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Letter

Photochemical (Hetero-)Arylation of Aryl Sulfonium Salts

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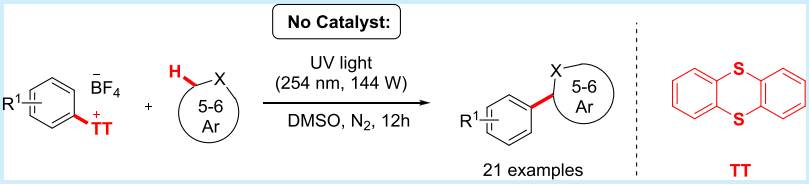
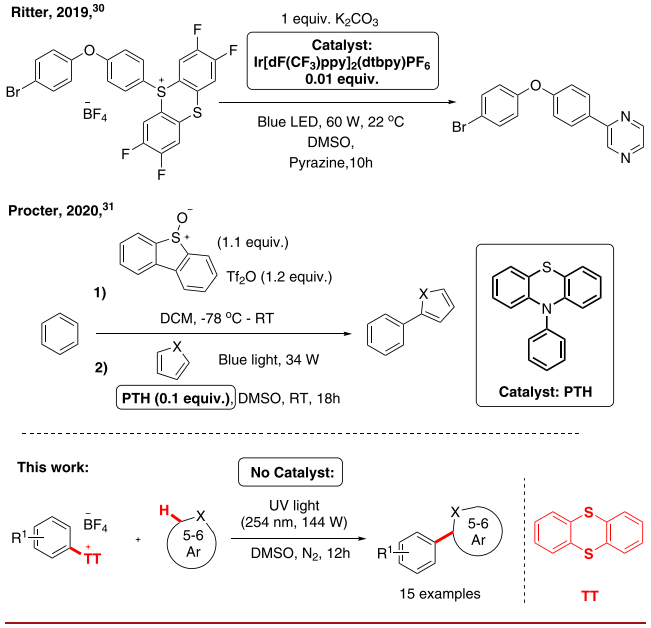


ABSTRACT: The construction of (hetero)biaryls, which are ubiquitous scaffolds among medical substances, functional materials, and agrochemicals, constitutes a key application of cross-coupling methods. However, these usually require multiple synthetic steps. Herein, we report a simple photoinduced and catalyst-free C−H/C−H (hetero)arylation cross-coupling through aryl thianthrenium salts, which are formed site-selectively by direct C−H functionalization. The key to this approach is the UV-light, which can disrupt the C−S bond to form thianthrene radical cations and aryl radicals.

Aryl−aryl cross-coupling methods, which allow access to (hetero)biaryls,[1−6] constitute one of the most widely utilized synthetic strategies for accessing materials, pharmaceuticals, organic electronics, and conducting polymers.[7−10] However, traditional cross-coupling reactions typically require tedious synthetic steps as well as often onerous catalysts or catalyst precursors. Moreover, these do not always provide the desired regioselectivity because of the electronic and steric similarity of the many C−H bonds usually contained in the building blocks.[11] In recent years, some inspiring selective C−H/C−H cross-coupling protocols have appeared, which can be utilized to construct (hetero)biaryls.[11−14] However, these usually still require onerous metal salts and/or complex ligand structures. In addition, arylations are often associated with high reactions temperatures, limited substrate scopes, and non-optimal functional group tolerance.[15−18] In this context, photochemistry, one of the cleanest and greenest activation methods because it is noninvasive and does not contaminate the system, has emerged. These often still require halides, pseudohalides, or alternatively diazonium salts, which are labile or difficult to synthesize.[19−28] In contrast, the recent and inspiring development of aryl sulfonium salts as arylation building blocks, which are themselves obtained directly from aromatic C−H bonds, has enabled considerably more efficient and more site selective biaryl synthesis.[29] For instance, Ritter recently developed an iridium catalyzed photochemical arylation method of aryl sulfonium salts (2019, Scheme 1),[30] while Procter utilized a phenothiazine derivative as a metal-free photocatalyst (2020, Scheme 1).[31] Nevertheless, these and related recent methods often still suffer from the use of onerous and/or transition metal-based photocatalysts, which not only increase the manufacturing costs but also limit their practical applications.[32,33]

Scheme 1. C−H/C−H Cross-Coupling, Selected Works



Thus, we propose here a simple, catalyst-free direct usage of UV-light (254 nm) to induce a site-selective C−H/C−H cross-coupling of simple arenes with DMSO as a solvent.[34,35]

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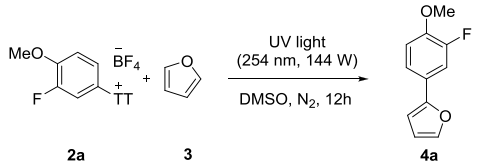
The key to this approach is the high-energy UV-light, which can directly cleave the C−S bond to form thianthrene radical cations and aryl radicals.

At the initial stage of the investigation, 2-fluoroanisole was chosen as a substrate to form aryl thianthrenium salt **2a**, which was utilized to explore the optimal conditions of a site-selective C−H/C−H cross-coupling of simple arenes (Table 1). The

Table 1. Screening of Reaction Conditions[a]



2a **3** **4a**

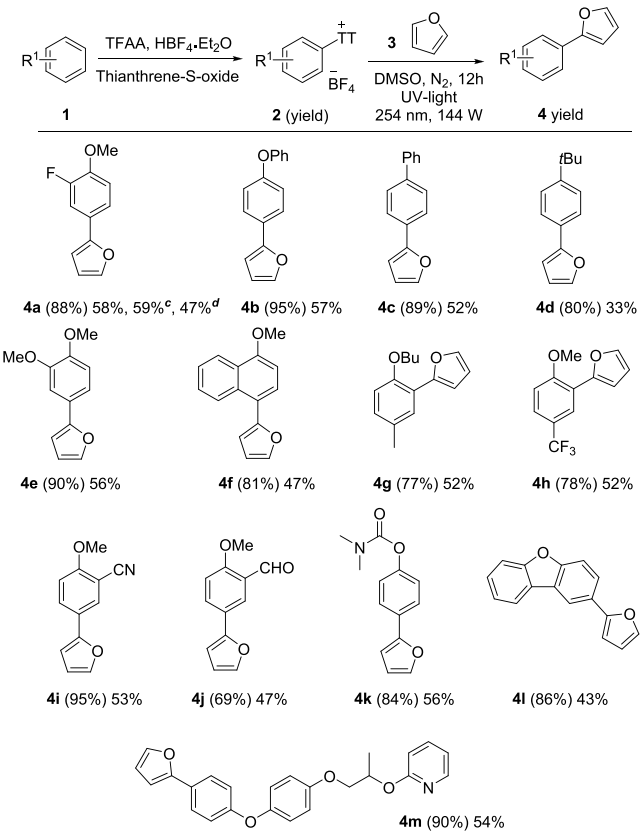
entry	variations from the optimal conditions[a]	yield (%)[b] of **4a**
1	none	62 (58)[c]
2[d]	no light	0
3[d]	390 nm instead of 254 nm	0
4[d]	72 W instead of 144 W	55
5[d]	K_2CO_3 as additive (72 W)	34
6[d]	Al_2O_3 as additive (72 W)	53
7[d]	SiO_2 as additive (72 W)	47
8[d]	phenothiazine as additive (72 W)	32
9[d]	air instead of N_2	35
10[d,e]	other solvent instead of DMSO	<30

[a]Reaction conditions: **2a** (0.2 mmol), **3** (2 mL), DMSO (3 mL), UV-light (254 nm, 144 W), quartz vial, rt, N_2, 12 h. [b]The yields were determined by ^{19}F NMR spectroscopy, with 4-fluorotoluene as an internal standard. [c]Yield of isolated product. [d]The reaction time is 48 h. [e]Other solvents: CH_3COOH, acetone, DMF, CH_3NO_2, CH_3CN, CCl_4, DCE, THF.

type of light, power, additive, reaction time, and solvent were notably evaluated. Typically, a 50 mL flat-bottom cylindrical quartz vial equipped with a magnetic stir bar is charged with aryl thianthrenium salts **2a** (0.2 mmol, 1.0 equiv), furan (2 mL), and DMSO (3 mL). The tube is sealed, and the mixture is then stirred at room temperature under UV-light (254 nm, 144 W) for 12 h. **4a** was obtained in 62% yield, as determined by ^{19}F NMR spectroscopy (Table 1, entry 1). In the absence of light or when we used 390 nm UV-light instead of 254 nm UV-light, **4a** was not detected (Table 1, entries 2 and 3). When the power of the light was reduced by half (72 W), the yield of **4a** dropped to 55%; moreover, it was associated with a longer reaction time of 48 h (Table 1, entry 4). None of the additives tested improved the yield (Table 1, entries 5−7). Interestingly, when the reaction was carried out under air, the yield dropped to 35%. Finally, among all other tested solvents, none afforded more than 30% of the desired product (Table 1, entry 10).

With the optimized reaction conditions in hand, we first set out to explore the scope of arenes **1**. Initially, a range of anisole derivatives was studied, affording promising yields. Various functional groups were well tolerated under standard conditions (**4a**−**4m**, Scheme 2), with the notable exception of halides, such as Br-substituents, presumably because of their incompatibility with the strong UV light. The high chemoselectivity observed in the first step is particularly noteworthy. Furthermore, performing the reaction on a 2 mmol scale afforded the target effectively (product **4a**, 47% isolated yield, Scheme 2). Subsequently, the substrate scope of intercepting (hetero)arenes was studied under the standard reaction

Scheme 2. Substrate Scope for Arenes 1[a,b]



[a]Reaction conditions for the first step (see SI); Reaction conditions for the second step: **2** (0.2 mmol), **3** (2 mL), DMSO (3 mL), UV-light (254 nm, 144 W), quartz vial, rt, N_2, 12 h. [b]Yield of isolated product; yield in parentheses for the first step. [c]59% ^{19}F NMR yield was obtained by increasing the reaction scale to 2 mmol, reaction time is 24h, DMSO (5 mL), furan (3 mL). [d]47% Yield of isolated product for 2 mmol scale.

conditions (Scheme 3). Various substituted nitrogen-containing heterocycles (**5a**, **6a**), furans (**7a**, **8a**), thiophene (**9a**, **10a**), and benzenes (**11a**, **12a**) can successfully provide the corresponding coupling products with encouraging yields. Moreover, high chemoselectivity (**5a**, **7a**, **8a**, **9a**, **10a**) and complete regiocontrol were observed.

In order to gain some insight into the reaction mechanism, a range of control experiments were then carried out. The reaction gave the desired product in low yields in the presence of a radical scavenger, such as TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) or 1,4-dinitrobenzene, suggesting that a radical pathway is likely involved (Scheme 4, eq 1). This is consistent with the aerobic condition experiment (Table 1, entry 9, **4a** in 35% yield). Next, the radical trapped adducts were identified and characterized (Scheme 4, eq 2). We could not extract the TEMPO trapped adduct **13a**. However, its reduction product **13b** was obtained in 44% isolated yield. Thus, **13a** might not survive the strong UV-light conditions of the reaction. Thereafter, several hydrogenation experiments were attempted (Scheme 5). In the presence of cyclohexa-1,4-diene, both **4a** and **1a** were obtained in 26% and 27% yield, respectively (Scheme 5, eq 3). In the absence of furan, **1a** was obtained in 69% yield (Scheme 5, eq 4). When **2c** was utilized in the otherwise same hydrogenation experiment, hydrogenation product **1c** was obtained in 58% isolated yield. Next, a UV

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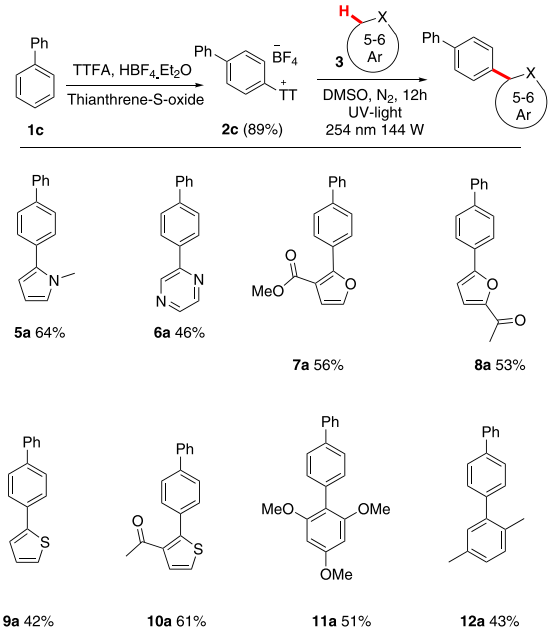
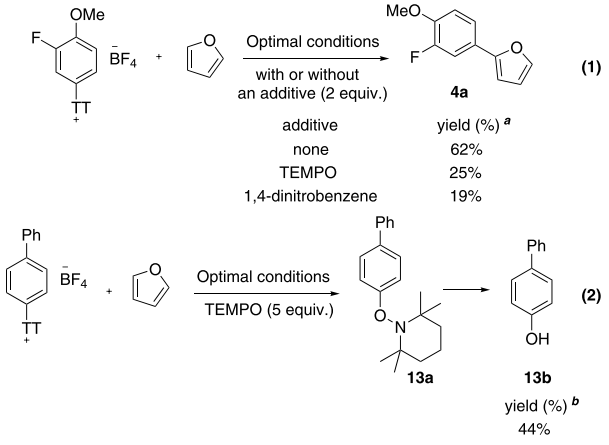
Scheme 3. Substrate Scope of (Hetero)Arenes 3[a,b]



[a]Reaction conditions for first step, see the Supporting Information; reaction conditions for second step: **2c** (0.2 mmol), **3** (20 equiv), DMSO (3 mL), UV-light (254 nm, 144 W), quartz vial, rt, N_2, 12 h. [b]Yield of isolated product.

Scheme 4. Mechanistic Experiments with TEMPO



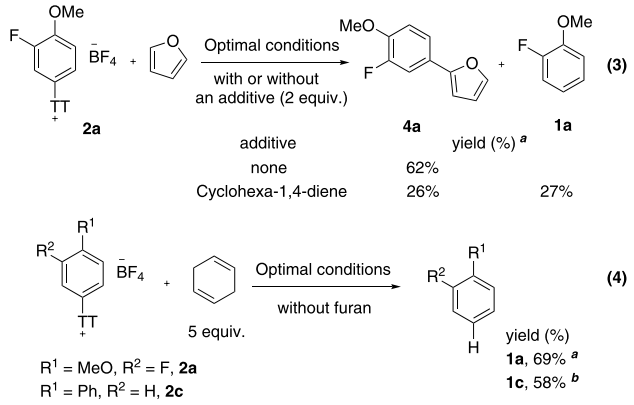
[a]The yield was determined by ^{19}F NMR spectroscopy. [b]Isolated yield.

absorption experiment was performed (Figure 1). As shown in Figure 1, compound **2a** has almost no absorption under a 254 nm wavelength. Thus, autocatalysis can be reasonably ruled out.

Combining our mechanistic experiments and previous reports,[30−32,36] we propose a possible mechanism in Scheme 6. Under UV-light, the C−S bond of the aryl thianthrenium salts (**A**) can be directly cleaved to form thianthrene radical cations (**B**) and aryl radical (**C**). In the presence of furan, adduct (**D**) is formed from aryl radical (**C**). Then **D** is oxidized by **B** to generate **F** and **E**. Elimination of HBF_4 generates thereafter **G** (coupling product).

In conclusion, we have reported here a photoinduced C−H/C−H cross-coupling (hetero)arylation reaction through aryl thianthrenium salts, which are formed site-selectively by direct C−H functionalization. The key to the approach is the UV-light, which can directly disrupt the C−S bond to form thianthrene radical cations and aryl radicals, in catalyst-free conditions. The method should be applicable to the late-stage functionalization of medicines, functional materials, and agrochemicals.

Scheme 5. Mechanistic Hydrogenation Experiments



[a]The yield was determined by ^{19}F NMR spectroscopy. [b]Isolated yield.

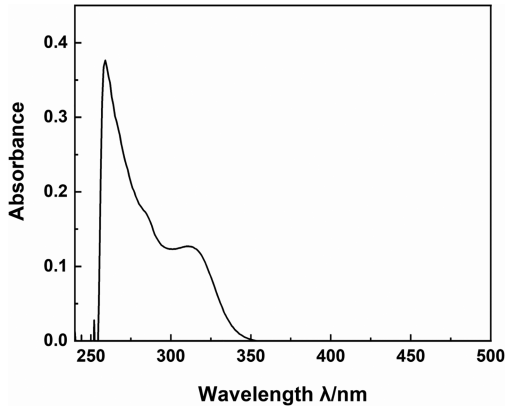
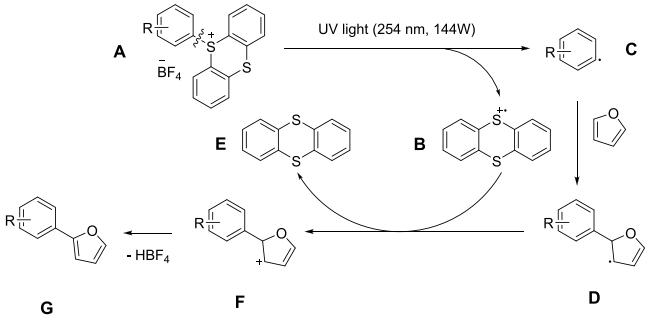


Figure 1. UV absorption experiment with **2a**.

Scheme 6. Possible Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01904.

Experimental procedures, characterization, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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