl, 6-fluoro, or 7-fluoro substituent were all tolerated. The coupling products (**3ab–3af**) were obtained in yields ranging from 59 to 91% and all with 12:1 → 20:1 rr. 1, 4-Dichloroisoquinoline, 1,5-dichloroisoquinoline and 1,6-dichloroisoquinoline were also selectively coupled with 2-phenylindole (**2a**) at the 1-position, yielding the corresponding products (**3ag–3ai**) with 42–56% yields and 10:1 → 20:1 rr. Additionally, dichlorinated quinolines (products **3aj**, **3ak**), dichlorinated pyridines (products **3al**, **3am**), dichlorinated pyrimidines (products **3an**, **3ao**), and a dichlorinated quinazoline (product **3ap**) proved to be compatible substrates, which yielded the products in 58–91% yields and with 5:1 → 20:1 rr. X-ray crystallography (CCDC 2249565, 2270451) confirmed that the reaction typically occurred at C–Cl sites closer to heterocyclic nitrogen atoms in the structures of products **3ak** and **3am**. Trichlorinated heteroarenes also demonstrated high reaction efficiency and regioselectivity. For example, the reaction of 2,4,7-trichloroquinoline gave rise to product **3aq** in a 95% yield with 12:3:1 rr, wherein the C–Cl bond at the 4-position was reacted, as conformed by X-ray crystallography (CCDC 2254507). Furthermore, a trichloro 2-butoxyethyl ester was successfully functionalized with 12.5:1 rr, furnishing the product (**3as**) in a moderate yield. Notably, electronically rich polychlorinated heteroarenes did not react, perhaps due to their inability to form effective EDA intermediates with indole substrates.

A variety of phenylindole derivatives were examined as coupling partners. The results indicated that those bearing an electron-donating group on the indolyl moiety (products **3ba–3bf**),

Scheme 2 Substrate scope. ^a 6 h. ^b 55 °C. ^c 36 h. ^d 40 h.

electron-donating, withdrawing substituents, or a fused ring on the phenyl fragment (products **3bg–3bk**) were all viable. The target products were obtained with yields ranging from 35 to 68% and regioselectivity ranging from 5:1 to >20:1 rr. Interestingly, *N*-methyl protected indole could be converted into the product (**3bl**) with lower yield (35%) and regioselectivity (6:1). Furthermore, electron-rich arenes were found to be useful coupling partners as well. For instance, the reaction of **1**, 3-dichloroisoquinoline (**1a**) with 2-aminonaphthalene (**2o**) gave the desired product (**3bn**) in a 56% yield with >20:1 rr.

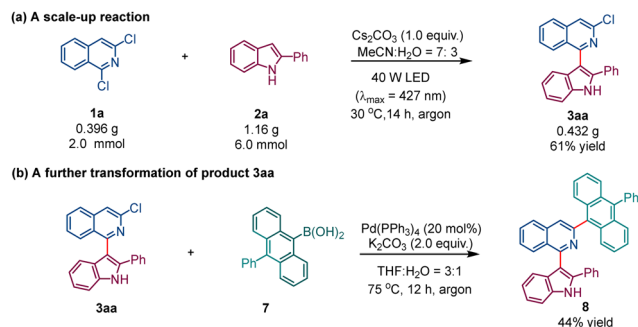
To gain a deeper understanding of the reaction mechanism, a series of experiments were designed and conducted (Scheme 3). The addition of a competitive radical acceptor, such as ethyl ((2-phenylallyl)sulfonyl)benzene, to the reaction of **1a** and **2a** completely inhibited the formation of **3aa**, but



Scheme 3 Mechanistic studies.

instead, an allylated isoquinoline product (**4**) was detected by high-resolution mass spectrometry (HRMS) (Scheme 3a). Furthermore, interference with triethoxyphosphine led to the observation of a phosphorylated indole derivative (**5**). These findings strongly suggest a radical pathway and highlight the possible involvement of heteroaryl and indolyl radical species in the photochemical reaction. Additionally, the existence of heteroaryl radicals was further supported by an electron paramagnetic resonance (EPR) experiment (Scheme 3b).

UV-Vis spectra were recorded to determine the light absorption of the reaction components (Scheme 3c). The individual substrates (**1a**, **2a**), as well as the basic additive and solvent, did not exhibit strong absorption in the visible-light region. However, when a mixture of **1a**, **2a** and Cs_2CO_3 in acetonitrile was examined, an obvious red-shift and absorption enhancement



Scheme 4 Synthetic utility of this method.

were observed, indicating possible interactions among the two substrates and the basic additive. This standpoint was further supported by ^1H NMR titration experiments (Scheme 3d). When Cs_2CO_3 was added to a mixture of **1a** and **2a**, significant changes in the N–H signal of **2a** were observed.

Based on the results of these mechanistic studies, our previous experience,¹³ and other literature sources,²³ we proposed a plausible mechanism (Scheme 3e). Initially, mixing **1**, 3-dichloroisoquinoline (**1a**), 2-phenylindole (**2a**), and Cs_2CO_3 in acetonitrile leads to the formation of an EDA complex – an isoquinoline-indole anion-cesium cation ternary complex. This EDA intermediate absorbs photons and undergoes an intramolecular SET, delivering a cesium cation-binding dichloroisoquinoline radical anion and 2-phenylindole radical. The subsequent C–Cl bond cleavage, followed by a radical–radical combination process, yields the final product (**3aa**). It is assumed that the mild intramolecular SET process is critical for achieving high reaction efficiency and site-selectivity. It is worth mentioning that an alternative mechanism, which involves the formation of hydrogen bonding EDA complexes, cannot be disregarded (refer to Section 4.5 in the ESI†).^{25–27}

To demonstrate the practical application of this method, a scale-up reaction was conducted (Scheme 4a). A mixture of **1a** (0.396 g, 2.0 mmol), **2a** (1.16 g, 6.0 mmol) and Cs_2CO_3 (0.650 g, 2.0 mmol) was subjected to LED irradiation under standard conditions, which resulted in the formation of 0.432 g of **3aa** (61% yield). The product can be easily converted into a polyaryl compound (**8**) through a Pd-catalyzed Suzuki coupling reaction (Scheme 4b).

In summary, we have developed a novel photochemical approach that utilizes unconventional heteroarene-indole anion-cesium cation EDA intermediates for the site-selective cross-coupling of polychlorinated heteroarenes with indole derivatives or electron-rich arenes. This reaction occurs under mild conditions, eliminates the need for transition metal catalysts or external photosensitizers, and provides a convenient means of accessing valuable chlorine-containing biaryl heterocyclic products. The controlled SET process that takes place in the EDA complexes, followed by the combination of

resulting radical species, facilitates high reaction efficiency and site-selectivity. These findings are expected to create new opportunities for achieving selective functionalization of polyhalide feedstocks.

Conflicts of interest

There are no conflicts to declare.

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