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

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Abstract

Disclosed is a mild, scalable, 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 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 its utility, this C–S coupling protocol was applied in drug synthesis and late-stage modifications of active pharmaceutical ingredients. UV–vis spectroscopy and time-dependent density functional theory calculations suggest that visible-light-promoted intermolecular charge transfer within 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 a strong base (e.g., *t*-BuONa), specific

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Supporting Information

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Notes

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or air-sensitive ligands, and high temperature. Such concerns motivate efforts to develop alternative approaches for C–S bond 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 formation (Scheme 1b).[4] In 2013, Noël and co-workers reported a one-pot Stadler–Ziegler process to form C–S bonds by employing $Ru(bpy)_3Cl_2 \cdot 6H_2O$ 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 for a nickel catalyst.[7] Nevertheless, ruthenium and iridium photoredox catalysts may introduce limitations in terms of the scalability and sustainability of these processes. In addition, UV-photoinduced[8] coupling of thiophenoxide with aryl iodides in liquid ammonia was also reported (Scheme 1c).[8a] However, the required high-energy UV irradiation can lead to side reactions.[8a] These side reactions could potentially be minimized by the use of lower-energy visible light, leading to increased functional group tolerance in producing aryl thioethers.

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 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*-diaryldihydrophenazines[9a] or *N*-arylphenoxazines[9b] as organic photoredox catalysts, which we previously developed for use in organocatalyzed atom transfer radical polymerization as well as in 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 light-emitting diode (LED) irradiation of a solution containing 4′-bromoacetophe-none (**1a**), 4-methylbenzenethiol (**2a**), Cs_2CO_3, and the organic photoredox catalyst 5,10-di-1-naphthyl-5,10-dihydrophenazine in dimethyl sulfoxide (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 h of white LED irradiation at room temperature (Table S1, entry 1).[11] Further studies revealed that white LED irradiation, the presence of base, and the 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] that are subsequently quenched to yield the C–S cross-coupled product (vide infra).

The effect of varying the base, base loading, and solvent was also investigated (Table S1). We obtained increasingly higher yields as the Cs_2CO_3 loading was increased from 0.0 equiv

(0%; entry 5) to 1.5 equiv (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 yields.[11] DMSO was determined to be the best solvent compared with other polar aprotic solvents (entries 1 and 9–11).

With the 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 yields (50–97%) with thiols containing hindered (**3c**), electron-rich (**3c**–**e**, **3h**, **3i**, **3l**), and electron-poor (**3f**, **3g**) 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 and suffered only a small loss in yield (9.71 g, 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]

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 with electron-poor aryl iodides (**3b**, **4g**–**o**). Aryl bromides also resulted in good reactivity (**4j**, **4l**, **4m**, **4o**–**v**, **4x**). Overall, this C–S cross-coupling method is compatible with aryl halides containing a wide range of functional groups, including carbonyl (**3b**, **4g**, **4h**, **4l**), formyl (**4i**), ester (**4j**), nitryl (**4k**), cyano (**4m**, **4n**), trifluoromethyl (**4o**), extended aromatic (**4p**– **u**), amide (**4v**, **4w**), and amino groups (**4x**, **4y**).

In comparison with aryl iodides and 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**–**l**), mercaptopyridines (**5a**, **5b**), mercaptopyrimidines (**5c**–**e**), 2-mercaptobenzimidazole (**5g**), 2-mercaptobenzothiazole (**5f**), and 7-mercapto-4-methylcoumarin (**5h**) were all effectively coupled in this protocol (70–92% yield).

To illustrate potential pharmaceutical applications (Scheme 5), we first applied our visible-light-promoted C–S cross-coupling methodology in the synthesis of the key structure of 11β-HSD1 inhibitors (**6**, 84%; **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. In particular, we subjected indometacin, fenofibrate, moclobemide, and hydrochlorothiazide pharmaceutical ingredients (containing an aryl chloride) to thiophenols under 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 × 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] Furthermore, 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] formed by the association of the thiolate anion and 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]

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 a π–π interaction with a shortest π-stacking distance of approximately 3.4 Å (Figure 1c). Additionally, time-dependent DFT (TD-DFT) calculations computed at the CAM-B3LYP/6-31+G(d,p) level 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) of 0.137. Specifically, 35% of the 306 nm absorption is contributed by a local excitation involving the thiolate π orbitals ($\pi_{HOMO} \rightarrow \pi_{LUMO+4}$) while 32% is contributed by a charge-transfer excitation from the thiolate to **1a** ($\pi_{HOMO} \rightarrow \pi_{LUMO+5}$). Moreover, TD-DFT calculations also predicted a significantly red-shifted peak at 383 nm, albeit with weaker absorption (f = 0.036). This peak has 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.

On the basis of these analyses, we propose the following visible-light-induced C–S cross-coupling mechanism (Figure 1d). A thiolate anion and an aryl halide first associate to form an EDA complex. As a result of the charge-transfer absorption of this EDA complex, visible-light-induced electron transfer from the thiolate anion to the aryl halide generates the intermediate halide anion, thiyl radical, and aryl radical; these radicals subsequently couple to yield the desired C–S cross-coupled product.

In summary, we have developed a mild, efficient, 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 TD-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. Furthermore, the potential utility of this transformation has been demonstrated by late-stage functionalization of active pharmaceutical reagents and by the synthesis of key structures of 11β-HSD1 inhibitors. The extension of this work to polymer synthesis is currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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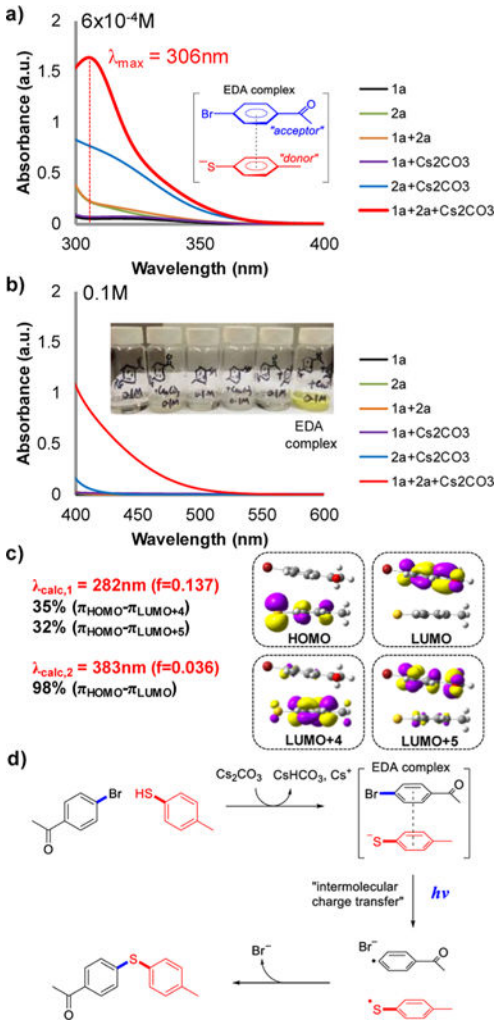
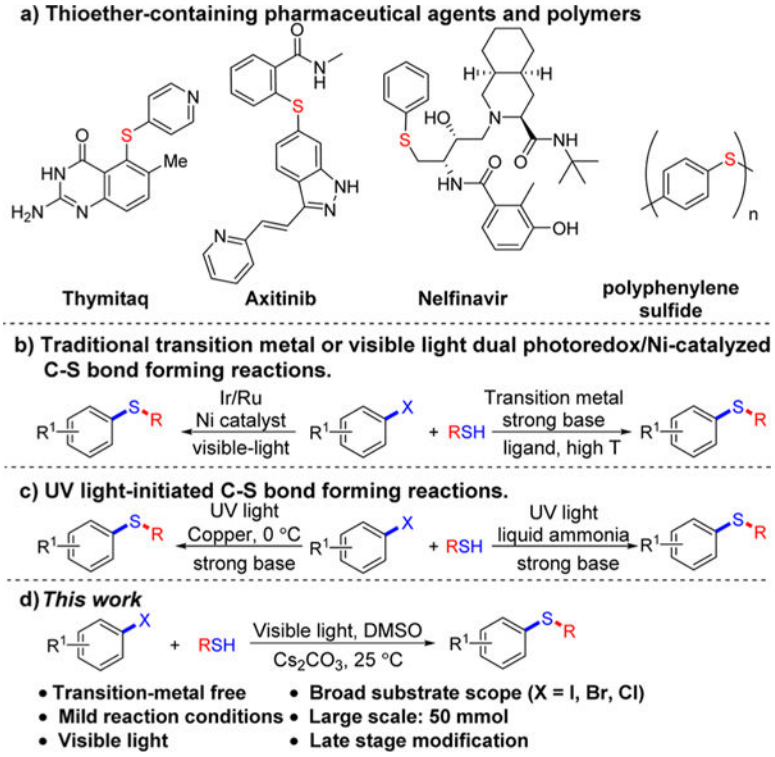


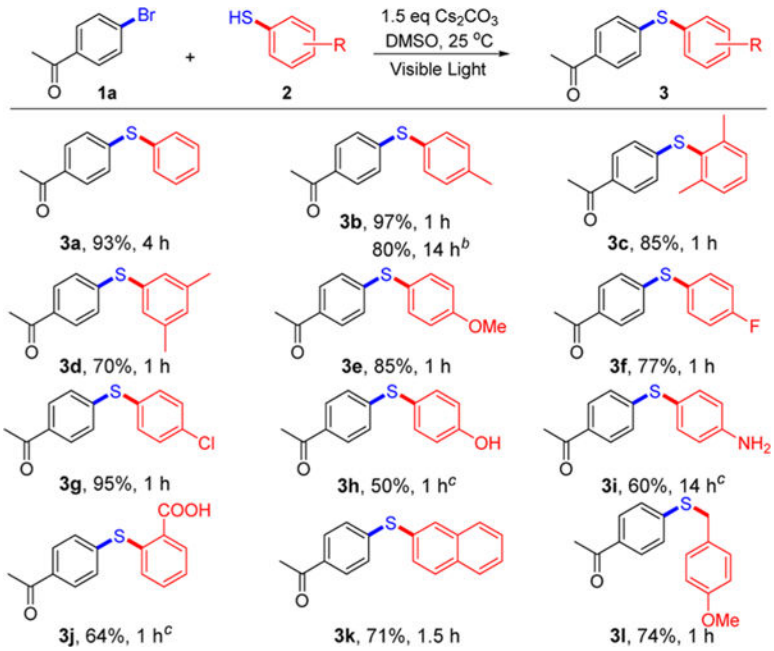
Figure 1.

(a, b) UV–vis absorption spectra of mixtures of **1a**, **2a**, and Cs_2CO_3 in DMSO (path length = 1 cm) at concentrations of (a) 6×10^{-4} M and (b) 0.1 M for each species. The inset of (b) shows the formation of a yellow compound (proposed EDA complex) upon mixing of **1a**, **2a**, and Cs_2CO_3. (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.



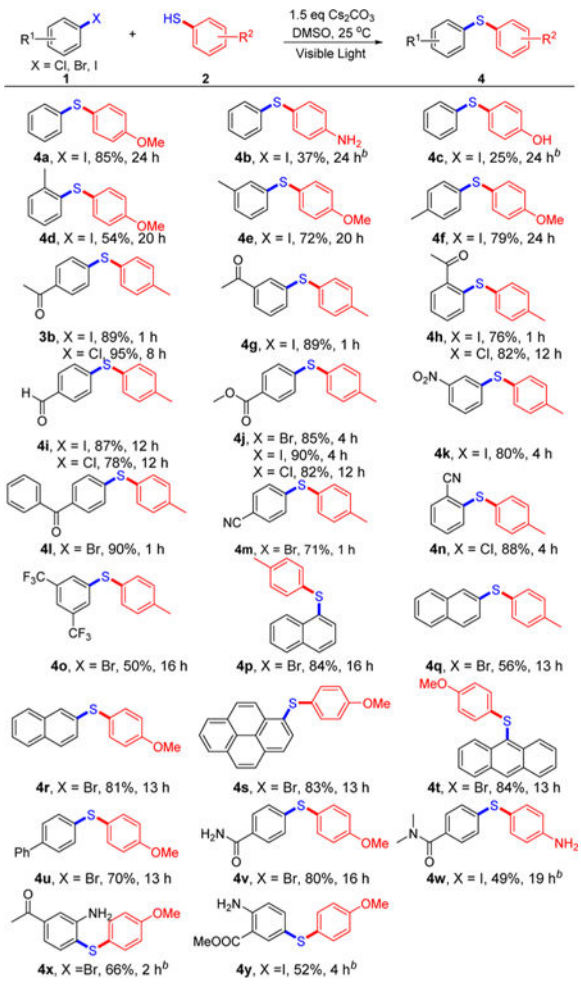
Scheme 1.

Importance of C–S Bonds and Approaches for Their Formation



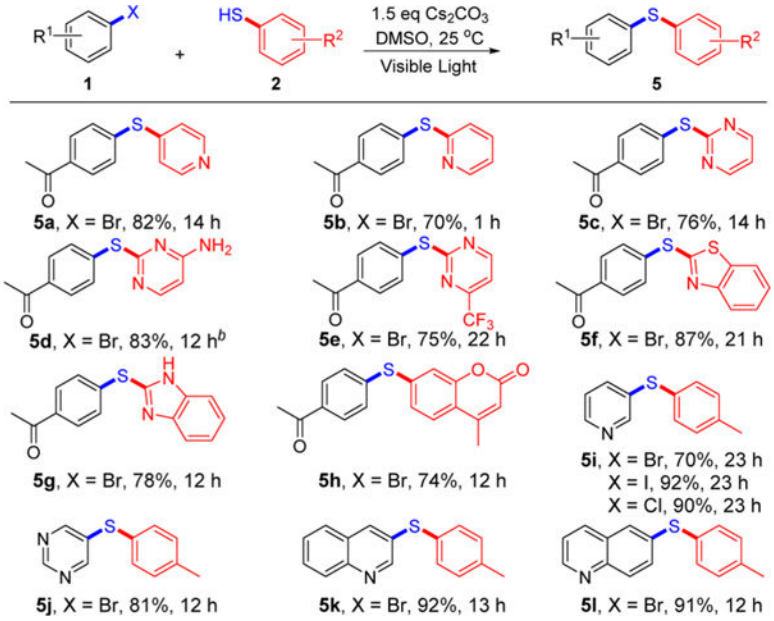
Scheme 2. Scope of Thiols[a]

[a]General conditions: **1a** (0.2 mmol), **2** (1.5 equiv), Cs_2CO_3 (1.5 equiv), DMSO (1.5 mL). Isolated yields are provided. [b]50 mmol scale. [c]2.0 equiv of Cs2CO3.



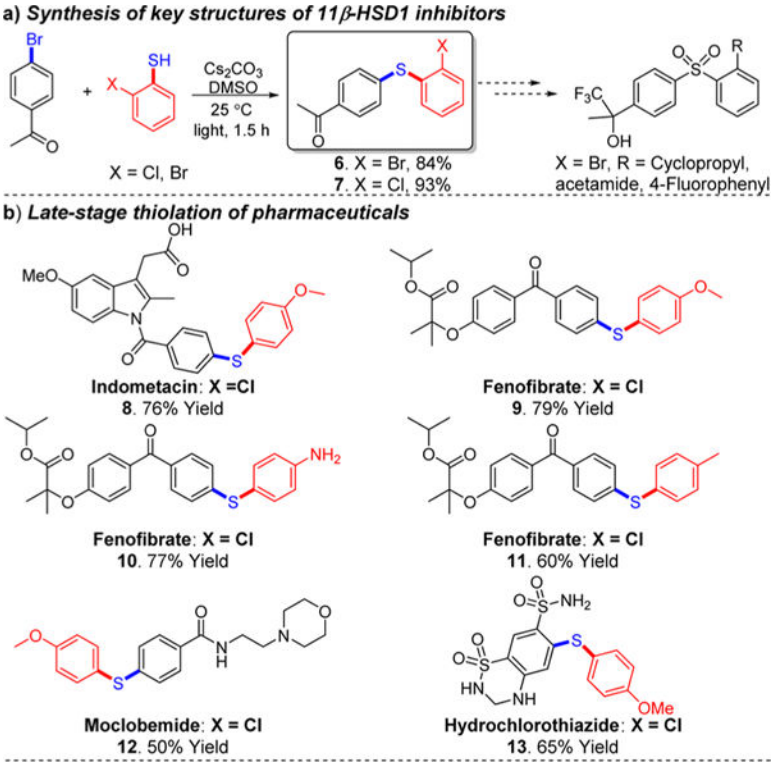
Scheme 3. Scope of Aryl Chlorides/Bromides/Iodides[a]

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



Scheme 4. Scope of (Hetero)arene Coupling Partners[a]

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



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