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Photocatalytic C–C bond thio(seleno)esterification of 1,2-diketone-derived pro-aromatic intermediates†

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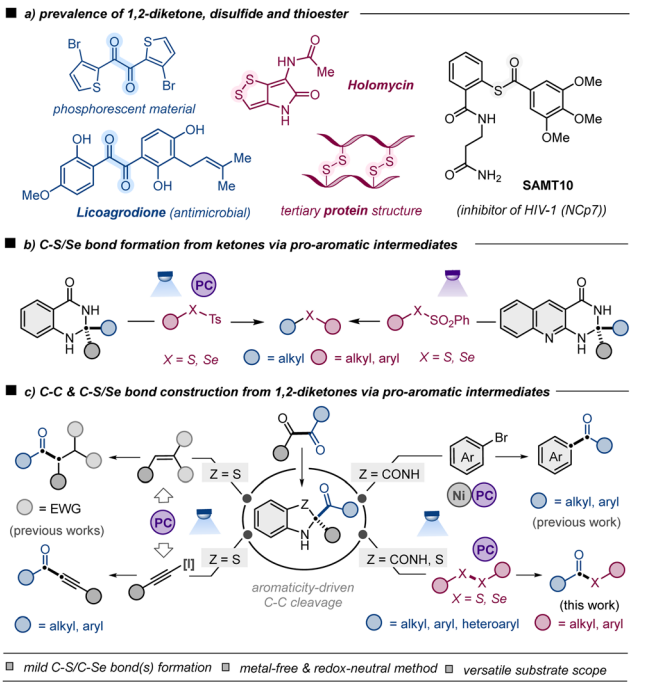
We report an organophotocatalyst-enabled oxidant-free C–S/C–Se bond coupling of (un)symmetrical 1,2-diketones *via* pro-aromatic dihydroquinazolinones/benzothiazolines, employing readily accessible disulfides/diselenides. In this scalable and redox-neutral method, various dialkyl, di(hetero)aryl, and alkyl-aryl 1,2-diketones are expediently converted to *S*-aryl (*S*-alkyl) alkyl/(hetero)aryl thioesters and Se-alkyl aryl selenoesters with broad functional group compatibility in high efficiency.

1,2-Diketones constitute a unique class of carbonyl compounds that are prevalent in various natural products[1] and synthetic materials[2] as well as easily prepared in the laboratory (Scheme 1a).[3] Due to their low-lying LUMO ($\pi^* + \pi^*$),[4] 1,2-dicarbonyl compounds serve as versatile synthetic intermediates in organic chemistry, including their use in the synthesis of heteroaromatic compounds and bisimine/bisoxime ligands among others.[5] Compared to the traditional reactivity, the exploration of C(C═O)–C(C═O) bond cleavage of 1,2-diketones is relatively underdeveloped in advanced organic synthesis.[6–8] Notably, the cleavage of the C(CO)–C(α) bond of aliphatic ketones *via* different pro-aromatic intermediates is rapidly evolving, enabling researchers to devise various innovative methods for C–C and C–X bond formation.[9] In this regard, Chen, Walsh, Shang and co-workers described a photoredox-catalyzed C–S/Se coupling of dihydroquinazolinones with thio(seleno)sulfonates, *en route* to thioethers and selenoethers (Scheme 1b).[9d] Later, Li *et al.* reported direct photo-excitation of a ketone-derived dihydropyrimidoquinolinone for C–S/Se coupling to deliver thioether/selenoether (Scheme 1b).[9e] Recently, 1,2-ketone-derived benzothiazolines[7] and dihydroquinazolinones[8] have emerged as efficient acyl radical precursors upon aromaticity-driven C(C═O)–C(C═O) bond cleavage, enabling access to a different set of molecular entities. In this respect, Zhu *et al.* and Akiyama *et al.* independently demonstrated the utilization of benzothiazolines in hydroacylation of alkenes or alkynylation of alkynyl hypervalent iodine reagents (Scheme 1b).[7] Alternatively, Liao *et al.* and Martin *et al.* described dihydroquinazolinones in the C–C cross-coupling of aryl bromides toward ketone synthesis enabled by Ni and photoredox catalysis (Scheme 1b).[8] Nonetheless, the full potential of these pro-aromatic intermediates from 1,2-diketones has yet to be realised, such as their application in carbon–heteroatom bond forming transformation.

The thioester functionality is widely present in natural products, pharmaceutical drugs and polymers.[10] Thio(seleno)esters



Scheme 1 (a) Prevalence of 1,2-diketones, disulfides and thioesters, (b) C–S/Se bond formation from ketones *via* pro-aromatic intermediates, and (c) construction of C–C and C–S/Se bonds from 1,2-diketones *via* pro-aromatic intermediates.

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have found extensive applications in native chemical ligation (NCL), biosynthesis of polyketides and non-ribosomal proteins as well as divergent organic synthesis.[11] Recently, the exploitation of advanced strategies for synthesizing thio(seleno)esters has seen substantial momentum in organic synthesis.[12] However, several of these methods involve: (a) the utilization of transition metal catalysts mediating acyl intermediate formation using toxic carbon monoxide;[12a,f] (b) CO alone at high pressure in the absence of metal catalyst;[12g] (c) the use of stoichiometric amount of oxidant;[12h,j,k] or (d) the utilization of $ArSO_2SR$(f) reagents.[12j,k] The development of noble-metal-free photocatalytic protocols is in high demand to achieve sustainability and to avoid metal (*e.g.* iridium) contamination[13] with compounds that are directly utilized in biological studies.

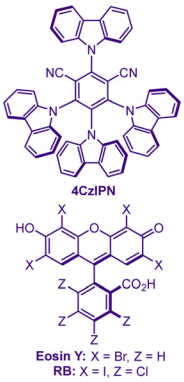
While C–C bond formation employing 1,2-diketone-derived pro-aromatic intermediates has recently been reported,[7,8] C–X bond formation from the same has not been reported to the best of our knowledge. Intrigued by the emerging reports on thioetherification,[9b,c] in the current work we envisage developing a mild and efficient C–X (X = S, Se)-bond-forming transformation of 1,2-diketones with readily accessible disulfides and diselenides, *en route* to thioesters/selenoesters, enabled by organophotoredox catalysis (Scheme 1c). Nonpolar or low-polarity C(C═O)–C(C═O) and S–S/Se–Se bonds would be cleaved to form more polar C(C═O)–S/Se bonds. This thio(seleno)esterification of envisaged method might be expected to preferentially fragment interior C–C skeleton rather than peripheral/terminal C–H, CHO, CO_2H and related groups.

The envisaged plan was realized upon an extensive optimization study, employing benzil-derived dihydroquinazolinone (**1a**) and diethyl 3,3′-disulfanediyldipropionate (**2h**) as model substrates. Blue light irradiation of DHQ (**1a**, 1 equiv.) with disulfide (**2h**, 2.5 equiv.) in the presence of 4CzIPN (1 mol%) in DMF afforded the desired thioester product in 96% yield (Table 1, entry 1). Changing the photocatalyst to Rose Bengal or eosin Y resulted in decreased yields of the thioester formation (Table 1, entries 2 and 3). Several solvents were screened: DMF was found to be superior at facilitating the reaction, whereas DMSO, DME and CH_2Cl_2 were less effective (Table 1, entries 4–6). Using fewer equivalents of **2h** led to diminished yields of **3ah** (Table 1, entries 7 and 8). Purple LED was less effective than blue LED in promoting the reaction (Table 1, entry 9). Control experiments showed the indispensable role of photocatalyst and light (Table 1, entries 10 and 11).

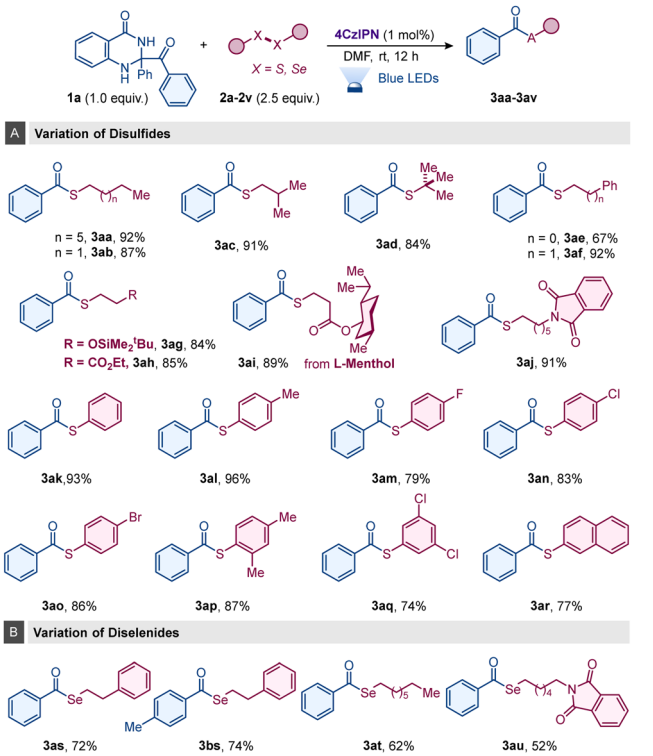
Having optimized conditions established, we set out to assess the versatility of disulfides and diselenides in reacting with dihydroquinazolinone (**1a**) (Scheme 2). Initially, an array of disulfides, namely **2a–2f** including *n*-octyl, *n*-butyl, isobutyl, *tert*-butyl, benzylic and homobenzylic thiols, were tested and provided thioester products **3aa–3af** in good to excellent yields (Scheme 2A). Additionally, disulfide **2g** and **2h** containing a silyl ether and ester functional groups respectively successfully furnished thioester products **3ag** and **3ah** in a good yield under the optimized protocol. Delightfully, disulfides **2i** and **2j** featuring menthol ester and phthalimide, respectively, performed efficiently, affording the corresponding thioesters **3ai** and **3aj** in good yields (Scheme 2A). Furthermore, a spectrum of aryl disulfides (**2k–2o**), decorated with electron-rich and electron-poor functionalities at the *para*-position were employed, and furnished

Table 1 Optimizationfor thioester formation[a]

Entry	Variation from standard conditions	Yield[b] (%) of **3ah**
1	**None**	**96**
2	**RB**, instead of **4CzIPN**	57
3	**Eosin Y**, instead of **4CzIPN**	81
4	DMSO, instead of DMF	71
5	1,2-DME instead of DMF	54
6	CH_2Cl_2, Instead of DMF	59
7	**2h** (2.0 equiv.), instead of **2h** (2.5 equiv.)	83
8	**2h** (1.5 equiv.), instead of **2h** (2.5 equiv.)	67
9	Purple LEDs instead of Blue LEDs	83
10	w/o **4CzIPN**	0
11	w/o light	0



[a] Reaction conditions: **1a** (0.1 mmol), **2h** (0.25 mmol), 4CzIPN (1 mol%), DMF (1 mL), rt, 12 h, blue LEDs. [b] Isolated yield. 4CzIPN = 2,3,4,6-tetrakis(9*H*-carbazole-9-yl)-isophthalo-nitrile, RB = Rose Bengal, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, DME = 1,2-dimethoxyethane.



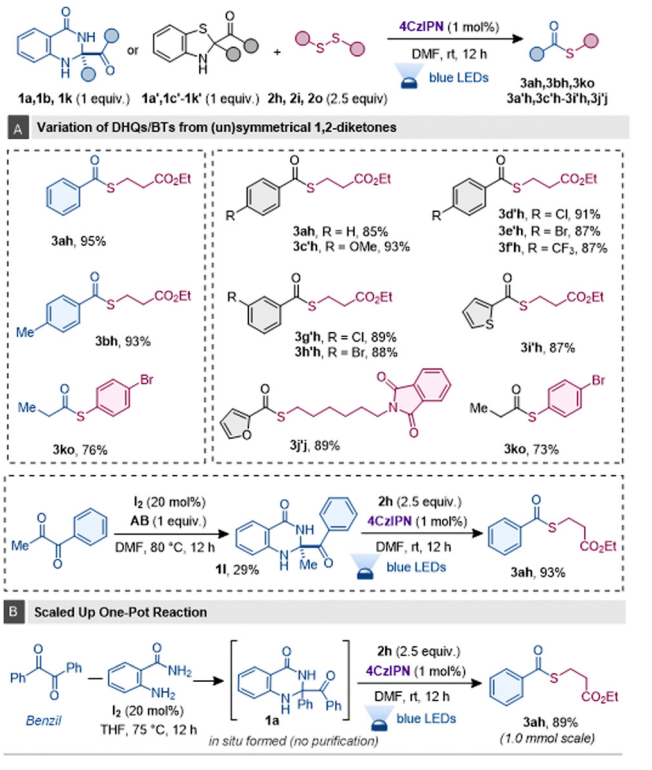
Scheme 2 Reaction conditions: (A) **1a** (0.2 mmol), **2a–2r** (0.5 mmol), 4CzIPN (1 mol%), DMF (2 mL), rt, 12 h, blue LEDs; isolated yields. (B) **1a,1b** (0.2 mmol), 2s–2u (0.5 mmol), 4CzIPN (1 mol%), DMF (2 mL), rt, 12 h, blue LEDs; isolated yields.

the desired thioester products **3ak–3ao** in good to excellent yields (Scheme 2A). Moreover, disubstituted aryl and polyaryl disulfides **2p–2r** were examined under the optimized conditions to deliver thioesters **3ap–3ar**, respectively (Scheme 2A). Prompted by the emerging interest of selenoester in native chemical ligation, we became interested in expanding the scope of chalcogen esters; in our test, alkyl and aryl diselenides (**2s–2u**) reacted smoothly with dihydro-quinazolinone (**1a** and **1b**) and satisfactorily delivered the corresponding selenoesters **3as–3au** and **3bs** (Scheme 2B).

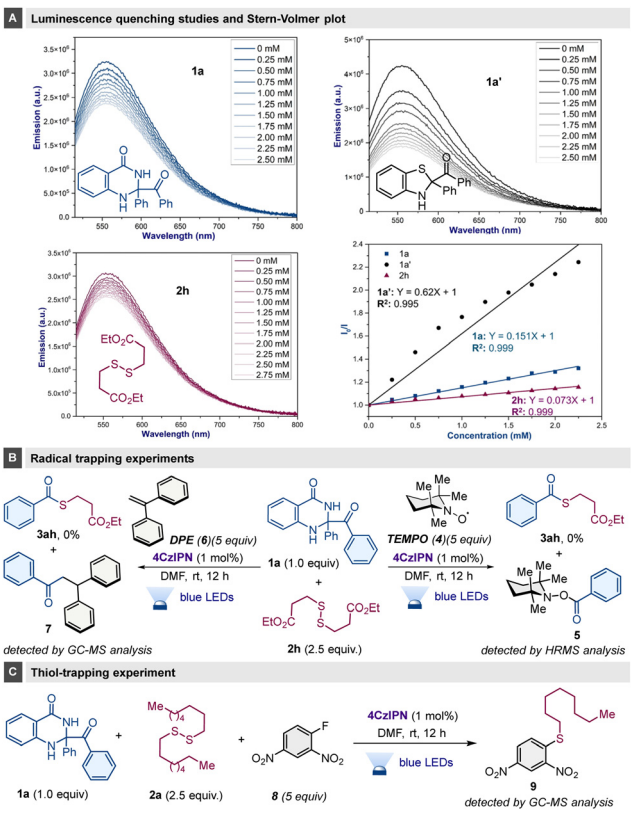
Afterwards, we tested symmetrical and unsymmetrical 1,2-diketones in the form of dihydroquinazolinones or benzothiazolines (Scheme 3A). Initially, benzil was converted to dihydroquinazolinone **1a** and benzothiazoline **1a'**, which afforded parent thioester **3ah** in good and comparable yields upon reaction with disulfide **2h** under standard conditions. Likewise, another dihydroquinazolinone, namely **1b**, reacted smoothly with disulfide **2h** to provide thioester product **3bh** in a good yield. While synthesis of dihydroquinazolinones from diaryl 1,2-diketones was attempted, these DHQs were not obtained in reasonable yield, presumably due to the competitive bisimine formation. We turned our attention to the synthesis of benzothiazolines from 1,2-diketones. Various benzothiazolines, namely **1c′–1h′**, prepared from *para-* and *meta*-substituted electron-rich and electron-deficient diaryl-1,2-diketones effectively participated in this reaction, delivering desired thioesters **3c′h–3h′h** in good to excellent yields and hence showcasing the functional group tolerance. Furthermore, benzothiazolines **1i′–1j′** from heteroaryl-1,2-diketones performed well under the optimized conditions to furnish **3i′h–3j′j** in good yields. Dihydroquinazolinone **1k** from aliphatic 1,2-diketone was also competent, with the desired thioester **3ko** obtained in good yield. Gratifyingly, an unsymmetrical ketone was selectively converted to dihydroquinazolinone **1l** in a decent yield, and the benzoyl motif of **1l** transformed to furnish thioester **3ah** in an excellent yield. To showcase the scalability and operational simplicity of the developed reaction, a one-pot telescopic synthesis of thioester **3ah** was performed on a 1-mmol scale without purification of dihydroquinazolinone **1a** (Scheme 3B).

To elucidate the mechanistic intricacies here, initially a light OFF–ON experiment was conducted to indicate the need for continuous light irradiation for effective reaction.[14] The photoluminescence quenching of 4CzIPN against the potential quenchers **1a**, **1a′** and **2h** and subsequent Stern–Volmer plot analysis were carried out, and revealed the substantial quenching ability of substrates **1a′** and **1a** (Scheme 4A). Radical inhibition tests in the presence of TEMPO (**4**) radical scavenger or 1,1-diphenylethene (DPE, **6**) provided indirect evidence of benzoyl rather than phenyl radical formation, with the corresponding adducts **5** and **7** having been detected (Scheme 4B). Furthermore, the standard reaction in the presence of Sanger's reagent (**8**) identified an alkyl aryl sulfide (**9**), providing evidence for the formation of thiolate in this reaction (Scheme 4C).

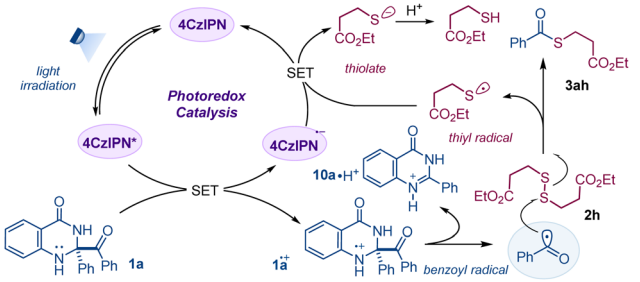
Based on the preliminary mechanistic information and literature reports, we have sketched a mechanistic scenario, shown in Scheme 5. Light irradiation of 4CzIPN leads to the formation of photo-excited 4CzIPN* ($E_{4CzIPN^*/4CzIPN^{\bullet-}}$ = +1.35 V *vs.* SCE),[15] which is reductively quenched by dihydroquinazolinone **1a**



Scheme 3 (A) Reaction conditions: **1a–1b**, **1k**, **1l**, **1a′**, **1c′–1k′** (0.2 mmol), **2h**, **2i**, **2o** (0.5 mmol), 4CzIPN (1 mol%), DMF (2 mL), rt, 12 h, blue LEDs; isolated yields. AB = 2-aminobenzamide. (B) Scale up one-pot reaction.



Scheme 4 Mechanistic studies: (A) luminescence studies and Stern–Volmer plot; (B) radical trapping experiments; (C) thiol-trapping experiment.



Scheme 5 Mechanistic proposal.

($E_{1a^{\bullet+}/1a}$ = +0.50 V *vs.* SCE)[8a] to generate radical cation **1a**$^{\bullet+}$ alongside the formation of 4CzIPN$^{\bullet-}$. Fragmentation of the C–C bond of the radical cation releases benzoyl (Bz$^{\bullet}$) radical, which is driven by aromatization.[7,8] Next, addition of benzoyl (Bz$^{\bullet}$) radical to the S–S bond of disulfide **2h** results in the formation of the C–S bond of thioester **3ah** and thiyl (RS$^{\bullet}$) radical.[12h] Lastly, the reduction of thiyl (RS$^{\bullet}$) ($E_{RS^{\bullet}/RS^{-}}$ = ∼ + 0.3 V *vs.* SCE)[16] by 4CzIPN$^{\bullet-}$ (E4CzIPN/4CzIPN$^{\bullet-}$ = −1.21 V *vs.* SCE)[15] liberates thiolate, regenerating 4CzIPN in the ground state. A similar mechanism for benzothiazoline is outlined in the ESI† (Fig. S12).[14]

In summary, we report a mild and efficient thioester and selenoester synthesis from symmetrical and unsymmetrical 1,2-diketones and readily accessible disulfides/diselenides enabled by organic photoredox catalysis. While 1,2-diketone-derived dihydroquinazolinones and benzothiazolines were previously demonstrated for C–C bond formation, the currently developed reaction is essentially characterized by polar C–S/C–Se bond construction upon successive cleavage of the nonpolar or low-polarity C(C═O)–C(C═O) bond of 1,2-diketones and nonpolar S–S/Se–Se bond cleavage of disulfides/diselenides. This oxidant-free and scalable C–C activation protocol enables various dialkyl, diaryl, diheteroaryl and alkyl-aryl 1,2-diketones to be transformed to numerous *S*-aryl (*S*-alkyl) alkyl/aryl/heteroaryl thioesters as well as Se-aryl (Se-alkyl) aryl selenoesters with diverse functional group tolerance and in high efficiency.

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Data availability

The data underlying this work are available in the published article and its ESI.†

Conflicts of interest

The authors declare no competing financial interest.

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