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An *N*-(acetoxy)phthalimide motif as a visible-light pro-photosensitizer in photoredox decarboxylative arylthiation†

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An efficient visible-light photoredox decarboxylative coupling of *N*-(acetoxy)phthalimides with aryl thiols has been developed. The reaction was performed well at room temperature with good tolerance of functional groups. Importantly, the visible-light photoredox decarboxylative arylthiation did not need an added photocatalyst.

Carbon–sulfur bond formation is of great concern in organic synthesis because sulfur-containing compounds widely occur in natural products, biologically active molecules, and materials,[1] so it is highly desirable to develop a convenient and efficient protocol for the formation of C–S bonds using readily available starting materials under mild conditions. Carboxylic acids and their derivatives are common chemicals and widely occur in organic molecules and natural products,[2] and some classical decarboxylative coupling reactions,[3] such as Heck-type reactions,[4] allylations,[5] redox-neutral cross-coupling reactions,[6] and oxidative arylations,[7] have been developed. In fact, C–S bond formation *via* decarboxylative couplings has been developed. Unfortunately, higher temperatures and oxidants are usually required.[8a] Barton and co-workers have developed decarboxylative arylthiation of thiohydroxamate esters,[8b,c] and Procopiou's group realized the formation of C–S bonds using Barton's thiohydroxamate esters under irradiation of two 200 W tungsten filament light bulbs at 0 °C.[8d] However, only disulfides were effective. Recently, visible-light photoredox catalysis has emerged as a powerful activation protocol in new chemical transformations,[9] and some achievements have been made in the visible-light photoredox decarboxylative couplings of carboxylic acids and their derivatives by some groups[10] and us.[11] However, visible-light photocatalysts usually are necessary. In 1989, Okada and co-workers reported their pioneering research on the decarboxylative coupling of *N*-(acetoxy)phthalimides under irradiation of UV.[12] Since this discovery, the direct photogeneration of radicals from the phthalimide derivatives with UV in the absence of a photocatalyst has been established.[13] Unfortunately, the visible-light photoredox decarboxylative coupling in the absence of a photocatalyst has been ignored thus far. Very recently, Overman's group observed the Michael addition of *N*-(acyloxy)-phthalimides to electron-deficient olefins with irradiation of low-energy blue LEDs without addition of a photocatalyst, and they thought that the transformation was poorly understood at the time.[14] Several photoinduced cross-couplings of aryl halides with aryl thiols have also been described in the presence of catalysts.[15] Herein, we report a photoredox arylthiation of *N*-(acetoxy)phthalimides at room temperature under irradiation of visible light without the requirement of an added photocatalyst, and the corresponding mechanism is explored.

Coupling of **1k** with 4-isopropylbenzenethiol (**2e**) was selected as the model to optimize the conditions of visible-light photoredox catalysis including photocatalysts, bases and solvents (see Table S1 in the ESI†). The results showed that the optimal photoredox conditions are as follows: 1.5 equiv. of Cs_2CO_3 as the base and DMF as the solvent under an Ar atmosphere and irradiation of visible light with a 40 W compact fluorescent lamp (CFL) or a 3 W blue LED. After obtaining the optimized visible-light photoredox conditions, the substrate scope for decarboxylative coupling of *N*-(acetoxy)phthalimides (**1**) with aryl thiols (**2**) was surveyed. As shown in Table 1, ten common organic carboxylic acid active esters were first tested, and the active esters of secondary and tertiary carboxylic acids displayed higher reactivity than the primary ones (see **3a–j**). A carboxylic acid containing an alkene gave a low yield with the production of unknown by-products (see **3f**). The reactivity of various *N*-protected amino acid active esters was investigated, and *N*-Boc/Cbz-Pro-OPht and *N*-Boc-pipecolinic acid active esters gave excellent yields (see **3k**, **3w–x**). Active esters of three neutral amino acids including alanine, leucine and phenylalanine were applied as the radical precursors, and a phenylalanine derivative provided a slightly lower yield than two other neutral amino acid derivatives (see **3y–aa**). *N*,*O*-Protected serine active ester gave arylthiation product **3ab** in 80% yield, and other amino

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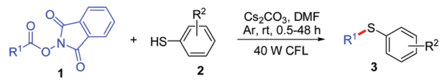
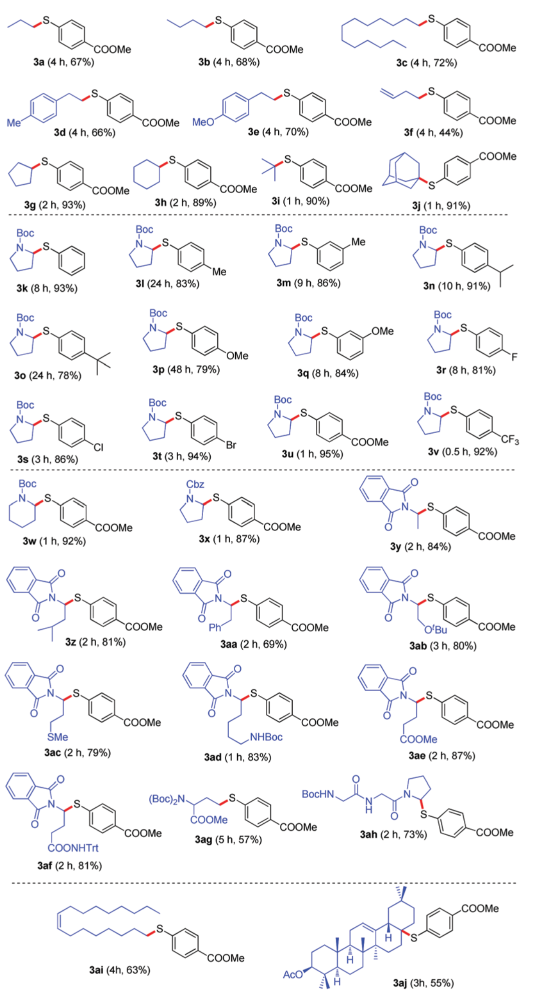
† Electronic supplementary information (ESI) available: Optimization of conditions, mechanistic investigations, synthetic procedures, characterization data and ^{15}N, ^{1}H, and ^{13}C NMR spectra of the synthesized compounds **3a–ah**. See DOI: 10.1039/c6cc06994k

Table 1 Scope for visible-light photoredox decarboxylative arylthiation[a]



3 (time, yield[b])


3a (4 h, 67%)
3b (4 h, 68%)
3c (4 h, 72%)
3d (4 h, 66%)
3e (4 h, 70%)
3f (4 h, 44%)
3g (2 h, 93%)
3h (2 h, 89%)
3i (1 h, 90%)
3j (1 h, 91%)
3k (8 h, 93%)
3l (24 h, 83%)
3m (9 h, 86%)
3n (10 h, 91%)
3o (24 h, 78%)
3p (48 h, 79%)
3q (8 h, 84%)
3r (8 h, 81%)
3s (3 h, 86%)
3t (3 h, 94%)
3u (1 h, 95%)
3v (0.5 h, 92%)
3w (1 h, 92%)
3x (1 h, 87%)
3y (2 h, 84%)
3z (2 h, 81%)
3aa (2 h, 69%)
3ab (3 h, 80%)
3ac (2 h, 79%)
3ad (1 h, 83%)
3ae (2 h, 87%)
3af (2 h, 81%)
3ag (5 h, 57%)
3ah (2 h, 73%)
3ai (4h, 63%)
3aj (3h, 55%)

[a] Reaction conditions: under an Ar atmosphere and irradiation of visible light, carboxylic acid active ester ($R^1COOPht$) (**1**) (0.15 mmol), aryl thiol (**2**) (0.18 mmol), Cs_2CO_3 (0.225 mmol), DMF (1.5 mL), temperature (rt, ∼25 °C), time (0.5–48 h) in a sealed Schlenk tube. [b] Isolated yield. Boc = *tert*-butyloxycarbonyl. Cbz = benzyloxycarbonyl. Trt = trityl. ^{t}Bu = *tert*-butyl. CFL = compact fluorescent lamp.

acid (methionine, lysine, glutamic acid and glutamine) derivatives containing different functional groups were also good substrates (see **3ac–af**). We also tested active ester of Glu on the side chain carboxyl, *N*-bis(Boc)-Glu(OPht)-OMe, and it afforded target product **3ag** in 57% yield. Interestingly, tripeptide active ester, *N*-Boc-Gly-Gly-Pro-OPht, was tested, and it yielded **3ah** containing a tripeptide fragment in 73% yield. Natural *cis*-9-octadecenoic acid and oleanic acid derivatives were used as the substrates, and they provided the corresponding arylthiation products **3ai** and **3aj** in 63% and 55% yields, respectively. The substrate scope of aryl thiols was explored using *N*-Boc-Pro-OPht as the partner (see **3k–v**), and aryl thiols containing electron-withdrawing groups exhibited faster reaction rate than those containing electron-donating groups. One main factor was that the aryl thiols containing electron-donating groups were of higher nucleophilicity and more easily formed carboxylic acid thiol esters, which was not favorable for subsequent visible-light photoredox decarboxylative arylthiation (see the reaction mechanism in Scheme 2). The visible-light photoredox decarboxylative arylthiation displayed tolerance of various functional groups including amides, esters, ethers, C–F bonds, C–Cl bonds, C–Br bonds and CF_3. It is worthwhile to note that some products contain amino acid fragments, and their further modification can provide diverse molecules after removal of the protective groups on them.

To explore the mechanism for the visible-light photoredox decarboxylative arylthiation, cyclopentanecarboxylic acid active ester [*c*-Pen-COOPht (**1g**)] was chosen as the model substrate to investigate its UV-visible absorption spectra under different conditions in the range of 200–800 nm (Fig. 1a). *c*-Pen-COOPht (**1g**) in DMF only exhibited UV absorption peaks between 200 and 330 nm (line **1g** in Fig. 1a). Addition of NaCl did not lead to any variation of the UV-visible absorption spectrum (line **1g** + NaCl in Fig. 1a), which showed that **1g** could not transform into a photosensitizer in the presence of the alkali-metal ion. Interestingly, different UV-visible absorption spectra were displayed when different bases, diisopropylethylamine (DIPEA) (line **1g** + DIPEA in Fig. 1a), Na_2CO_3 (line **1g** + Na_2CO_3 in Fig. 1a) and Cs_2CO_3 (line **1g** + Cs_2CO_3 in Fig. 1a), were added to DMF solution of **1g**, respectively, and some absorption peaks in the range of 400–800 nm were observed, in which the effect of Cs_2CO_3 was the most conspicuous. To make out what happened with **1g**, we prepared ^{15}N-labeled *N*-(acetoxy)phthalimide, cyclohexanecarboxylic

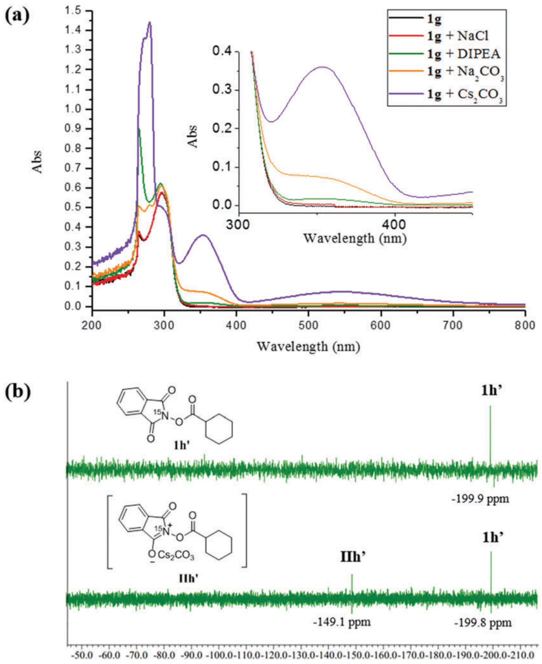
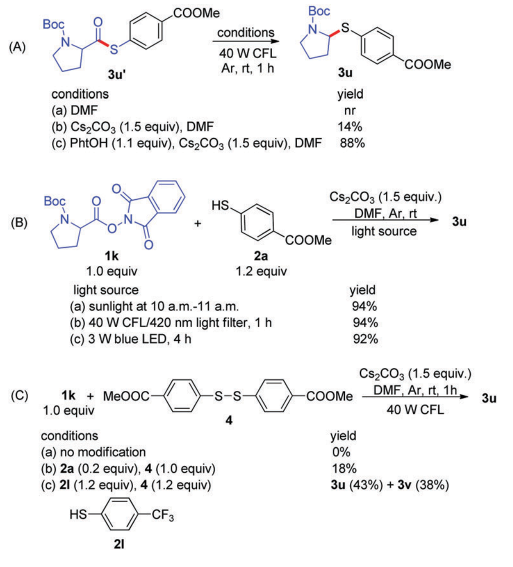


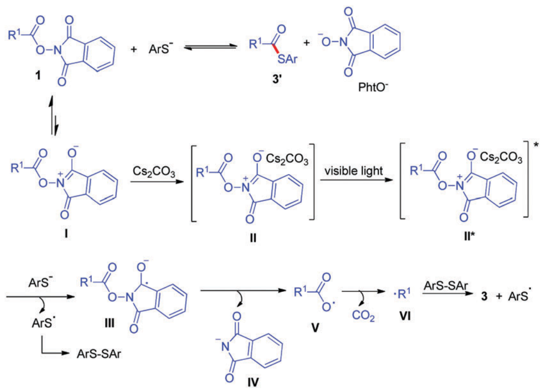
Fig. 1 (a) The UV-visible absorption spectra of cyclopentanecarboxylic acid active ester (*c*-Pen-COOPht (**1g**)) under different conditions. (b) ^{15}N NMR spectra of ^{15}N-cyclohexanecarboxylic acid active ester [*c*-Hex-COOPht (**1h′**)] (0.02 M in DMF) in the absence or presence of Cs_2CO_3 (using $Me^{15}NO_2$ as the external standard).

acid active ester [*c*-Hex-COOPht (**1h′**)] (see the ESI† for the details), and its ^{15}N NMR spectrum in DMF showed a peak at −199.9 ppm (Fig. 1b). When Cs_2CO_3 was added to a DMF solution of **1h′**, a new peak at −149.1 ppm corresponding to complex **IIh′** of **Ih′** with Cs_2CO_3 was observed (see Fig. 1b). It is worthwhile to note that the signal at −149.1 ppm is not intense because Cs_2CO_3 is not highly soluble in DMF. The UV-visible absorption spectra of 4-(trifluoromethyl)thiophenol (TFTP) (**2l**) and 1,2-bis(4-(trifluoromethyl)phenyl)disulfane (BTFPD) were detected in the absence or presence of Cs_2CO_3, and no new absorption peak was observed beyond 400 nm (see Fig. S1-I, II in the ESI†), which implied that neither aryl thiols nor disulfides could be the visible light photosensitizers in the reactions. Investigation on treatment of cyclopentanecarboxylic acid active ester (*c*-Pen-COOPht (**1g**)) with 4-cyanobenzyl bromide by HRESI-MS exhibited that another resonance structure **Ig** of **1g** could occur in the solution (see Fig. S2, S3 and Scheme S1 in the ESI†). The radical-trapping experiments displayed that the reactions involved a free-radical intermediate process (see Fig. S4 and Scheme S2 in the ESI†). We performed Stern–Volmer fluorescence quenching experiments (see Fig. S5–S9 in the ESI†), and the results showed that complex **IIg** of **Ig** with Cs_2CO_3 could be a photosensitizer of visible light.

Furthermore, several control experiments were performed under different conditions. (A) Using *N*-Boc-proline thiol ester (**3u′**) as the substrate: (a) no reaction took place for **3u′** in DMF under irradiation of visible light (Scheme 1Aa); (b) addition of 1.5 equiv. of Cs_2CO_3 (relative to the amount of **3u′**) led to the formation of a small amount of product **3u** (Scheme 1Ab), but the transformation is poorly understood at this time; and (c) the reaction provided **3u** in 88% yield in the presence of 1.1 equiv. of *N*-hydroxyphthalimide (PhtOH) and 1.5 equiv. of Cs_2CO_3 (Scheme 1Ac). The results demonstrated that the formation of *N*-(acetoxy)phthalimide derivatives through displacement of the thiol ester by PhtOH was of great concern for the visible-light photoredox decarboxylative arylthiation. (B) Using *N*-Boc-Pro-OPht (**1k**) as the substrate irradiated with different light sources: (a) a similar yield was achieved with sunlight instead of a 40 W CFL (Scheme 1Ba); (b) the reaction was performed well when lights below 420 nm were filtered under irradiation of a 40 W CFL (Scheme 1Bb); and (c) irradiation with 3 W blue LEDs provided **3u** in 92% yield (Scheme 1Bc). The latter two experiments showed that the reaction was not activated by UV-light from CFLs. (C) In the presence of dimethyl 4,4′-disulfanediyldibenzoate (**4**): (a) reaction of **1k** with **4** did not work under the standard conditions (Scheme 1Ca); (b) treatment of **1k** (1.0 equiv.), **2a** (0.2 equiv.) and **4** (1.0 equiv.) provided **3u** in only 18% yield (Scheme 1Cb); and (c) reaction of **1k** (1.0 equiv.), 4-(trifluoromethyl)thiophenol (**2l**) (1.2 equiv.) and **4** (1.2 equiv.) gave **3u** and **3v** in 43% and 38% yields, respectively (Scheme 1Cc), and the result exhibited that coupling of carbon radicals with diaryl disulfide was reasonable.



Scheme 1 Control experiments for mechanistic investigations.



Scheme 2 A possible mechanism for visible-light photoredox decarboxylative arylthiation.

A possible mechanism for the visible-light photoredox decarboxylative arylthiation is proposed in Scheme 2 according to the results above. Reversible treatment of **1** with aryl thiol (**2**) in the presence of a base (Cs_2CO_3) leads to thiol ester (**3′**) and a PhtO$^-$ anion. Two resonance structures of **1** and **I** occur in the solution,[16] and complexation of **I** with Cs_2CO_3 provides **II**. Irradiation of **II** as a photosensitizer with visible light gives the excited-state **II***, and a single electron transfer from ArS$^-$ to phthalimide of **II*** delivers two radicals, **III** and ArS$^\bullet$, in which dimerization of ArS$^\bullet$ forms diaryl disulfide.[17] Elimination of the phthalimide anion (**IV**) from **III** provides carboxyl radical **V**, and release of carbon dioxide in **V** provides radical **VI**. Reaction of **VI** with diaryl disulfide leads to the target product (**3**).[18]

In summary, we have developed a novel and efficient visible-light photoredox decarboxylative arylthiation. The coupling performed well at room temperature and exhibited great universality of substrates. Importantly, no extra photocatalyst was required in the photoredox decarboxylative arylthiation. The mechanistic investigations show that an *N*-(acetoxy)phthalimide unit is a pro-photosensitizer, and its complex with the inorganic base can absorb visible light. Therefore, the novel and efficient method will find widespread application in the synthesis of aryl sulfides.

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