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Direct Synthesis of Thioesters from Feedstock Chemicals and Elemental Sulfur

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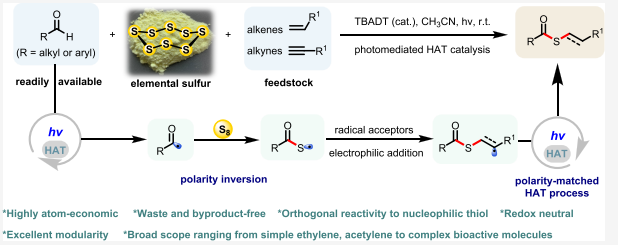
ABSTRACT: The development of a mild, atom- and step-economical catalytic strategy that effectively generates value-added molecules directly from readily available commodity chemicals is a central goal of organic synthesis. In this context, the thiol−ene click chemistry for carbon−sulfur (C−S) bond construction has found widespread applications in the synthesis of pharmaceuticals and functional materials. In contrast, the selective carbonyl thiyl radical addition to carbon−carbon multiple bonds remains underdeveloped. Herein, we report a carbonyl thiyl radical-based thioester synthesis through three-component coupling from feedstock aldehydes, alkenes, or alkynes and elemental sulfur by direct photocatalyzed hydrogen atom transfer. This method represents an orthogonal strategy to the conventional thiol-based nucleophilic substitution and exhibits a remarkably broad substrate scope ranging from simple commodity chemicals such as ethylene and acetylene to complex pharmaceutical molecules. This protocol can be easily extended to the synthesis of thiolactones, oligomer/polymers, and thioacids. Its synthetic utility has been demonstrated by a two-step synthesis of the drug esonarimod. Mechanistic studies indicate that the use of elemental sulfur to trap acyl radicals is both thermodynamically and kinetically favored, illustrating its great potential for the synthesis of sulfur-containing molecules.



INTRODUCTION

The development of benign yet atom- and step-economical catalytic methods for effective access to value-added compounds from inexpensive and readily available feedstock chemicals is a central goal of synthetic chemistry. In particular, thioesters are of vital importance not only in organic synthesis but also in materials, foods, cosmetics, antibiotics, and biology.[1−5] They serve as versatile synthetic intermediates for acyl transfer reactions such as native chemical ligation[6,7] and Fukuyama reduction/coupling.[8] In nature, acetyl coenzyme A, a biologically important thioester, plays a crucial role in protein, carbohydrate, and lipid metabolic processes.[9] Current methods for the synthesis of thioesters, however, mainly rely on the condensation of carboxylic acids and thiols in the presence of dehydrating reagents[10] or acylation of thiols in the presence of stoichiometric acylating reagents or metallic additives,[11,12] with considerable waste and byproducts generated (Figure 1A). Greener processes have been developed using aldehydes and thiols as the starting materials, but stoichiometric amounts of oxidants are required in these oxidative couplings.[13,14] Notably, Milstein's group recently reported a waste-free catalytic dehydrogenative coupling of alcohols or aldehydes and thiols to generate thioesters with hydrogen gas as the sole byproduct.[15] Although elegant, the use of thiols as the starting material is not ideal due to their unpleasant odor, unstable nature, limited commercial scope, and high coordinating ability, which can deactivate transition-metal catalysts.[16]

Elemental sulfur, the oldest fungicide, exists in ambient conditions primarily as an eight-membered ring (S_8). The worldwide production of S_8 exceeds 70 million metric tons per year.[17] Its abundant, nontoxic, nonvolatile, nonhygroscopic, and odorless nature makes it an ideal source to introduce sulfur atoms into organic molecules. Moreover, there is a strong motivation to use elemental sulfur as a chemical feedstock since a huge surplus of this material (approximately 7 million tons annually) is in storage unused.[18] However, elemental sulfur exhibits limited solubility in most organic solvents, and conventional activation of S_8 normally involves high temperature or strong acidic or basic conditions,[17,19] which are not compatible with thioesters.

Recent sporadic studies have shown that S_8 can participate in radical transformations to introduce sulfur atoms into molecular scaffolds under mild conditions.[18,20−25] Thiol−ene click chemistry,[26−28] in which thiyl radical species regioselectively undergo anti-Markovnikov addition to a carbon−carbon double bond, is among the most prominent and efficient pathways to construct carbon−sulfur bonds. Inspired

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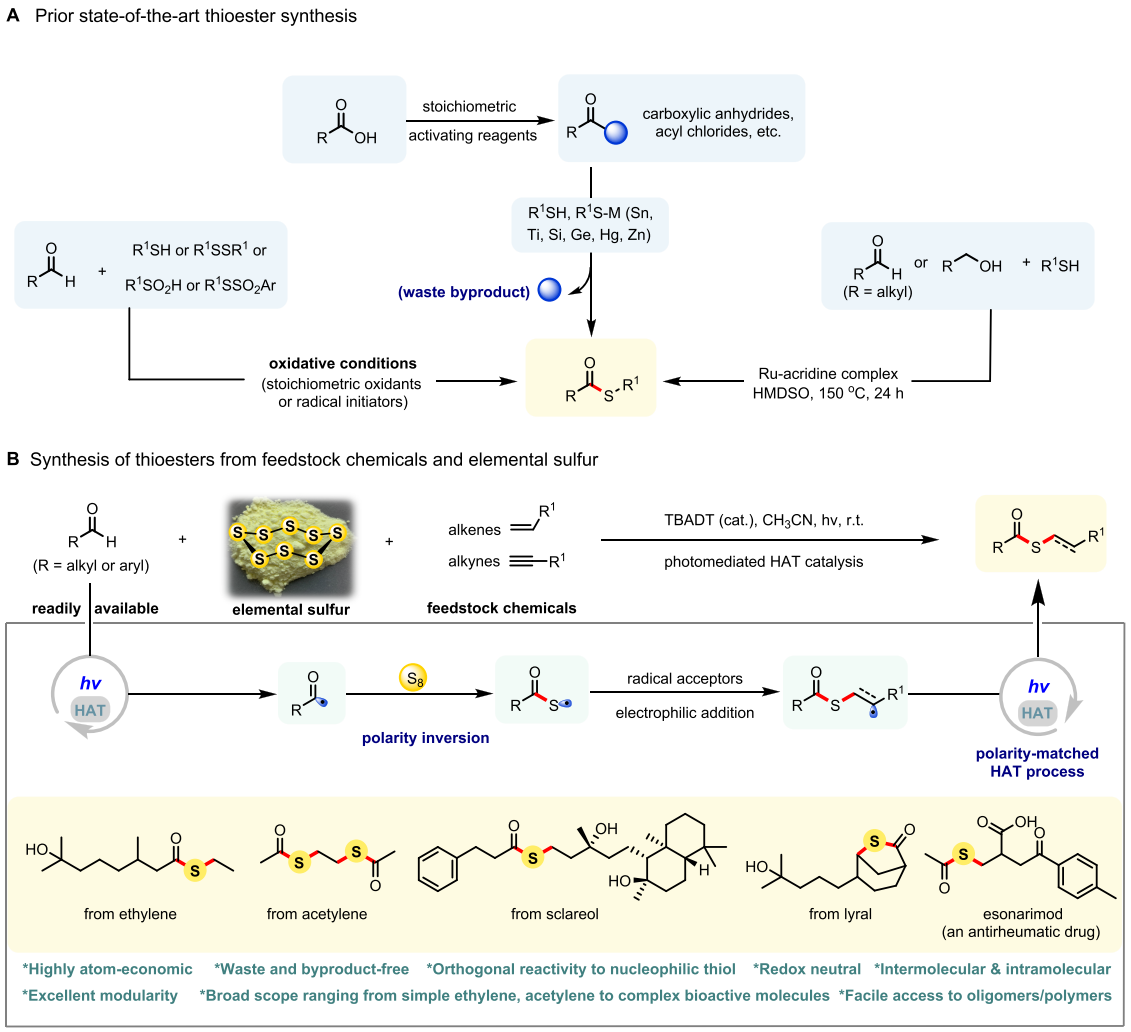

Figure 1. Sustainable synthesis of thioesters. (A) Prior state-of-the-art thioester synthesis. (B) Synthesis of thioesters from feedstock chemicals and elemental sulfur. HMDSO: hexamethyldisiloxane.

by the thiol−ene click chemistry, we wondered whether the carbonyl thiyl radical intermediates were capable of similar reactivity. While pursuing methods for photo-mediated direct hydrogen atom transfer (HAT) catalysis,[29−33] we envisioned that an acyl radical generated from hydrogen abstraction from aldehydes could add to S_8 to deliver an electrophilic carbonyl thiyl radical after S−S bond homolytic cleavage, at the same time achieving radical polarity inversion. The electrophilic nature of the carbonyl thiyl radical will unlock the reactivity with a wide range of electron-rich feedstock chemicals (e.g., alkenes and alkynes) to produce various types of thioesters. The cleaved polysulfur radical or carbonyl thiyl radical intermediates formed *in situ* undergo reduction and protonation with the reduced photocatalyst to deliver thiol or thioacid intermediates, which will facilitate the reverse HAT step in a polarity-matched fashion to accomplish the catalytic cycle (Figure 1B). We herein report efficient three-component coupling, which produces a wide range of thioesters from feedstock aldehydes, alkenes, or alkynes and elemental sulfur through direct photo-HAT catalysis based on decatungstate anions ($[W_{10}O_{32}]^{4-}$). Compared to existing protocols for thioester synthesis, our method features not only orthogonal reactivity to nucleophilic thiols but also a highly modular synthesis using some of the most readily available feedstocks (aldehydes, alkenes, alkynes, and elemental sulfur) as the coupling partners in an atom-, step-, and redox-economical fashion.

RESULTS AND DISCUSSION

We initiated our study using S_8 as the sulfur source in combination with 3-phenylpropanal **1a** and alkene **2a** possessing a hydroxyl group that is sensitive in the conventional nucleophilic thioester synthesis.[34,35] After optimization of the conditions, it was found that *tetra-n*-butylammonium decatungstate (TBADT) was the optimal photo-HAT catalyst delivering the desired thioester product **3a** in 83% isolated yield using CH_3CN as the solvent at room temperature under 390 nm light irradiation for 24 h (Table 1, entry 1). Other typical photo-HAT catalysts, such as eosin Y (**Cat. 1**) and diaryl ketone sensitizer (**Cat. 2**) could also promote this transformation in moderate efficiency in a metal-free manner (entries 2 and 3). However, no reaction occurred with pentacenetetrone (**Cat. 3**) or phenylglyoxylic acid (**Cat. 4**) as the photocatalyst (entry 4). The amount of sulfur was investigated (entries 5 and 6). Notably, product **3a** was still obtained with good yield when the amount of S_8 was reduced to 0.125 equivalent (entry 6), demonstrating the excellent atom-efficiency of the transformation. The use of other

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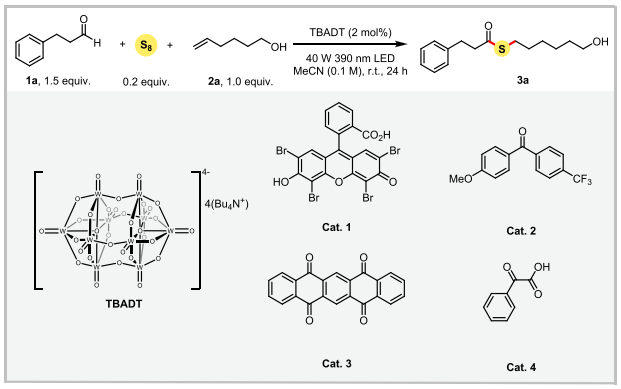
Table 1. Optimization of Three-Component Coupling to Access Thioesters



entry	variation from the standard conditions[a]	yield[b]
1	none	83%
2	**Cat. 1** (4 mol %) instead of TBADT, 456 nm kessil light (40 W)	38%
3	**Cat. 2** (5 mol %) instead of TBADT, white LED (18 W)	53%
4	**Cat. 3** (5 mol %) or **Cat. 4** (5 mol %) instead of TBADT, white LED (18 W)	0%
5	S_8 (0.375 equiv)	83%
6	S_8 (0.125 equiv)	66%
7	acetone (0.1 M)	68%
8	DMF (0.1 M)	55%
9	MeOH (0.1 M)	20%
10	CH_2Cl_2 (0.1 M)	16%
11	without TBADT or light	0%

[a]Standard conditions: all reactions were carried out with **1a** (0.3 mmol) and **2a** (0.2 mmol) under the irradiation of 40 W 390 nm LED light unless otherwise noted. [b]Isolated yields (based on **2a**). LED: light-emitting diode.

solvents led to inferior product yields (entries 7−10 and Table S4). For instance, the use of either dimethylformamide (DMF) or methanol resulted in the formation of by-products under TBADT-based photocatalytic conditions (Figure S2). Further control experiments illustrated that the photocatalyst and light were all essential for achieving an effective transformation (entry 11).

Having established the optimal reaction conditions, we explored the scope of alkenes and alkynes, as well as the aldehyde partners. An extremely broad range of thioesters was effectively synthesized with moderate to excellent yields from the corresponding alkenes, alkynes, or aldehydes as illustrated in Figure 2. Unactivated alkenes containing unprotected polar groups such as free OH or COOH that are problematic in the conventional ionic pathway gave the desired thioester products (**3a** and **3b**) in excellent yields. The reaction could be applied to a series of unactivated α-olefins bearing different functionalities such as ether (**3c**), chloride (**3d**), ester (**3e**−**3h**), amide (**3i**), ketone (**3j**), pentafluoroarene (**3k**), indole (**3l**), silane (**3m**), and boronic ester (**3n**) groups, giving rise to the corresponding thioester products in good yields. High yields of products (**3o**−**3w**) were obtained from unactivated 1,1-disubstituted alkenes possessing different functional groups such as nitrile (**3q**), benzenesulfonate (**3r**), ester (**3s**), amide (**3t**), or ether (**3u**). Heterocycles such as benzimidazole (**3v**) could be readily used. Base-sensitive terminal alkynes could also be tolerated under our reaction conditions (**3w**). When a cyclic alkene was subjected to the standard conditions, the desired product (**3x**) could be obtained in 63% yield. Notably, sterically demanding tri- or tetra-substituted unactivated alkenes also reacted smoothly under the standard conditions, providing the thioester products (**3y** and **3z**) in moderate yields. When activated alkenes containing either electron-donating or electron-withdrawing groups were used as radical acceptors, the desired thioester products (**3aa** and **3ab** or **3ac** and **3ad**) were obtained in moderate to good yields. Styrene-type substrates such as styrene, 2-vinylnaphthalene, and 4-vinylpyridine were also feasible to deliver the thioester products **3ae**−**3ag** in moderate yields. 1,4-Di(prop-1-en-2-yl)benzene employed as a substrate gave the difunctionalized product **3ah** in 45% yield.

Importantly, gaseous ethylene was a competent partner for this three-component coupling, accomplishing the ethyl thioesters (**3ai**−**3al**) in good to excellent yields simply with an ethylene balloon. This protocol offers a new avenue for the direct conversion of ethylene into value-added chemicals in an operationally simple and atom-efficient way. C_2-C_3 alkenes possessing halogen atoms (bromine, iodine, and chlorine) underwent the coupling reaction smoothly (**3am**−**3ao**). The halogens are useful as synthetic handles for further derivatization, e.g., through cross-couplings. This protocol can also be extended to alkynes, and terminal alkynes were effectively converted into the corresponding enethioates (**3ap** and **3aq**) in a mixture of Z/E isomers. Internal alkynes also gave the desired enethioate (**3ar**) with low Z/E selectivity (E/Z = 3:1). Notably, gaseous feedstock acetylene could undergo consecutive difunctionalization to achieve dithioesters (**3as** and **3at**) by simply using an acetylene balloon, probably due to the steric accessibility of the acetylene molecule.[36,37]

We subsequently evaluated the scope with respect to aldehydes. Primary and secondary aliphatic aldehydes proved to be competent starting materials to furnish the desired thioesters in moderate to good yields. These aldehydes tolerate a wide range of functional groups, such as ester (**3av**−**3ax**), furan (**3ay**), free alcohol (**3az**), amide (**3ba**), and carbamate (**3be**) groups. The tertiary alkyl aldehydes represent a challenging class of aldehydes to generate acyl radicals, which tend to decarbonylate to form a stable tertiary alkyl radical.[29−31] However, under our reaction conditions, tertiary alkyl aldehydes exhibited good efficiency without the formation of any decarbonylation byproduct (**3bf** and **3bg**), indicating an efficient radical trapping by elemental sulfur when compared to decarbonylation. An α,β-unsaturated aldehyde was also used to generate thioester **3bh**, albeit in a lower yield, due to the plausible oligomerization. Notably, thioesters **3bi** or **3bj** could be obtained from acetaldehyde or trioxane, respectively. Aromatic aldehydes are also suitable substrates for the three-component coupling reaction.

Both electron-rich (e.g., methoxy) and electron-poor (e.g., trifluoromethyl, fluoro, and chloro) substituents were well tolerated, and the corresponding products (**3bk**−**3br**) were obtained in good yields. Heteroaromatic compounds, such as thiophene, benzofuran, and pyrimidine, which are prevalent in pharmaceutical molecules, can be incorporated in the aldehydes, leading to the corresponding thioesters (**3bs**−**3bu**) in moderate to good yields. Although competitive HAT from other activated sites to excited TBADT can also occur as a minor pathway (see below), the observation that when cyclohexane, ethylbenzene, and tetrahydropyran instead of aldehydes were subjected to the optimal reaction conditions, only trace amounts or very low yields of thioether products

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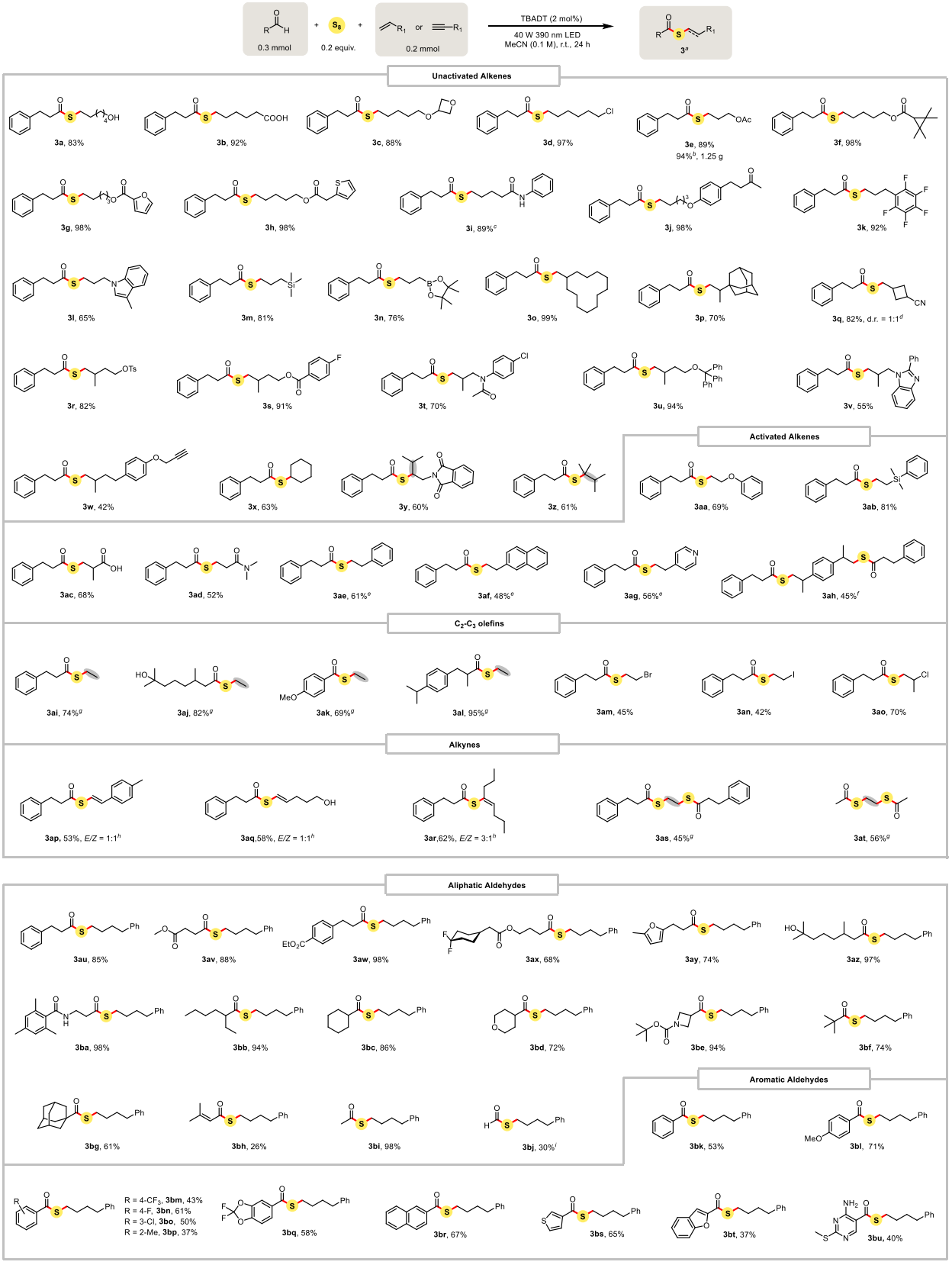

Figure 2. Substrate scope of three-component coupling to directly access thioesters. Superscript *a*: Unless otherwise noted, reactions were conducted under the standard conditions and isolated yields are given. Superscript *b*: For the gram-scale synthesis, 5 mmol of **2e** was used and the reaction was conducted for 36 h. Superscript *c*: Reactions were conducted for 48 h. Superscript *d*: Diastereomeric ratio (d.r.) was determined by the analysis of the ^{1}H NMR spectrum of the crude reaction mixture. Superscript *e*: Reactions were conducted with 0.4 equiv S_8 and 4 mol % TBADT. Superscript *f*: 0.6 mmol of aldehyde and 0.8 equiv S_8 was used. Superscript *g*: 0.2 mmol of aldehyde and a balloon filled with ethylene or acetylene gas were applied. The yield was determined based on the aldehyde substrate. Superscript *h*: 0.2 mmol of aldehyde and 0.3 mmol of alkyne

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Figure 2. continued

were used. *E*/*Z* ratios were determined by the ^{1}H NMR analysis of the crude reaction mixture. Superscript *i*: Trioxane was used as the formaldehyde equivalent and BCl_3 was added into the reaction mixture upon completion.

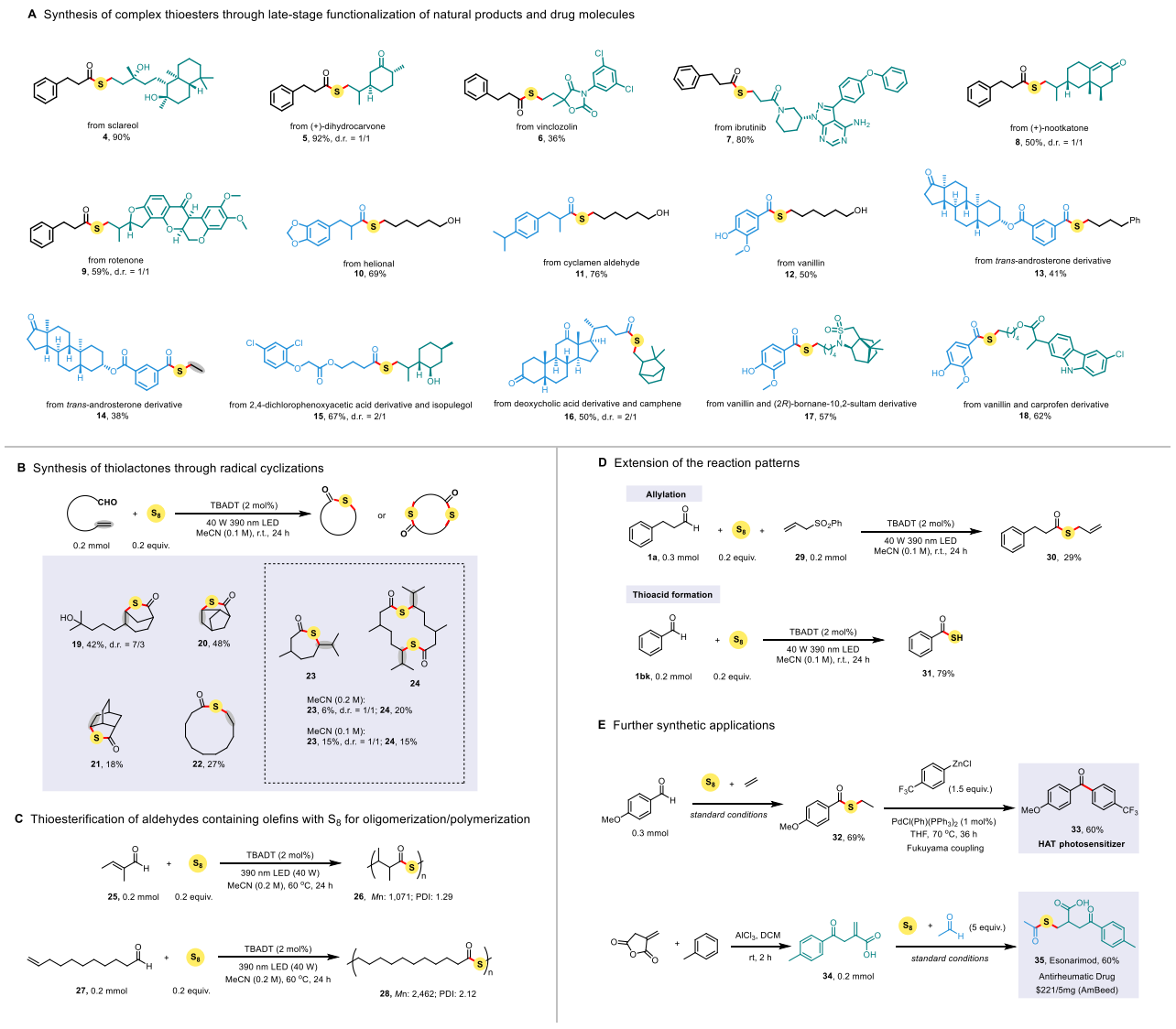

Figure 3. Synthetic extensions and applications of thioester generation by HAT photocatalysis. (A) Incorporation of pharmaceutical molecules. (B) Synthesis of thiolactones through radical cyclization. (C) Synthesis of oligomers/polymers through thioesterification. (D) Extension of the reaction patterns. (E) Other synthetic applications.

were detected (Figure S10), indicates that S_8 is preferentially trapped by the acyl radical, accounting for the selective functionalization of aldehydic C−H bonds in the presence of other activated C(sp^3)−H bonds.

To showcase the synthetic practicability and robustness, we further applied this protocol to direct late-stage modification of a variety of complex pharmaceutical drugs and natural products in a chemo- and regioselective fashion with excellent functional group compatibility (Figure 3A). Olefin-containing natural products and drug molecules such as sclareol (**4**), dihydrocarvone (**5**), vinclozolin (**6**), ibrutinib (**7**), nootkatone (**8**), and rotenone (**9**) or aldehydes including helional (**10**), cyclamen aldehyde (**11**), vanillin (**12**), and derivatives from *trans*-androsterone (**13** and **14**) readily participated in this three-component transformation. Sensitive functionalities such as free alcohols (**4**, **10**−**12**, and **15**), ketones (**5**, **8**, **9**, **13**, and **14**), and *N*-heteroaryl amine (**7**) were well tolerated, highlighting reactivity orthogonal to the conventional thiol-based nucleophilic substitution. When two competing alkenes were presented in a single molecule, a site-specific thioester was obtained from a reaction at the electron-rich and more sterically accessible alkene site (**8**). Importantly, two pharmaceutical aldehydes and alkenes could be simultaneously incorporated into one molecule through the thioester linker (**15**−**18**), suggesting the rich potential to apply the present protocol to the preparation of antibody-drug conjugates and biomolecule labeling.[38] With their intrinsic three-dimensional conformation, cyclic thioesters have been found to play a pivotal role in multidisciplinary areas varying from bioactive pharmaceutical ingredients to functional materials,[1,39−41] but

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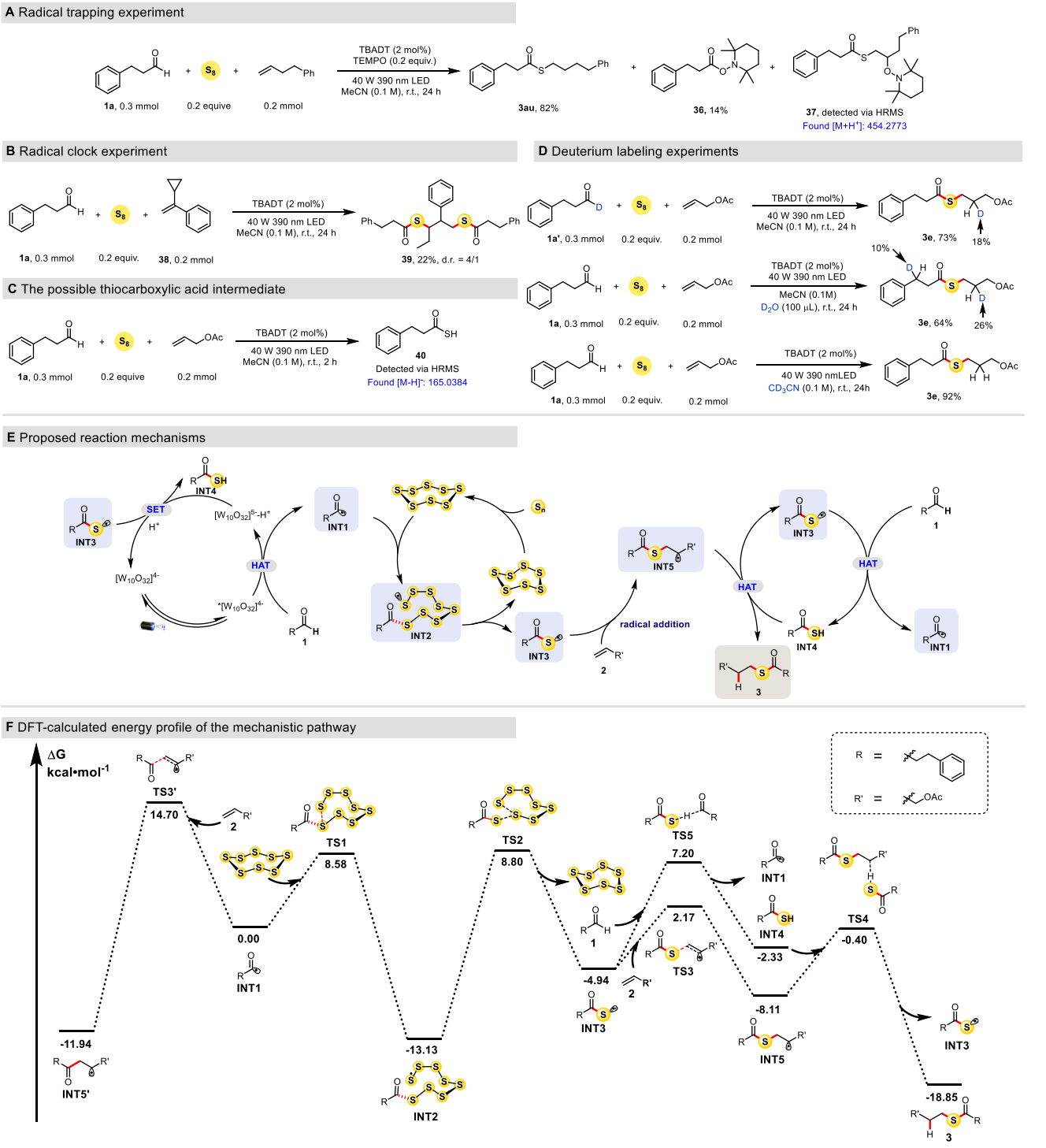

Figure 4. Proposed mechanisms with supporting evidence. (A) Radical trapping experiment. (B) Radical clock experiment. (C) Investigation of the possible thiocarboxylic acid intermediate. (D) Deuterium labeling experiments. (E) Plausible reaction mechanisms. (F) DFT-calculated energy profile of the mechanistic pathway.

their synthesis remains challenging. We anticipated that the application of this direct photo-HAT strategy to aldehydes bearing an alkene unit would lead to cyclization through intramolecular carbonyl thiyl radical addition (Figure 3B). In fact, various fused-ring and monocyclic thioesters with different ring sizes were successfully constructed (**19**–**24**). Concentration-dependent intramolecular and intermolecular cyclization of generated carbonyl thiyl radicals (**23** and **24**) was observed.

We next examined the photo-HAT-initiated polymerization using monomeric aldehydes bearing an alkene moiety (Figure 3C). Both 2-methylbut-2-enal and undec-10-enal underwent polymerization to provide the polythioesters **26** (M_n: 1071; PDI: 1.29) and **28** (M_n: 2462; PDI: 2.12) in 9−13 units of monomers. It is worth noting that these thioester-based polymers can easily undergo degradation or upcycling through hydrolysis, aminolysis, thiolysis, and oxidative cleavage,[42] which indicated an intriguing potential of our method for

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the synthesis of eco-friendly materials. This three-component coupling protocol can be further extended by trapping the generated carbonyl thiyl radical intermediates by other SOMOphiles, indicating an enormous potential to produce various patterns of sulfur-containing value-added chemicals (Figure 3D). For instance, the allylthioester (**30**) was generated, albeit in a relatively lower yield by using allyl phenyl sulfone (**29**) as a radical scavenger. In addition, in the absence of an alkene, thiocarboxylic acids (**31**), an important family of acylsulfur reagents, can be prepared in high yields under our standard protocols.

The capacity of the present strategy was also illustrated by the preparation of *S*-ethyl benzothioate **32** from 4-methoxybenzaldehyde and ethylene, which can be directly converted to the commonly used photo-HAT catalyst **33**[43] through Fukuyama coupling (Figure 3E). To further exhibit the potential in pharmaceutical synthesis, esonarimod, an anti-rheumatic drug,[44] was assembled in a two-step fashion (Figure 3E). First, alkenoic acid **34** was readily synthesized from 3-methylenedihydrofuran-2,5-dione and toluene through Friedel−Crafts acylation. Subsequently, a three-component coupling of acetaldehyde, elemental sulfur, and alkenoic acid **34** successfully yielded esonarimod **35** in 60% yield.

To shed light on the reaction mechanisms, a variety of control experiments were performed (Figure 4). The addition of TEMPO (0.2 equiv) as a radical scavenger into the reaction system generated the TEMPO-acyl adduct (**36**) in 14% yield, revealing the involvement of an acyl radical intermediate in the reaction process (Figure 4A). Meanwhile, a TEMPO-carbon adduct (**37**) was detected by HRMS measurement, supporting the formation of the carbon radical adduct by the addition of the carbonyl thiyl radical to the alkene (Figure 4A). Notably, a radical clock experiment led to the ring-opened dithioester **39** (Figure 4B) by consecutive difunctionalization involving double carbonyl thiyl radical addition to the C═C double bond of **38**. Thiocarboxylic acid **40** was detected by HRMS, revealing its presence during the reaction process (Figure 4C), and it might serve as a HAT reagent to provide hydrogen to the carbon-centered radical intermediates. Deuterium labeling experiments indicated that the hydrogen source for a reverse HAT could be the aldehyde or water, instead of the solvent CH_3CN (Figure 4D). The deuterium incorporation ratios could be rationalized by a D/H exchange between water, D_2O, and $[W_{10}O_{32}]^{5-}$-D^+/H^+.[45,46]

Based on the experiments described above, a possible mechanism of this three-component coupling is proposed in Figure 4E. The photo-excited $*[W_{10}O_{32}]^{4-}$ can abstract a hydrogen atom from an aldehyde to give the acyl radical **INT1** and a reductive intermediate $H^+[W_{10}O_{32}]^{5-}$ (E_{red} = −0.97 V *vs* SCE in MeCN).[47] Then, the nucleophilic acyl radical **INT1** reacts with elemental sulfur, giving rise to the sulfur radical intermediate **INT2**. Compared to the reported data related to the process of decarbonylation of pivaloyl radical and acyl radical cyclization to form six-member rings,[48,49] the rate constant for an acyl radical trapped by S_8 should be over 1.3×10^5 s^{-1}. This intermediate is fragmented into a carbonyl thiyl radical **INT3** through intramolecular cyclization (for more discussion, see the Supporting Information, Section 10). Subsequently, the electrophilic carbonyl thiyl radical **INT3** adds to alkenes to deliver the carbon-centered radical **INT5**.[26−28] In addition, the carbonyl thiyl radical **INT3** behaves as an oxidant and triggers a single electron transfer event with $H^+[W_{10}O_{32}]^{5-}$ to provide thiocarboxylic acid **INT4** with concomitant regeneration of $[W_{10}O_{32}]^{4-}$. A polarity-matched HAT between the nucleophilic carbon-centered radical **INT5** and the generated thiocarboxylic acid **INT4** furnishes the desired thioester **3**.[50] The electrophilic carbonyl thiyl radical **INT3** might also serve as a HAT reagent and abstract the hydrogen atom from an aldehyde, giving nucleophilic acyl radicals **INT1**. A measured quantum yield of 6.34 indicated a radical chain mechanism (for details, see the Supporting Information).

To further validate the proposed reaction mechanisms, quantum chemical calculations were conducted at the density functional theory (DFT) level. As shown in Figure 4F, the obtained energy profile starts from the acyl radical **INT1** generated *in situ*, which reacts with either an alkene or elemental sulfur. Compared to the addition of **INT1** to an alkene via the transition state **TS3′**, the barrier of reacting with elemental sulfur is only 8.58 kcal·mol^{-1} via transition state **TS1** in acetonitrile, which is about 3×10^4 times faster judging by its $\Delta\Delta G^*$ = 6.12 kcal·mol^{-1}. In addition, **INT2** is a very stable intermediate, indicating a both thermodynamically and kinetically favored process. This again underlines the fact that elemental sulfur is a great scavenger for acyl radicals. The intramolecular cyclization of **INT2**, with its highest global barrier in this reaction process, is the rate-determining step.[51] The energy barrier for addition of the carbonyl thiyl radical **INT3** to an alkene was determined to be only 7.11 kcal·mol^{-1}. The barrier of HAT between thiocarboxylic acid **INT4** and carbon-centered radical **INT5** is low, and this step is both kinetically and thermodynamically favored due to the polarity match (ΔG(**INT5** → **INT3**) = −10.74 kcal·mol^{-1}), and the final thioester product can be obtained with the generation of the carbonyl thiyl radical **INT3**. In addition, the radical **INT3** could readily abstract a hydrogen atom from an aldehyde to reproduce an acyl radical via **TS5**, supporting the radical chain propagation in this reaction process.

CONCLUSIONS

We have developed efficient three-component coupling to synthesize structurally diverse thioesters from readily available aldehydes, alkenes, alkynes, and elemental sulfur through direct photo-HAT catalysis. This protocol features several merits including atom-, step-, and redox-economical synthesis, a remarkably broad scope of available feedstocks, applicability to late-stage functionalization of complex pharmaceuticals, and reactivity orthogonal to conventional thiol-based nucleophilic additions. The reaction can be easily diversified for the synthesis of thiolactones, degradable thioester-based polymers, and thioacids. We suggest that the establishment of carbonyl thiyl radical chemistry based on the usage of elemental sulfur through photo-HAT catalysis will unlock new opportunities in organic synthesis, pharmaceuticals, and functional materials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c13157.

General procedures, tables of reaction optimizations, analytical data, calculation details, and characterization data for all the products (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Bannin, T. J.; Kiesewetter, M. K. Poly(thioester) by Organocatalytic Ring-Opening Polymerization. *Macromolecules* **2015**, *48*, 5481−5486.

(2) Chandru, K.; Gilbert, A.; Butch, C.; Aono, M.; Cleaves, H. J. The Abiotic Chemistry of Thiolated Acetate Derivatives and the Origin of Life. *Sci. Rep.* **2016**, *6*, 29883.

(3) Martin, N.; Neelz, V.; Spinnler, H.-E. Suprathreshold Intensity and Odour Quality of Sulphides and Thioesters. *Food Qual. Prefer.* **2004**, *15*, 247−257.

(4) Kanda, Y.; Ashizawa, T.; Kakita, S.; Takahashi, Y.; Kono, M.; Yoshida, M.; Saitoh, Y.; Okabe, M. Synthesis and Antitumor Activity of Novel Thioester Derivatives of Leinamycin. *J. Med. Chem.* **1999**, *42*, 1330−1332.

(5) Wang, N.; Saidhareddy, P.; Jiang, X. Construction of Sulfur-Containing Moieties in the Total Synthesis of Natural Products. *Nat. Prod. Rep.* **2020**, *37*, 246−275.

(6) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. Synthesis of Proteins by Native Chemical Ligation. *Science* **1994**, *266*, 776−779.

(7) Agouridas, V.; El Mahdi, O.; Diemer, V.; Cargoet, M.; Monbaliu, J. C. M.; Melnyk, O. Native Chemical Ligation and Extended Methods: Mechanisms, Catalysis, Scope, and Limitations. *Chem. Rev.* **2019**, *119*, 7328−7443.

(8) Sikandar, S.; Zahoor, A. F.; Naheed, S.; Parveen, B.; Ali, K. G.; Akhtar, R. Fukuyama Reduction, Fukuyama Coupling and Fukuyama-Mitsunobu Alkylation: Recent Developments and Synthetic Applications. *Mol. Diversity* **2022**, *26*, 589−628.

(9) Pietrocola, F.; Galluzzi, L.; Bravo-San Pedro, J. M.; Madeo, F.; Kroemer, G. Acetyl Coenzyme A: a Central Metabolite and Second Messenger. *Cell Metab.* **2015**, *21*, 805−821.

(10) Iimura, S.; Manabe, K.; Kobayashi, S. Direct Thioesterification from Carboxylic Acids and Thiols Catalyzed by a Bronsted Acid. *Chem. Commun.* **2002**, *1*, 94−95.

(11) Kazemi, M.; Shiri, L. Thioesters Synthesis: Recent Adventures in the Esterification of Thiols. *J. Sulfur Chem.* **2015**, *36*, 613−623.

(12) Santi, C.; Battistelli, B.; Testaferri, L.; Tiecco, M. On Water Preparation of Phenylselenoesters. *Green Chem.* **2012**, *14*, 1277−1280.

(13) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. The Direct Synthesis of Thioesters Using an Intermolecular Radical Reaction of Aldehydes with Dipentafluorophenyl Disulfide in Water. *Chem. Commun.* **2002**, *10*, 1082−1083.

(14) Yi, C. L.; Huang, Y.-T.; Lee, C.-F. Synthesis of Thioesters through Copper-Catalyzed Coupling of Aldehydes with Thiols in Water. *Green Chem.* **2013**, *15*, 2476−2484.

(15) Luo, J.; Rauch, M.; Avram, L.; Diskin-Posner, Y.; Shmul, G.; Ben-David, Y.; Milstein, D. Formation of Thioesters by Dehydrogenative Coupling of Thiols and Alcohols with H_2 Evolution. *Nat. Catal.* **2020**, *3*, 887−892.

(16) Hegedus, L. L.; McCabe, R. W. Catalyst Poisoning. *Stud. Surf. Sci. Catal.* **1980**, *6*, 471−505.

(17) Nguyen, T. B. Recent Advances in Organic Reactions Involving Elemental Sulfur. *Adv. Synth. Catal.* **2017**, *359*, 1066−1130.

(18) Chung, W. J.; Griebel, J. J.; Kim, E. T.; Yoon, H.; Simmonds, A. G.; Ji, H. J.; Dirlam, P. T.; Glass, R. S.; Wie, J. J.; Nguyen, N. A.; Guralnick, B. W.; Park, J.; Somogyi, A.; Theato, P.; Mackay, M. E.; Sung, Y.-E.; Char, K.; Pyun, J. The Use of Elemental Sulfur as an Alternative Feedstock for Polymeric Materials. *Nat. Chem.* **2013**, *5*, 518−524.

(19) Liu, H.; Jiang, X. Transfer of Sulfur: From Simple to Diverse. *Chem. − Asian J.* **2013**, *8*, 2546−2563.

(20) Zhang, J. R.; Liao, Y. Y.; Deng, J. C.; Feng, K. Y.; Zhang, M.; Ning, Y. Y.; Lin, Z. W.; Tang, R. Y. Oxidative Dual C-H Thiolation of Imidazopyridines with Ethers or Alkanes Using Elemental Sulphur. *Chem. Commun.* **2017**, *53*, 7784−7787.

(21) Murakami, S.; Nanjo, T.; Takemoto, Y. Photocatalytic Activation of Elemental Sulfur Enables a Chemoselective Three-Component Thioesterification. *Org. Lett.* **2021**, *23*, 7650−7655.

(22) Lee, T.; Dirlam, P. T.; Njardarson, J. T.; Glass, R. S.; Pyun, J. Polymerizations with Elemental Sulfur: From Petroleum Refining to Polymeric Materials. *J. Am. Chem. Soc.* **2022**, *144*, 5−22.

(23) Zhang, G.; Yi, H.; Chen, H.; Bian, C.; Liu, C.; Lei, A. Trisulfur Radical Anion as the Key Intermediate for the Synthesis of Thiophene via the Interaction between Elemental Sulfur and NaO*t*Bu. *Org. Lett.* **2014**, *16*, 6156−6159.

(24) Wang, M.; Dai, Z.; Jiang, X. Design and Application of Alpha-Ketothioesters as 1,2-Dicarbonyl-Forming Reagents. *Nat. Commun.* **2019**, *10*, 2661.

(25) Jia, J.; Liu, J.; Wang, Z. Q.; Liu, T.; Yan, P.; Gong, X. Q.; Zhao, C.; Chen, L.; Miao, C.; Zhao, W.; Cai, S.; Wang, X. C.; Cooper, A. I.; Wu, X.; Hasell, T.; Quan, Z. J. Photoinduced Inverse Vulcanization. *Nat. Chem.* **2022**, *14*, 1249−1257.

(26) Hoyle, C. E.; Bowman, C. N. Thiol−Ene Click Chemistry. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540−1573.

(27) Denes, F.; Pichowicz, M.; Povie, G.; Renaud, P. Thiyl Radicals in Organic Synthesis. *Chem. Rev.* **2014**, *114*, 2587−2693.

(28) Teders, M.; Henkel, C.; Anhäuser, L.; Strieth-Kalthoff, F.; Gómez-Suárez, A.; Kleinmans, R.; Kahnt, A.; Rentmeister, A.; Guldi, D.; Glorius, F. The Energy-Transfer-Enabled Biocompatible Disulfide−Ene Reaction. *Nat. Chem.* **2018**, *10*, 981−988.

(29) Yan, J.; Tang, H.; Kuek, E. J. R.; Shi, X.; Liu, C.; Zhang, M.; Piper, J. L.; Duan, S.; Wu, J. Divergent Functionalization of Aldehydes PhotoCatalyzed by Neutral Eosin Y with Sulfone Reagents. *Nat. Commun.* **2021**, *12*, 7214.
(30) Cao, H.; Kuang, Y.; Shi, X.; Wong, K. L.; Tan, B. B.; Kwan, J. M. C.; Liu, X.; Wu, J. Photoinduced Site-Selective Alkenylation of Alkanes and Aldehydes with Aryl Alkenes. *Nat. Commun.* **1956**, *2020*, 11.
(31) Yan, J.; Cheo, H. W.; Teo, W. K.; Shi, X.; Wu, H.; Idres, S. B.; Deng, L. W.; Wu, J. A Radical Smiles Rearrangement Promoted by Neutral Eosin Y as a Direct Hydrogen Atom Transfer Photocatalyst. *J. Am. Chem. Soc.* **2020**, *142*, 11357−11362.
(32) Fan, X. Z.; Rong, J. W.; Wu, H. L.; Zhou, Q.; Deng, H. P.; Tan, J. D.; Xue, C. W.; Wu, L. Z.; Tao, H. R.; Wu, J. Eosin Y as a Direct Hydrogen-Atom Transfer Photocatalyst for the Functionalization of C-H Bonds. *Angew. Chem., Int. Ed.* **2018**, *57*, 8514−8518.
(33) Cao, H.; Kong, D.; Yang, L. C.; Chanmungkalakul, S.; Liu, T.; Piper, J. L.; Peng, Z.; Gao, L.; Liu, X.; Hong, X.; Wu, J. Brønsted Acid-Enhanced Direct Hydrogen Atom Transfer Photocatalysis to Enable Selective Late-Stage Functionalization of Unactivated C(sp^3)-H Bonds. *Nat. Synth.* **2022**, *1*, 794−803.
(34) Chavan, S. P.; Subbarao, Y. T.; Dantale, S. W.; Sivappa, R. Transesterification of Ketoesters Using Amberlyst-15. *Synth. Commun.* **2001**, *31*, 289−294.
(35) Maheswara, M.; Kim, M.; Yun, S. J.; Ju, J. J.; Do, J. Y. A New Strategy for Chemoselective *O*-acylation of *β*-mercapto Alcohols via Alkylsilyl and Stannyl Protection. *Tetrahedron Lett.* **2009**, *50*, 480−483.
(36) Lü, S.; Wang, Z.; Zhu, S. Thiol-Yne Click Chemistry of Acetylene-Enabled Macrocyclization. *Nat. Commun.* **2022**, *13*, 5001.
(37) Dietel, T.; Lukas, F.; Kretschmer, W. P.; Kempe, R. Elongation and Branching of *α*-Olefins by Two Ethylene Molecules. *Science* **2022**, *375*, 1021−1024.
(38) Agarwal, P.; Bertozzi, C. R. Site-Specific Antibody-Drug Conjugates: The Nexus of Biorthogonal Chemistry, Protein Engineering, and Drug Development. *Bioconjugate Chem.* **2015**, *26*, 176.
(39) Newman, D. J.; Cragg, G. M. Bioactive Macrocycles from Nature. In *Macrocycles in Drug Discovery*, J., Levin, ed. Royal Society of Chemistry 2014, pp. 1−36.
(40) Yue, T. J.; Zhang, M. C.; Gu, G. G.; Wang, L. Y.; Ren, W. M.; Lu, X. B. Precise Synthesis of Poly(thioester)s with Diverse Structures by Copolymerization of Cyclic Thioanhydrides and Episulfides Mediated by Organic Ammonium Salts. *Angew. Chem., Int. Ed.* **2018**, *58*, 618−623.
(41) Yuan, P.; Sun, Y.; Xu, X.; Luo, Y.; Hong, M. Towards High-Performance Sustainable Polymers via Isomerization-Driven Irreversible Ring-Opening Polymerization of Five-Membered Thionolactones. *Nat. Chem.* **2022**, *14*, 294−303.
(42) Bingham, N. M.; Nisa, Q. U.; Chua, S. H.; Fontugne, L.; Spick, M. P.; Roth, P. J. Thioester-Functional Polyacrylamides: Rapid Selective Backbone Degradation Triggers Solubility Switch Based on Aqueous Lower Critical Solution Temperature/Upper Critical Solution Temperature. *ACS Appl. Polym. Mater.* **2020**, *2*, 3440−3449.
(43) Shen, Y.; Gu, Y.; Martin, R. Sp^3 C−H Arylation and Alkylation Enabled by the Synergy of Triplet Excited Ketones and Nickel Catalysts. *J. Am. Chem. Soc.* **2018**, *140*, 12200−12209.
(44) Noguchi, T.; Onodera, A.; Ito, M.; Yoshida, M.; Yokomori, S. A Practical Procedure for the Synthesis of Esonarimod, (*R,S*)-2-Acetylthiomethyl-4-(4-Methylphenyl)-4-Oxobutanoic Acid, An Anti-rheumatic Agent. II. *Synth. Commun.* **2003**, *33*, 2657−2670.
(45) Kuang, Y.; Cao, H.; Tang, H.; Chew, J.; Chen, W.; Shi, X.; Wu, J. Visible Light Driven Deuteration of Formyl C−H and Hydridic C(sp^3)−H Bonds in Feedstock Chemicals and Pharmaceutical Molecules. *Chem. Sci.* **2020**, *11*, 8912−8918.
(46) Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Albini, A. Atom-Economical Synthesis of Unsymmetrical Ketones through Photocatalyzed C-H Activation of Alkanes and Coupling with CO and Electrophilic Alkenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 1869−1872.
(47) Renneke, R. F.; Pasquali, M.; Hill, C. L. Polyoxometalate Systems for the Catalytic Selective Production of Nonthermodynamic Alkenes from Alkanes. Nature of Excited-State Deactivation Processes and Control of Subsequent Thermal Processes in Polyoxometalate Photoredox Chemistry. *J. Am. Chem. Soc.* **1990**, *112*, 6585−6594.
(48) Lunazzi, L.; Ingold, K. U.; Scaiano, J. C. Absolute Rate Constants for the Decarbonylation of the Phenylacetyl Radical. *J. Phys. Chem.* **1983**, *87*, 529−530.
(49) Hancock, A. N.; Schiesser, C. H. The Kinetics of Carbonyl Radical Ring Closures. *Chem. Sci.* **2014**, *5*, 1967−1973.
(50) Roberts, B. Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25−35.
(51) Cheng, Y.; Zong, L.; López-Andarias, J.; Bartolami, E.; Okamoto, Y.; Ward, T. R.; Sakai, N.; Matile, S. Cell-Penetrating Dynamic-Covalent Benzopolysulfane Networks. *Angew. Chem., Int. Ed.* **2019**, *58*, 9522−9526.

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