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A general electron donor–acceptor complex for photoactivation of arenes *via* thianthrenation†

Kai Sun, [a] Anzai Shi,[a] Yan Liu,[b] Xiaolan Chen, *[a] Panjie Xiang,[a] Xiaotong Wang,[a] Lingbo Qu[a] and Bing Yu *[a]

General photoactivation of electron donor–acceptor (EDA) complexes between arylsulfonium salts and 1,4-diazabicyclo[2.2.2]octane with visible light or natural sunlight was discovered. This practical and efficient mode enables the production of aryl radicals under mild conditions, providing an unrealized opportunity for two-step *para*-selective C–H functionalization of complex arenes. The novel mode for generating aryl radicals *via* an EDA complex was well supported by UV-vis absorbance measurements, nuclear magnetic resonance titration experiments, and density functional theory (DFT) calculations. The method was applied to the regio- and stereo-selective arylation of various *N*-heterocycles under mild conditions, yielding an assembly of challengingly linked heteroaryl–(hetero)aryl products. Remarkably, the meaningful couplings of bioactive molecules with structurally complex drugs or agricultural pharmaceuticals were achieved to display favorable *in vitro* antitumor activities, which will be of great value in academia or industry.

Introduction

Aryl radicals have proven to be versatile synthetic intermediates in organic synthesis, displaying an important role in materials science, agricultural chemistry, and especially pharmaceutical chemistry.[1] Classically, the generation of aryl radicals depends heavily on the reduction of aromatic halides by AIBN/*n*-Bu_3SnH or energy-intensive diazonium salts by transition metal reductants.[2] The oxidation of arylhydrazines and boronic acids emerged as an alternative to access aryl radicals in the presence of strong oxidants.[3] However, site-selective synthesis of these active precursors from the corresponding arenes is challenging.[4] The range of substrates is limited to simple arenes in most of the reported systems. Further disadvantages of these conventional reactions include the employment of toxic or expensive reagents and harsh oxidants (or reductants). Therefore, the development of sustainable approaches for the generation of aryl radicals that can exploit more general precursors without harsh oxidants or reductants would be highly desirable.

Photocatalysis,[5] which directly converts sustainable solar energy into chemical energy,[6] now emerges as a promising technology to achieve diverse organic transformations in an environmentally friendly and energy-saving methodology.[7] Some elegant methods for photocatalytic generation of aryl radicals have been reported.[8] Very recently, it has been reported that sulfonium salts[9] offer a feasible transformative platform for the late-stage functionalization of complex scaffolds. In particular, triarylsulfonium salts derived from aromatic C–H bonds are promising candidates for photocatalytic organic transformations. However, direct photochemical activation of triarylsulfonium salts requires strong energy such as ultraviolet light.[10] The high energy of ultraviolet light will destroy more chemical bonds, resulting in low selectivity. Moreover, special light sources and equipment, such as high-pressure mercury lamps, lamp boxes, quartz reactors, *etc.*, are usually required. Recently, some elegant visible-light mediated activations of triarylsulfonium salts have been reported.[11] For example, the Ritter group disclosed an elegant arylation method of aryl sulfonium salts using the iridium complex as the photocatalyst (Scheme 1a).[12] The Procter group reported a metal-free strategy for formal C–H/C–H cross-couplings using 10-phenylphenothiazine as the optimal photocatalyst (Scheme 1b).[13] These strategies rely on the employment of an exogenous photocatalyst that harvests the energy of visible light to activate triarylsulfonium salts for the generation of aryl radicals under mild reaction conditions.

Photoinduced intermolecular charge transfer through the association of an electron-donating substrate (*D*) and an electron acceptor molecule (*A*) *via* noncovalent interactions is a well-known process in photochemistry (Scheme 1c).[14] Although each component itself (*D* or *A*) might not absorb visible light, the molecular aggregate formed between the donor and acceptor molecules in the ground state establishes a new charge-transfer

[a]*Green Catalysis Center, College of Chemistry, Zhengzhou University, Zhengzhou 450001, China. E-mail: chenxl@zzu.edu.cn; bingyu@zzu.edu.cn*

[b]*Henan International Joint Laboratory of Rare Earth Composite Material, College of Materials Engineering, Henan University of Engineering, Zhengzhou 451191, China*

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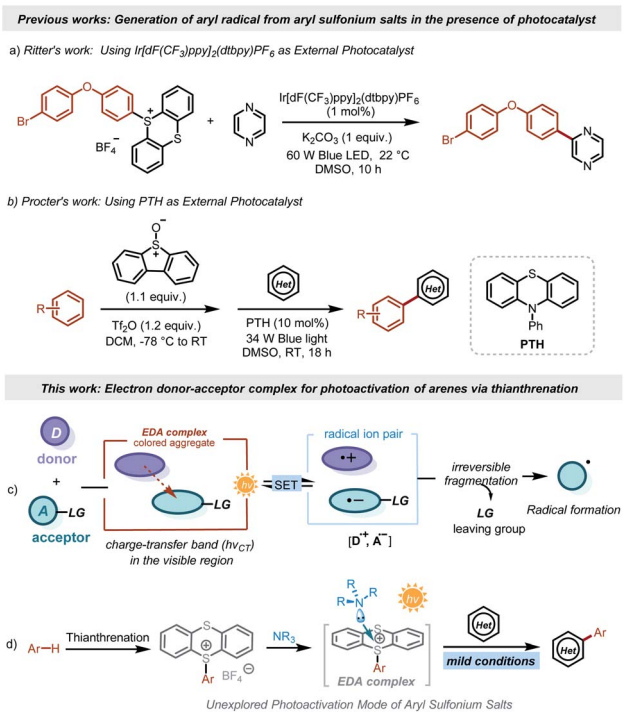


Scheme 1 Photocatalytic arylation of aryl sulfonium salts.

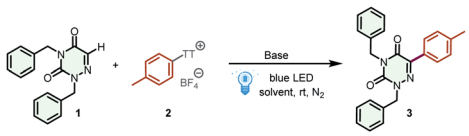
band ($h\nu_{CT}$) related to single electron transfer (SET) from the donor to the acceptor, enabling the ability for absorption of visible light.[15] Upon light irradiation, the SET events in the electron-donor–accepter (EDA) complex can generate reactive open-shell intermediates, which act as valuable synthons for novel synthetic routes under mild conditions.[16] In 2021, the Shi group disclosed the generation of alkyl radicals from EDA complexes between alkyl thianthrenium salts and the B_2cat_2-·DMA adduct.[17] During the preparation of our manuscript, the Procter group described the use of photoactive EDA complexes between arylsulfonium and triarylamines for the production of aryl radicals, leading to the formation of alkylation and cyanation of arenes.[18] Such irradiation-induced intermolecular charge transfer would provide fresh opportunities for generating aryl radicals from arylthianthrenium salts. This virtually unexplored approach can significantly expand the synthetic toolbox of modern chemists.

Herein, we provide a practical approach for the photocatalytic generation of aryl radicals from EDA complexes between arylsulfonium salts and 1,4-diazabicyclo[2.2.2]octane (DABCO), enabling the preparation of high-value-added (hetero) biaryls under mild conditions (Scheme 1d). Through this simple strategy, bioactive molecules can be meaningfully coupled with structurally complex drugs or agricultural pharmaceuticals. The resulting compounds display favorable *in vitro* antitumor activities, providing great value in academia or industry. Moreover, this novel mode for generating aryl radicals *via* EDA complexes was comprehensively studied through UV–vis absorbance measurements, nuclear magnetic resonance (NMR) titration experiments, and density functional theory (DFT) calculations.

Results and discussion

As an azapyrimidinone analog of uracil, azauracil is a promising microbiological inhibitor that has been widely studied by chemists and pharmacists.[19] In particular, the ribonucleosides of 6-azauracil display significant antiviral, antitumor, and antifungal activities. New synthetic methods that enrich the structural diversity of azauracils and nucleosides would significantly advance research in this area. We hypothesized that electron-deficient arylthianthrenium salts can serve as electron acceptors, forming EDA complexes with tertiary amines. This scheme provides an unrealized opportunity to access aryl radicals for the alkylation of azauracils and nucleosides. The feasibility of our hypothesis was evaluated by selecting toluene as a model substrate to produce aryl thianthrenium salt **2** to react with 2,4-dibenzyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**1**) for the synthesis of 2,4-dibenzyl-6-(*p*-tolyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**3**) (Table 1). Initially, various commercially available tertiary amines, including *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine (DMAP), Et_3N, 1,1,3,3-tetramethylguanidine (TMG), and 1,4-diazabicyclo[2.2.2]octane (DABCO) (entries 1–6 in Table 1) were investigated. All of these

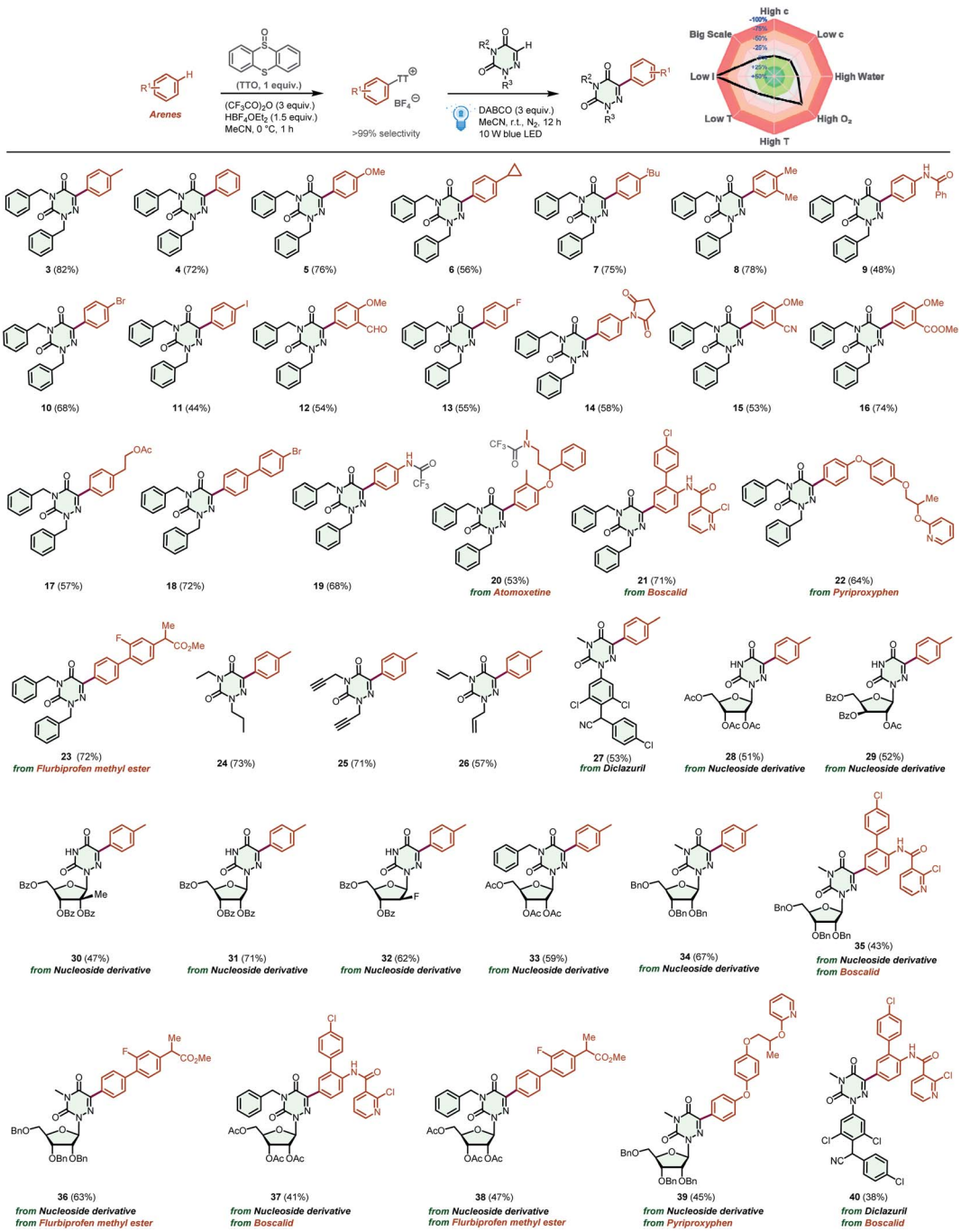
Table 1 Optimization of the reaction conditions[a]



Entry	Base	Solvent	Yield (%)
1	TMEDA	MeCN	42
2	DBU	MeCN	50
3	DMAP	MeCN	32
4	Et_3N	MeCN	50
5	TMG	MeCN	59
6	DABCO	MeCN	72
7	Triphenylamine	MeCN	Trace
8	Tri-*p*-tolylamine	MeCN	21
9	PPh_3	MeCN	N.D
10	Tricyclohexylphosphine	MeCN	N.D
11	DABCO	DMSO	57
12	DABCO	Acetone	61
13	DABCO	DCM	32
14	DABCO	DMF	Trace
15	DABCO	EtOH	Trace
16	DABCO	DCE	40
17	DABCO	THF	21
18[b]	DABCO	MeCN	52
19[c]	DABCO	MeCN	82
20[d]	—	MeCN	N.D
21[e]	DABCO	MeCN	N.D

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), base (2 equiv.), and an appropriate solvent (1.5 mL) were irradiated with a 10 W blue LED (430 nm) at room temperature under a N_2 atmosphere for 12 h. Yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard based on **1**. N.D = not detected. [b] DABCO (1 equiv.). [c] DABCO (3 equiv.). [d] No base. [e] In the dark.

tertiary amines effectively promoted the reaction, and the desired product **3** was obtained in 72% yield when DABCO was employed (entry 6). However, when triphenylamine or tri-*p*-tolylamine was employed as the electron-donating reagents, the yield of product **3** was significantly reduced (entries 7 and 8). Moreover, no desired product could be detected when PPh_3 or tricyclohexylphosphane was used instead of tertiary amines (entries 9 and 10). Then, a series of other solvents, including dimethyl sulfoxide (DMSO), acetone, dichloromethane (DCM), dimethylformamide (DMF), ethanol (EtOH), 1,2-dichloroethane (DCE), and tetrahydrofuran (THF), were screened (entries 11–17). Unfortunately, these attempts failed to improve the yield, and no positive results were obtained. Next, the dosage of tertiary amine was optimized to further improve the reaction efficiency (entries 18 and 19). The best dosage was 3 equiv. of DABCO, which afforded the desired product **3** in 82% yield. The control experiments conducted in the absence of tertiary amines and visible light gave no desired product, indicating the important roles of tertiary amine and light in this transformation (entries 20 and 21). Furthermore, additional experiments showed that the donor loading could be decreased below 1 equivalent by adding other bases (for details, see Table S1†).



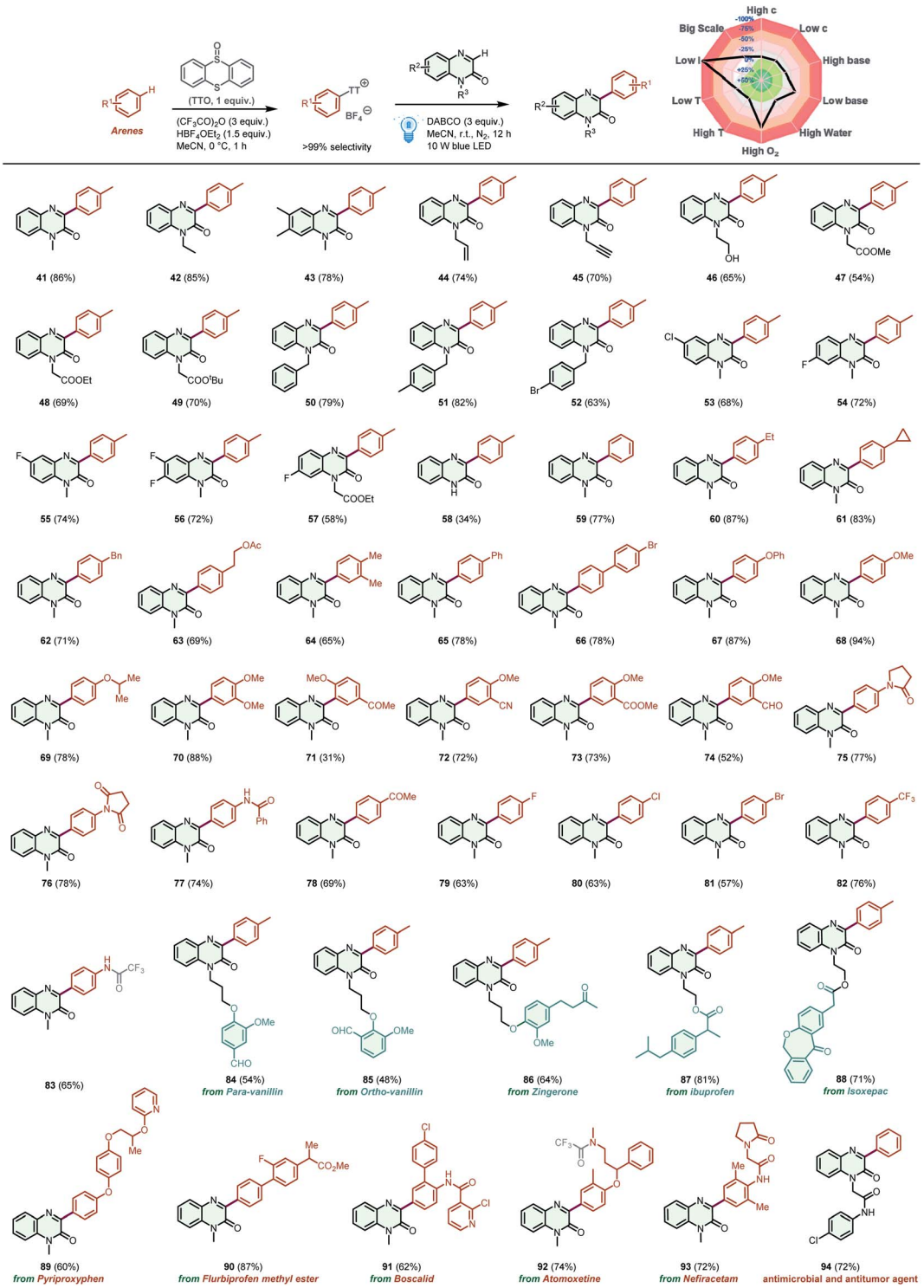
Scheme 2 Substrate scope of the alkylation of azauracils and nucleosides.

Having optimized the reaction conditions, we then turn our attention to examining the generality of our practical protocol. Initially, arenes bearing a wide range of functional groups were reacted with 2,4-dibenzyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**1**) (Scheme 2). To our delight, all of these arenes were suitable substrates for the two-step site-selective C–H arylation reaction, obtaining the desired products **3**–**19** in moderate to good yields (44–82%). It is worth emphasizing that various functional groups were tolerated in these cases, and some sensitive functional groups such as –CHO, –CN, and $-COCH_3$ were compatible with the transformation. The acid-sensitive free amino group was trifluoroacylated to product **19** in 68% yield. The straightforward and selective modification of biorelevant compounds are of importance in research and development campaigns.[20] These conditions can be used in the late-stage diversification of drugs and agricultural pharmaceuticals, such as the multi-use insecticide pyriproxyphen, the fungicide boscalid, and atomoxetine for the treatment of attention deficit and hyperactivity disorder, affording the corresponding products **20**–**22** in satisfactory yields (53–71%). Flurbiprofen methyl ester, a drug derivative, was also amenable to this transformation, affording product **23** in 72% yield. Afterward, the scope of 6-azauracils was assessed. Gratifyingly, *N*,*N*′-disubstituted 6-azauracils were smoothly arylated with thianthrenium salt **2**, affording the corresponding products **24**–**26** in satisfactory yields (57–73%). Moreover, the new anticoccidial drug diclazuril was also compatible with this efficient methodology, giving the product **27** in 53% yield. It is noteworthy that convenient C(sp^2)–H arylation of 6-azauridine nucleosides was successfully achieved, furnishing the arylated 6-azauridine nucleosides **28**–**34** in moderate yields (47–71%). In these cases, the free secondary N–H group in the 6-azauridine nucleosides was tolerated with no significant effects on the reaction efficiency. Additionally, this protocol provides a feasible way for the effective coupling of 6-azauridine nucleosides and pharmaceuticals, leading to the corresponding nucleoside derivatives **35**–**39** in moderate yields (41–63%). Diclazuril was also coupled with boscalid to afford the corresponding product **40** in 38% yield. More importantly, in all of the above cases, thianthrene was recovered by separation and reused in subsequent cycles. Additionally, the model reaction efficiency of product **3** was investigated under different reaction parameters.[21] In a comprehensively condition-based sensitivity assessment, this photocatalytic transformation was sensitive to low light intensity and high oxygen concentrations, which was generally tolerant toward the substrate concentration, reaction temperature, water, and scale (see the radar diagram in Scheme 2 and the ESI† for details).

The proposed photoactivation of arenes *via* thianthrenation was then applied to the arylation of quinoxalin-2(1*H*)-ones (Scheme 3), which play a significant role in antimicrobial compounds, antitumor agents, and semiconductors.[22] Through this protocol, various quinoxalin-2(1*H*)-ones bearing different functional groups afforded the corresponding products **41**–**57** with excellent site selectivity and reactivity. Owing to the mild reaction conditions, sensitive alkenyl, alkynyl, and hydroxy groups were well tolerated under the optimized conditions (**44**–**46**). Notably, *N*-unsubstituted quinoxalin-2(1*H*)-one was also a suitable substrate to furnish the desired product **58** in 34% yield. To explore the arene generality of the protocol, various electron-rich, neutral, and electron-poor arenes were reacted with *N*-methylquinoxalin-2(1*H*)-one under the optimized reaction conditions. Remarkably, the functional groups –Me, –Et, –Bn, –OAc, –Ph, –OMe, –OPh, –F, –Cl, –Br, –CN, –CHO, –COOMe, and $-COCH_3$ were transformed into their corresponding products **59**–**82** in average to good yields, highlighting the compatibility of the protocol with a wide range of functional groups. Likewise, when aniline participated in this reaction, product **83** was generated in 65% yield, in which trifluoroacylation of the free amino group occurs. The scope of the protocol was further extended to facile late-stage functionalization of valuable scaffolds containing drug-like molecules and natural isolates. For example, quinoxalin-2(1*H*)-ones containing *o*-vanillin, *p*-vanillin, zingerone, ibuprofen, and isoxepac were selectively arylated to the desired products **84**–**88** in 48–81% yields. Nefiracetam, pyriproxyphen, flurbiprofen methyl ester, boscalid, and atomoxetine were all efficient arylation reagents in this two-step C–H alkylation reaction to produce products **89**–**93**, demonstrating the utility of this transformation. Finally, the application of this methodology for the preparation of antimicrobial and antitumor agent **94** was achieved, and a 72% yield of the desired product was obtained. Likewise, in a condition-based sensitivity assessment, low light intensity, high oxygen concentrations, and the DABCO amount were the main factors influencing the preparation reproducibility of product **41** (for details, see the ESI†).

Encouraged by the above results, we further examined the generality of the proposed protocol by screening other simple yet significant (hetero)aryl cycles (Scheme 4). To our delight, coumarin, 1-(fluoromethyl)cinnolin-4(1*H*)-one, and 2-phenylimidazo[1,2-*a*]pyridine were successfully arylated under the optimized reaction conditions, producing the corresponding products **95**-**97** in acceptable yields. Moreover, 3-methylene-1-phenylpyrrolidine-2,5-dione, which could be transformed into 3-methyl-1-phenyl-1*H*-pyrrole-2,5-dione in the presence of base,[23] was a suitable substrate to access product **98** in 36% yield. Additionally, this method was also applied to the direct C–H arylation of tangeretin and 1,3,5-trimethoxybenzene, leading to the formation of desired products **99** and **100** in 36% and 61% yields, respectively. Unfortunately, some other (hetero) aromatic cycles, including pyridine, quinoline, benzothiazole, benzoxazole and indole were not suitable substrates for this transformation, and no desired products could be detected (for details, see Scheme S1†).

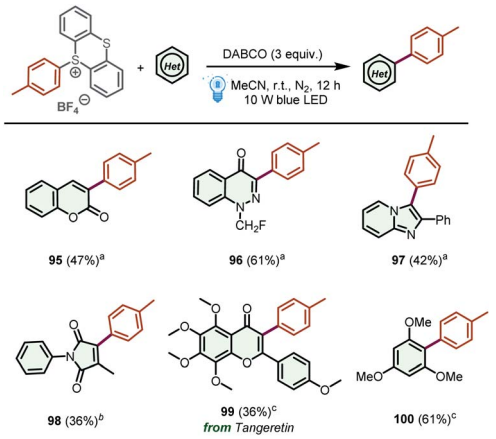
To clarify the practicality of these transformations, the gram-scale synthesis of products **3** and **41** was performed on 4 mmol and 5 mmol scales, respectively. To our delight, the reactions proceeded smoothly to provide the desired products with no significant reduction in yields only by increasing the light intensity and reaction time (Scheme 5). Furthermore, natural sunlight-driven experiments were performed, leading to the formation of substantial amounts of products **3** and **41** in 79% and 76% yields, respectively. A one-pot sequence was also explored, and product **3** could be obtained in 37% yield (for details, see the ESI†).



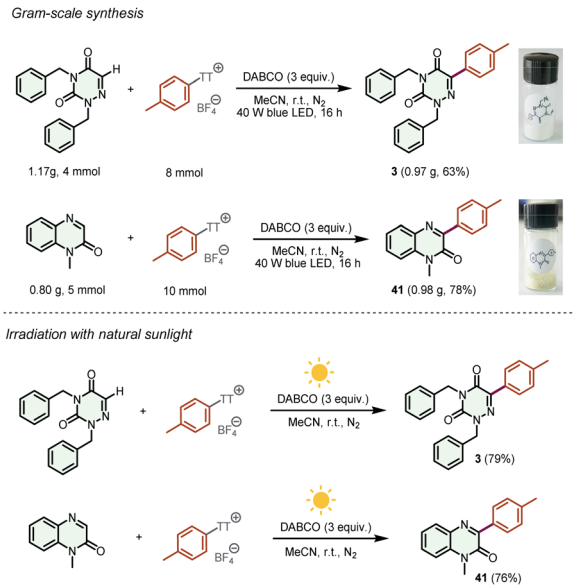
Scheme 3 Substrate scope for the arylation of quinoxalin-2(1*H*)-ones.

Importantly, the *in vitro* antitumor activities of the synthetic compounds **37** and **92** were evaluated in Ramos cells. The results indicated that compounds **37** and **92** exhibited excellent antitumor activities (Fig. S7†). In the aspect of anti-lymphoma activity, the IC_{50} values of compounds **37** and **92** against Ramos cells are slightly lower than that of the approved drug fluorouracil (5-FU, 13.7 μM), indicating the potential of our method in the development of novel drugs.

To get deep insight into the reaction mechanism, some radical trapping experiments were conducted (Scheme 6). When the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl) oxidanyl (TEMPO) or 1,1-diphenylethylene was added to the

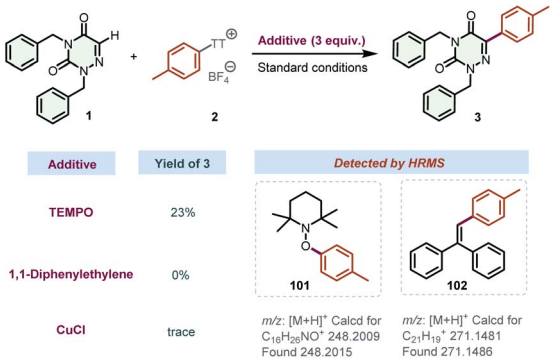


Scheme 4 Screening of other (hetero)aromatic cycles. (a) Reaction conditions: (hetero)aromatic cycle (0.1 mmol) was reacted with thianthrenium salt (0.2 mmol) in the presence of DABCO (3 equiv.) under 10 W blue LED irradiation. (b) 3-Methylene-1-phenylpyrrolidine-2,5-dione (0.1 mmol) is used as a substrate to react with thianthrenium salt (0.2 mmol) in the presence of DABCO (3 equiv.) under 10 W blue LED irradiation. (c) Thianthrenium salt (0.1 mmol) was reacted with (hetero)aromatic cycle (10 equiv.) in the presence of DABCO (3 equiv.) under 10 W blue LED irradiation.



Scheme 5 Synthetic applications.

model reaction, the reactions were severely inhibited. Moreover, CuCl was also proven to be an effective inhibitor of this transformation. All of these results indicated the possible involvement of a radical pathway. Additionally, the reaction mixtures were analyzed by high-resolution mass spectrometry (HRMS), and the adducts **101** and **102** were successfully detected, respectively. These results strongly support the generation of aryl radicals in the photocatalytic transformation, which might be initiated by the photo-activated EDA complexes between arylsulfonium salts and DABCO. The preparation of product **41**



Scheme 6 Control experiments.

was also severely inhibited by TEMPO, 1,1-diphenylethylene, or CuCl (for details, see the ESI†).

The formation of the EDA complex was confirmed in additional mechanism investigations (Fig. 1). When DABCO was added to a solution of arylthianthrenium salt **2** in CH_3CN, the solution developed a marked yellow color. The UV-vis absorbance experimental results showed that the absorption peaks of the DABCO and arylthianthreniumsalt **2** mixture appeared at 430–460 nm, while those of control groups can only be observed in the near UV-region. This might be caused by the formation of a new EDA molecular aggregate. Moreover, ^{1}H NMR titration experiments and a Job's plot analysis confirmed the formation of a 1 : 1 complex between the arylthianthrenium salt **2** and DABCO. The binding constant K_a of complexation was 1.04 M^{-1} in $CDCl_3$ (for details, see the ESI†). Additionally, DFT calculations were carried out to better understand the intermolecular charge transfer between arylthianthrenium salt **2** and DABCO. In the equilibrium structure, the distance *d* of the *N*/*S*

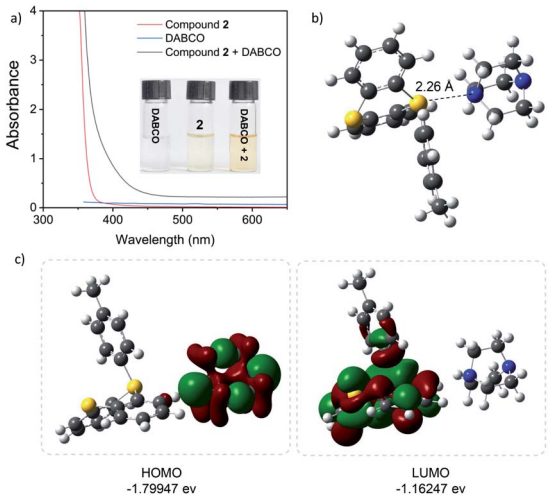
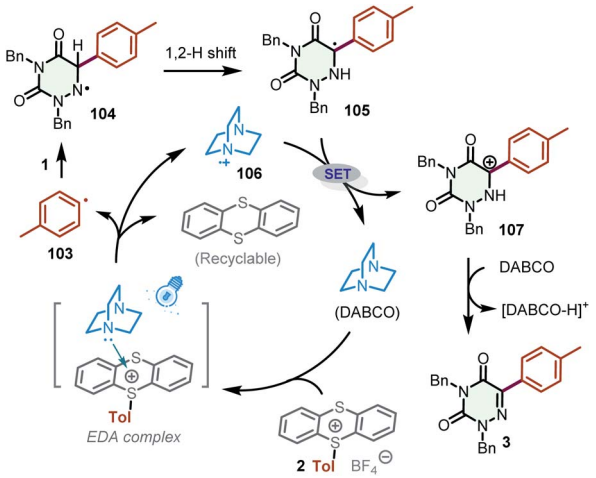


Fig. 1 (a) UV-Vis absorption spectra of reactant mixtures recorded in CH_3CN in 1 mm path-length quartz cuvettes, and visual appearance of the separate reaction components and the colored EDA complex between compound **2** and DABCO. (b) Calculated bond distances of arylsulfonium salt **2** and DABCO. (c) Calculated HOMO and LUMO of the EDA complex.



Scheme 7 Proposed mechanism.

interactions was 2.26 Å, shorter than the summed van der Waals radii of the two interacting atoms (3.78 Å).[24] The binding energy was calculated to be 3.73 kcal mol^{-1}, implying a feasible interaction between the arylthianthrenium salt **2** and DABCO. The low energy gap (0.64 eV) between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) indicated a favorable electron-transfer process under visible light irradiation.

Based on the above observations and previous reports,[25] a plausible mechanism containing EDA complexes for the generation of aryl radicals was proposed (Scheme 7). Initially, DABCO combines with the aryl thianthrenium salt **2** to generate the EDA complex, which produces the aryl radical **103**, thianthrene, and $DABCO^{\bullet+}$ (**106**). Afterward, the addition of aryl radical **103** to the C=N bond of 2,4-dibenzyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione (**1**) affords radical **104**, which undergoes a 1,2 H shift to furnish radical **105**. Radical **105** can be oxidized by $DABCO^{\bullet+}$ (**106**) to the carbon cation **107**, which transforms into the desired product **3** in the presence of DABCO by deprotonation.

Conclusions

In conclusion, we have developed a novel mode for the generation of aryl radicals by photoactivation of arenes *via* thianthrenation. When the EDA complex between arylsulfonium salts and DABCO is excited by weak visible light or natural sunlight, it forms aryl radicals that can be leveraged in synthetically useful transformations for the arylation of various *N*-heterocycles. The high versatility of the EDA complex facilitates an assembly of challengingly linked heteroaryl–(hetero) aryl products. More importantly, this practical protocol can efficiently and selectively combine bioactive molecules with structurally complex drugs or agricultural pharmaceuticals. The resulting compounds displayed favorable *in vitro* antitumor activities. The proposed methodology is promising for the development of novel synthetic methods and antitumor drugs in academia or industry. We believe that photoactivation of arenes to aryl radicals *via* thianthrenation will facilitate further arylation processes, providing meaningful compounds under mild reaction conditions.

Data availability

The data that support the findings of this study are available in the ESI† or on request from the corresponding author.

Author contributions

K. S., X. L. C. and B. Y. designed the subject and guided the experiments throughout. K. S., A. Z. S., Y. L., P. J. X. and X. T. W. conducted the organic synthesis and characterization. Y. L. conducted the DFT calculations, and K. S. performed the *in vitro* antitumor activity analysis. K. S., L. B. Qu and B. Y. completed the article writing together.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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