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A general method for site-selective Csp^3–S bond formation *via* cooperative catalysis†

Yuman Qin,‡ Yujie Han,‡ Yongzhen Tang, Junfa Wei and Mingyu Yang *

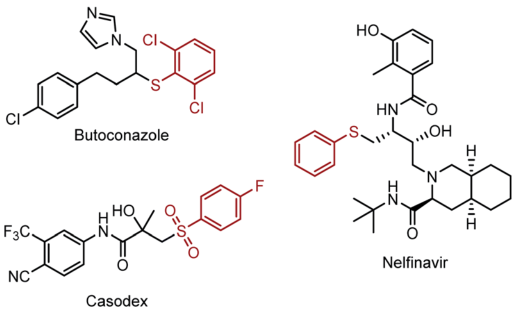
Herein, we report a copper-catalysed site-selective thiolation of Csp^3–H bonds of aliphatic amines. The method features a broad substrate scope and good functional group compatibility. Primary, secondary, and tertiary C–H bonds can be converted into C–S bonds with a high efficiency. The late-stage modification of biologically active compounds by this method was also demonstrated. Furthermore, the one-pot preparation of pyrrolidine or piperidine compounds *via* a domino process was achieved.

Introduction

The sp^3 carbon–sulfur bond plays a pivotal role in modern organic synthesis, natural products and pharmaceuticals. For example, Butoconazole is an imidazole antifungal used in gynaecology, and Nelfinavir is an antiretroviral drug which was used in the treatment of the human immunodeficiency virus (HIV) (Scheme 1). Clinical trials demonstrated that the introduction of Csp^3–S moieties could improve their biological activities, such as anti-tumour, anti-inflammatory and immunomodulatory properties.[1] Besides that, the Csp^3–S bond can also be found in the natural amino acid, such as cysteine, and facilitate the metabolism process of the related protein in the organism.[2] Given the importance of Csp^3–S containing compounds, methods that can directly assemble the Csp^3–S bond through direct C–H functionalization with a high efficiency and selectivity are highly demanded. Moreover, these methods could facilitate the late-stage functionalization of complex molecules that enable the rapid diversification and construction of a library of molecule analogues.

Csp^3–S bonds are usually constructed by nucleophilic substitution of the alkyl halides with metal thiolate (Scheme 2a). Also, similar to other kinds of nucleophilic substitution reactions, these methods are sensitive to the sterics.[3] With the development of transition-metal catalysis, more efficient protocols to introduce the Csp^3–S bond were realized *via* the transition-metal catalysed cross-coupling of organo halides/alkene and thiols/thioethers.[4] For example, Li reported the palladium catalysed cross-coupling of aryl halides and thiols; however, only primary and secondary thiols were shown to be suitable substrates.[5] Furthermore, the preparation of alkyl halide substrates was tedious and was not step- and atom-economic (Scheme 2b). Alternatively, hydrothiolation of alkenes has been developed to construct the Csp^3–S bond. However, pre-functionalization of the substrates is necessary, and the regioselectivity greatly depends on the structure of the substrate (Scheme 2c).[6] Recently, the direct thiolation *via* the alpha-sp^3 C–H bonds of ether and amine was achieved by Li,[7] Yuan and Xiang,[8] independently (Scheme 2d). The thiolation of Csp^3–H was also developed, facilitated by a directing group strategy (Scheme 2e).[9] However, to date, a general method to realize the C–H bond thiolation remains a significant challenge.

Inspired by the Hofmann–Löffler–Freytag (HLF) reaction,[10] C–H bond functionalization *via* a radical pathway provides a new route to construct different types of targeted molecules.[11] Elegant related works have been documented by Suárez,[12] Muñiz[13] and Nagib[14] independently by using the stoichiometric amounts of iodine, catalytic iodine, and triiodide for the HLF type reaction. More recently, a breakthrough of metallaphotoredox-catalysed remote functionalization of amides was demonstrated by the groups of Knowels,[15] Rovis,[16] and Meggers.[17] In addition, Cu-modified HLF-type reactions with a simple NH substrate are particularly valuable in primary



Scheme 1 Pharmaceutical molecules containing sp^3 C–S thiol moieties.

Key Laboratory of Applied Surface and Colloid Chemistry of MOE, School of Chemistry and Chemical Engineering, Shaanxi Normal University, 620 West Chang'an Ave, Xi'an, 710119, China. E-mail: yangmy05@snnu.edu.cn; yangmy05@gmail.com

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‡ These authors contributed equally to this work.

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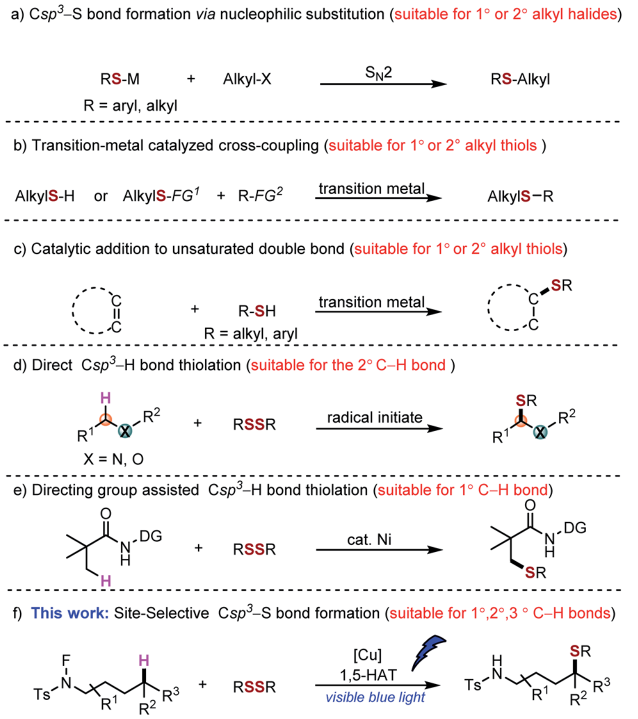


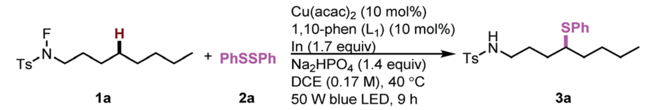
Scheme 2 The strategies to construct the Csp^3–S bond: (a) Csp^3–S bond formation *via* nucleophilic substitution. (b) Transition-metal catalysed cross-coupling. (c) Catalytic addition to unsaturated double bond. (d) Direct Csp^3–H bond thiolation. (e) Directing group assisted Csp^3–H bond thiolation. (f) Site selective Csp^3–S bond formation.

C–H bond amination.[18] Although the generated amidyl radical induced 1,5-HAT (HLF reaction) process is well established, further transformation of C-centred radicals is limited to the halogenation, cyclization or interceptions by alkenes or heteroaryls.[19] The metal mediated C-centred radical resulted in the functionalization of unactivated Csp^3–H bond selectively and efficiently, a great challenge. We proposed that by using a N–F precursor, the low tendency toward N–F homolysis and instability of the fluorine radical, can enable the 1,5-HAT process to facilitate Csp^3–H bond functionalization over C–F bond formation. Previously, and independently, Zhu[20] and Nagib[21] have reported a remote arylation of an aliphatic amine *via* activation of the N–F precursors. Very recently, Muñiz demonstrated a cyclization reaction of an aliphatic amine *via* N–F bond activation by a copper catalyst, albeit under a high temperature.[22] Li has successfully achieved a copper catalysed trifluoromethylation by using N–F precursors.[23] Given the importance of thiol moieties in functional molecules, here we describe a protocol for the site-selective thiolation of aliphatic amines through the combination of light-driven and copper-facilitated 1,5-hydrogen atom transfer (Scheme 2f). This strategy enables the transformation of primary, secondary and tertiary C–H bonds into C–S bonds with a high efficiency. Meanwhile, a late-stage modification of biologically active compounds was demonstrated to show the synthetic utility of such a methodology.

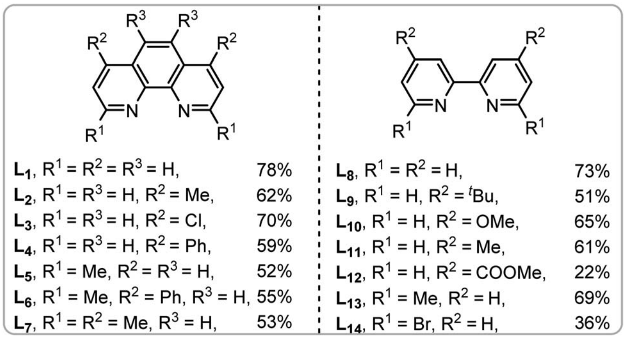
Results and discussion

To initiate our proposal, *N*-fluoro-tosylamide **1a** and phenyl disulfide **2a** were chosen as the model substrates. After extensive optimization, we found that a cocktail containing 10 mol% of $Cu(acac)_2$, 10 mol% of 1,10-phenanthroline (**L**$_1$), 1.4 equivalent Na_2HPO_4 and 1.7 equivalent of indium powder as additives could promote the desired δ thiolated product **3a** in 75% isolated yield in the presence of blue LED. Control experiments were conducted to determine the role of each ingredient (Table 1, entries 2–5). Without a copper catalyst or ligand, the yield decreased significantly (Table 1, entries 2 and 3). The desired product was only observed in 36% yield, indicating the pivotal role of light in this transformation (Table 1, entry 4). Moreover, a lower yield was obtained in the absence of indium powder and base (Table 1, entry 5). Other copper complexes were also tested in this reaction, resulting in low yields (Table 1, entries 6–8). The aliphatic amines are generally regarded as good reducing reagents in photoredox reactions. However, the addition of triethylamine inhibited this reaction (Table 1, entry 9). To determine the role of copper complexes in

Table 1 Effect of reaction parameters[a]



Entry	Variations from "standard" conditions	Yield[b] (%)
1	None	78 (75)
2	Without $Cu(acac)_2$	27
3	Without **L**$_1$	13
4	Under dark	36
5	Without In powder and Na_2HPO_4	65
6	$Cu(OTf)_2$ instead of $Cu(acac)_2$	47
7	cat.$[Cu]_1$[c] instead of $Cu(acac)_2$	31
8	cat.$[Cu]_2$[d] instead of $Cu(acac)_2$	20
9	Et_3N instead of Na_2HPO_4	0
10	2,6-Lutidine instead of Na_2HPO_4	19
11	$Ir(ppy)_3$ instead of $Cu(acac)_2$	10
12	$Ru(1,10\text{-phen})_3Cl_2$ instead of $Cu(acac)_2$	7



[a] Reaction was conducted on a 0.1 mmol scale. [b] Yields were determined by ^1H NMR analysis *versus* 1,1,2,2-tetrachloroethane as the internal standard. Isolated yield in parentheses. [c] cat.$[Cu]_1$ is $Cu(CH_3COCHCOCF_3)_2$. [d] cat.$[Cu]_2$ is $Cu(CF_3COCHCOCF_3)_2$.

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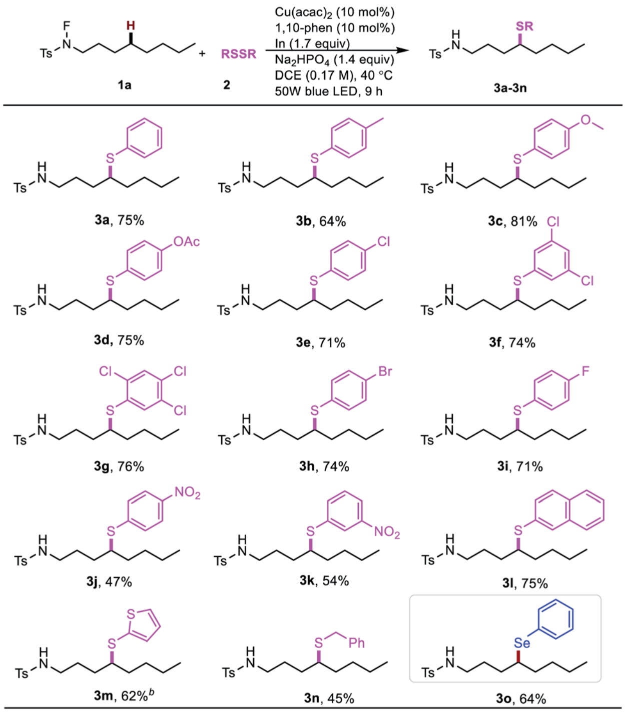
this transformation,[24] we replaced the copper with an Ir complex or Ru complex, and no desired results were obtained, indicating the role of copper is more than as a photoredox catalyst in this reaction (Table 1, entries 11 and 12).

With the optimal conditions in hand, we examined the scope of different disulfides with *N*-fluoro-tosylamide **1a** (Table 2). The substituted disulfides with electron-donating groups, such as methyl (**3b**), methoxyl (**3c**) and acetoxyl (**3d**), were all well tolerated. Moreover, the halide-substituted aryl disulfides also underwent this thiolation reaction (**3e**–**3i**), even with multi-halides or fluoro substituents. Remarkably, the electron-withdrawing nitro-group on the disulfide led to a moderate drop in reactivity (**3j**, **3k**). Interestingly, the thiophenyl group generally has special properties in optoelectronic materials, and can afford the desired product in an acceptable yield (**3m**). Furthermore, to our satisfaction, the benzyl disulfide can give the δ benzyl thioether in a slightly compromised yield (**3n**, 45%). Interestingly, the δ-selenation could also be achieved when using diselenide instead of disulfide (**3o**).

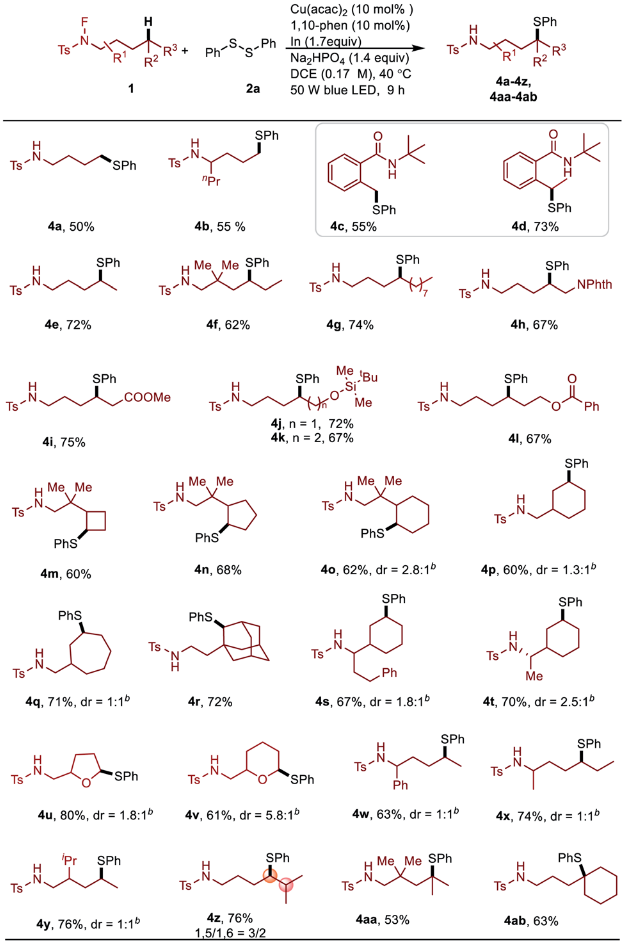
This C–H thiolation protocol was also successfully applied to functionalize a wider range of electronically and sterically diverse primary, secondary and tertiary aliphatic C–H bonds (Table 3). The thiolation yield for primary C–H bond is slightly increased with a *N*-fluorotosylamide substrate containing a substituent at the α-position (**4a**, **4b**). *N*-Fluorocarboxamides are also good substrates for this transformation (**4c**, **4d**). Notably, functionalization of the secondary C–H bond afforded a series of thiolether derivatives selectively. Even with longer carbon chains in the substrates (**4e**–**4g**), the reaction occurred only at the δ position. Surprisingly, a *gem*-dialkyl group on the linear *N*-fluoroamide substrates at the β-position does not improve the product yield (**4f**). The biologically relevant functionalities, such as Nphth (**4h**), carboxylic ester (**4i**) and OTBDMS (**4j**, **4k**), as well as OBz (**4l**) are well tolerated. Specifically, exclusive δ-selectivity was observed in the case of **4h** and **4j** bearing a heteroatom near the reaction centres. Cycloalkanes with various ring sizes ranging from four to seven carbons were thiolated in good yields (**4m**–**4q**, **4s**–**4t**). The adamantyl group can be functionalized selectively on secondary C–H bonds rather than tertiary ones (**4r**). Obviously, in heteroatom-containing cycles, functionalized products were obtained at the α-position with a better diastereoselectivity for the six-member ring than the five-member ring (**4u**, **4v**). Disappointingly, the steric hindered substituents at the α- or β-position of *N*-fluoroamides led to a poor diastereoselectivity (**4w**–**4y**). Both the 1,5-HAT and 1,6-HAT processes occurred in a substrate

Table 2 Substrate scope of disulfides[a]



[a] Unless otherwise noted, the reaction conditions were as follows: **1a** (0.1 mmol), **2** (1.2 equiv.), Cu(acac)$_2$ (10 mol%), 1,10-phen (10 mol%), In powder (1.7 equiv.), Na$_2$HPO$_4$ (1.4 equiv.), DCE 0.6 mL, blue LED (50 W), 40 °C, 9 h. [b] 80 °C.

Table 3 Selective thiolation of aliphatic amides[a]



[a] Unless otherwise noted, the reaction conditions were as follows: **1** (0.1 mmol), **2** (1.2 equiv.), Cu(acac)$_2$ (10 mol%), 1,10-phen (10 mol%), In powder (1.7 equiv.), Na$_2$HPO$_4$ (1.4 equiv.), DCE 0.6 mL, blue LED (50 W), 40 °C, 9 h. [b] dr was determined by crude ^{1}H NMR.

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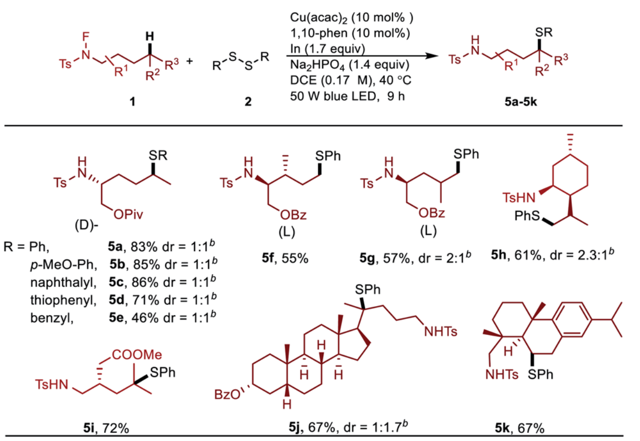
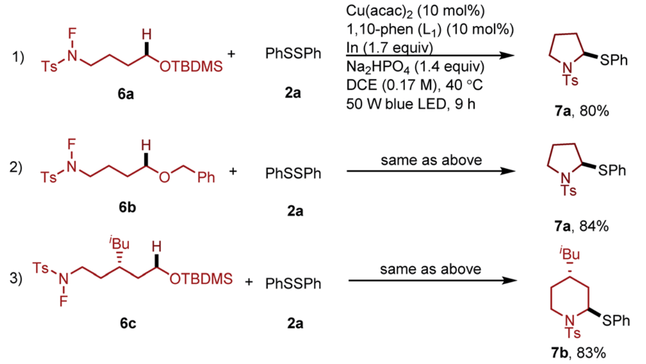
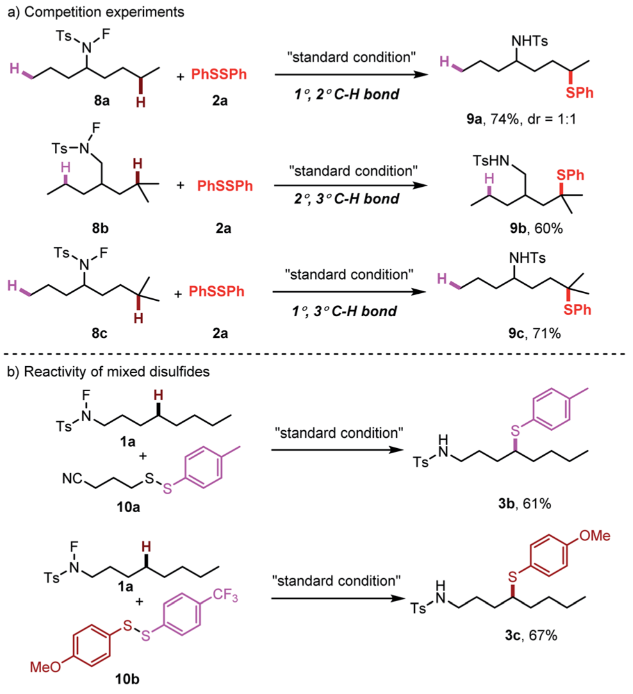
Table 4 Selective thiolation of biologically active compounds[a]



[a] Unless otherwise noted, the reaction conditions were as follows: **1** (0.1 mmol), **2a** (1.2 equiv.), Cu(acac)$_2$ (10 mol%), 1,10-phen (10 mol%), In powder (1.7 equiv.), Na$_2$HPO$_4$ (1.4 equiv.), DCE 0.6 mL, blue LED (50 W), 40 °C, 9 h. [b] dr was determined by crude ^{1}H NMR.



Scheme 3 Preparation of pyrrolidine or piperidine derivatives *via* remote thiolation.



Scheme 4 Control experiments: (a) competition experiments; (b) reactivity of mixed disulfides.

which involved a tertiary C–H bond at the ε-position (**4z**). Finally, this transformation can be successfully applied to construct the quaternary carbon centre with a thiol group, highlighting the synthetic utility of this methodology (**4aa**, **4ab**).

Having demonstrated the applicability of this remote Csp^3–H thiolation protocol, late-stage functionalization of biologically active molecules was carried out (Table 4). The amino alcohol derivatives can be coupled with varieties of disulfides, which greatly demonstrated the powerful utility of this method (**5a–5g**). These functionalized amino alcohols have a great potential in the synthesis of biological compounds. A non-symmetric thiolation of the methyl group occurred on the menthol derived *N*-fluoroamide substrate (**5h**). It's important to note that pharmaceutical molecular (**5i**) and complex natural products (**5j**, **5k**) can be readily modified with excellent regioselectivity.

Furthermore, to illustrate the utility of this new transformation with respect to constructing drug scaffolds, we tested a type of substrates which can proceed by a domino process involving the 1,5-HAT followed by cyclization and sequence thiolation, affording thiol substituted pyrrolidine or piperidine derivatives (Scheme 3).

To gain insight into the reaction mechanism, competition experiments between 1°/2° C–H bonds, 2°/3° C–H bonds and 1°/3° C–H bonds were carried out independently (Scheme 4a). The total reactivity of the hydrogen atoms decreased in the order tertiary > secondary > primary. Furthermore, to test the selectivity of thiolation reagents, the mixed disulfides were subjected to this transformation (Scheme 4b). For an alkyl phenyl disulfide, only the phenyl thioether product was observed. For a mixed aryl disulfide with an electron-donating group OMe and an electron-withdrawing group CF$_3$, the thiolation occurred only with the electron-donating OMe substituted thiol group.[25] These selectivities may result from the electron density on different sulfur moieties. Based on this selectivity, we developed a direct cross-coupling between two biologically interesting molecules to give the corresponding conjugated compounds (Scheme 5a). Subsequently, the thioether group can be directly oxidized to a sulphone group, which broadly exist in pharmaceuticals (Scheme 5b).

Moreover, radical control experiments were carried out to uncover evidence for the presence of radical intermediates. Radical-clock experiments were conducted (Scheme 6a), the observation of products **15a**, **17a** and **19a** indicating the formation of a carbon-centred radical in the transformation. Especially for **19a**, the observed linear selectivity deduced that a η^1- or η^3 metal allylic intermediate maybe involved in this process. Subsequently, the radical process was further demonstrated by the results in the presence of TEMPO and BHT. Furthermore, the experiments of PhSH and In(SPh)$_3$ were conducted to test the

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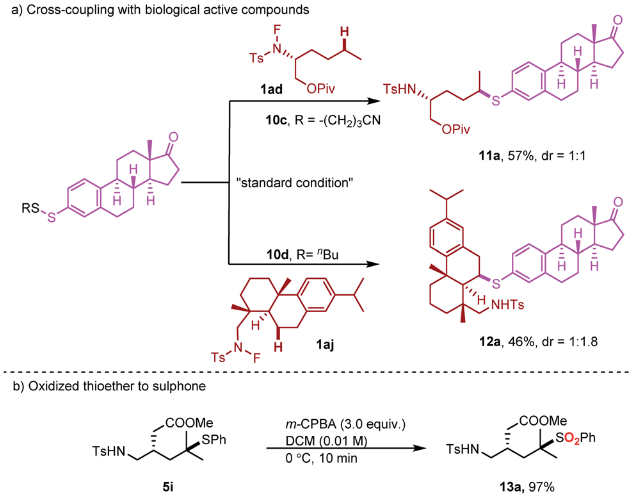
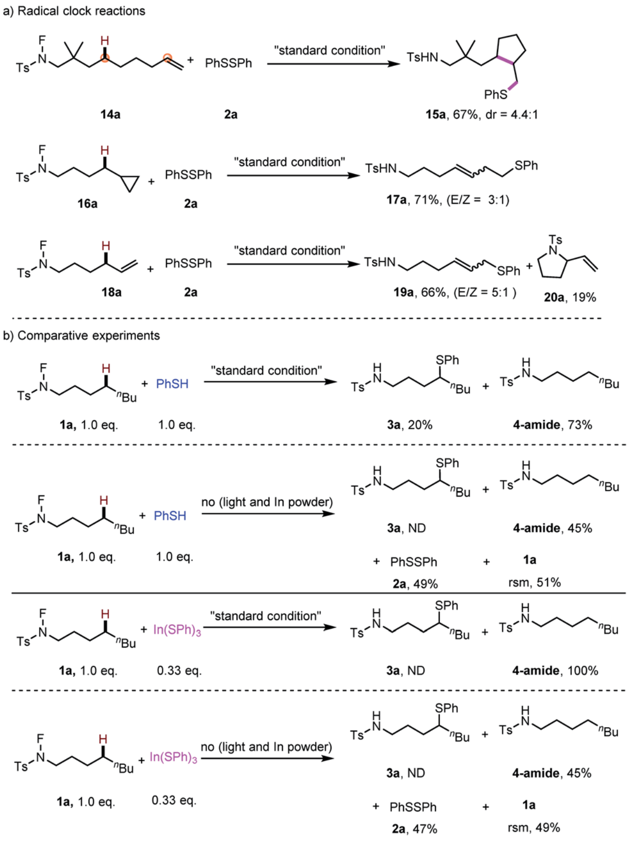
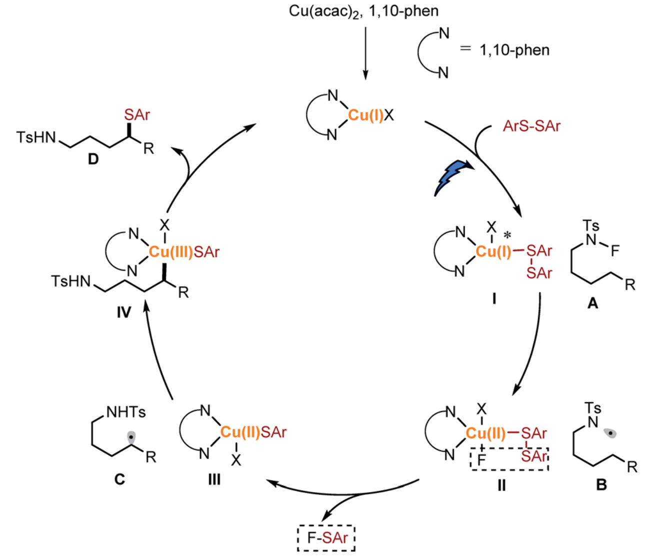


Scheme 5 Late-stage functionalization of biological active compounds: (a) cross-coupling with biological active compounds; (b) oxidized thioether to sulphone.

possible active species of this thiolation reaction. The results indicated that by using PhSH, 20% of the desired product was obtained, while no desired product was observed by using In(SPh)$_3$ as the thiolation reagent (Scheme 6b). Finally, blank experiments were carried out to confirm the effective role of each additive in this transformation (details in the ESI†).



Scheme 6 Mechanistic investigation: (a) radical clock reactions; (b) comparative experiments.



Scheme 7 Proposed mechanism.

Based on these results, we propose that this transformation is preferred by a light-driven, copper initiated 1,5-HAT process (Scheme 7). Ligand exchange between an *in situ* generated Cu(I) catalyst and disulfide occurred to generate Cu(I)–**I** species, which could be excited by visible light followed by reducing the N–F amide **A** to afford the N-centred radical **B** and Cu(II)–**II** intermediate. The Cu(II)–**II** released one molecular of F-SAr[26] through a metathesis process to afford the Cu(II)–**III**. The selective formation of F-SAr is likely to result from the coordination ability of the sulfur group. The electron-rich sulfur group coordinated to form the Cu(I)–**I** species. This selectivity is in conjunction with the result of the mixed disulfide. Translocation of the N-centred radical **B** to the C-centred radical **C** *via* 1,5-HAT occurred, and then the δ C-radical was intercepted by the Cu(II)–**III** to form the Cu(III)–**IV** intermediate. Finally, the reductive elimination of Cu(III)–**IV** gave the desired product **D** and regenerated active Cu(I) catalyst. Furthermore, efforts to expand the scope of this transformation are underway.

Conclusions

In summary, we have developed a light-driven, copper-catalysed site-selective thiolation of Csp^3–H bonds for aliphatic amines. Primary, secondary and tertiary C–H bonds can all be successfully converted into C–S bonds. The broad amine scope, good functional compatibility, and late-stage modification of biologically active intermediates underscore the unique synthetic potential of this method.[27]

Conflicts of interest

The authors declare no conflicts of interest.

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Notes and references

1 (*a*) M. Feng, B. Tang, S. H. Liang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200; (*b*) D. Xiao, Y.-J. Wang, X.-B. Hu, W.-J. Kan, Q. Zhang, X. Jiang, Y.-B. Zhou, J. Li and W. Lu, *Eur. J. Med. Chem.*, 2019, **176**, 419; (*c*) C. E. Hoyle, A. B. Lowe and C. N. Bowman, *Chem. Soc. Rev.*, 2010, **39**, 1355; (*d*) H. Guo, B. Sun, H. Gao, X. Chen, S. Liu, X. Yao, X. Liu and Y. Che, *J. Nat. Prod.*, 2009, **72**, 2115; (*e*) J.-M. Wang, G.-Z. Ding, L. Fang, J.-G. Dai, S.-S. Yu, Y.-H. Wang, X.-G. Chen, S.-G. Ma, J. Qu, S. Xu and D. Du, *J. Nat. Prod.*, 2010, **73**, 1240.

2 (*a*) J. Zhao and X. Jiang, *Chin. Chem. Lett.*, 2018, **29**, 1079; (*b*) M. C. Bagley, J. W. Dale, E. A. Merritt and X. Xiong, *Chem. Rev.*, 2005, **105**, 685; (*c*) X. Just-Baringo, F. Albericio and M. Álvarez, *Angew. Chem., Int. Ed.*, 2014, **53**, 6602.

3 (*a*) Q. W. Decker and H. W. Post, *J. Org. Chem.*, 1957, **22**, 1957; (*b*) F. M. Menger and L. Shi, *J. Am. Chem. Soc.*, 2006, **128**, 9338.

4 (*a*) T. Kondo and T.-A. Mitsudo, *Chem. Rev.*, 2000, **100**, 3205; (*b*) I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2011, **111**, 1596; (*c*) H. Liu and X. Jiang, *Chem.–Asian J.*, 2013, **8**, 2546.

5 (*a*) G. Y. Li, *Angew. Chem., Int. Ed.*, 2001, **40**, 1513; (*b*) G. Y. Li, G. Zhang and A. F. Noonan, *J. Org. Chem.*, 2001, **66**, 8677.

6 (*a*) T. Tamai, K. Fujiwara, S. Higashimae, A. Nomoto and A. Ogawa, *Org. Lett.*, 2016, **18**, 2114; (*b*) X.-H. Yang, R. T. Davison, S.-Z. Nie, F. A. Cruz, T. M. McGinnis and V. M. Dong, *J. Am. Chem. Soc.*, 2019, **141**, 3006.

7 R.-Y. Tang, Y.-X. Xie, Y.-L. Xie, J.-N. Xiang and J.-H. Li, *Chem. Commun.*, 2011, **47**, 12867.

8 S.-R. Guo, Y.-Q. Yuan and J.-N. Xiang, *Org. Lett.*, 2014, **15**, 4654.

9 (*a*) X. Wang, R. Qiu, C. Yan, V. P. Reddy, L. Zhu, X. Xu and S.-F. Yin, *Org. Lett.*, 2015, **17**, 1970; (*b*) S.-Y. Yan, Y.-J. Liu, B. Liu, Y.-H. Liu, Z.-Z. Zhang and B.-F. Shi, *Chem. Commun.*, 2015, **51**, 7341.

10 (*a*) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 558; (*b*) A. W. Hofmann, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 5; (*c*) K. Löffler and C. Freytag, *Ber. Dtsch. Chem. Ges.*, 1910, **42**, 3427; for selected review, see: (*d*) M. E. Wolff, *Chem. Rev.*, 1963, **63**, 55; (*e*) R. S. Neal, *Synthesis*, 1971, 1.

11 For selected examples on remote C–H bond activation *via* N-radical chemistry, see: (*a*) Z. Li, L. Song and C. Li, *J. Am. Chem. Soc.*, 2013, **135**, 4640; (*b*) B. J. Groendyke, D. I. AbuSalim and S. P. Cook, *J. Am. Chem. Soc.*, 2016, **138**, 12771; (*c*) S. P. Morcillo, E. M. Dauncey, J. H. Kim, J. J. Douglas, N. S. Sheikh and D. Leonori, *Angew. Chem., Int. Ed.*, 2018, **57**, 12945; (*d*) E. M. Dauncey, S. P. Morcillo, J. J. Douglas, N. S. Sheikh and D. Leonori, *Angew. Chem., Int. Ed.*, 2018, **57**, 744; (*e*) E. A. Wappes, K. M. Nakafuku and D. A. Nagib, *J. Am. Chem. Soc.*, 2017, **139**, 10204; (*f*) C. Zhu, Y. Liang, X. Hong, H. Sun, W.-Y. Sun, K. N. Houk and Z. Shi, *J. Am. Chem. Soc.*, 2015, **137**, 7564; (*g*) Y. Tang, Y. Qin, D. Meng, C. Li, J. Wei and M. Yang, *Chem. Sci.*, 2018, **9**, 6374; (*h*) L. Wang, Y. Xia, K. Bergander and A. Studer, *Org. Lett.*, 2018, **20**, 5817; (*i*) W. Shu and C. Nevado, *Angew. Chem., Int. Ed.*, 2017, **56**, 1881; (*j*) H. Zhang, Y. Zhou, P. Tian and C. Jiang, *Org. Lett.*, 2019, **21**, 1921; (*k*) X.-Q. Mou, X.-Y. Chen, G. Chen and G. He, *Chem. Commun.*, 2018, **54**, 515; (*l*) L. M. Stateman, E. A. Wappes, K. M. Nakafuku, K. M. Edwards and D. A. Nagib, *Chem. Sci.*, 2019, **10**, 2693; (*m*) Y. Kumar, Y. Jaiswai and A. Kumar, *Org. Lett.*, 2018, **20**, 4964; (*n*) H. Jiang and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 1692; (*o*) F. Wang and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2019, **58**, 6385; (*p*) Y.-R. Gu, X.-H. Duan, L. Chen, Z.-Y. Ma, P. Gao and L.-N. Guo, *Org. Lett.*, 2019, **21**, 917. For selected review, see: (*q*) S. Z. Zard, *Chem. Soc. Rev.*, 2008, **37**, 1603; (*r*) L. M. Stateman, K. M. Nakafuku and D. A. Nagib, *Synthesis*, 2018, **50**, 1569; (*s*) J. Davies, S. P. Morcillo, J. J. Douglas and D. Leonori, *Chem.–Eur. J.*, 2018, **24**, 12154.

12 (*a*) R. Hernández, A. Rivera, J. A. Salazar and E. Suárez, *J. Chem. Soc., Chem. Commun.*, 1980, 958; (*b*) C. Betancor, J. I. Concepcion, R. Hernandez, J. A. Salazar and E. Suárez, *J. Org. Chem.*, 1983, **48**, 4430; (*c*) C. G. Francisco, A. J. Herrera and E. Suárez, *J. Org. Chem.*, 2003, **68**, 1012.

13 (*a*) C. Martínez and K. Muńiz, *Angew. Chem., Int. Ed.*, 2015, **54**, 8287; (*b*) C. Q. O'Broin, P. Fernández, C. Martínez and K. Muńiz, *Org. Lett.*, 2016, **18**, 436; (*c*) P. Becker, T. Duhamel, C. J. Stein, M. Reiher and K. Muñiz, *Angew. Chem., Int. Ed.*, 2017, **56**, 8004; (*d*) H. Zhang and K. Muñiz, *ACS Catal.*, 2017, **7**, 4122; (*e*) T. Duhamel, C. J. Stein, C. Martínez, M. Reiher and K. Muñiz, *ACS Catal.*, 2018, **8**, 3918.

14 E. A. Wappes, S. C. Fosu, T. C. Chopko and D. A. Nagib, *Angew. Chem., Int. Ed.*, 2016, **55**, 9974.

15 G. C. Choi, Q. Zhu, D. Miller, C. Gu and R. R. Knowels, *Nature*, 2016, **539**, 268.

16 J. C. K. Chu and T. Rovis, *Nature*, 2016, **539**, 272.

17 W. Yuan, Z. Zhou, L. Gong and E. Meggers, *Chem. Commun.*, 2017, **53**, 8964.

18 (*a*) C. Yamamoto, K. Takamatsu, K. Hirano and M. Miura, *J. Org. Chem.*, 2016, **81**, 7675; (*b*) F. Pan, B. Wu and Z.-J. Shi, *Chem.–Eur. J.*, 2016, **22**, 6487.

19 For selected examples on amidyl radical induced HAT, see: for halogenation, see: (*a*) Q. Qin and S. Yu, *Org. Lett.*, 2015, **17**, 1894; (*b*) T. Liu, M. C. Myers and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **129**, 313; (*c*) M. A. Short, J. M. Blackburn and J. L. Roizen, *Angew. Chem., Int. Ed.*, 2017, **57**, 296. For cyclization, see:(*d*) R. Fan, D. Pu, F. Wen and J. Wu, *J. Org. Chem.*, 2007, **72**, 8994; (*e*) P. Becker, T. Duhamel, C. Martínez and K. Muñiz, *Angew. Chem., Int. Ed.*, 2018, **57**, 5166; (*f*) N. R. Paz, D. Rodíguez-Sosa, H. Valdés, R. Marticorena, D. Melián, M. B. Copano, C. C. González and A. J. Herrera, *Org. Lett.*, 2015, **17**, 2370; (*g*) M. Yang, B. Su, Y. Wang, K. Chen, X. Jiang, Y.-F. Zhang, X.-S. Zhang, G. Chen, Y. Cheng, Z. Cao, Q.-Y. Guo, L. Wang and Z.-J. Shi, *Nat. Commun.*, 2014, **5**, 4707; (*h*) D. Meng, Y. Tang, J. Wei, X. Shi and M. Yang, *Chem. Commun.*, 2017,

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53, 5744. Reacted with alkenes, see: (*i*) M. A. Ashley, C. Yamauchi, J. C. K. Chu, S. Otsuka, H. Yorimitsu and T. Rovis, *Angew. Chem., Int. Ed.*, 2019, **58**, 4002; (*j*) S. T. Nguyen, Q. Zhu and R. R. Knowles, *ACS Catal.*, 2019, **9**, 4502; (*k*) Z.-Y. Ma, L.-N. Guo, Y. You, F. Yang, M. Hu and X.-H. Duan, *Org. Lett.*, 2019, **21**, 5500. Reacted with heteroaryl, see: (*l*) N. Tang, X. Wu and C. Zhu, *Chem. Sci.*, 2019, **10**, 6915.

20 Z. Li, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 13288.

21 Z. Zhang, L. M. Stateman and D. A. Nagib, *Chem. Sci.*, 2019, **10**, 1207.

22 D. Bafaluy, J. M. Muñoz-Molina, I. Funes-Ardoiz, S. Herold, A. J. de Aguirre, H. Zhang, F. Maseras, T. Belderrain, P. J. Pérez and K. Muñiz, *Angew. Chem., Int. Ed.*, 2019, **58**, 8912.

23 Z. Liu, H. Xiao, B. Zhang, H. Shen, L. Zu and C. Li, *Angew. Chem., Int. Ed.*, 2019, **58**, 2510.

24 For selected copper photoredox catalysis, see: (*a*) Q. M. Kainz, C. D. Matier, A. Bartoszewicz, S. L. Zultanski, J. C. Peters and G. C. Fu., *Science*, 2016, **351**, 681; (*b*) D. B. Bagal, G. Kachkovskyi, M. Knorn, T. Rawner, B. M. Bhanage and O. Reiser, *Angew. Chem., Int. Ed.*, 2015, **54**, 6999.

25 The results was detected by MS-ESI.

26 For the preparation and characterization of F-SPh, see: (*a*) F. Seel, R. Budenz, R. D. Flaccus and R. Staab, *J. Fluorine Chem.*, 1978, **12**, 437; (*b*) H. Poleschner and K. Seppelt, *Chem.–Eur. J.*, 2004, **10**, 6565; (*c*) S. Liu, *J. Chem. Phys.*, 2014, **141**, 194109.

27 When our manuscript is in revision, a similary type reaction was reported: A. Modak, E. N. Pinter and S. P. Cook, *J. Am. Chem. Soc.*, 2019, **141**, 18405.

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