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Metal-Free, Visible-Light-Mediated Direct C−H Arylation of Heteroarenes with Aryl Diazonium Salts

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Supporting Information

ABSTRACT: Visible light along with 1 mol % eosin Y catalyzes the direct C−H bond arylation of heteroarenes with aryl diazonium salts by a photoredox process. We have investigated the scope of the reaction for several aryl diazonium salts and heteroarenes. The general and easy procedure provides a transition-metal-free alternative for the formation of aryl−heteroaryl bonds.

Arylated heteroarenes are widely used in materials science because of their interesting optical and electronic properties,[1] but they also find biomedical applications as peptide mimetics[2] or drugs.[3] The most efficient synthesis of aryl−heteroaryl bonds is the direct arylation of heteroarenes by C−H bond activation. In contrast to the well-known cross-coupling reactions, such C−H activation methods do not require preactivation of the heteroarene, and a variety of transition-metal-catalyzed processes using aryl halides, arylboronic acids, aryltin reagents, and diazonium salts as coupling partners (Figure 1) have been developed.[4] However, photocatalysis may provide a valuable alternative that avoids the use of transition metals, ligands, bases, or elevated temperatures. Recent reports have demonstrated the formation of C−C,[5] C−P,[5m,6] and C−N[7] bonds using visible light and ruthenium or iridium complexes or organic dyes as photoredox catalysts.

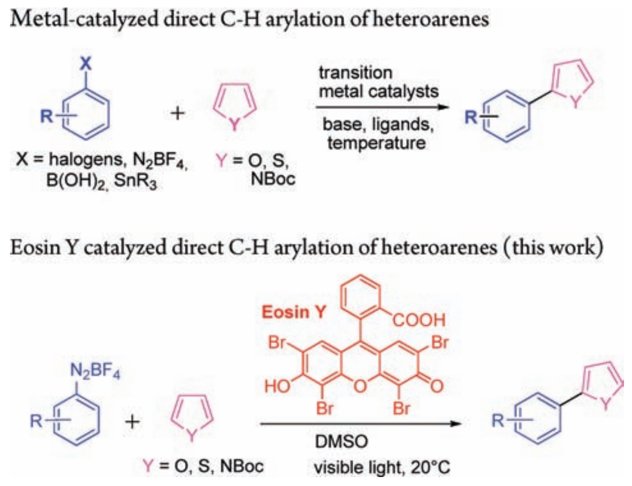

Figure 1. Metal-catalyzed and photocatalytic approaches for direct C−H arylation of heteroarenes.

Aryl diazonium salts are an excellent source of aryl radicals because of their relatively high reduction potentials.[8] The long-known Meerwein arylation uses this in a copper-mediated redox process for the coupling of aryl diazonium salts to alkenes or heteroarenes. However, the reaction suffers from low yields (typically in the 20−40% range), high catalyst loadings, and restriction to aqueous reaction media. The Meerwein arylation has therefore not widely been used in synthesis.[9] Heinrich and co-workers[10] reported the direct arylation of phenols, anilines, and furans with aryl diazonium salts using $TiCl_3$ catalysis; the reaction possibly proceeds through a radical mechanism. Recently, Sanford and co-workers[11] merged palladium catalysis with photocatalysis for C−H arylation. Aryl diazonium salts are well-known oxidative quenchers in photoredox chemistry,[5k,12] which was first applied by Cano-Yelo and Deronzier[13] in the visible-light-mediated Pschorr cyclization to convert stilbene diazonium salts into the corresponding phenanthrene derivatives using $Ru(bpy)_3^{2+}$ as a photoredox catalyst. The same authors also used a ruthenium complex in an oxidative quenching cycle for the transformation of benzyl alcohol to aldehyde with aryl diazonium salts as oxidative quenchers.[14] We report now a photocatalyzed single-electron transfer (SET)-mediated direct C−H bond arylation of heteroarenes with aryl diazonium salts that requires only green light and the organic dye eosin Y as a catalyst.

First, the reaction conditions were optimized for the direct arylation of furan (**2a**) with diazonium salt **1a**, 530 nm light-emitting diode (LED) irradiation, and 1 mol % eosin Y as a photoredox catalyst. Various solvents, additives, and amounts of **2a** were examined at room temperature, and the desired product was obtained in all cases. Dimethyl sulfoxide (DMSO) was found to be a good solvent for the photoreaction. The arylated product was obtained in good yield using an excess of 10 equiv of **2a** (Table 1, entry 2). Excess base decreased the product yield (Table 1, entries 10−12), which was attributed to direct reaction of the base with **1a**. Control reactions confirmed that both light and eosin Y are required for significant conversion to the product (Table 1, entries 13 and 14).

Having optimized the reaction conditions, we examined the scope of the reaction of **2a** with different aryl diazonium salts **1**. Among the aryl diazonium salts used for direct arylation of furan, electron-acceptor- (Table 2, entries 2−6) and neutral-substituted (Table 2, entries 1 and 7) diazonium salts were

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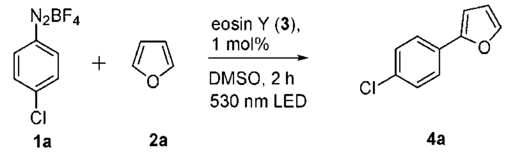
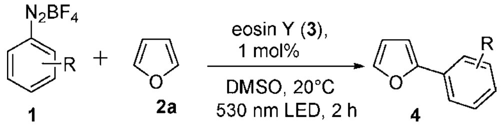
Table 1. Optimization of the Reaction Conditions

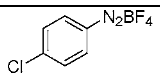
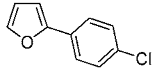
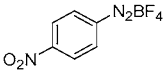
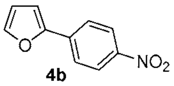
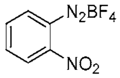
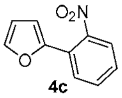
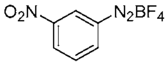
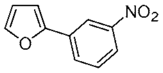
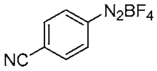
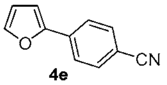
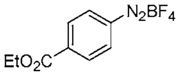
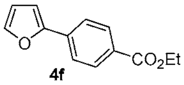
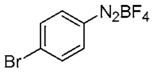
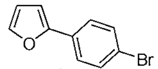
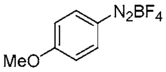
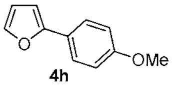
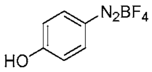
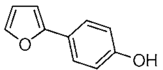
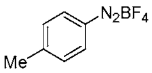
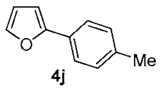
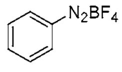
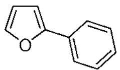


entry	conditions	yield [%][a]
1	**2a** (5 equiv), DMSO	73
2	**2a** (10 equiv), DMSO	80
3	**2a** (15 equiv), DMSO	80
4	**2a** (10 equiv), DMF	48
5	**2a** (10 equiv), MeOH	55
6	**2a** (10 equiv), CH_3CN	12
7	**2a** (10 equiv), EtOAc	17
8	**2a** (10 equiv), THF	10
9	**2a** (10 equiv), DMSO/H_2O (3:1)	73
10	**2a** (10 equiv), DMSO, pyridine (2 equiv)	66
11	**2a** (10 equiv), DMSO, NaOAc (2 equiv)	54
12	**2a** (10 equiv), DMSO, ^{t}BuOK (2 equiv)	45
13	**2a** (10 equiv), DMSO, no light, 72 h	14
14	**2a** (10 equiv), DMSO, no catalyst, 72 h	19

[a] Yieds were determined by ^{1}H NMR analysis.

Table 2. Scope of Aryl Diazonium Salts[a]



entry	substrate	product	yield [%][b]
1	 **1a**	 **4a**	74
2	 **1b**	 **4b**	85
3	 **1c**	 **4c**	86
4	 **1d**	 **4d**	65
5	 **1e**	 **4e**	72
6	 **1f**	 **4f**	78
7	 **1g**	 **4g**	84
8	 **1h**	 **4h**	54
9	 **1i**	 **4i**	40
10	 **1j**	 **4j**	58
11	 **1k**	 **4k**	60

[a] The reaction was performed with **1** (0.23 mmol), **2a** (10 equiv), and eosin Y (0.01 equiv) in 1.0 mL of DMSO. [b] Isolated yields after purification on SiO_2.

found to be more efficient for product formation than electron-donor-substituted ones (Table 2, entries 8–10). Moreover, a range of functional groups, such as nitro, ester, cyano, and hydroxyl groups were tolerated in this photoreaction. Notably, halogen-substituted aryl diazonium salts successfully underwent C–H bond arylation leaving the C–halogen bond intact, which is useful for further synthetic elaboration.

The metal-free, photocatalyzed C–H arylation was also effective for other heteroarenes, such as thiophene and pyrrole, and the corresponding products were obtained in moderate to good yields (Table 3).

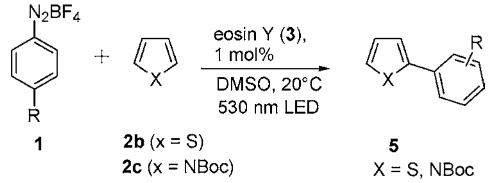
Thienyl diazonium salt **6** led to heterobiaryls **7** and **8**, which are typical structural motifs of organic semiconductors (Scheme 1a). In addition to heteroarenes, nitrobenzene was converted in 50% yield into compound **10** and other regioisomers (10%) after 20 h of irradiation with green light (Scheme 1b).

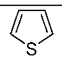
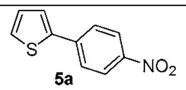
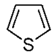
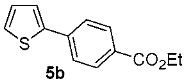
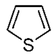
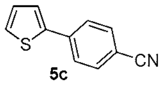
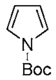
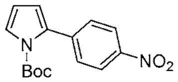
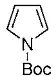
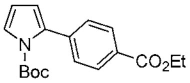
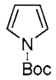
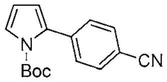
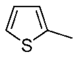
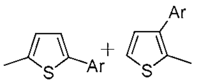
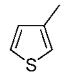
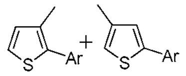
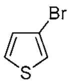
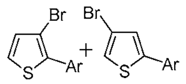
The C–H arylation of heteroarenes with aryl diazonium salts using eosin Y was expected to proceed through a radical mechanism, and preliminary mechanistic investigations supported this assumption. When the reaction of aryl diazonium salts was conducted in the absence of furan but with added 2,2,6,6-tetramethylpiperidinoxyl (TEMPO), compound **11** (Figure 2) was obtained. Furthermore, addition of TEMPO to the reaction mixture of aryl diazonium salts, furan, and eosin Y stopped the arylation process, and the TEMPO-trapped intermediate **12** (Figure 2) was detected. The identified compounds suggest that the photoreaction proceeds via a radical pathway (see the Supporting Information for more details).

On the basis of the above observations and literature reports,[10,11,13,15] a plausible mechanism for this photoreaction is proposed (Scheme 2). Initially, aryl radical **13** is formed by SET from the excited state of eosin Y to aryl diazonium salt **1**. Addition of aryl radical **13** to heteroarene **2** gives radical intermediate **14**, which is further transformed to carbocation intermediate **15** by two possible pathways: (a) oxidation of the radical intermediate **14** by the eosin Y radical cation to give **15** and (b) the oxidation of **14** by aryl diazonium salt **1** in a radical chain transfer mechanism. Finally, intermediate **15** is deprotonated, regenerating the aromatic system and leading to the desired coupling product **16**.

In summary, we have reported a metal-free, direct intermolecular C–H arylation of heteroarenes by photoredox catalysis with green light. The reaction proceeds smoothly at room temperature, does not require transition-metal catalysts or bases, and displays a broad scope toward diazonium salts and heterocycles with a wide range of functional group tolerance. This SET cross-coupling represents an efficient alternative to the known transition-metal-catalyzed (Pd, Ru, Ir, Rh, and Ti) and ^{t}BuOK-promoted strategies for C–H

Table 3. Scope of Heteroarenes[a]

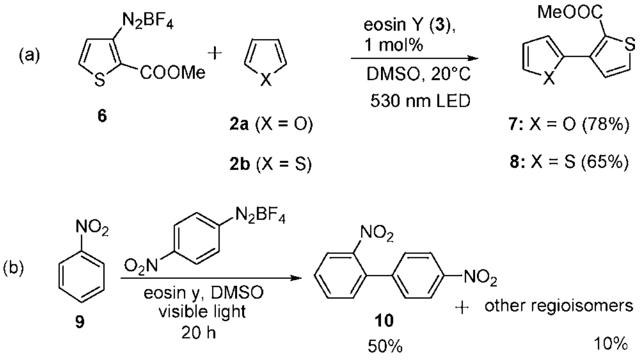


entry	R		t [h]	product	yield [%][b]
1	NO$_2$	 2b	4	 5a	70
2	CO$_2$Et	 2b	14	 5b	60
3	CN	 2b	16	 5c	52
4	NO$_2$	 2c	14	 5d	61
5	CO$_2$Et	 2c	18	 5e	51
6	CN	 2c	16	 5f	55
7	NO$_2$	 2d	16	 5g 5g^1 (5:1) Ar = 4-NO$_2$-C$_6$H$_4$	53
8	NO$_2$	 2e	24	 5h 5h^1 (5:1) Ar = 4-NO$_2$-C$_6$H$_4$	67
9	NO$_2$	 2f	24	 5i 5i^1 (5:1) Ar = 4-NO$_2$-C$_6$H$_4$	60

[a] Reactions were carried out using **1** (0.23 mmol), heteroarene (5 equiv in the case of thiophene derivatives, 2 equiv in the case of pyrrole derivatives), and eosin Y (0.01 equiv) in 1.0 mL of DMSO. [b] Isolated yields after purification on SiO$_2$.

arylation, and it overcomes the significant drawbacks of the Meerwein arylation that have prevented its broader application in organic synthesis. The induction of the reaction by visible light may find applications beyond synthesis, such as in the chemical patterning of surfaces. Further investigations of the mechanism of the reaction and its application are ongoing in our laboratory.

Scheme 1. C−H Photoarylation of (a) Heteroarenes with a Thienyl Diazonium Salt and (b) Nitrobenzene with an Aryl Diazonium Salt



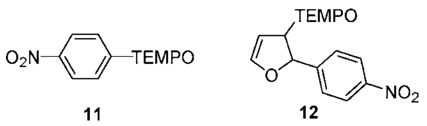
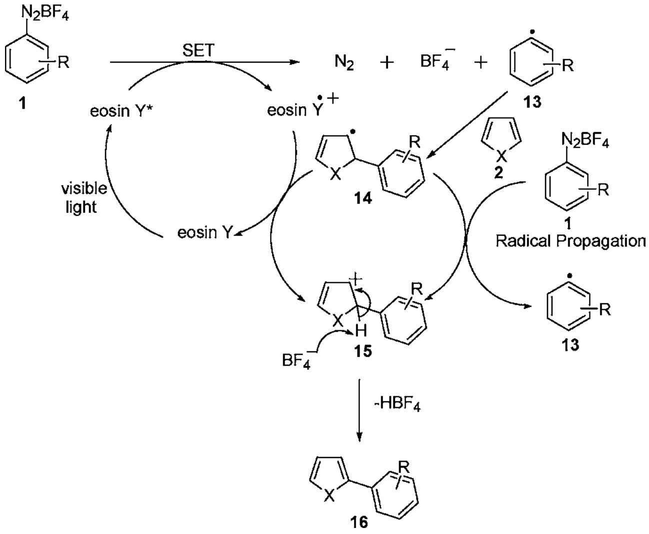


Figure 2. TEMPO-trapped reaction intermediates.

Scheme 2. Suggested Mechanism for Photocatalytic Direct C−H Arylation of Heteroarenes



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all compounds. 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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