Divergent functionalization of aldehydes photocatalyzed by neutral eosin Y with sulfone reagents

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While aldehydes represent a classic class of electrophilic synthons, the corresponding acyl radicals are inherently nucleophilic, which exhibits umpolung reactivity. Generation of acyl radicals typically requires noble metal catalysts or excess oxidants to be added. Herein, we report a convenient and green approach to access acyl radicals, capitalizing on neutral eosin Y-enabled hydrogen atom transfer (HAT) photocatalysis with aldehydes. The generated acyl radicals underwent SOMOphilic substitutions with various functionalized sulfones (X-SO₂R') to deliver value-added acyl products. The merger of eosin Y photocatalysis and sulfone-based SOMOphiles provides a versatile platform for a wide array of aldehydic C–H functionalizations, including fluoromethylthiolation, arylthiolation, alkynylation, alkenylation and azidation. The present protocol features green characteristics, such as being free of metals, harmful oxidants and additives; step-economic; redox-neutral; and amenable to scale-up assisted by continuous-flow technology.
Acyl radicals are versatile synthetic intermediates in C–C bond-forming reactions, such as Giese addition\(^1,2\) and Minisci acylation\(^3\), as well as transition metal-mediated cross-coupling reactions\(^4-6\). The exploration of acyl radical chemistry greatly expanded the scope of accessible carbonyl-containing functional molecules\(^7\). However, conventional approaches to accessing acyl radicals normally require harsh conditions such as high temperature, ultraviolet irradiation, or the use of hazardous reagents. Emerging and rapidly expanding photocatalysis has offered enormous opportunities to access acyl radicals in a greener and sustainable fashion from a variety of precursors, including aldehydes, carboxylic acids, acid derivatives, and acylsilanes\(^8-13\). Among them, the use of aldehydes for acyl radical generation represents the most straightforward and atom-economic pathway.

By taking advantage of aldehyde feedstocks as acyl radical precursors\(^14-16\), a plethora of acyl–C bond-forming reactions have been developed. This bond formation is normally realized by acyl radical addition to unsaturated alkenes or (hetero)aromatics, have been developed. This bond formation is normally realized by acyl radical addition to unsaturated alkenes or (hetero)aromatics, leading to acyl–C(sp\(^2\)) or acyl–C(sp\(^3\)) bond formation. In stark contrast, the construction of acyl–X (X = S, N, D) and acyl–C(sp\(^3\)) bonds from aldehydes is largely unexplored (Fig. 1a). Excess oxidants\(^17,18\), additives\(^19,20\), or noble metal catalysts\(^21-24\) are usually required to achieve such transformations.

Direct photocatalyzed hydrogen atom transfer (HAT) has enabled a remarkable breakthrough in C–H functionalizations\(^25,26\). Capitalizing on HAT activity of C–O biradical of excited ketones or quinones, a series of HAT photocatalysts were developed\(^27-31\). Although anionic eosin Y was commonly used as a photoredox catalyst\(^32-34\), a previous study by our group established neutral eosin Y as an excellent direct HAT photocatalyst that can activate a wide range of C–H bonds to access the corresponding carbon radicals under simple and mild conditions\(^35\). Eosin Y was capable of providing access to acyl radicals from aldehyde feedstocks, which have been employed to react with alkenes and alkenes for asymmetric 1,4-addition\(^36\) and a radical Smiles rearrangement\(^37\), respectively. With the cumulative insights gained from the eosin Y-HAT photocatalytic system\(^38\), we envisioned that its merger with sulfone SOMOphiles\(^39,40\) can provide a general platform for aldehydic C–H functionalization to access various types of functional acyl compounds. Acyl radicals generated by photoinduced HAT undergo nucleophilic substitution with X-SO\(_2\)R, which will benefit from polarity matching\(^41\), delivering diverse functionalized acyl compounds accompanied by electrophilic sulfonyl radical species. The sulfonyl radical then participates in a reversed HAT (RHAT) process with eosin Y-H to complete the catalytic cycle.

In this work, by using different SOMOphilic sulfone reagents as acyl radical traps in HAT photocatalysis, we achieve aldehydic C–H fluoromethylthiolation, arylthiolation, alkynylation, alkenylation, and azidation (Fig. 1b). Notably, arylsulfinic acid is utilized as an odorless thiolation reagent for thioester generation. Compared to existing protocols for aldehydic C–H functionalizations, eosin...
Y-HAT photocatalysis features operationally simple, inexpensive, and metal-, oxidant-, and additive-free green attributes.

Results

Development of aldehydic C–H fluoromethylthiolation. The monofluoroethylthio moiety (SCH₂F) widely exists in a variety of biologically active compounds (Supplementary Fig. 1)⁴⁴,⁴⁵. Previous reports to achieve aldehydic C–H monofluoroethylthiolation relied on the use of stoichiometric oxidants such as 2,2′-azodi(2-methylbutyronitrile) (AMBN)⁴⁶ or PhI(O₂CCF₃)₂/NaN₃.¹⁷ We envisioned that eosin Y-based HAT photocatalysis may enable this transformation in a redox-neutral fashion. After extensive condition optimization using benzaldehyde 1a and S-(fluoromethyl) benzenesulfonfthioate (PhSO₂–SC₂H₃F) 2a as the model substrates (Supplementary Table 1), we found that neutral eosin Y (4 mol%) in tert-butanol (tBuOH) under blue light (18 W, 470 nm LED) irradiation at ambient temperature afforded desired product 3a in optimal yield (88%). Notably, no product was generated using anionic eosin Y as the photocatalyst, while other photocatalytic systems for HAT⁴²,²²,²⁴,²⁷,⁴⁷ gave inferior product yields (Supplementary Table 4), highlighting the effectiveness of eosin Y catalysis. Light irradiation was essential, as no product was detected when the reaction was performed in darkness.

With the optimized conditions, the scope of aldehydes amenable to monofluoroethylthiolation was investigated (Fig. 2). Electron-rich (3b–f) and electron-deficient (3g–k) arone derivatives possessing ortho-, meta-, or para-substituents all provided the corresponding monofluoroethyl thioester products in 55–78% yields. A wide range of functionalities, including ether (3b–e), phenol (3d), thioether (3f), halide (3h, 3i), and cyanide (3j), were well tolerated. Naphthalene- or heterocyclic (such as benzodioxole and benzo[b]thiophene)-substituted aldehydes smoothly participated in the transformation to afford products 3l–n in good yields (72–92%). The scope with respect to aliphatic aldehydes was evaluated next. Both linear (3o–r) and branched (3s, 3t) alkyl aldehydes afforded the desired products in good yields (67–88%). The incorporation of amide (3q), terminal alkene (3r) and piperidine (3t) substrates was compatible with our conditions. However, tertiary aldehydes such as pivaldehyde failed to give the corresponding product (not shown), probably due to the facile decarboxylation of the unstable tert-alkyl acyl radical.¹⁸ Moreover, the protocol can be applied to late-stage functionalization of natural product derivatives. Useful yields (46–54%) of monofluoroethylthiolation products were obtained with complex molecules derived from (−)-menthol (3u), (+)-fenchol (3v), and lthioc acid (3w). Importantly, by simply changing fluoromethylthio-sulfone reagents 2a to 2b (PhSO₂–SC₂H₃F) and 2c (PhSO₂–SC₂F₃), this protocol could be successfully extended to aldehydic C–H difluoromethylthiolation (3x) and trifluoromethylthiolation (3y, 3z), respectively, representing a general method to access diverse fluoromethylthioesters in a simple and green manner.

Development of aldehydic C–H thiolation using arylsulfonic acid as an odorless sulfur reagent. During the study of aldehydic C–H fluoromethylthiolation, we found that the eosin Y photocatalyzed reaction between 4-methoxybenzaldehyde 1b and 2a gave major product 3b accompanied by S-phenyl thioester 4b in >20% yield (Fig. 3a). In light of our previous study on HAT photocatalysis and related reports on photocascade catalysis⁴⁹–⁵¹, we speculated that S-phenyl thioester 4b might be derived from benzenesulfonic acid 5a generated in situ (Fig. 3b). The photo-generated acyl radical A underwent radical substitution with 2a to deliver monofluorothiolation product 3 and benzenesulfonfyl radical B simultaneously. RHAT with eosin Y-H would convert benzenesulfonyl radical B to benzenesulfonic acid 5a, which accumulated in the reaction mixture and served as the sulfur reagent for thiolation. This hypothesis was verified by treatment of 1b with 5a under eosin Y photocatalysis conditions, which delivered thioester 4b in 68% yield (Fig. 3c).

Given the synthetic value of thioesters⁵² and the appealing property of arylsulfonic acid as an odorless and readily available sulfur reagent, we attempted to examine the thiolation scope of this operationally simple method (Fig. 4). A diverse set of aromatic aldehydes took part in this transformation to give moderate to good yields (46–71%) of thioester products (4a–k), tolerating a variety of functional moieties such as amide (4d), ester (4e, 4j), halide (4h), trifluoromethyl (4i), and 2,2-difluorobenzodioxide (4k) groups. Aromatic aldehydes with para-, meta-, or ortho-substituents smoothly participated in the transformation. Heteroaryl (4l, 4m) and alkyl (4n, 4o) aldehydes were also amenable to thiolation, but with lower yields (22–50%), where a substantial amount of sulfonic acids was observed as the side-products. Furthermore, variation with respect to arylsulfonic acids was evaluated, illustrating that a broad scope of (hetero) arylsulfonic acids afforded the corresponding thioesters (4p–u) in useful yields (40–61%).

To gain a mechanistic understanding of the aldehydic C–H arthiolation, a range of control experiments were performed to elucidate the reaction intermediates. Various S-phenyl sources were examined (Fig. 5a). Both benzenesulfonic acid 5a and S-phenyl benzenesulfonfthioate 9a could afford thioester 4b in good yields, while other S-aryl sources such as benzenesulfonic acid 6, thiol 7, disulfide 8, and disulfone 10 were not effective at all or delivered 4b in very low yields. These results indicated that arylthiosulfonate 9 may act as a key intermediate in the reaction. This was further supported by the fact that benzenesulfonic acid 5a could be converted to S-phenyl benzenethiosulfonate 9a under eosin Y photocatalytic conditions, but 9a could not be generated in the absence of eosin Y (Fig. 5b). The reaction became sluggish with the addition of radical scavengers such as 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and butylated hydroxylcione (BHT), supporting a radical-based mechanism. When 1,1-diphenylethylene was added as an additive, adducts 11 and 12 were detected by electrospray ionization mass spectrometry (ESI-MS), indicating the presence of arylsulfonfyl radicals and acyl radicals, respectively (Fig. 5c). Moreover, ¹⁸O incorporation was not observed when ¹⁸O-labeled 4-methylbenzenesulfonic acid 18O₅b was employed, which suggested that the carbonyl oxygen in the thioester product was derived from the aldehyde (Fig. 5d).

In light of all the experimental data and related literature, a tentative mechanistic pathway for aldehydic C–H arthiolation is proposed (Fig. 5e). Photo-excited *eosin Y undergoes HAT with benzenesulfonic acid 5a to generate benzenesulfonfyl radical B⁵⁴, which dimerizes to give disulfone species 10. 10 is reduced by benzenesulfonic acid 5a to give thiosulfonate 9a.⁵⁵,⁵⁶ 9a then participates in radical substitution with acyl radical A, which is formed via eosin Y-HAT photocatalysis with aldehyde 1. Arythioester product 4 is obtained together with arylsulfonfyl radical B, which closes the photocatalytic cycle and regenerates benzenesulfonic acid 5a (see Supplementary Fig. 12 for more discussion).

Development of Aldehydic C–H Alknylation. To further demonstrate HAT photocatalysis by eosin Y with sulfone reagents as a versatile platform for aldehydic C–H functionalizations, we found that methanesulfonfyl alkyn 13aa was a suitable alknylation reagent to deliver synthetically valuable ynone compounds (Fig. 6). A series of alkyn sulfones bearing different R’
SO₂ group were examined and methanesulfonyl alkyne 13aa was identified as the optimal reagent, probably due to the small steric hindrance (see Supplementary Tables 2 and 3 for optimization study). Diverse substituents (e.g., F, Cl, Br, CF₃) could be incorporated in arylaldehydes to produce ynones 14a–g in moderate yields (41–69%). Aldehydes possessing heteroaromatics such as thiophene (14h) were suitable substrates as well. Aliphatic aldehydes including both linear (14i, 14j) and branched (14k–m) alkyl substituents participated in the alkynylation more efficiently to afford ynones in good yields (70–84%). Moreover, aldehydes derived from lithocholic acid and dihydrocholesterol underwent the transformations smoothly, leading to the facile formation of 14n (73%) and 14o (22%), respectively. Next, the scope regarding alkynyl sulfone 13 was explored. The protocol was feasible for both arylalkynyl sulfones (14p–u) bearing a variety of functionalities (e.g., Cl, CO₂Me, OMe) and heteroarylalkynyl sulfones (14v) to produce the corresponding ynones with moderate to good yields (42–72%).

Preliminary study on aldehydic C–H azidation and alkenylation and scale-up in continuous-flow reactors. To further showcase the versatility of eosin Y-HAT photocatalysis with sulfone reagents, aldehydic C–H azidation and alkenylation were investigated (Fig. 7a). Our preliminary study illustrated that triflic azide (CF₃SO₂N₃) 15 could be applied to forge C–N bonds, delivering acyl azides (16a, 16b) in moderate yields (55–58%). This protocol provides a mild alternative to previous aldehydic C–H azidation reactions, which require either excess oxidants

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or inconvenient reagents. Aldehydic C–H alkenylation was also feasible using (E)-1,2-bis(phenylsulfonyl)ethene as the alkenylation reagent, delivering enone in 40% yield. Finally, the aldehydic C–H monofluoromethylation reaction was smoothly transferred to an operationally simple continuous-flow reactor to achieve >15 g per day production, indicating the potential of our strategy for large-scale synthesis (Fig. 7b).

Discussion

In summary, we have demonstrated a versatile platform for aldehydic C–H functionalization by merging neutral eosin Y-HAT photocatalysis with a variety of sulfone-based SOMOphilic reagents to directly construct acyl–S, acyl–C and acyl–N bonds. The eosin Y-sulfone system will serve as a more green and sustainable method with easier handling for aldehydic functionalization compared to existing catalytic/stoichiometric systems and has several practically or mechanistically notable features. First, PhSO2–SCH2F 2 proved particularly effective for metal-, additive- and oxidant-free fluoromethylthiolation with diverse aldehydes, including complex natural product derivatives. The fluoromethylthiolation reaction was performed under continuous-flow conditions to achieve a productivity of 15 g per day. Second, arylsulfonic acid (ArSO2H), as an odorless and easily accessible reagent, was employed for arylthiolation of aldehydes. A preliminary mechanistic study supported that an in situ-generated arylthiosulfonate (ArSO2–SAr) species participated in the subsequent radical substitution step. Third, the acyl–C(sp2) bond was successfully forged via acyl radical addition-sulfonyl radical elimination with a methanesulfonyl alkyne. Finally, exploiting the versatility of radical addition-elimination, the present strategy was further extended to aldehydic C–H azidation and alkenylation. Extension of the C–H substrate scope to abundant alkanes and expanding the chemical space of sulfone SOMOphilic reagents to new reaction patterns are currently under investigation in our laboratory.

Methods

General procedure of neutral-eosin Y-photocatalyzed aldehydic C–H fluoromethylthiolation. A 20 mL Schlenk tube equipped with a magnetic stir bar was charged with eosin Y (0.008 mmol, 5.2 mg), aldehyde (0.3 mmol), and fluoroalkylthiolation reagents (0.2 mmol). Then, 2.0 mL of anhydrous tert-butanol was added. The Schlenk tube was connected to Schlenk line and freeze–pump–thaw was performed for three times to completely remove air.
General procedure of neutral-eosin Y-photocatalyzed aldehydic C-H thiolation. A 20 mL Schlenk tube equipped with a magnetic stir bar was charged with eosin Y (0.008 mmol, 5.2 mg), aldehyde 1 (0.4 mmol), and arylsulfonyl chloride (0.2 mmol). Then, 2.0 mL of anhydrous tert-butanol was added. The Schlenk tube was connected to Schlenk line and freeze–pump–thaw was performed for three times to completely remove air inside the reaction mixture. Eventually the Schlenk tube was filled with an atmosphere of tert-butanol and sealed. The reaction vessel was surrounded by a coil of blue LED strip (2 m, 18 W). Then the reaction was running at ambient temperature (~27 °C) using a fan to cool down the reaction mixture and stopped after 48 h. The solvent was removed under reduced pressure and the crude mixture was purified by silica gel column chromatography or prepared TLC (eluent: hexane/diethyl ether or hexane/ethyl acetate; 10/1–3/1) to give the corresponding product 3. Note that the workup procedure was performed under weak vacuum (~50 mbar) and low temperature (~30 °C) due to volatility of the corresponding product 3.

**General procedure of neutral-eosin Y-photocatalyzed aldehydic C-H alkynylation.** A 20 mL Schlenk tube equipped with a magnetic stir bar was charged with eosin Y (0.008 mmol, 5.2 mg), aldehyde 1 (0.4 mmol), and acetylenic sulfone reagents 2 (0.2 mmol), eosin Y (4 mol%), and tert-butanol (2.0 mL) in an argon-filled Schlenk tube (20 mL) at room temperature (~27 °C) under 470 nm light (18 W LED) irradiation.

Computational details. Density functional theory calculations were performed to shed light on the mechanism of eosin Y regeneration (Supplementary Fig. 17). RHAT (red line) is the favored pathway, which features a barrier 2.1 kcal/mol lower than an alternative single electron transfer (SET, black line). The geometries optimization in this study was performed at the uB3LYP density functional with a standard def2-SVP basis set. The nature of the stationary points (minima with no imaginary frequency or transition states with one imaginary frequency) were confirmed. The free energies of the optimized geometries were calculated at the same level of theory, considering the solvent effect of acetone using an SMD continuum solvation model. Unless specified otherwise, the Gibbs free energy was used throughout. For

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**Fig. 4 Scope of the odorless aldehydic C-H thiolation.** [a] Reaction conditions unless otherwise noted: 1 (0.4 mmol), 2 (0.2 mmol), eosin Y (4 mol%), and tert-butanol (2.0 mL) in an argon-filled Schlenk tube (20 mL) at room temperature (~27 °C) under 470 nm light (18 W LED) irradiation.

Inside the reaction mixture. Eventually the Schlenk tube was refilled with an atmosphere of argon at room temperature and sealed. The reaction vessel was surrounded by a coil of blue LED strip (2 m, 18 W). Then the reaction was running at ambient temperature (~27 °C) using a fan to cool down the reaction mixture and stopped after 48 h. The solvent was removed under reduced pressure and the crude mixture was purified by silica gel column chromatography or prepared TLC (eluent: hexane/diethyl ether or hexane/ethyl acetate; 10/1–3/1) to give the corresponding product 3. Note that the workup procedure was performed under weak vacuum (~50 mbar) and low temperature (~30 °C) due to volatility of the corresponding product 3.
transition state, intrinsic reaction coordinate calculations were performed to verify whether it connected with correct reactants and products or intermediates. All calculations were performed using the Gaussian 16 Rev. A.03 software suite.

Data availability
The authors declare that all other data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon request. Source data are provided with this paper.
**Fig. 6 Substrate scope of aldehydic C–H alkynylation.** [a] Reaction conditions: 1 (0.4 mmol), 13 (0.2 mmol), eosin Y (4 mol%), and tert-butanol (2.0 mL) in an argon-filled Schlenk tube (20 mL) at 60 °C under 470 nm light (18 W LED) irradiation.

**Fig. 7 Aldehydic C–H diversification and scale-up synthesis in flow.** a Aldehydic C–H azidation and vinylation. Reaction conditions unless otherwise noted: 1 (0.4 mmol), sulfone (0.2 mmol), eosin Y (4 mol%), and solvent (2.0 mL) in an argon-filled Schlenk tube (20 mL) under 470 nm light (18 W LED) irradiation. [a] Reaction was performed in CH3CN at room temperature. [b] Reaction was performed in ethyl acetate at 80 °C. b Reaction scale-up in continuous-flow microtubing reactors. Psi pound per square inch.
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Author contributions
J.Y. discovered and developed the reaction. J.Y., J.L.P., S.D., and J.W. conceived and designed the investigations. X.S. conducted DFT calculations. J.Y., H.T., E.J.R.K., and C.L. performed the experiments. J.Y., H.T., M.Z., and J.W. wrote the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
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