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Perylenequinonoid-Catalyzed [4 + 1] and [4 + 2] Annulations of Azoalkenes: Photocatalytic Access to 1,2,3-Thiadiazole/1,4,5,6-Tetrahydropyridazine Derivatives

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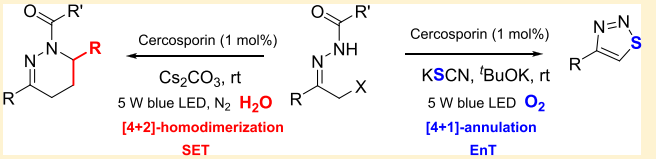
Supporting Information

ABSTRACT: Nitrogen-containing heterocycles are especially considered "privileged" structural scaffolds for the development of new drugs. However, traditional methods of organic synthesis are mainly based on thermal cycloaddition reaction; thus, the exploration of new strategies for the rapid assembly of N-heterocycles under mild conditions is highly desirable. Here, we developed a new method that visible light along with 1 mol % cercosporin, which is one of the perylenequinonoid pigments with excellent properties of photosensitization and can be easily produced by a new isolated endophytic fungus *Cercospora sp. JNU001* strain with high yield through microbial fermentation, catalyzes the synthesis of 1,2,3-thiadiazoles and 1,4,5,6-tetrahydropyridazines by a photocatalytic process with good regioselectivity and broad functional-group compatibility under mild conditions. Thus, a bridge between microbial fermentation and organic photocatalysis for the construction of nitrogen-containing heterocycles was set up in a sustainable, environmentally friendly manner.



INTRODUCTION

Nitrogen-containing heterocycles are the most abundant and integral scaffolds that frequently occur in bioactive natural products, synthetic agrochemicals, and pharmaceuticals.[1] Among them, 1,2,3-thiadiazoles[2] and 1,4,5,6-tetrahydropyridazines[3] are privileged and valuable N−N-bond-containing heterocyclic scaffolds and serve as versatile intermediates in organic synthesis (Figure 1). In most cases, they demonstrate diverse pharmacological activities owing to their substitution patterns and function groups. Consequently, a great deal of research effort has been devoted to development of elegant and creative strategies to construct these nitrogen heterocycles, of which most methods are based on thermal cycloaddition reactions.[4] Owing to energy shortage and environmental pollution, the utilization of solar energy as a sustainable and renewable energy resource to drive synthetic transformations has become a hotspot in green chemistry.[5] Additionally, photocatalysis has been recognized as a useful routine[6] with the generation of various reactive species under mild conditions, frequently without stoichiometric activation reagents.[7] To date, azoalkenes (1,2-diaza-1,3-dienes),[8] powerful and versatile four-unit intermediates, have seldom been employed as synthons in photocatalytic annulations by using metal-based $Ru(bpy)_3Cl_2$ as the photocatalyst with high efficiency for radical cyclization of α-halogeno hydrazine with β-ketocarbonyls,[9] whereas metal-free photocatalyst eosin Y showed only 7% yield. Compared with transition-metal-based photocatalysts, metal-free photocatalysts exhibit more environmentally friendly properties.[6d,e] Therefore, the exploration of new strategies or new catalysts to develop greener methodologies for the rapid assembly of N-heterocycles based on metal-free photocatalysis is highly desirable.

Naturally occurring perylenequinonoid pigments (PQPs), such as cercosporin (CP),[10] hypocrellin,[11] elsinochrome,[12] and phleichrome[13] (Figure 2), produced by endophytic fungi, have

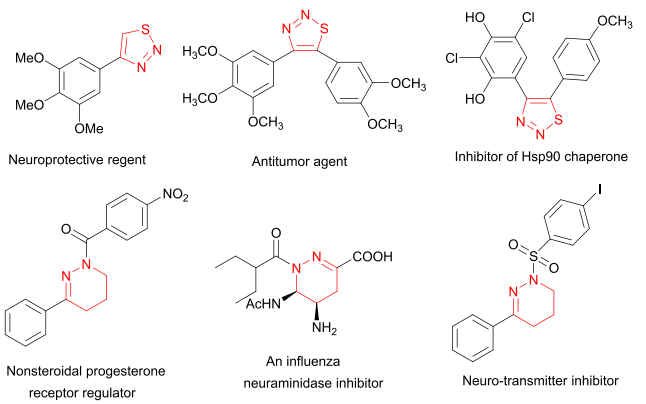


Figure 1. Biologically active 1,2,3-thiadiazole and 1,4,5,6-tetrahydropyridazine derivatives.

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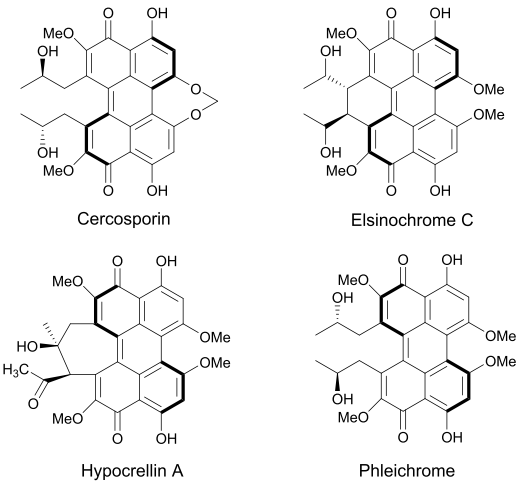
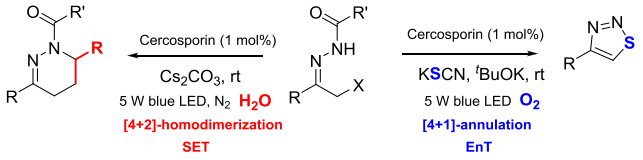


Figure 2. Representatives of the naturally occurring mold perylenequinones.

aroused considerable attention owing to their excellent properties of photosensitization, which function as new potential compounds in photodynamic therapy and photophysical diagnosis.[11a,14] These photosensitizers can be activated to excited state by visible light absorption and then undergo energy transfer (EnT) and electron transfer (ET),[10e,11c,14a,15] implying that these natural product PQPs can be used as "metal-free" photocatalysts for organic synthesis, but have never been investigated.[15]

Herein, we report an unprecedented photocatalytic [4 + 1] annulation of azoalkenes with thiocyanate salt as the "S" source and [4 + 2] cyclodimerization of azoalkenes. It afforded 1,2,3-thiadiazoles and 1,4,5,6-tetrahydropyridazines with excellent yields under mild reaction conditions by using one of the naturally occurring PQPs cercosporin (CP) as a metal-free photocatalyst. Notable features of our finding include (a) a natural product cercosporin as an organic photocatalyst for synthesis of N-heterocycles, (b) mild reaction conditions and broad substrate scope, and (c) great conversions of substrates in the gram-scale reactions (Scheme 1).

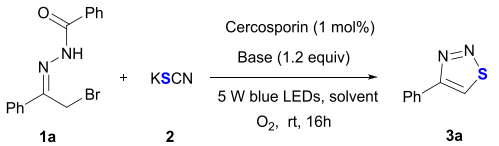
Scheme 1. Cercosporin-Catalyzed [4 + 1] and [4 + 2] Annulations of Azoalkenes



RESULTS AND DISCUSSION

Thiocyanate salts have been proved to be attractive and versatile reagents in organic transformations[16] because of their easy availability, low cost, and low toxicity. As an ambident nucleophilic unit, thiocyanate salts can introduce the "SCN" source to afford thiocyanate products.[17] Meanwhile, in recent years, thiocyanate salts can also be found as a sulfur transfer reagent[18] or a stable "CN" source in organic transformations.[19] Thus, carbon−sulfur bond and nitrogen−sulfur bond formations play important roles in the constructions of organosulfur compounds. Here, an unprecedented photocatalytic [4 + 1] annulation of azoalkenes with thiocyanate salt as the S source and C−S/S−N bond formation in one pot was realized with cercosporin as a photocatalyst, which was produced by a new isolated endophytic fungus *Cercospora sp. JNU001* strain with high yield through microbial fermentation (Supporting Information). Initially, α-bromo-*N*-benzoyl-hydrazone **1a** was employed as the model substrate to react with potassium thiocyanate (KSCN) **2** in the presence of CP (1 mol %) and K_2CO_3 (1.2 equiv) in 2.0 mL of MeCN with the photoirradiation of 5 W blue LED at room temperature under an O_2 atmosphere. Gratifyingly, the desired product **3a** was given in 50% yield after 16 h of irradiation (Table 1, entry 1). Then,

Table 1. Optimization of Reaction Conditions[a]



1a 2 3a

entry	photocatalyst	base	solvent	yield (%)[b]
1	cercosporin	K_2CO_3	MeCN	50
2	cercosporin	KOH	MeCN	62
3	cercosporin	*t*BuOK	MeCN	88
4	cercosporin	Cs_2CO_3	MeCN	72
5	cercosporin	DBU	MeCN	59
6	cercosporin	*t*BuOK	EtOH	49
7	cercosporin	*t*BuOK	$CHCl_3$	38
8	cercosporin	*t*BuOK	DMSO	65
9	cercosporin	*t*BuOK	toluene	trace
10	cercosporin	*t*BuOK	CH_2Cl_2	21
11	hypocrellin A	*t*BuOK	MeCN	12
12	hypocrellin B	*t*BuOK	MeCN	25
13[c]	cercosporin	*t*BuOK	MeCN	82
14	cercosporin		MeCN	trace
15		*t*BuOK	MeCN	trace
16[d]	cercosporin	*t*BuOK	MeCN	trace
17[e]	cercosporin	*t*BuOK	MeCN	trace
18[f]	cercosporin	*t*BuOK	MeCN	69

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), photocatalyst (1 mol %), base (0.24 mmol), solvents (2.0 mL), 5 W blue LEDs, 16 h, at room temperature under an O_2 atmosphere. [b]Isolated yield. [c]NaSCN was used as the S source. [d]Without visible light irradiation. [e]The reaction was conducted in Ar. [f]Performed with 0.5 mol % of cercosporin.

several experiments were performed to investigate the effect of base, solvent, and S source on the reaction. The use of *t*BuOK gave a superior performance and afforded **3a** in 88% yield, whereas altering the base from *t*BuOK to Cs_2CO_3 led to a slightly lower yield of **3a** at 72% (entries 2−5). A brief survey of reaction media showed that acetonitrile remained the best solvent for the photocatalytic cyclization. Other solvents such as ethanol, $CHCl_3$, dimethyl sulfoxide (DMSO), toluene, methanol, and dichloromethane either gave inferior results or completely impeded the reaction (entries 6−10). We also tested other commercially available perylenequinonoid pigments, hypocrellin A and hypocrellin B, but giving extremely poor catalytic activity (entries 11−12). Although NaSCN as the S source also delivered 82% yield of **3a** (entry 13), KSCN was believed to be more suitable as the S source in light of the low cost and similar yields. Control experiments showed that a base was essential for the reaction because no reaction occurred without a base (entry 14). No expected product **3a**

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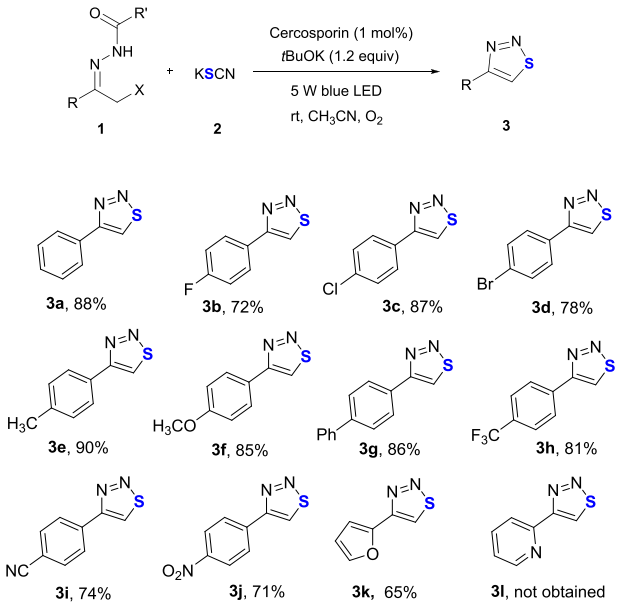
was detected as substrate **1a** remained in the absence of a photocatalyst, light irradiation, or O_2, thus indicating that the reaction should proceed via a photocatalytic process (entries 15 and 17). These experiments demonstrated that light, CP, *t*BuOK, and O_2 were all essential for the reaction. Attempts to decrease the amount of photocatalyst led to a reduction in yield (entry 18).

With the optimized reaction conditions in hand, the scope of *α*-halo-*N*-acyl-hydrazone **1** was studied as shown in Scheme 2.

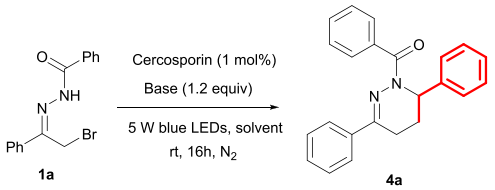
Scheme 2. Cercosporin-Catalyzed [4 + 1] Annulations of Azoalkenes with KSCN



As expected, the procedure was applicable for substrates with both electron-donating and -withdrawing groups in the phenyl ring, providing 4-aryl-1,2,3-thiadiazoles in moderate to good yields. The procedure also tolerated the functional groups, such as trifluoromethyl and cyano (**3h**, **3i**). The Cl and Br groups were well tolerated in this reaction, providing the possibility for further functionalization (**3c**, **3d**). The electron-withdrawing groups such as NO_2 (**3j**) can also afford the desired sulfone products in excellent yields. The furan analogue of hydrazone (**3k**) proceeded smoothly with 65% yield. However, the pyridine analogue of hydrazone (**3l**) did not work under this reaction condition.

Interestingly, 5% yield of 1,4,5,6-tetrahydropyridazine **4a** derived from [4 + 2] cyclodimerization of azoalkene was detected with liquid chromatography–mass spectrometry during the optimization process. 1,2-Diaza-1,3-dienes bearing no substituents at C4 show a tendency of self-condensation. It gave cyclic dimers in the presence of the base when unsuitable or inefficient partners for the cycloaddition reaction are present.[20] In view of the important pharmacological activity of 1,4,5,6-tetrahydropyridazines as valuable N–N-bond-containing heterocyclic scaffolds, this result inspired us to optimize the photocatalytic reaction conditions and examine the scope and generality of the present methodology. We started our investigation by taking **1a** as a model substrate to determine the optimal reaction conditions for the cyclodimerization reaction to form **4a**. Several experiments were performed to investigate the effect of solvent and base on the reaction (Table 2). As a result, we were pleased to find that the cyclo-

Table 2. Optimization of Cyclodimerization Conditions[a]



entry	photocatalyst	base	solvent	yield (%)[b]
1	cercosporin	K_2CO_3	MeCN	60
2	cercosporin	KOH	MeCN	51
3	cercosporin	*t*BuOK	MeCN	31
4	cercosporin	Cs_2CO_3	MeCN	65
5	cercosporin	DBU	MeCN	22
6	cercosporin	Cs_2CO_3	EtOH	58
7	cercosporin	Cs_2CO_3	$CHCl_3$	48
8	cercosporin	Cs_2CO_3	DMSO	12
9	cercosporin	Cs_2CO_3	toluene	25
10	cercosporin	Cs_2CO_3	MeCN/H_2O = 20:1	73
11	cercosporin	Cs_2CO_3	MeCN/H_2O = 10:1	80
12	cercosporin		MeCN/H_2O = 10:1	trace
13		Cs_2CO_3	MeCN/H_2O = 10:1	trace
14[c]	cercosporin	Cs_2CO_3	MeCN/H_2O = 10:1	trace
15[d]	cercosporin	Cs_2CO_3	MeCN/H_2O = 10:1	61
16[e]	cercosporin	Cs_2CO_3	MeCN/H_2O = 10:1	69

[a]Reaction conditions: **1a** (0.5 mmol), photocatalyst (1 mol %), base (0.24 mmol), solvents (2.0 mL), 5 W blue LEDs, 16 h, at room temperature under a nitrogen atmosphere. [b]Isolated yield. [c]Without visible light irradiation. [d]Performed with 0.5 mol % of cercosporin. [e]Performed with 0.5 equiv of Cs_2CO_3.

dimerization reaction proceeded well in the presence of Cs_2CO_3 (2.0 equiv) and CP (1 mol %) in the mixed solvent (MeCN/H_2O = 10:1) under a nitrogen atmosphere and gave an 80% yield of **4a**. The addition of water has an important effect on the yield of the reaction, indicating that water may participate in the [4 + 2] cyclodimerization reaction as a reactant. Attempts to decrease the amounts of both the photocatalysis CP and the base resulted in much lower yields of **4a**.

Next, we tested a variety of *α*-halo-*N*-acyl-hydrazones **1** to investigate the generality of this optimized reaction. As illustrated in Scheme 3, the reaction proceeded effectively with several substrates and was not found to be much dependent on the electronic nature of the substituents. They afforded a wide range of 1,4,5,6-tetrahydropyridazines (**4a–4q**) in good to excellent yields. In most cases, 1,4,5,6-tetrahydropyridazines were isolated in greater than 70% yield. Importantly, the flexibility of the process allows the strategic placement of functional groups. For instance, **4c**, **4d**, **4i**, **4k**, **and 4n–4o**, which contain chlorine and bromine atoms, can be easily prepared and could be additionally derivatized, thereby providing a convenient alternative for the generation of a broad range of analogues. To our delight, not much electronic effect of *R′* on the aromatic ring was observed. Electron-donating, -withdrawing, and -neutral groups gave almost similar yields at ~80% of 1,4,5,6- tetrahydropyridazines, but alkyl-substituted hydrazones failed to give the desired products.

Last, to demonstrate the synthetic utility of the photocatalytic [4 + 1] annulation of azoalkenes with thiocyanate salt and cyclodimerizations, the gram-scale reactions were carried out (Scheme 4). Comparable yields were obtained, thus

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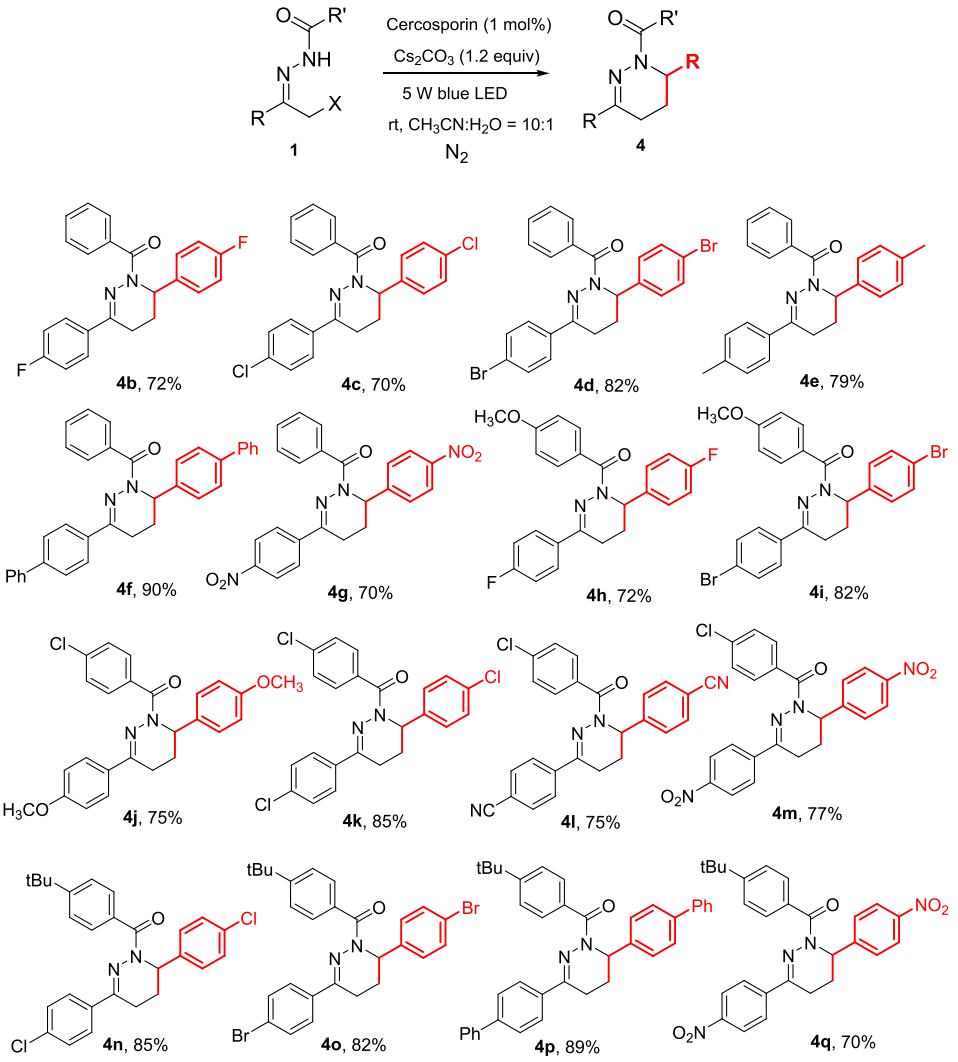
Scheme 3. Cercosporin-Catalyzed [4 + 2] Homocyclodimerizations of Azoalkenes

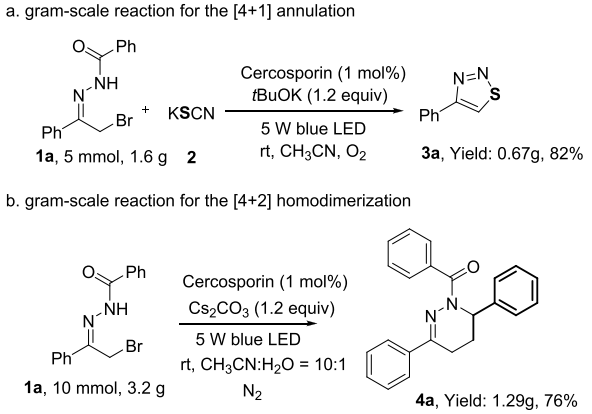


providing a possibility for large-scale synthesis of heterocycles in a sustainable, environmentally friendly manner.

To further get some insights into the mechanisms, several control experiments were conducted. The on/off light experiments of the photoreactions (Supporting Information) revealed that the reactions were inhibited in the absence of light. For the [4 + 2] homocyclodimerization of azoalkene, addition of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-ditert-butyl-4-methylphenol (BHT) led to the obvious inhibition of the reaction (Scheme 5a). We also employed the electron spin resonance (ESR) spin-trap technique (with 5,5-dimethyl-1-pyrroline N-oxide—DMPO) to probe the nature of the reactive oxygen species generated in the reaction under visible irradiation, and four characteristic peaks of DMPO−•OH were obviously observed (Scheme 5b). These results suggested that a radical pathway should be involved in the transformation process. However, when 1.5 equiv of TEMPO was introduced to the [4 + 1] annulation reaction, the desired product was not significantly inhibited. Furthermore, the effect of DABCO (1,4-diazabicyclo[2.2.2]-octane, a singlet oxygen scavenger) on the [4 + 1] annulation reaction was also studied, and the photo-oxidative reaction of sulfide can be significantly suppressed (Scheme 5c). Therefore, we propose that the presence of $^1O_2$ is responsible for the [4 + 1] annulation reaction through an energy transfer (EnT) process.

On the basis of our results and previous literature studies,[4b,c,20a,21] a plausible mechanism is proposed in Scheme 6. Treatment of the α-halo hydrazone **1** with a base generates azoalkene **5** (1,2-diaza-1,3-diene). For the [4 + 1] annulation

Scheme 4. Gram-scale Reactions for the Cercosporin-Catalyzed Annulations



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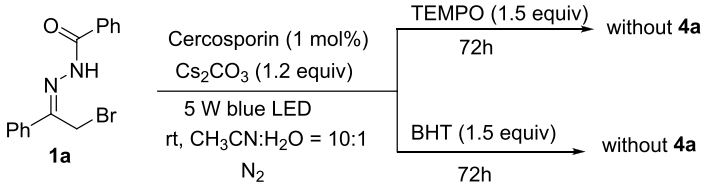
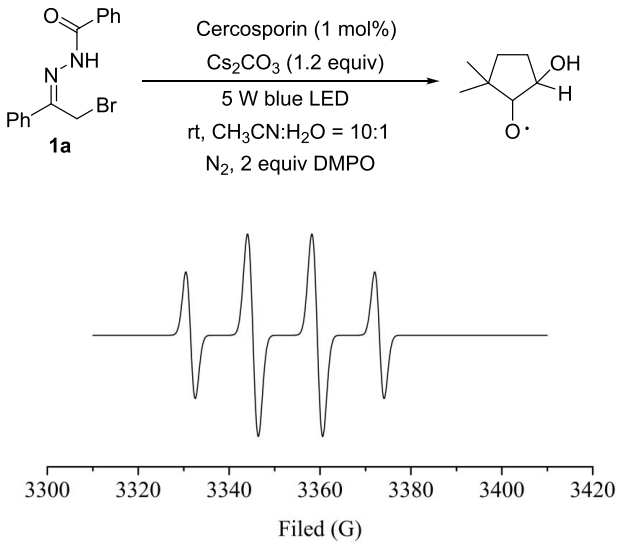
Scheme 5. Control Experiment and ESR Spin-trap

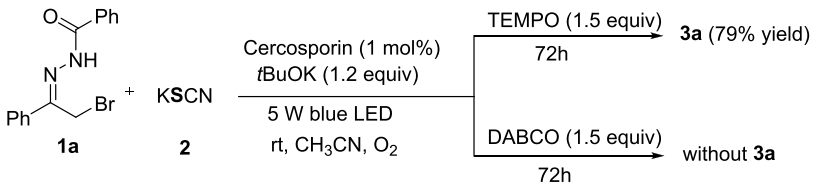
(a) Effect of TEMPO and BHT on the cercosporin-catalyzed [4+2] homocyclodimerizations of azoalkenes



(b) ESR spin-trap of cercosporin-catalyzed [4+2] homocyclodimerizations of azoalkenes with DMPO



(c) Effect of TEMPO and DABCO on the cercosporin-catalyzed [4+1] annulations of azoalkenes with KSCN



reaction, azoalkene **5** undergoes aza-Michael addition with the SCN− to generate a nucleophilic reaction product, which is isomerized to afford intermediate **6**. After that, intramolecular nucleophilic substitution reaction takes place to afford compound **7**.[21] The CN group is hydrolyzed by a base under the reaction conditions.[22] Oxidative aromatization[23] of intermediate **7** in the presence of $^1O_2$ generated from CP through the EnT process[10e] affords the [4 + 1] annulation product **3**. For the [4 + 2] homocyclodimerization, a radical pathway should be involved in the transformation process. Azoalkene **5** undergoes regioselective intermolecular [4 + 2] cycloaddition to give pyridazine **8**. Similar to the effect of CsF,[20a] the OH radical,[24] which was formed by CP self-electron transfer,[11a] may be the only active nucleophilic species supported by the results of optimization reaction and control experiments. Regioselective attack of the OH radical at one of the acyl carbonyls of **8** followed by nitrogen elimination and breaking of the C−N bond resulted in the intermediate radical **9**. Oxidative quenching of the excited state of the photocatalyst (CP*) by **9** via a single electron transfer process leads to the formation of an unstable carbanion intermediate, which undergoes protonation to afford the desired 1,4,5,6-tetrahydropyridazine. The catalyst turnover may be accomplished by the oxidation of water, together with the generation of the OH radical and the ground state of the photocatalyst CP.

CONCLUSIONS

In summary, we have developed a new method for the construction of nitrogen-containing heterocycles by using one of the perylenequinonoid derivatives, cercosporin, as a metal-free, cost-effective, and environmentally friendly photocatalyst under mild conditions. It selectively photocatalyzed [4 + 1] annulation of azoalkenes with thiocyanate salt as the S source and [4 + 2] cyclodimerization of azoalkenes to afford 1,2,3-thiadiazoles and 1,4,5,6- tetrahydropyridazines, respectively. The use of inexpensive household lights and the ease of handling make the developed methods particularly attractive for applications in synthesis. In particular, we set up a connection between microbial fermentation and organic photocatalysis for the construction of nitrogen-containing heterocycles in a sustainable, environmentally friendly manner.

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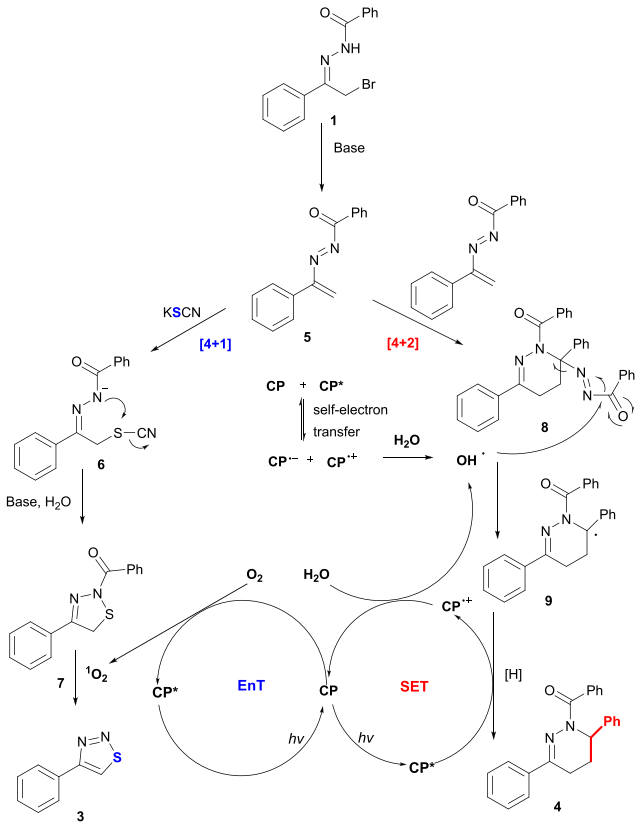
Scheme 6. Proposed Mechanism



Given the excellent properties of photosensitization, we expect that this new class of photoredox catalyst can be used for other chemical reactions, awaiting further investigation.

EXPERIMENTAL SECTION

General Methods. Cercosporin was biosynthesized by a new cercosporin producing strain in our laboratory. Hypocrellin A and hypocrellin B were commercially available and used without further purification. α-Halo-*N*-acyl-hydrazones **1** were synthesized according to a previously described method (α-Halo-*N*-acyl-hydrazones **1** were not stable in the ambient temperature).[25] All other commercially available reagents and solvents were used without further purification. Thin-layer chromatography was performed using silica gel plates F254. Visualization was accomplished with short-wavelength UV light (254 nm) and near-UV light (366 nm) sources. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 (400 MHz) spectrometer in $CDCl_3$ solution with internal solvent signals (for ^{1}H and ^{13}C) as the reference (7.26 and 77.2, respectively). Data for ^{13}C NMR are reported in terms of chemical shift, and no special nomenclature is used for equivalent carbons. High-resolution mass spectra (HRMS) were recorded on Waters Xevo G2 Q-TOF instrument. UV−vis and fluorescence measurements were performed with a Shimadzu UV-3600 plus spectrophotometer and an F-2700 spectrofluorometer. Electron spin resonance (ESR) was recorded on EMXplus-10/12. The lifetime was measured on an Edinburgh FLS920 fluorescence spectrometer. Cyclic voltammetry was performed using a CHI600E electrochemical workstation: Au wire (φ = 1.6 mm) sealed in a Teflon jacket as the working electrode, Pt wire as the counter electrode, Ag/AgCl (KCl, 3 M) electrode as the reference electrode, and ferrocenium/ferrocene (Fc^+/Fc) as the internal standard. The scan rate was 50 mV/s (in the range −1 to +2.2 V). Bu_4NPF_6 (0.1 M in MeCN) was used as the supporting electrolyte. Photochemical reaction was carried out in the borosilicate glass bottle under visible light by a PHILIPS 5 W blue LED at room temperature. The sample was placed at an approximate distance of 5 cm from the lamp. The light intensity was measured to be 6.51 mW/cm^2. The emission spectrum of each light source was measured with a Hitachi F-2700 spectrofluorometer. The intensity of irradiation was measured by an FZ-A radiometer (Photoelectric Instrument Factory of Beijing Normal University) equipped with a 400−1000 nm sensor.

General Procedure for the Cercosporin-Catalyzed [4 + 1] Annulations of Azoalkenes with KSCN. In a 10 mL Schlenk tube with a magnetic stirring bar, the cercosporin (0.01 equiv), α-halo-*N*-acyl-hydrazone **1** (0.2 mmol), KSCN **2** (2 equiv), and *t*BuOK (1.2 equiv) were dissolved in dry CH_3CN (2 mL), and the resulting mixtures were placed under 5 W blue LED for 16 h under an O_2 atmosphere. When the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography to afford the desired product **3**.

*4-Phenyl-1,2,3-thiadiazole (**3a**).*[4d] The representative procedure was followed using *N*′-(2-bromo-1-phenylethylidene) benzohydrazide (**1a**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3a** (28 mg, 88%) as a yellow solid. Mp = 74.2−75.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.66 (s, 1H), 8.07−8.05 (m, 2H), 7.55−7.44 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 162.9, 130.8, 129.9, 129.4, 129.2, 127.4. HRMS (ESI-Q-TOF) exact mass calcd for $C_8H_7N_2S$ [M + H]$^+$ 162.0330, found 163.0349.

*4-(4-Fluorophenyl)-1,2,3-thiadiazole (**3b**).*[4d] The representative procedure was followed using *N*′-(2-chloro-1-(4-fluorophenyl)-ethylidene)benzohydrazide (**1b**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3b** (25 mg, 72%) as a yellow solid. Mp = 94.5−95.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.60 (s, 1H), 8.09−8.02 (m, 2H), 7.23−7.19 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 164.3, 161.9, 161.3, 133.6, 129.8 (d, J_{C-F} = 9.0 Hz), 127.8 (d, J_{C-F} = 3.0 Hz), 116.3 (d, J_{C-F} = 22.0 Hz). HRMS (ESI-Q-TOF) exact mass calcd for $C_8H_6FN_2S$ [M + H]$^+$ 181.0236, found 181.0231.

*4-(4-Chlorophenyl)-1,2,3-thiadiazole (**3c**).*[4d] The representative procedure was followed using *N*′-(2-chloro-1-(4-chlorophenyl)-ethylidene)benzohydrazide (**1c**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3c** (33 mg, 87%) as a yellow solid. Mp = 131.3−133.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.65 (s, 1H), 8.00 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 162.6, 135.5, 132.4, 129.4, 128.9, 128.7. HRMS (ESI-Q-TOF) exact mass calcd for $C_8H_6ClN_2S$ [M+H]$^+$ 196.9940, found 196.9940.

*4-(4-Bromophenyl)-1,2,3-thiadiazole (**3d**).*[4d] The representative procedure was followed using *N*′-(2-bromo-1-(4-bromophenyl) ethylidene) benzohydrazide (**1d**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3d** (37 mg, 78%) as a yellow solid. Mp = 145.5−147.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.66 (s, 1H), 7.94 (d, *J* = 8 Hz, 2H), 7.65 (d, *J* = 8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 161.2, 134.3, 132.7, 130.4, 129.6, 123.1. HRMS (ESI-Q-TOF) exact mass calcd for $C_8H_6BrN_2S$ [M + H]$^+$ 240.9435, found 240.9429.

*4-(p-Tolyl)-1,2,3-thiadiazole (**3e**).*[4d] The representative procedure was followed using *N*′-(2-bromo-1-(*p*-tolyl) ethylidene) benzohydrazide (**1e**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3e** (31 mg, 90%) as a yellow solid. Mp = 65.4−67.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.59 (s, 1H), 7.94 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 8 Hz, 2H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 162.4, 139.4, 132.9, 130.2, 128.5, 127.5, 21.4. HRMS (ESI-Q-TOF) exact mass calcd for $C_9H_9N_2S$ [M + H]$^+$ 177.0486, found 177.0501.

*4-(4-Methoxyphenyl)-1,2,3-thiadiazole (**3f**).*[4d] The representative procedure was followed using *N*′-(2-chloro-1-(4-methoxyphenyl)-ethylidene)benzohydrazide (**1f**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3f** (32 mg, 85%) as a yellow solid. Mp = 82.6−84.2 °C.

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^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.52 (s, 1H), 7.99 (d, J = 8 Hz, 2H), 7.04 (d, J = 8 Hz, 2H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 162.3, 160.5, 131.8, 129.0, 123.8, 115.0, 55.7. HRMS (ESI-Q-TOF) exact mass calcd for $C_9H_9N_2OS$ $[M + H]^+$ 193.0436, found 193.0429.

*4-([1,1′-Biphenyl]-4-yl)-1,2,3-thiadiazole (**3g**).*[26] The representative procedure was followed using *N*′-(1-([1,1′-biphenyl]-4-yl)-2-bromoethylidene) benzohydrazide (**1g**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3g** (40 mg, 86%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.68 (s, 1H), 8.13 (d, J = 8 Hz, 2H), 7.75 (d, J = 8 Hz, 2H), 7.66 (d, J = 8 Hz, 2H), 7.50−7.46 (m, 2H), 7.41−7.37 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 162.0, 141.3, 139.8, 133.6, 130.2, 128.3, 128.2, 127.9, 127.2. HRMS (ESI-Q-TOF) exact mass calcd for $C_{14}H_{11}N_2S$ $[M + H]^+$ 239.0643, found 239.0652.

*4-(4-(Trifluoromethyl)phenyl)-1,2,3-thiadiazole (**3h**).*[4b] The representative procedure was followed using *N*′-(2-chloro-1-(4-(trifluoromethyl)phenyl)ethylidene)benzohydrazide (**1h**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3h** (37 mg, 81%) as a yellow solid. Mp = 105.4−107.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.77 (s, 1H), 8.19 (d, J = 8 Hz, 2H), 7.79 (d, J = 8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 160.8, 135.8, 135.0, 130.1, 128.3, 127.3 (t, J_{C-F} = 271.0 Hz), 126.6 (t, J_{C-F} = 4.0 Hz), 115.1. HRMS (ESI-Q-TOF) exact mass calcd for $C_9H_6F_3N_2S$ $[M + H]^+$ 231.0204, found 231.0226.

*4-(1,2,3-Thiadiazol-4-yl)benzonitrile (**3i**).*[4c] The representative procedure was followed using *N*′-(2-bromo-1-(4-cyanophenyl)-ethylidene)benzohydrazide (**1i**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3i** (27 mg, 74%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.80 (s, 1H), 8.19 (d, J = 8 Hz, 2H), 7.82 (d, J = 8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 160.5, 136.3, 135.3, 133.7, 128.3, 119.0, 1121. HRMS (ESI-Q-TOF) exact mass calcd for $C_9H_6N_3S$ $[M + H]^+$ 188.0282, found 188.0290.

*4-(4-Nitrophenyl)-1,2,3-thiadiazole (**3j**).*[27] The representative procedure was followed using *N*′-(2-bromo-1-(4-nitrophenyl) ethylidene) benzohydrazide (**1j**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3j** (29 mg, 71%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.66 (s, 1H), 7.94 (d, J = 12 Hz, 2H), 7.65 (d, J = 8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 161.2, 134.3, 132.7, 130.4, 129.6, 123.1. HRMS (ESI-Q-TOF) exact mass calcd for $C_8H_6N_3O_2S$ $[M + H]^+$ 208.0181, found 208.0181.

*4-(Furan-2-yl)-1,2,3-thiadiazole (**3k**).*[4b] The representative procedure was followed using *N*′-(2-bromo-1-(furan-2-yl)ethylidene)-benzohydrazide (**1k**) (0.2 mmol) and KSCN (0.4 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **3k** (19 mg, 65%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.62 (s, 1H), 7.58 (s, 1H), 7.19−7.18 (m, 1H), 6.62−6.61 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 154.0, 146.5, 144.7, 132.2, 112.5, 109.9. HRMS (ESI-Q-TOF) exact mass calcd for $C_6H_5N_2OS$ $[M + H]^+$ 153.0123, found 153.0140.

General Procedure for the Cercosporin-Catalyzed [4+2] Homocyclodimerizations of Azoalkenes. In a 10 mL Schlenk tube with a magnetic stirring bar, the cercosporin (0.01 equiv), α-halo-*N*-acyl-hydrazone **1** (0.5 mmol), and Cs_2CO_3 (1.2 equiv) were dissolved in a mixed solvent (CH_3CN/H_2O = 10:1, 2 mL), and the resulting mixtures were placed under 5 W blue LED for 16 h under a N_2 atmosphere. When the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography to afford the desired product **4**.

*(3,6-Diphenyl-5,6-dihydropyridazin-1(4H)-yl)(phenyl)-methanone (**4a**).*[20a] The representative procedure was followed using *N*′-(2-bromo-1-phenylethylidene) benzohydrazide (**1a**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 15:1) yielded **4a** (68 mg, 80%) as a yellow solid. Mp = 146.2−148.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.84−7.82 (m, 2H), 7.60−7.58 (m, 2H), 7.49−7.44 (m, 3H), 7.33−7.30 (m, 5H), 7.26−7.24 (m, 1H), 7.18 (d, J = 8 Hz, 2H), 6.09 (s, 1H), 2.71−2.67 (m, 1H), 2.43−2.16 (m, 3H).

*(3,6-Bis(4-fluorophenyl)-5,6-dihydropyridazin-1(4H)-yl) (phenyl)-methanone (**4b**).* The representative procedure was followed using *N*′-(2-chloro-1-(4-fluorophenyl) ethylidene) benzohydrazide (**1b**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **4b** (67 mg, 72%) as a yellow solid. Mp = 189.8−192.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.80−7.78 (m, 2H), 7.57−7.55 (m, 2H), 7.52−7.43 (m, 3H), 7.16−7.12 (m, 2H), 7.03−6.97 (m, 4H), 6.05 (s, 1H), 2.69−2.65 (m, 1H), 2.40−2.25 (m, 2H), 2.22−2.13 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 170.2, 163.4 (d, $^1J_{C-F}$ = 248.1 Hz), 162.0 (d, $^1J_{C-F}$ = 244.1 Hz), 146.0, 135.5 (d, $^4J_{C-F}$ = 3.1 Hz), 135.1, 133.2 (d, $^4J_{C-F}$ = 3.2 Hz), 130.4, 129.9, 127.5, 127.2 (d, $^3J_{C-F}$ = 8.2 Hz), 127.1 (d, $^3J_{C-F}$ = 8.0 Hz), 115.7 (d, $^2J_{C-F}$ = 21.5 Hz), 115.4 (d, $^2J_{C-F}$ = 21.6 Hz), 50.9, 24.0, 18.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −111.7, −115.5. HRMS (ESI-Q-TOF) exact mass calcd for $C_{23}H_{19}F_2N_2O$ $[M + H]^+$ 377.1465, found 377.1482.

*(3,6-Bis(4-chlorophenyl)-5,6-dihydropyridazin-1(4H)-yl)(phenyl)-methanone (**4c**).* The representative procedure was followed using *N*′-(2-chloro-1-(4-chlorophenyl)ethylidene)benzohydrazide (1c) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded 4c (71 mg, 70%) as a yellow solid. Mp = 176.9−180.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.78 (d, J = 4 Hz, 2H), 7.50−7.43 (m, 5H), 7.30−7.26 (m, 5H), 7.10 (d, J = 8 Hz, 2H), 6.03 (s, 1H), 2.68−2.63 (m, 1H), 2.39−2.26 (m, 2H), 2.20−2.11 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 170.2, 145.8, 138.3, 135.4, 135.3, 134.9, 133.2, 130.5, 129.9, 129.0, 128.6, 127.5, 126.9, 126.6, 51.2, 29.7, 23.8, 18.6. HRMS (ESI-Q-TOF) exact mass calcd for $C_{23}H_{19}Cl_2N_2O$ $[M + H]^+$ 409.0874, found 409.0864.

*(3,6-Bis(4-bromophenyl)-5,6-dihydropyridazin-1(4H)-yl)(phenyl)-methanone (**4d**).* The representative procedure was followed using *N*′-(2-bromo-1-(4-bromophenyl) ethylidene) benzohydrazide (1d) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded 4d (101 mg, 82%) as a yellow solid. Mp =176.1−179.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.78 (d, J = 8 Hz, 2H), 7.52−7.40 (m, 9H), 7.04 (d, J = 8 Hz, 2H), 6.01 (s, 1H), 2.67−2.62 (m, 1H), 2.39−2.25 (m, 2H), 2.20−2.11 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 170.2, 145.9, 138.9, 135.8, 134.8, 132.0, 131.6, 130.5, 129.9, 127.5, 127.2, 126.9, 123.6, 121.2, 51.3, 29.7, 23.8, 18.5. HRMS (ESI-Q-TOF) exact mass calcd for $C_{23}H_{19}Br_2N_2O$ $[M + H]^+$ 498.9845, found 498.9799.

*(3,6-Di-p-tolyl-5,6-dihydropyridazin-1(4H)-yl)(phenyl)-methanone (**4e**).* The representative procedure was followed using *N*′-(2-bromo-1-(*p*-tolyl) ethylidene) benzohydrazide (**1e**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **4e** (72 mg, 79%) as a yellow solid. Mp =192.6−194.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.81 (d, J = 8 Hz, 2H), 7.48−7.40 (m, 5H), 7.12−7.05 (m, 6H), 6.04 (s, 1H), 2.68−2.63 (m, 1H), 2.61 (s, 3H), 2.41−2.15 (m, 3H), 2.33 (s, 3H), 2.30 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 170.1, 146.9, 139.2, 137.0, 136.8, 135.5, 134.5, 130.2, 130.1, 129.4, 129.1, 127.3, 125.4, 125.3, 51.5, 24.0, 21.2, 21.0, 18.7. HRMS (ESI-Q-TOF) exact mass calcd for $C_{25}H_{25}N_2O$ $[M + H]^+$ 369.1967, found 369.1965.

*(3,6-Di([1,1′-biphenyl]-4-yl)-5,6-dihydropyridazin-1(4H)-yl)-(phenyl)methanone (**4f**).* The representative procedure was followed using *N*′-(1-([1,1′-biphenyl]-4-yl)-2-bromoethylidene) benzohydrazide (**1g**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 10:1) yielded **4f** (110 mg, 90%) as a yellow solid. Mp = 209.6−210.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.88−7.86 (m, 2H), 7.68 (d, J = 8 Hz, 2H), 7.59−7.53 (m, 8H), 7.48 (d, J = 8 Hz, 2H), 7.45−7.39 (m, 5H), 7.36−7.30 (m, 2H), 7.27 (d, J = 8 Hz, 2H), 6.14 (s, 1H), 2.80−2.72 (m, 1H), 2.49−2.26 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 170.3, 146.7, 141.9, 140.7, 140.3, 139.0, 136.1, 135.3, 130.3, 130.1, 129.0, 128.8, 127.6, 127.4, 127.3, 127.1, 127.0, 125.9, 125.8, 51.6, 29.7, 24.0, 18.8. HRMS (ESI-Q-TOF) exact mass calcd for $C_{35}H_{29}N_2O$ $[M + H]^+$ 493.2280, found 493.2260.

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*(3,6-Bis(4-nitrophenyl)-5,6-dihydropyridazin-1(4H)-yl)(phenyl)-methanone (**4g**).* The representative procedure was followed using *N*′-(2-bromo-1-(4-nitrophenyl) ethylidene) benzohydrazide (**1j**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4g** (75 mg, 70%) as a yellow solid. Mp = 71.2−73.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.22−8.16 (m, 4H), 7.80 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H), 7.57−7.48 (m, 3H), 7.34 (d, J = 8 Hz, 2H), 6.15 (s, 1H), 2.81−2.75 (m, 1H), 2.54−2.38 (m, 2H), 2.24−2.15 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 170.4, 148.1, 147.5, 147.0, 144.6, 142.4, 134.1, 131.1, 130.0, 127.7, 126.5, 126.1, 124.3, 123.8, 51.8, 29.7, 23.6, 18.7. HRMS (ESI-Q-TOF) exact mass calcd for $C_{23}H_{19}N_4O_5$ [M + H]$^+$ 431.1356, found 431.1327.

*(3,6-Bis(4-fluorophenyl)-5,6-dihydropyridazin-1(4H)-yl)(4-methoxyphenyl)methanone (**4h**).* The representative procedure was followed using *N*′-(2-chloro-1-(4-fluorophenyl)ethylidene)-4-methoxybenzohydrazide (**1m**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4h** (73 mg, 72%) as a yellow solid. Mp = 71.8−72.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.86 (d, J = 8 Hz, 2H), 7.63−7.59 (m, 2H), 7.14−7.11 (m, 2H), 7.04−6.94 (m, 6H), 6.03 (s, 1H), 3.89 (s, 3H), 2.69−2.64 (m, 1H), 2.39−2.25 (m, 2H), 2.22−2.13 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 169.4, 163.4 (d, $^1J_{C-F}$ = 248.1 Hz), 162.0 (d, $^1J_{C-F}$ = 243.9 Hz), 161.5, 145.6, 135.6 (d, $^4J_{C-F}$ = 3.3 Hz), 133.3 (d, $^4J_{C-F}$ = 3.2 Hz), 132.5, 127.2 (d, $^3J_{C-F}$ = 8.3 Hz), 127.1 (d, $^3J_{C-F}$ = 8.0 Hz), 115.7 (d, $^2J_{C-F}$ = 21.5 Hz), 115.4 (d, $^2J_{C-F}$ = 21.6 Hz), 112.7, 55.4, 51.2, 29.7, 24.0, 18.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −111.7, −115.5. HRMS (ESI-Q-TOF) exact mass calcd for $C_{24}H_{21}F_2N_2O_2$ [M + H]$^+$ 407.1571, found 407.1557.

*(3,6-Bis(4-bromophenyl)-5,6-dihydropyridazin-1(4H)-yl)(4-methoxyphenyl)methanone (**4i**).* The representative procedure was followed using *N*′-(2-bromo-1-(4-bromophenyl)ethylidene)-4-methoxybenzohydrazide (**1n**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4i** (107 mg, 82%) as a yellow solid. Mp = 185.2−187.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.85 (d, J = 8 Hz, 2H), 7.50−7.42 (m, 6H), 7.03 (d, J = 8 Hz, 2H), 6.96 (d, J = 8 Hz, 2H), 5.99 (s, 1H), 3.89 (s, 3H), 2.68−2.62 (m, 1H), 2.39−2.24 (m, 2H), 2.22−2.11 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 182.1, 169.2, 165.0, 162.0, 144.4, 141.8, 135.5, 133.3, 132.5, 132.0, 131.6, 127.1, 126.5, 123.7, 121.5, 114.4, 112.8, 85.9, 55.6, 31.8, 18.0. HRMS (ESI-Q-TOF) exact mass calcd for $C_{24}H_{21}Br_2N_2O_2$ [M + H]$^+$ 528.9951, found 528.9954.

*(3,6-Bis(4-methoxyphenyl)-5,6-dihydropyridazin-1(4H)-yl)(4-chlorophenyl)methanone (**4j**).* The representative procedure was followed using *N*′-(2-bromo-1-(4-methoxyphenyl) ethylidene)-4-chlorobenzohydrazide (**1o**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4j** (85 mg, 75%) as a yellow solid. Mp = 187.5−188.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.78 (d, J = 8 Hz, 2H), 7.53 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 2H), 6.87−6.83 (m, 4H), 5.99 (s, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.70−2.62 (m, 1H), 2.36−2.15 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 168.8, 160.6, 158.8, 147.3, 136.2, 133.8, 131.8, 131.6, 130.4, 129.7, 127.6, 126.8, 126.6, 114.3, 113.9, 55.4, 51.2, 24.1, 18.7. HRMS (ESI-Q-TOF) exact mass calcd for $C_{25}H_{24}ClN_2O_3$ [M + H]$^+$ 435.1476, found 435.1485.

*(3,6-Bis(4-chlorophenyl)-5,6-dihydropyridazin-1(4H)-yl)(4-chlorophenyl)methanone (**4k**).* The representative procedure was followed using 4-chloro-*N*′-(2-chloro-1-(4-chlorophenyl)ethylidene)-benzohydrazide (**1p**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4k** (93 mg, 85%) as a yellow solid. Mp = 195.8−197.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.76 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 7.43 (d, J = 8 Hz, 2H), 7.32−7.28 (m, 4H), 7.08 (d, J = 8 Hz, 2H), 6.00 (s, 1H), 2.69−2.64 (m, 1H), 2.39−2.25 (m, 2H), 2.21−2.12 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 169.0, 146.4, 138.2, 136.7, 135.5, 135.2, 133.3, 131.6, 129.1, 128.8, 127.8, 126.6, 51.3, 23.8, 18.6. HRMS (ESI-Q-TOF) exact mass calcd for $C_{23}H_{18}Cl_2N_2O$ [M + H]$^+$ 443.0485, found 443.0491.

*4,4′-(1-(4-Chlorobenzoyl)-1,4,5,6-tetrahydropyridazine-3,6-diyl) Dibenzonitrile (**4l**).* The representative procedure was followed using *N*′-(2-bromo-1-(4-cyanophenyl)ethylidene)-4-chlorobenzohydrazide (**1q**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4l** (79 mg, 75%) as a yellow solid. Mp = 89.3−91.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.75 (d, J = 8 Hz, 2H), 7.67−7.63 (m, 6H), 7.46 (d, J = 8 Hz, 2H), 7.26 (d, J = 8 Hz, 2H), 6.07 (s, 1H), 2.76−2.71 (m, 1H), 2.47−2.33 (m, 2H), 2.24−2.12 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 169.1, 145.4, 144.9, 140.5, 137.3, 132.9, 132.4, 131.5, 128.0, 126.2, 125.8, 118.3, 112.9, 111.8, 52.0, 23.5, 18.6. HRMS (ESI-Q-TOF) exact mass calcd for $C_{25}H_{18}ClN_4O$ [M + H]$^+$ 425.1169, found 425.1201.

*(3,6-Bis(4-nitrophenyl)-5,6-dihydropyridazin-1(4H)-yl)(4-chlorophenyl)methanone (**4m**).* The representative procedure was followed using *N*′-(2-bromo-1-(4-nitrophenyl)ethylidene)-4-chlorobenzohydrazide (**1r**) (0.2 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4m** (89 mg, 77%) as a yellow solid. Mp = 205.9−207.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.75 (d, J = 8 Hz, 2H), 7.48−7.41 (m, 8H), 7.02 (d, J = 8 Hz, 2H), 5.98 (s, 1H), 2.69−2.64 (m, 1H), 2.39−2.25 (m, 2H), 2.21−2.12 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 169.0, 146.4, 138.7, 136.7, 135.6, 133.1, 132.0, 131.7, 131.6, 127.8, 127.2, 126.9, 123.9, 121.3, 51.4, 23.7, 18.6. HRMS (ESI-Q-TOF) exact mass calcd for $C_{23}H_{18}ClN_4O_5$ [M + H]$^+$ 465.0865, found 465.0842.

*(3,6-Bis(4-chlorophenyl)-5,6-dihydropyridazin-1(4H)-yl)(4-(tert-butyl)phenyl)methanone (**4n**).* The representative procedure was followed using *N*′-(2-bromo-1-(4-chlorophenyl)ethylidene)-4-(*tert*-butyl)benzohydrazide (**1s**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4n** (98 mg, 85%) as a yellow solid. Mp = 249.6−251.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.78 (d, J = 8 Hz, 2H), 7.53 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H), 7.30−7.27 (m, 4H), 7.09 (d, J = 8 Hz, 2H), 6.03 (s, 1H), 2.68−2.63 (m, 1H), 2.39−2.26 (m, 2H), 2.21−2.10 (m, 1H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 170.0, 154.1, 145.7, 138.4, 135.5, 135.2, 133.1, 131.7, 130.1, 129.0, 128.6, 126.9, 126.7, 124.4, 51.3, 34.9, 31.2, 29.7, 23.8, 18.6. HRMS (ESI-Q-TOF) exact mass calcd for $C_{27}H_{27}Cl_2N_2O$ [M + H]$^+$ 465.1501, found 465.1480.

*(3,6-Bis(4-bromophenyl)-5,6-dihydropyridazin-1(4H)-yl)(4-(tert-butyl)phenyl)methanone (**4o**).* The representative procedure was followed using *N*′-(2-bromo-1-(4-chlorophenyl)ethylidene)-4-(*tert*-butyl)benzohydrazide (**1t**) (0.5 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4o** (113 mg, 82%) as a white solid. Mp = 192.4−196.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.78 (d, J = 8 Hz, 2H), 7.48−7.42 (m, 8H), 7.03 (d, J = 8 Hz, 2H), 6.01 (s, 1H), 2.67−2.62 (m, 1H), 2.39−2.25 (m, 2H), 2.20−2.10 (m, 1H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 169.9, 154.1, 145.7, 138.9, 136.0, 132.0, 131.7, 131.6, 130.2, 131.7, 131.6, 130.2, 127.2, 126.9, 124.4, 123.6, 121.2, 51.3, 34.9, 31.2, 23.8, 18.6. HRMS (ESI-Q-TOF) exact mass calcd for $C_{27}H_{27}Br_2N_2O$ [M + H]$^+$ 555.0472, found 555.0427.

*(4-(tert-Butyl)phenyl)(3,6-di([1,1′-biphenyl]-4-yl)-5,6-dihydropyridazin-1(4H)-yl) Methanone (**4p**).* The representative procedure was followed using *N*′-(1-([1,1′-biphenyl]-4-yl)-2-bromoethylidene)-4-(*tert*-butyl)benzohydrazide (**1u**) (0.2 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4p** (121 mg, 89%) as a yellow solid. Mp = 189.2−190.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 7.87 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.60−7.58 (m, 3H), 7.56−7.49 (m, 7H), 7.45−7.39 (m, 5H), 7.37−7.27 (m, 4H), 6.14 (s, 1H), 2.80−2.72 (m, 1H), 2.48−2.21 (m, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ ppm 170.0, 153.8, 146.4, 141.9, 140.8, 140.4, 140.2, 139.1, 136.2, 132.1, 130.3, 128.8, 127.6, 127.2, 127.1, 127.0, 126.0, 125.9, 124.4, 51.7, 34.9, 31.3, 24.1, 18.9. HRMS (ESI-Q-TOF) exact mass calcd for $C_{39}H_{37}N_2O$ [M + H]$^+$ 549.2906, found 549.2922.

*(3,6-Bis(4-nitrophenyl)-5,6-dihydropyridazin-1(4H)-yl)(4-(tert-butyl)phenyl)methanone (**4q**).* The representative procedure was followed using *N*′-(2-bromo-1-(4-nitrophenyl)ethylidene)-4-(*tert*-butyl)benzohydrazide (**1v**) (0.2 mmol) as the substrate. Isolation by column chromatography (PE/EtOAc: 5:1) yielded **4q** (85 mg, 70%) as a yellow solid. Mp = 70.2−72.3 °C. ^{1}H NMR (400 MHz,

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$CDCl_3$): δ ppm 8.21−8.17 (m, 4H), 7.81−7.74 (m, 4H), 7.52 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 6.14 (s, 1H), 2.80−2.75 (m, 1H), 2.52−2.39 (m, 2H), 2.24−2.14 (m, 1H), 1.40 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ ppm 170.1, 154.9, 148.0, 147.5, 147.1, 144.3, 142.5, 130.9, 130.2, 126.5, 126.1, 124.6, 124.3, 123.8, 51.8, 35.0, 31.2, 23.6, 18.7. HRMS (ESI-Q-TOF) exact mass calcd for $C_{27}H_{27}N_4O_5$ $[M + H]^+$ 487.1982, found 487.1989.

Gram-Scale Reaction for the Cercosporin-Catalyzed [4 + 1] Annulation. In a 50 mL Schlenk bottle with a magnetic stirring bar, the cercosporin (0.01 equiv), α-bromo-*N*-acyl-hydrazone **1a** (5 mmol), KSCN **2** (2 equiv), and *t*BuOK (1.2 equiv) were dissolved in dry CH_3CN (20 mL), and the resulting mixtures were placed under 5 W blue LED for 24 h under an O_2 atmosphere. When the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography to afford the desired product **3a** (0.67 g, 82%).

Gram-Scale Reaction for the Cercosporin-Catalyzed [4 + 2] Homodimerization. In a 50 mL Schlenk bottle with a magnetic stirring bar, the cercosporin (0.01 equiv), α-bromo-*N*-acyl-hydrazone **1a** (10 mmol), and Cs_2CO_3 (1.2 equiv) were dissolved in a mixed solvent (CH_3CN/H_2O = 10:1, 20 mL), and the resulting mixtures were placed under 5 W blue LED for 24 h under a N_2 atmosphere. When the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography to afford the desired product **4a** (1.29 g, 76%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00545.

Biosynthesis, photochemical, and electrochemical characterizations of cercosporin; spectra of the light source; on/off light experiment; copies of spectral data for compounds **3** and **4** (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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