Multimodal Acridine Photocatalysis Enables Direct Access to Thiols from Carboxylic Acids and Elemental Sulfur

Arka Porey, Seth O. Fremin, Sachchida Nand, Ramon Trevino, William B. Hughes, Shree Krishna Dhakal, Viet D. Nguyen, Samuel G. Greco, Hadi D. Arman, Oleg V. Larionov*

The University of Texas at San Antonio, Department of Chemistry, One UTSA Circle, San Antonio, TX, 78249, USA, e-mail: oleg.larionov@utsa.edu

Abstract: Development of photocatalytic systems that facilitate mechanistically different steps in complex catalytic manifolds by distinct activation modes can enable previously inaccessible synthetic transformations. However, multimodal photocatalytic systems remain understudied, impeding their implementation in catalytic methodology. We report herein a photocatalytic access to thiols that directly merges the structural diversity of carboxylic acids with the ready availability of elemental sulfur without substrate preactivation. The photocatalytic transformation provides a direct radical-mediated segue to one of the most biologically important and synthetically versatile organosulfur functionalities, whose synthetic accessibility remains largely dominated by two-electron-mediated processes based on toxic and uneconomical reagents and precursors. The two-phase radical process is facilitated by a multimodal catalytic reactivity of acridine photocatalysis that enables both the singlet excited state PCET-mediated decarboxylative carbon–sulfur bond formation and the previously unknown radical reductive disulfur bond cleavage by a photoinduced HAT process in the silane–triplet acridine system. The study points to a significant potential of multimodal photocatalytic systems in providing new directions to previously inaccessible transformations.

Introduction

Recent advances in the development of homogeneous photocatalytic systems have enabled a variety of new synthetic transformations. In particular, complex photocatalytic manifolds that combine two or more catalysts that independently facilitate several catalytic cycles through relay or cooperative modes have emerged as powerful tools for the discovery of novel functionalizations.[1] By contrast, photocatalytic systems that entail mechanistically distinct catalytic cycles enabled by the same photocatalyst operating from different excited states in each process remain underexplored, despite the potential to unlock previously inaccessible catalytic interconversions and provide insight into the mechanisms of complex photocatalytic systems (Figure 1.A).[1,2]

Development of new catalytic methods that enable access to broad and diverse chemical space of key functionalities from abundant organic and inorganic feedstocks have emerged at the forefront of current synthetic methodology.[3] Thiols have centrally important roles in chemistry, drug discovery, biochemistry, and materials science, because of the favorable combination of physicochemical properties, Lewis basicity, facile interconversion with higher oxidation state organosulfur functionalities, and the propensity to form disulfide bonds (Figure 1.B).[4] Given the cross-disciplinary importance of thiols, catalytic reactions that enable their construction from structurally diverse precursors using simple sulfur-centered reagents will improve the efficiency of organic synthesis and facilitate access to new medicinal chemical space. Current synthetic approaches to thiols are largely based on two-electron processes that typically involve nucleophilic substitution and addition reactions, requiring toxic and malodorous reagents.[5] By contrast, one-electron processes remain less developed, limiting the accessible thiol chemical space.

Elemental sulfur that predominantly exists as a cyclic octoatomic allotope S_8 is produced on a scale of over 80 million tons as a by-product of petroleum refining, and an unutilized surplus of several million tons is generated every year.[6] The enormous abundance of inexpensive elemental sulfur ($120/ton) combined with the operational facility of handing the nontoxic, odorless, and nonhygroscopic solid S_8 provide a strong impetus for the development of new catalytic methodologies that leverage the reactivity and ubiquity of elemental sulfur. Yet, advances in S_8-based approaches remain limited. Notably, despite the weak sulfur–sulfur bond (BDE 39 kcal/mol),[7] reactions that are based on S_8-mediated one-electron processes are largely underdeveloped.[8]

The structural diversity of carboxylic acids that is evident from the broad span of their chemical space across the domains of molecular complexity,[9] fraction of sp^3 carbon atoms (Fsp^3),[10] and geometric diversity[11,12] renders them some of the most effective alkyl radical precursors for the purpose of accessing the chemical space of diverse functionalities that is not achievable by currently available transformations.[13-15]

Acridine photocatalysis is an emergent catalytic platform that has enabled direct decarboxylative functionalization of carboxylic acids, providing previously unavailable synthetic shortcuts to bioisosteric functional groups, synthetic intermediates, and new advanced materials.[8i,14,15] The photocatalytic radical generation is facilitated by photoinduced proton-coupled electron transfer (PCET) within the singlet excited state of the acridine–carboxylic acid hydrogen bond complex,[14] obviating stepwise preactivation of the carboxylic group that is typically required to bypass the challenging oxidative decarboxylation. However, the scope of the

direct decarboxylative functionalization remains narrow, and the primary catalytic mode of 9-arylacridines is confined to PCET with carboxylic acids, while the possibility of catalyzing other types of reactions, e.g., hydrogen atom transfer (HAT) from other substrates is understudied.[16]

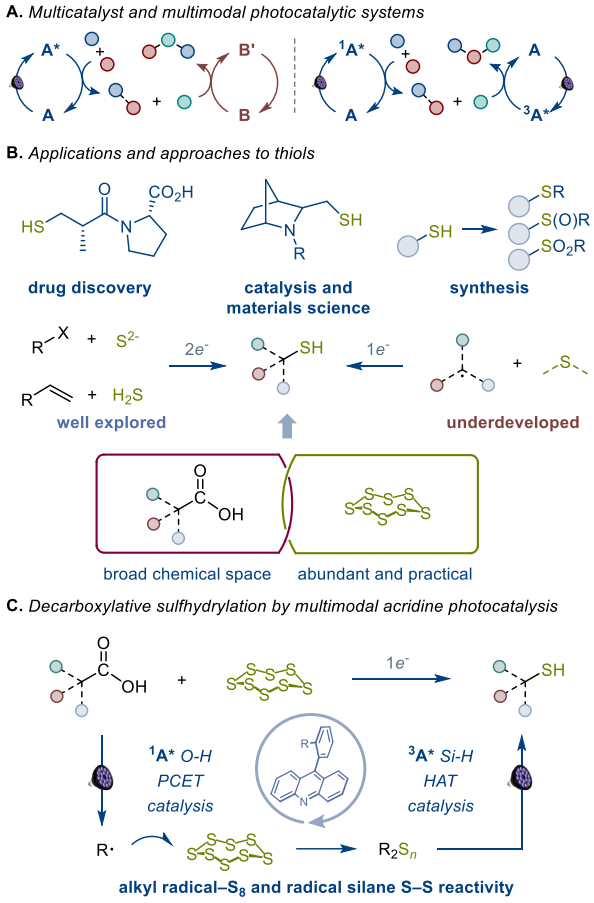


Figure 1. Multimodal acridine photocatalysis for decarboxylative sulfhydrylation with elemental sulfur.

A direct decarboxylative reaction of carboxylic acids with elemental sulfur would enable an efficient segue to thiols, because it would provide access to a broad thiol chemical space, leveraging the structural diversity of carboxylic acids and the abundance of the common inorganic feedstock (Figure 1.C). This approach would represent a departure from currently available methods that require an additional step for the conversion of carboxylic acids to reactive derivatives to facilitate the decarboxylation, as well as the use of organic sulfur synthons.[17] The development of such a direct synthetic shortcut between carboxylic acids and thiols is especially important in view of the diverse medicinal applications of sulfur-centered functional groups as bioisosteres of the carboxylic group,[18] and the facility of conversion of thiols to other sulfur functionalities. We hypothesized that the intermediate oligosulfides formed in the process could be directly converted to thiols in a reaction with silanes and acridine serving as a photocatalyst. The excited acridine catalyst would effect a HAT from the silane, generating the reactive silyl radical that could mediate a homolytic cleavage of the disulfide bonds. Although radical reduction of disulfide bonds with silanes was unknown and no example of a HAT from a Si–H bond by acridine was described, if successful, this process would facilitate direct conversion of carboxylic acids to thiols by a two-phase multimodal catalytic process with acridine catalyzing two distinct reactions.

We report herein the development of a direct decarboxylative sulfhydrylation that enables preactivation-free conversion of carboxylic acids to thiols in a reaction with elemental sulfur. The synthetic method leverages the multimodal catalytic reactivity of 9-arylacridines both in the photoinduced direct decarboxylation of carboxylic acids and the previously unknown hydrogen atom transfer from the Si–H bond in a silane.

Results and Discussion

Optimization studies with carboxylic acid **1**, revealed that the formation of the C–S bond can indeed be achieved in a reaction with sulfur in the presence of acridine **A1** under 400 nm LED irradiation and at 100 °C (Figure 2.A), producing dialkyl oligosulfides **2** in 80% yield, with the disulfide accounting for 44% of the mixture. While other acridine catalysts also afforded comparable yields, the reaction did not proceed without light or the photocatalyst.

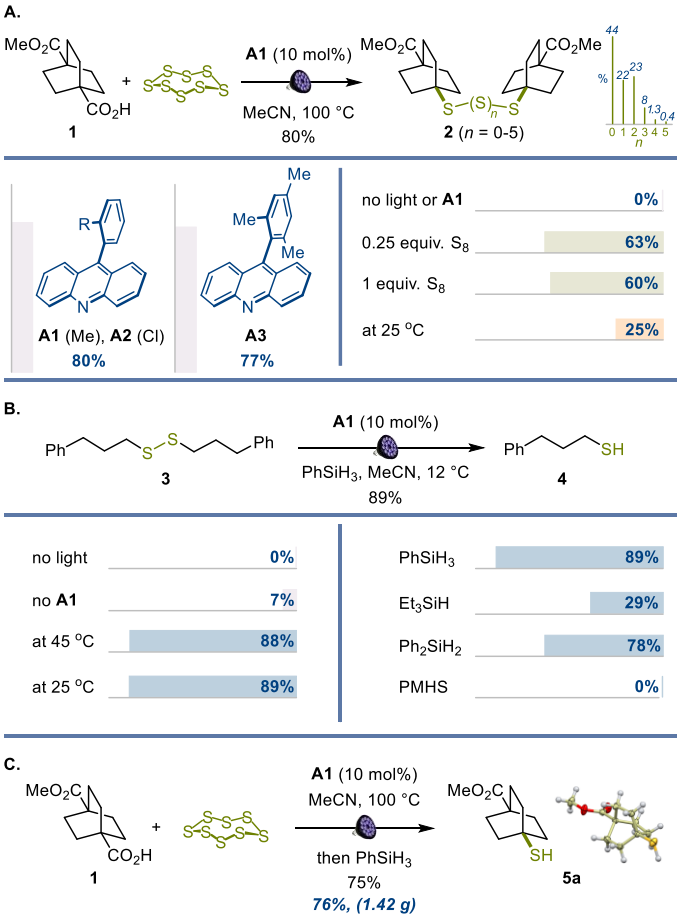


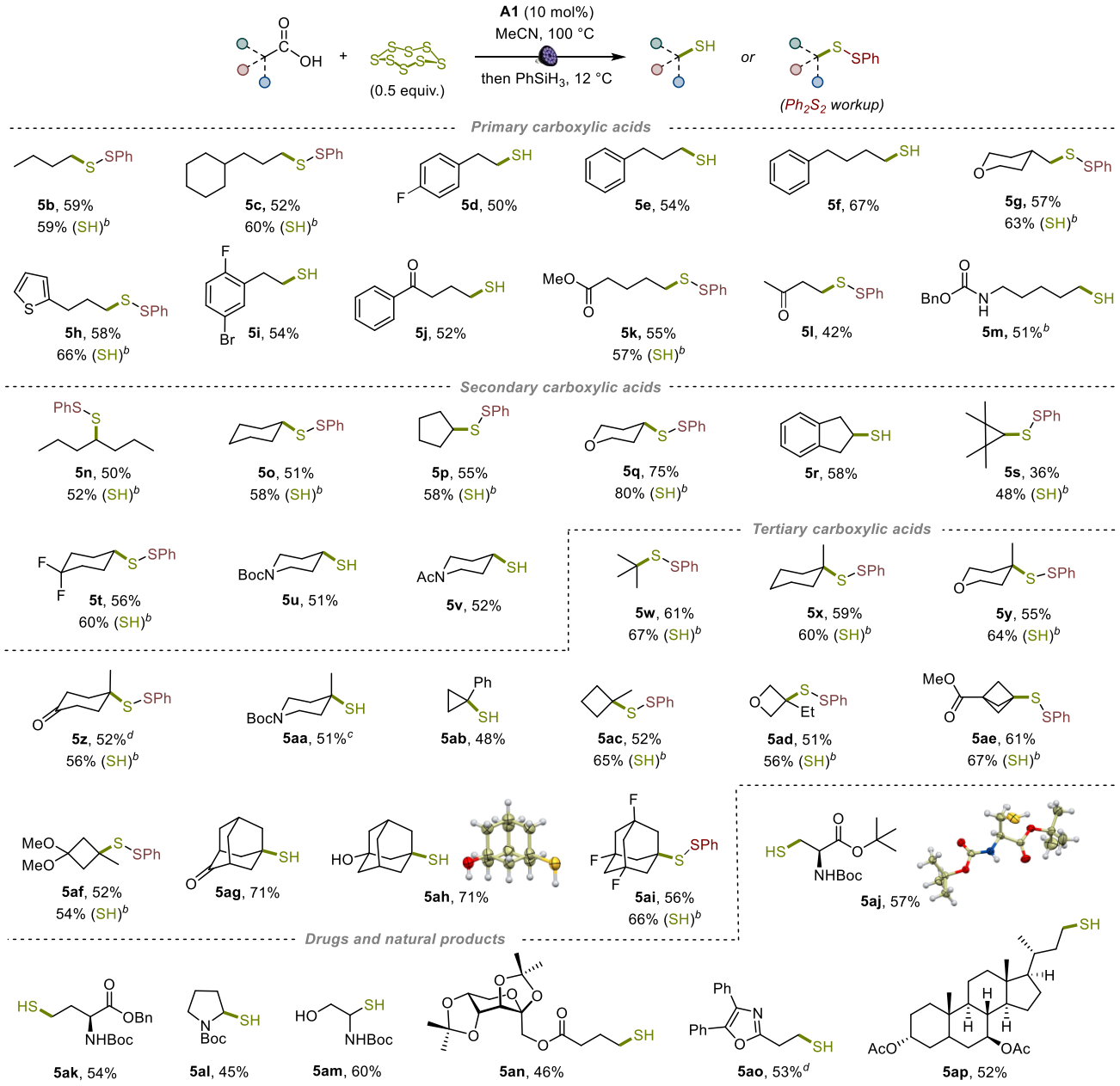
Figure 2. A. Acridine-catalyzed C–S bond formation. Reaction conditions: carboxylic acid **1** (0.2 mmol), sulfur (0.1 mmol), **A1** (10 mol%), acetonitrile (2.0 mL), LED (400 nm), 100 °C 12 h. **B.** Acridine-catalyzed reduction to thiol **4**. Reaction conditions: disulfide **3** (0.1 mmol), phenylsilane (0.4 mmol), **A1** (10 mol%), acetonitrile (1.0 mL), LED (400 nm), 12 °C, 12 h. Yields were determined by ^{1}H and ^{13}C NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. **C.** Decarboxylative

sulfhydrylation by multimodal acridine photocatalysis. Isolated yields. PMHS = polymethylhydrosiloxane.

Importantly, other types of photocatalysts, including acridinium salts, Ir- and Ru-based complexes, 4-CzIPN, and eosin Y failed to furnish the desired product under the reaction condition (Table S1). Lower and higher loadings of sulfur afforded the product in synthetically useful albeit lower yields. Likewise, lower temperature was detrimental to the reaction efficiency due to diminished sulfur solubility.

We next sought to identify a method for an in situ conversion of the oligosulfide intermediates to thiols. Although photocatalytic reduction of di- and oligosulfides with silanes was unknown, we surmised that the reduction could be enabled by acridine photocatalysis via a hydrogen atom transfer mechanism that can trigger S–S bond homolysis. Indeed, an optimization study with disulfide **3** indicated that thiol **4** was readily produced with phenylsilane in the presence of acridine **A1** and under 400 nm LED irradiation (Figure 2.B). Notably, a substantially lower yield was observed in the absence of acridine **A1**, and no product was formed without the LED light. Similarly, lower yields were observed with other silanes.

Table 1. Scope of direct decarboxylative thiol construction with sulfur[a]



[a] Reaction conditions: carboxylic acid (0.2 mmol), sulfur (0.1 mmol), A1 (10 mol%), acetonitrile (2.0 mL), LED (400 nm), 100 °C, 12 h, then $PhSiH_3$ (0.8 mmol), LED (400 nm), 12 °C, 24 h. Disulfide workup: Ph_2S_2 (0.4 mmol), K_2CO_3 (0.4 mmol), MeCN, 25 °C, 12 h. Isolated yields. [b] NMR yield of the thiol product; determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c] The reaction was carried out with A2 as a photocatalyst at 110 °C. [d] The reaction was carried out at 110 °C.

The sulfur- and phenylsilane-mediated reactions enabled by acridine photocatalysis could be readily merged in a synthetic method that directly afforded thiol **5a** in 75% yield (Figure 2.C). The reaction could also be carried out on a gram scale, pointing to the preparative potential of the method.

The scope of the decarboxylative sulfhydrylation was investigated next with a range of carboxylic acids (Table 1). While many thiol products were suitable for isolation, some thiols were too volatile and were conveniently secured after end-capping with a phenylthio group. An array of primary carboxylic acids featuring acyclic as well as cyclic saturated and aromatic groups were readily converted to corresponding thiols and disulfide derivatives (**5b-5f**). Heterocyclic groups and halogen substitution in the aromatic rings were also equally well tolerated (**5g-5i**).

Likewise, keto, ester, and amide-substituted carboxylic acids were suitable substrates (**5j-5m**). Furthermore, a range of acyclic and cyclic secondary carboxylic acids were compatible with the decarboxylative sulfhydrylation (**5n-5p**). Thus, products **5q-5s** bearing tetrahydropyran, indane, as well as strained and sterically encumbered tetramethylcyclopropane were readily accessed. Additionally, the decarboxylative sulfhydrylation could be used for the construction of thiols bearing medicinally important *gem*-difluorocyclohexane and piperidine rings (**5t-5v**).[19] Tertiary carboxylic acids also readily afforded corresponding products **5w-5ab**, including a variety of strained and medicinally relevant cyclic derivatives, featuring cyclobutane, oxetane, and bicyclo[1.1.1]pentane systems (**5ac-5af**). Similarly, functionalized adamantanecarboxylic acids were also converted to their corresponding thiol derivatives (**5ag-5ai**). The reaction performance was next explored in the more structurally complex settings of natural products and active pharmaceutical ingredients. Notably, medicinally important cysteine and homocysteine derivatives **5aj**

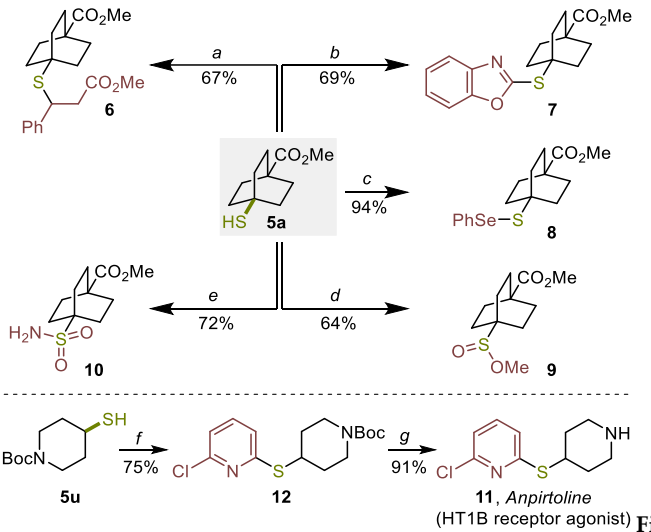


Figure 3. S-Functionalization of carboxylic acid-derived thiols. Reaction condition: a) methyl cinnamate, DBU, THF, rt. b) 2-chlorobenzo[*d*]oxazole, K_2CO_3, iPrOH, 100 °C. c) Ph_2Se_2, K_2CO_3, CH_3CN, rt. d) NBS, MeOH / DCM (1:1), 0 °C. e) $PhI(OAc)_2$, $(NH_4)_2CO_3$, MeOH, rt. f) 2,6-dichloropyridine, K_2CO_3, iPrOH, reflux. g) TFA, Et_3SiH, DCM, rt.

and **5ak**, as well as proline- and serine-derived thiols **5al** and **5m** could be readily produced. Likewise, thiol derivatives of fructose (**5an**), anti-inflammatory drug oxaprozin (**5ao**), and choleretic ursodeoxycholic acid (**5ap**) were accessed in a reaction with sulfur. The decarboxylative sulfhydrylation can enable access to a range of other organosulfur functionalities, as demonstrated for carboxylic acid-derived thiol **5a** (Figure 3). For example, sulfides **6** and **7** can be produced by base-mediated conjugate addition and substitution reactions, while S–Se bond formation can be readily achieved in a coupling with diselenide (**8**). Similarly, sulfinate ester **9** and sulfonamide **10** can be generated under oxidative conditions. The synthetic usefulness of the decarboxylative sulfhydrylation was further demonstrated by the metal-free synthesis of HT1B receptor agonist anpirtoline **11** via intermediate **12** by appending a pyridine fragment to carboxylic acid-derived thiol **5u**.

Computational studies point to a fast alkyl radical ring opening of S_8 that is followed by a thermodynamically favorable regeneration of the acridine catalyst by a hydrogen atom transfer from acridinyl radical **HA** to thiyl radical **13**, as well cross-termination between the alkyl radical and **13** (Figure 4.A). Subsequent kinetically facile homolytic substitution in the oligosulfide chain leads to the formation of shorter chain homologs. Furthermore, COPASI kinetic modeling (Figure 4.B) indicated that the radical-mediated oligosulfide chain redistribution leads to the experimentally observed ratio of oligosulfides (Figure 2.A), underscoring the key role of the homolytic substitution in the oligosulfide chain on the reaction efficiency.

Previous studies indicated that the acridine-catalyzed decarboxylation occurs via a proton-coupled electron transfer in the singlet excited state of the acridine–carboxylic acid hydrogen bond complex.[14a] Given that acridine and silane cannot form stable hydrogen bond complexes (Figure S1), the interaction of singlet excited acridine and phenylsilane may not be efficient enough, because the short lifetime of the acridine singlet excited state renders the bimolecular encounter on the singlet excited hypersurface sufficiently unlikely, pointing to the triplet excited acridine in the photocatalytic oligosulfide reduction. Indeed, while the presence of *trans*-stilbene as a triplet quencher did not have any negative effect on the acridine-catalyzed decarboxylative reactivity of carboxylic acids (Figure 4.C), the efficiency of the disulfide reduction was diminished in a concentration-dependent manner, indicating that the process is mediated by the triplet excited state of acridine. Furthermore, Stern-Volmer quenching experiments suggested that phenylsilane is the most efficient quencher of the acridine photocatalyst (Figure S2). EPR studies revealed formation of DMPO-derived radical **14** in a solution of phenylsilane and acridine under LED irradiation (Figure 4.E). Both acridine and phenylsilane, as well as LED irradiation were necessary to observe the radical, pointing to a photoinduced hydrogen atom transfer from phenylsilane to acridine with subsequent HAT to DMPO from the intermediate acridinyl radical. Additionally, kinetic experiments with $PhSiH_3$ and $PhSiD_3$ showed a significant kinetic isotope effect (k_H/k_D = 2.35, Figure 4.D). Collectively, these results suggest the involvement of the triplet acridine-mediated Si–H HAT process. Computational studies show that the hydrogen atom abstraction by triplet acridine from

phenylsilane is kinetically and thermodynamically facile (Figure 4.F), giving rise to hydrolytically labile[20] silyl sulfide **15** and weakly delocalized silyl radical **16** that can engage the disulfide in homolytic substitution. The resulting thiyl radical **17** is converted to the thiol product by an exergonic HAT from the acridinyl radical, regenerating the acridine catalyst.

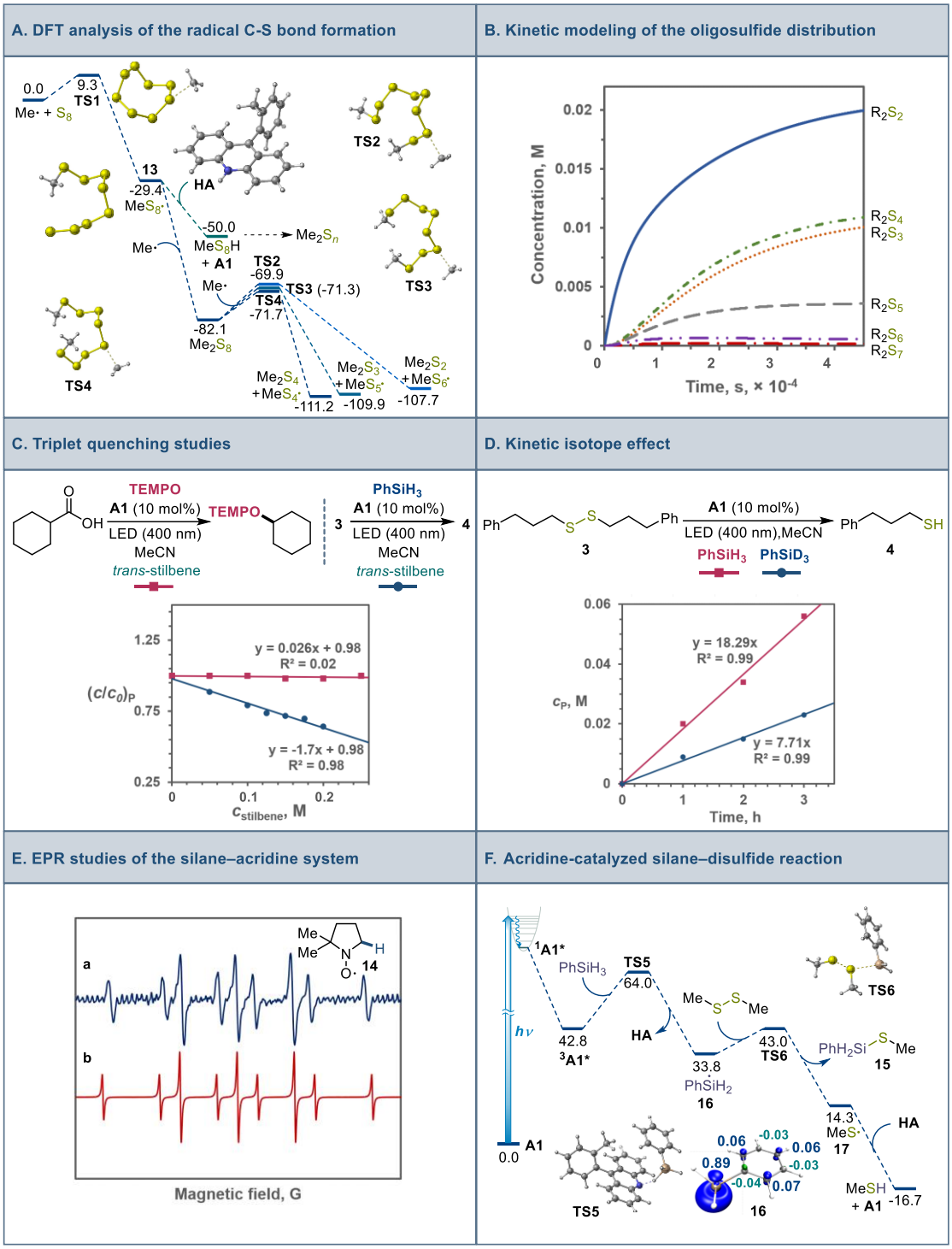


Figure 4. Mechanistic studies of the decarboxylative sulfhydrylation. **A.** DFT analysis of the C–S bond-forming processes, ΔG, kcal/mol. **B.** COPASI kinetic modelling of the oligosulfide distribution. **C.** Triplet quenching studies of the decarboxylative reaction with TEMPO (—■—) and the acridine-catalyzed phenylsilane–disulfide reaction (—●—) with *trans*-stilbene; $(c/c_0)_P$ denotes the ratio of the product concentration in the presence and in the absence of *trans*-stilbene. **D.** Kinetic isotope effect in the acridine-catalyzed disulfide bond cleavage with $PhSiH_3$ (—■—) and $PhSiD_3$ (—●—). **E.** EPR studies of the acridine–phenylsilane system under the LED irradiation, experimental (**a**) and simulated (**b**) spectra. **F.** DFT analysis of the acridine-catalyzed phenylsilane–disulfide reaction, ΔG, kcal/mol.

Conclusion

In conclusion, we have developed a multimodal photocatalytic system for decarboxylative sulfhydrylation that enables the construction of thiols from carboxylic acids and elemental sulfur without preactivation of carboxylic acids. The two-phase process is facilitated by the previously unknown multimodal catalytic reactivity of acridine photocatalysts that orchestrate both the PCET-mediated decarboxylative stage and the unprecedented HAT-mediated oligosulfide reductive cleavage. The functional group tolerance and scope of the reaction were demonstrated with a range of functionalized substrates, including more structurally and functionally complex natural products and active pharmaceutical ingredients. Mechanistic studies and kinetic modeling unveil the important roles of the alkyl-mediated homolytic substitution in the oligosulfide chain redistribution and the divergent triplet acridine-catalyzed silane–oligosulfide HAT reactivity.

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