Communication

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Visible Light-Promoted C-S Cross-Coupling via Intermolecular Charge-Transfer

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Supporting Information Placeholder

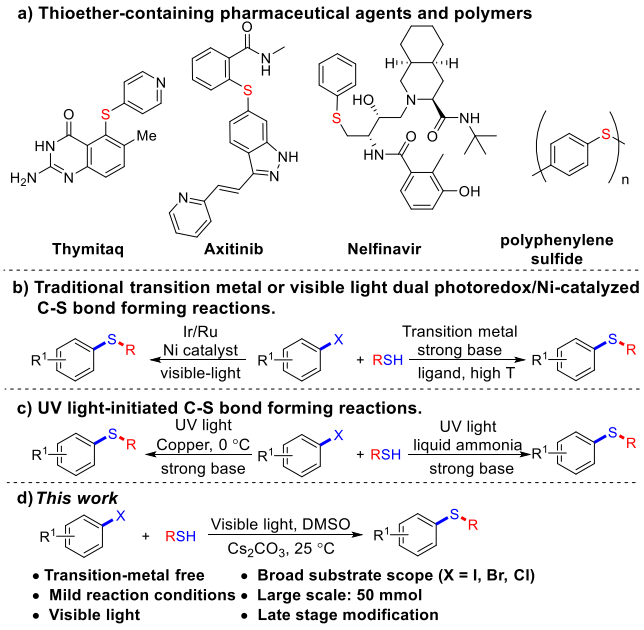
ABSTRACT: Disclosed is a mild, scalable, and visible light-promoted cross-coupling reaction between thiols and aryl halides for the construction of C–S bonds in the absence of both transition metal and photoredox catalysts. The scope of the aryl halides and thiol partners includes over 60 examples and therefore provides an entry point into various aryl thioether building blocks of pharmaceutical interest. Furthermore, to demonstrate utility, this C-S coupling protocol was applied in drug synthesis and in late stage modifications of active pharmaceutical ingredients. Combined UV-Vis spectroscopy and time-dependent density functional theory calculations suggest that visible light-promoted intermolecular charge transfer between the thiolate-aryl halide electron donor-acceptor complex permits the reactivity in the absence of catalyst.

Aromatic thioethers are prevalent in a wide range of bioactive natural products and pharmaceuticals, including thymitaq, axitinib and nelfinavir (**Scheme 1a**).[1a] Furthermore, aromatic thioethers are also valuable architectures in drug development,[1b-c] organic materials,[1d] and polymers.[1e] Therefore, the development of environmentally friendly and atom economical methods for constructing C-S bonds is of significant importance with broad impact across the areas of small molecule synthesis and materials.[2]

Traditionally, transition-metal catalysts are employed to catalyze cross-coupling reactions of thiols with aryl halides, providing a useful approach for C−S bond construction (**Scheme 1b**).[3] However, most of the reported methods require strong bases (e.g. *t*-BuONa), specific or air sensitive ligands, and high temperature. Such concerns motivate efforts to develop alternative approaches for C-S bonds formation.

Recently, photoredox catalysis has become a powerful strategy for the development of a wide range of reactions under mild conditions, including C-S bond formations (**Scheme 1b**).[4] In 2013, Noël and coworkers reported a one-pot Stadler–Ziegler process to form C-S bonds by employing $Ru(bpy)_3Cl_2·6H_2O$ as a photoredox catalyst.[5] Dual photoredox/Ni-catalyzed cross-coupling of thiols with (hetero)aryl halides was then developed in 2016.[6] More recently, [*fac*-Ir(ppy)$_3$] was implemented to catalyze the arylation of thiols with aryl halides without the need of nickel catalyst.[7] Nevertheless, ruthenium and iridium photoredox catalysts may introduce limitations in terms of the scalability and sustainability of these processes. In addition, ultraviolet (UV) photoinduced[8] coupling of thiophenoxide with aryl iodides in liquid ammonia was also reported (**Scheme 1c**).[8a] However, the requirement of high energy UV irradiation can lead side reactions[8a]. These side reactions could potentially be minimized by use of lower energy visible-light, leading to increased functional group tolerance in producing aryl thioethers.

Scheme 1: The Importance of C-S Bonds and Approaches for Their Formation.



Herein we report the visible light-induced C-S cross-coupling reactions between (hetero)aryl halides (ArX, where X = I, Br, or Cl) and (hetero)aryl thiols across a broad substrate scope (>60 examples). Notably, these C-S bond formations were carried out at room temperature and in the absence of both photoredox catalysts and transition metals typically required to effect cross-coupling reactions (**Scheme 1d**).

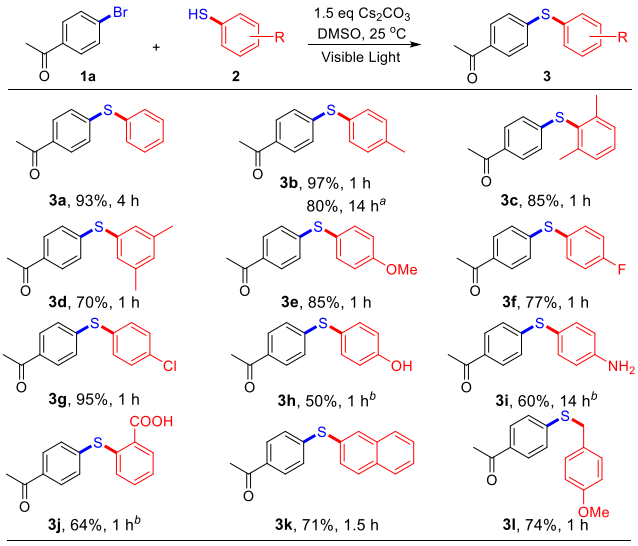
In our early attempts to achieve visible light-promoted and transition metal-free conditions for C-S cross-coupling, we applied strongly reducing *N*,*N*-diaryl dihydrophenazines[9a] or *N*-Aryl phenoxazines[9b] organic photoredox catalysts, which we previously developed for the applications of organocatalyzed atom transfer radical polymerization as well as for that of small molecule transformations.[9c,d] We hypothesized that these organic photoredox catalysts, in the photoexcited state, could directly reduce an aryl halide and generate a radical anion capable of partaking in C-S

bond formation.[10] Encouragingly, we observed the C-S cross-coupled product in high yield with white LED irradiation of a solution containing 4'-bromoacetophenone (**1a**), 4-methylbenzenethiol (**2a**), Cs_2CO_3 and organic photoredox catalyst 5,10-di(1-naphthyl)-5,10-dihydrophenazine in DMSO.

However, control experiments revealed that desired product was also isolated in high yield (97%) in the absence of the organic photoredox catalyst after 1 hour of white LED irradiation at room temperature (**Table S1**, entry 1).[11] Further studies revealed that white LED irradiation, presence of base, and absence of oxygen were each essential for this transformation (entries 2, 5, and 6). These control experiments suggest a radical mechanism involving thiyl and aryl radicals formed as a result of visible light-promoted intermolecular charge transfer[12] which are subsequently quenched to yield the C-S cross-coupled product (*vide infra*).

The effect of varying base, base loading, and solvent was also investigated (**Table S1**). We obtained increasingly higher yield as Cs_2CO_3 loading was increased from 0.0 eq (0%, entry 5) to 1.5 eq (97%, entry 1). It is noteworthy that K_2CO_3, which is much less expensive than Cs_2CO_3, is also an excellent base for this transformation (91%, entry 7) although Na_2CO_3 gave a much lower yield (24%, entry 8). To eliminate the possibility of trace impurities being responsible for this transformation, we employed other sources of base, including Cs_2CO_3 (99.995%) and K_2CO_3 (99.997%) and observed similarly high yield.[11] DMSO was determined to be the best solvent compared to other polar aprotic solvents (entries 1, 9-11).

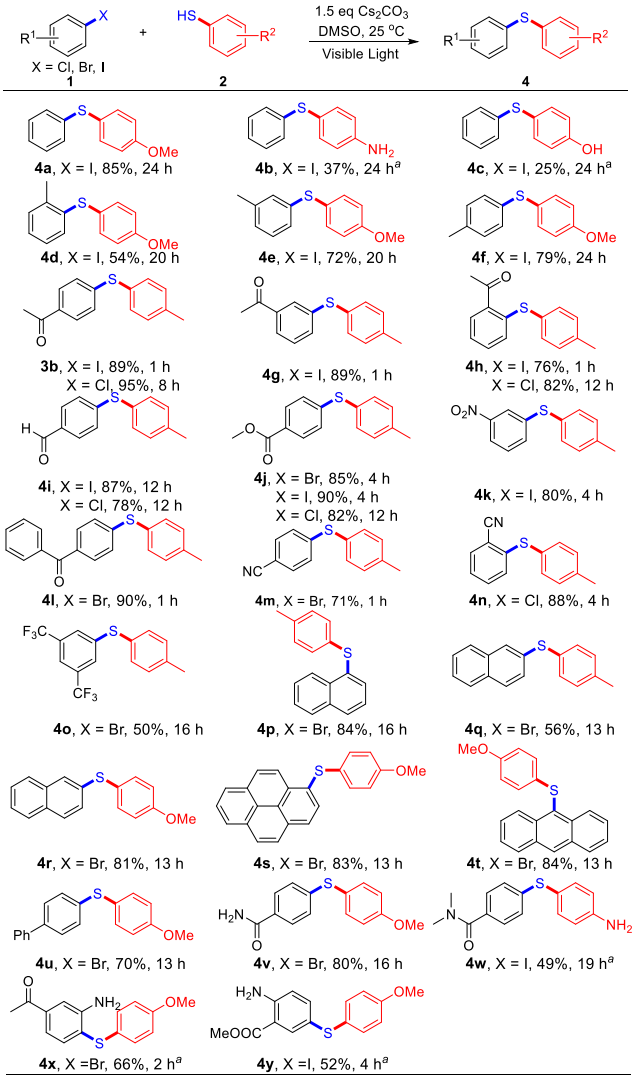
Scheme 2: Scope of Thiols.



General conditions: **1a** (0.2 mmol), **2** (1.5 equiv), Cs_2CO_3 (1.5 equiv), DMSO (1.5 mL), isolated yields provided. [a]50 mmol scale [b]2.0 equiv Cs_2CO_3.

With optimized conditions in hand, the scope of this mild, visible light-promoted, and procedurally simple C−S cross-coupling method was further explored. With respect to aryl thiols, diverse thiophenols (**2**) served as effective cross-coupling partners with **1a** to form C−S bonds (**Scheme 2**). C-S coupled products were obtained in good to excellent yield (50 - 97%) with thiols containing hindered (**3c**), electron-rich (**3c-e**, **h-i**, **l**), and electron-poor (**3f-g**) functional groups. Alkyl thiols were also successfully coupled (**3l**). It is worth highlighting that aryl thiol substrates containing free hydroxyl, amine or carboxyl groups were also tolerated under our C-S coupling conditions (products **3h-j**), eliminating the need for protecting groups. To illustrate the robustness and preparative scale utility of this C−S cross-coupling method, we scaled up the production of **3b** to 50 mmol while only suffering a small loss in yield (9.71g, 80%). In addition, **3b** was produced in high yield (86%) under sunlight irradiation, demonstrating the potential for sustainable preparation of aromatic thiothers using solar energy.[11]

Scheme 3: Scope of Aryl Chlorides/Bromides/Iodides.



General conditions: **1** (0.2 mmol), **2** (1.5 equiv), Cs_2CO_3 (1.5 equiv), DMSO (1.5 mL), isolated yields provided. [a]2.0 equiv Cs_2CO_3.

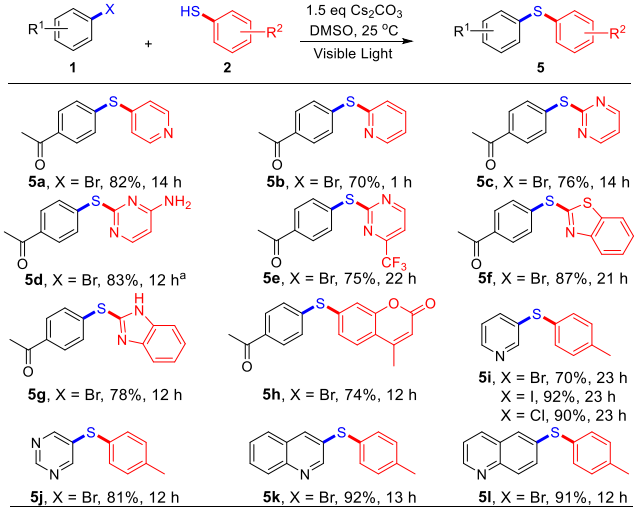
Various aryl iodides, bromides and chlorides were successfully coupled to thiol nucleophiles (**Scheme 3**). The electronic effects of the aryl iodides resulted in significant differences in reactivity. For example, both longer irradiation times (e.g. 20-24 h) and the use of electron-rich thiophenols were required to obtain reasonable yields with electron-neutral or rich aryl iodides (**4a-f**). Conversely, shorter reaction times and higher yields were obtained when electron-poor aryl iodides were employed (**3b**, **4g-o**). Aryl bromides also resulted in good reactivity (**4j, l-m, o-v, x**). Overall, this C-S cross-coupling method is compatible with aryl halides containing a wide range of functional groups, including carbonyl(**3b**, **4g-h**, **4l**), formyl(**4i**), ester (**j**), nitryl (**4k**), cyano (**4m-n**), trifluoromethyl (**4o**), extended aromatic systems (**4p-u**), amide (**4v-w**), or amino groups (**4x-y**).

In comparison to aryl iodides or bromides, aromatic chlorides are more attractive for synthetic applications because they are

inexpensive and available in great structural diversity.[13] However, aromatic chlorides as cross-coupling partners in photoredox-catalyzed thioether formation are less common.[7] Here, we extended the visible light-promoted arylation of thiols to aryl chloride substrates. A number of aryl chlorides containing electron withdrawing groups were successfully coupled to **2a** and the corresponding products (**3b**, **4h-j, 4n, 5i**) were isolated in good to excellent yields.

We next investigated C-S cross-couplings involving various heterocycles, which are ubiquitous among pharmaceutical products (**Scheme 4**). (Hetero)aryl halides (5i-j, 5k-l) and mercaptopyridines (**5a-b**), mercaptopyrimidines (**5c-e**), 2-mercaptobenzimidazole (**5g**), 2-mercaptobenzothiazole (**5f**), 7-mercapto-4-methylcoumarin (**5h**) were all effectively coupled in this protocol (yield = 70-92%).

Scheme 4: Scope of (Hetero)arene Coupling Partners.

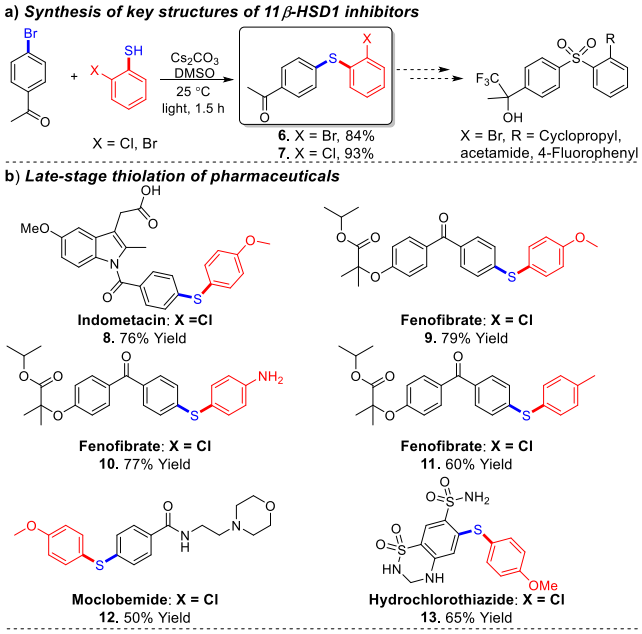


General conditions: **1** (0.2 mmol), **2** (1.5 equiv), Cs_2CO_3 (1.5 equiv), DMSO (1.5 mL), isolated yields provided. [a]2.0 equiv Cs_2CO_3.

To illustrate potential pharmaceutical applications (**Scheme 5**), we first applied our visible light C-S cross-coupling methodology in the synthesis of the key structure of 11β-HSD1 inhibitors (**6**, 80%; **7**, 93%). Compared with reported methods,[14] our transformation involves milder conditions and requires less time. Moreover, we evaluated our method for late-stage functionalization applications. Particularly, we subjected indometacin, fenofibrate, moclobemide and hydrochlorothiazide pharmaceutical ingredients (containing an aryl chloride) to thiophenols in our reaction conditions and obtained the thiolated compounds **8-13** in 50%–79% yield.

To gain insight into the C-S cross-coupling mechanism, we performed UV-Vis spectroscopic measurements on various combinations of **1a**, **2a**, and Cs_2CO_3 in DMSO at 6 x 10^{-4} M concentration for each species (**Figure 1a**). A red-shift in **2a**'s absorption upon Cs_2CO_3 addition was observed. This shift was attributed to the thiolate anion's absorption (deprotonated **2a**) and is supported by the upfield shift of the NMR signal when **2a** and Cs_2CO_3 were mixed.[11] Further, we observed the formation of a new peak (λ_{max} = 306 nm) when **1a**, **2a**, and Cs_2CO_3 were combined; this peak is proposed to result from the absorption of an electron donor–acceptor (EDA) complex[12] resulting from the association of the thiolate anion and the aryl bromide **1a**. At the higher concentration of 0.1 M, a solution containing this EDA complex is visibly yellow and has visible light absorption tailing to the 400-515 nm region (**Figure 1b**).[15]

Scheme 5: Synthetic Applications of the Visible Light-Promoted C-S Bond Formation.



Density functional theory (DFT) calculations support the proposed EDA complex formation. The electron-rich thiolate anion (deprotonated **2a**) and the electron-poor aryl bromide **1a** interact via the π - π interaction with the closest π -stack distance at approximately 3.4 Å (**Figure 1c**). Additionally, time-dependent DFT calculations computed at the CAM-B3LYP/6-31+G(d,p) level of theory assigned the observed λ_{max} = 306 nm to have both local and charge transfer excitation characteristics; this peak was predicted to be $\lambda_{calc,1}$ = 282 nm with an oscillator strength (f value) of 0.137. Specifically, 35% of the 306 nm absorption is contributed by a local excitation involving the thiolate π orbitals (π_{HOMO}-π_{LUMO+4}) while 32% is contributed by a charge transfer excitation from the thiolate to **1a** (π_{HOMO}-π_{LUMO+5}). Moreover, time-dependent DFT calculations also predicted a significantly red-shifted peak at 383nm albeit with weaker absorption (f = 0.036). This peak consists of almost exclusively charge transfer character (98%) involving π orbitals of the thiolate (π_{HOMO}) and **1a** (π_{LUMO}) and is proposed to be responsible for the observed visible light absorption.

Based on these analyses, we propose the following visible light-induced C-S cross-coupling mechanism as shown in **Figure 1d**. A thiolate anion and an aryl halide first associate to form an EDA complex. Due to the charge transfer absorption of this EDA complex, visible light-induced electron transfer from the thiolate anion to the aryl halide generates the intermediary halide anion, thiyl radical, and aryl radical; these radicals subsequently couple to yield the desired C-S cross-coupled product.

In sum, we have developed a mild, efficient, and visible light-promoted protocol for the C-S cross-coupling of thiols and aryl halides. A wide range of C-S bonds were constructed (> 60 examples) under visible light irradiation without the use of either transition-metal or photoredox catalysts. UV-Vis spectroscopy and time-dependent DFT calculations suggest the formation of an EDA complex between the electron-rich thiolate anion and the electron-poor aryl halide. The EDA complex absorbs visible light to effect intermolecular charge transfer; the subsequently formed thiyl and aryl radicals then couple to form the desired C-S cross-coupled product. Further, the potential utility of this transfor-

mation has been demonstrated by late-stage functionalization of active pharmaceutical reagents and by synthesis of key structures of 11β-HSD1 inhibitors. The extension of this work to polymer synthesis is currently in progress.

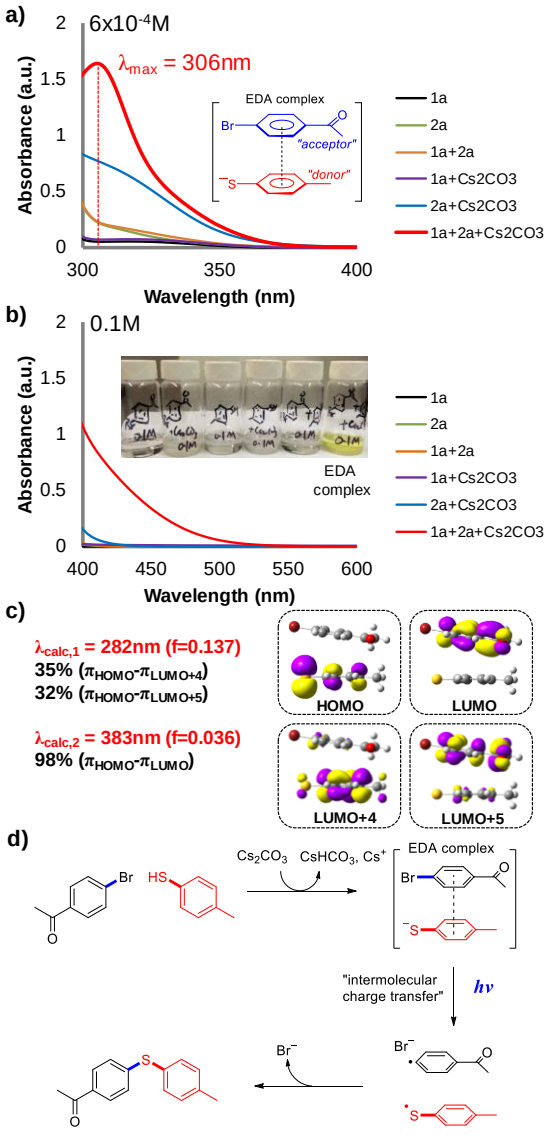


Figure 1: UV-Vis absorption spectra of mixtures of **1a**, **2a** and Cs_2CO_3 in DMSO (path length = 1cm) at concentrations of (a) $6x10^{-4}$ M and (b) 0.1 M for each species; (inset) a photograph showing the formation of a yellow compound (proposed EDA complex) when **1a**, **2a**, and Cs_2CO_3 were mixed together. (c) Time-dependent DFT calculations to predict UV-Vis absorptions of the EDA complex. (d) Proposed mechanism for visible-light induced C-S cross-coupling.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, mechanistic experiments, and spectral data. 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 interests.

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