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Organophotocatalytic Arene Functionalization: C−C and C−B Bond Formation

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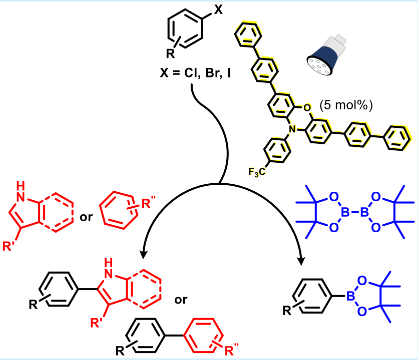
Supporting Information

ABSTRACT: Organophotocatalytic C−C and C−B bond formation reactions of aryl halides have been developed in the presence of an organophotosensitizer, 3,7-di([1,1′-biphenyl]-4-yl)-10-(4-(trifluoromethyl)phenyl)-10*H*-phenoxazine that has highly negative reduction potential at its photoexcited state. The developed reaction conditions are mild and allow the intermolecular C−C bond formation of the generated aryl radical with electron-rich (hetero)arenes and C−B bond formation with bis(pinacolato)diboron.



Arenes are the most prevalent structural motifs in functional organic molecules, and the synthesis of functionalized arenes has consequently received significant attention.[1] With the growth of organometallic chemistry, significant advances have been achieved in the transition-metal-catalyzed coupling of aryl (pseudo)halides toward the synthesis of valuable functionalized arenes.[2] The recent use of photosensitizers (PS), such as the polypyridyl ligand-based metal complexes, has enabled arene functionalization through homolytic aromatic substitution under visible light irradiation.[3] Photocatalytic arene functionalizations are attractive alternatives, with distinct advantages such as milder and eco-friendly reaction conditions. Furthermore, the use of organophotosensitizers circumvents the typical limitations associated with transition metal catalysis, such as their high costs and toxicity, which are particularly beneficial for expanding their applications in the synthesis of pharmaceuticals.[4] However, the reported organophotocatalytic reactions are mainly limited to the use of highly functionalized aryl precursors such as aryl diazonium salts, diaryliodonium salts, and aryl sulfonyl chlorides that have less negative reduction potentials (Scheme 1a).[5] Considering the facile preparation of a wide range of aryl halides, the formation of aryl radicals via cleavage of the Ar−X bond would be more desirable. Despite the reported use of aryl halides in photocatalytic transformations,[6] the use of aryl chlorides[7] is still challenging due to their high bond dissociation energy (BDE of Ar−Cl is ~407 kJ mol^{-1}) and highly negative reduction potentials (−1.7 V vs SCE > E_{red} > −2.8 V vs SCE).[7e]

We recently developed an organophotosensitizer, 3,7-di([1,1′-biphenyl]-4-yl)-10-(4-(trifluoromethyl)phenyl)-10*H*-phenoxazine (**A**), which has a highly negative photoexcited reduction potential [$E^*(\mathrm{PS}^{\bullet+}/\mathrm{PS}^*) = -1.98$ V vs SCE, and the calculated potential is $E^*(\mathrm{PS}^{\bullet+}/\mathrm{PS}^*) = -2.56$ V].[8] We envisioned the use of the strong reducing power of **A*** for the generation of aryl radicals via reduction of aryl halides, including some aryl chlorides. However, the successful aryl radical generation does not guarantee arene functionalization via the desired sequence of intermolecular reactions, as dehalogenation

Scheme 1. Highly Negative Photoexcited Reduction Potential of Photosensitizer A and Its Reactions

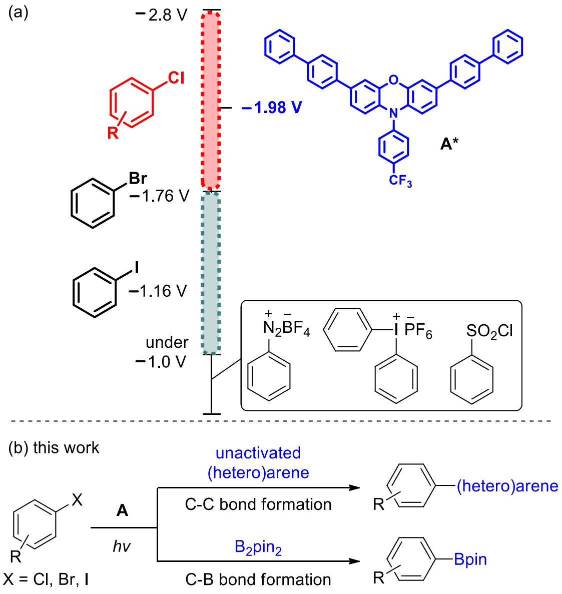


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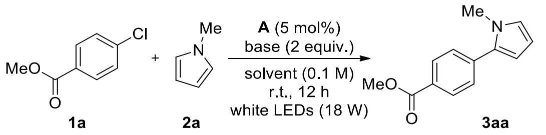
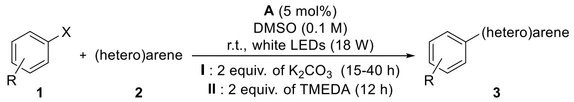
Table 1. Optimization of C−C Bond Formation[a]

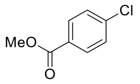
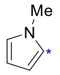
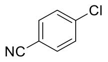
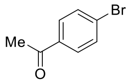
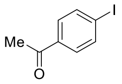
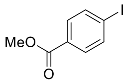
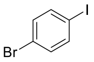
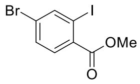
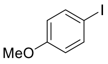
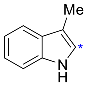
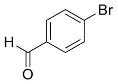
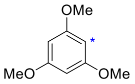
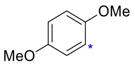


entry	solvent	base	variations	**3aa** (%)[b,c]
1	DMSO			27 (trace)
2	DMSO	K_2CO_3		47 (3)[d]
3	DMSO	K_2CO_3	30 h	91 (5)
4	DMSO	TEA		74 (14)
5	DMSO	DIPEA		82 (6)
6	DMSO	TMEDA		88 (10)
7	DMSO	DBU		44 (12)
8	DMSO		no **A**	0
9	DMSO		no *hν*	0
10	DMSO	(TMEDA)	$[Ru(bpy)_3]Cl_2$	0
11	DMSO	(TMEDA)	eosin Y	0
12	DMF			19 (21)
13	DCM			0
14	THF			0
15	TFE			0
16	DMA			17 (18)
17	MeCN			0

[a] Reaction scale: **1a** (0.1 mmol) and **2a** (1.0 mmol). [b] Yields were determined by GC using *n*-dodecane as the internal standard. [c] Numbers in parentheses indicate the yield of dechlorinated product, methyl benzoate. [d] 47% of **1a** remained unreacted.

Table 2. Substrate Scope of C−C Bond Formation[a]



entry	**1**	**2**	**3**, yield (%)[b] **con. I / con. II**
1	 **1a**	 **2a**	**3aa** (90 / 88[c])
2	 **1b**	**2a**	**3ba** (60 / 65)
3	 **1c**	**2a**	**3ca** (72 / 65)
4	 **1d**	**2a**	**3da** (= **3ca**) (40 / 58)
5	 **1e**	**2a**	**3ea** (= **3aa**) (62 / 96)
6	 **1f**	**2a**	**3fa** (59 / 67)
7	 **1g**	**2a**	**3ga** (32 / 81)
8	 **1h**	**2a**	**3ha** (42 / 84)
9	**1a**	 **2b**	**3ab** (49 / 88)
10	**1b**	**2b**	**3bb** (17 / 46)
11	**1c**	**2b**	**3cb** (16 / 65)
12	 **1i**	**2b**	**3ib** (12 / 50)
13	**1d**	**2b**	**3db** (= **3cb**) (7 / 59)
14	**1h**	**2b**	**3hb** (7 / 98)
15	**1a**	 **2c**	**3ac** (72 / 59)
16	**1b**	**2c**	**3bc** (52 / 51)
17	**1a**	 **2d**	**3ad** (18 / 50)

[a] Reaction scale: **1** (0.5 mmol) and **2** (5 mmol) under inert atmosphere (argon bubbling). [b] Isolated yield. [c] A 5 mmol scale reaction provided **3aa** in 80% yield under condition II.

is facile via the competing rapid hydrogen atom abstraction, which makes the development of intermolecular photocatalytic functionalizations highly challenging.[6a,b,g−i] Herein, we report the development of the phenoxazine **A**-mediated intermolecular C−C and C−B bond formations with aryl halides (Scheme 1b).

We began the investigation for the photosensitizer **A**-mediated C−C bond formation with methyl-4-chlorobenzoate (**1a**) and *N*-methylpyrrole (**2a**) as the model substrates under light irradiation with 18 W white light-emitting diodes (Table 1). The reaction of **1a** and **2a** proceeded in the presence of 5 mol % of **A** in dimethyl sulfoxide (DMSO) and produced the C−C coupled product **3aa** (entry 1) in 27% yield. The use of base significantly improved the reactivity and afforded **3aa** in high yields (entries 2−7). Particularly, the high yield realized with the inorganic base, K_2CO_3, supports the oxidative quenching pathway for the formation of the aryl radical by the reduction of the aryl chloride **1a** through direct electron transfer from the highly reducing photoexcited **A*** (entries 2 and 3). Next, we evaluated the use of tertiary amines, which are known to act as sacrificial electron donors, anticipating a switch in the photoredox cycle to a reductive quenching pathway. Interestingly, the use of triethylamine (TEA), diisopropylethylamine (DIPEA), tetramethylethylenediamine (TMEDA), or 1,8-diazabicycloundec-7-ene (DBU) led to the C−C bond formation in a shorter time (12 h) but accompanied the formation of methyl benzoate by further dechlorination (entries 4−7). Among the tertiary amine bases, TMEDA showed the best reactivity and afforded **3aa** in 88% yield (entry 6). Control experiments revealed that the reaction requires both photosensitizer **A** and visible light irradiation (entries 8 and 9). Next, we evaluated the use of $[Ru(bpy)_3]Cl_2$ ($E^*(Ru(III)/Ru(II)^*) = -0.81$ V vs SCE),[3d] which is the most widely used photosensitizer, and an organic dye, eosin Y ($E^*(EY^{\bullet+}/EY^*) = -1.11$ V vs SCE)[9] instead of **A**. As expected, the reactions did not proceed regardless of the presence of TMEDA, which is attributed to their less negative photoexcited reduction potential

Scheme 2. Proposed Mechanism

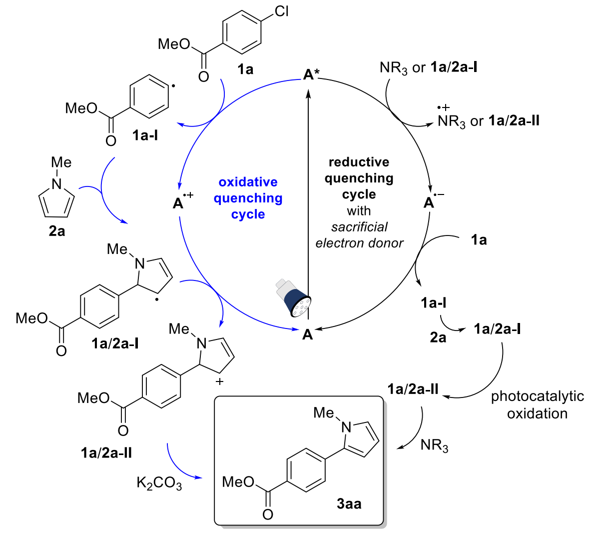
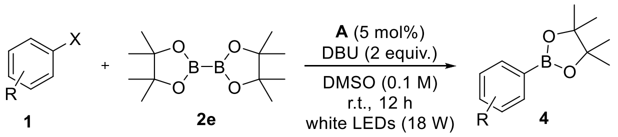
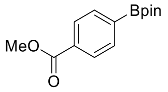
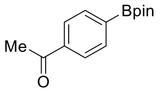
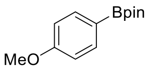
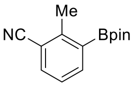
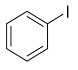
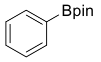
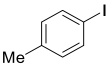
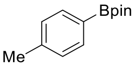
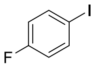
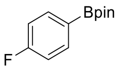
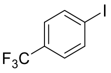
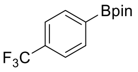


Table 3. Optimization of C−B Bond Formation[a]



entry	1	product 4 (%)[b]	
1[c]	**1a**		**4ae** (83)
2	**1c**		**4ce** (40)
3	**1h**		**4he** (68)
4	**1j**		**4je** (44)
5	 **1k**		**4ke** (71)
6	 **1l**		**4le** (46)
7	 **1m**		**4me** (44)
8	 **1n**		**4ne** (42)

[a]Reaction scale: **1** (0.5 mmol) and **2e** (3 mmol) under inert atmosphere (argon bubbling). [b]Isolated yield. [c]Reaction in the absence of DBU generated 37% of the product **4ae**.

(entries 10 and 11). Next, we screened a variety of common solvents for carrying out the reaction, which revealed the sensitivity of the reaction to the solvent system and the effectiveness of DMSO in comparison to other solvents (entries 12−17). We optimized the conditions further, including the concentration and stoichiometry of reagents, but these alterations in the reaction conditions were not fruitful (see Table S2 in the Supporting Information). Notably, the developed methodology displayed higher efficiency and required only 10 equiv of **2a**, in comparison to the previous reports,[6e,f,k] wherein more than 50 equiv of the coupling partner was required.

With the optimization of the reaction complete, we turned to the investigation of the substrate scope for the C−C bond formation using various aryl halides (**1**) and (hetero)arenes (**2**). We evaluated all reactions under two different conditions, which comprised the use of K$_2$CO$_3$ (condition I) and TMEDA (condition II) (Table 2). As emphasized, the highly negative photoexcited reduction potential of **A*** allowed the use of aryl chlorides as substrates despite limited scope to electron-deficient aryl chlorides (−CO$_2$Me, −CN). Several aryl bromide and iodides were evaluated and proved to be suitable substrates for the transformation. In addition, the pattern of the substitutions did not affect the reactivity, and the *ortho*-, *meta*-, and *para*-substituted aryl halides were all suitable. As coupling partners, unactivated *N*-heteroarenes and electron-rich arenes were successfully employed without any prefunctionalizations, which is a significant advantage of the radical transformation. The mild reaction conditions of the transformation tolerated the presence of various functional groups, such as the aldehyde, ketone, ester, and nitrile groups. Importantly, reactions of dihalogenated substrates containing bromide and iodide functionalities displayed excellent chemoselectivity in the C−C bond formation via reaction at the iodide moiety alone (**1f** and **1g**). The reaction conditions were amenable to a large-scale reaction: **3aa** could be prepared on a 5 mmol scale in a yield similar to that of a 0.5 mmol scale reaction.

A proposed mechanism for the C−C bond formation with **1a** and **2a** is shown in Scheme 2. The photoexcitation of **A** with visible light produces **A***, which reacts via two possible pathways. In the absence of sacrificial electron donors, **A*** is oxidatively quenched by single-electron transfer (SET) to **1a**, producing **A**$^{•+}$ and the key aryl radical intermediate **1a-I**. The C−C bond formation by the addition of **1a-I** to **2a** generates the radical species **1a/2a-I**. Then, SET from **1a/2a-I** to **A**$^{•+}$ regenerates the organophotosensitizer **A** and produces the aryl cation intermediate **1a/2a-II**. Finally, deprotonation of **1a/2a-II** by K$_2$CO$_3$ yields the coupled aryl heteroarene **3aa**. On the other hand, in the presence of an amine which acts as sacrificial electron donor, the photoexcited species **A*** participates in a reductive quenching process, wherein **A*** is reduced by SET from the amine and forms the radical anion **A**$^{•-}$, which in turn delivers its extra electron to **1a** to form **1a-I**. The subsequent coupling of **1a-I** with **2a** forms C−C coupled intermediate **1a/2a-I** and its photocatalytic oxidation by the SET process generates **1a/2a-II**. Finally, the deprotonation of **1a/2a-II** by the amine generates **3aa**. This is supported by the additional Stern−Volmer analysis using **1a** and TMEDA with **A** (see Figures S4 and S5 in the Supporting Information).

Having successfully used the radical intermediates for coupling with arenes, we turned our attention to investigate their use for C−B bond formation. Arylboronates are versatile synthons for a wide range of transition-metal-catalyzed transformations and are extensively used in synthetic chemistry.[10,11] We envisioned that the aryl radical generated by organocatalytic photocatalysis with **A** would react with diboronate through the oxidative quenching pathway in the absence of other additives.

Indeed, the reaction of **1a** with bis(pinacolato)diboron, B$_2$pin$_2$ (**2e**) proceeded in the presence of 5 mol % of **A** in DMSO (0.1 M), albeit, in a slow 37% conversion to the boronated product **4ae** in 12 h, with a significant level of **1a** remaining unreacted. Interestingly, the use of sacrificial electron donors significantly shortened the reaction time. Among the tertiary amines evaluated, DBU showed the best reactivity to give **4ae** in 92% yield (0.1 mmol scale; see Table S3 in the Supporting Information for the optimization process). Under the optimized conditions, we investigated the substrate scope of the transformation for the preparation of arylboronates by using various aryl halides (**1**) and B$_2$pin$_2$ (**2e**) (Table 3). Similar to the C−C bond formations, the C−B bond formation also proceeded well with various aryl halides (−Cl, −Br, −I) containing both electron-withdrawing and electron-donating substituents.

In conclusion, we developed a methodology for the organophotocatalytic C−C and C−B bond formation with aryl halides. The photoexcited 3,7-di([1,1′-biphenyl]-4-yl)-10-(4-(trifluoromethyl)phenyl)-10*H*-phenoxazine (**A**) has highly negative reduction potential and is capable of reducing aryl halides, including aryl chlorides, and generates the corresponding aryl radical intermediates. The developed transformations encompass a broad substrate scope, are mild and chemoselective, and deliver a wide range of functionalized arenes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03877.

Experimental details, additional experimental results, analytical data of the synthesized compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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