Copper-catalyzed intermolecular functionalization of unactivated C(sp^3)-H bonds and aliphatic carboxylic acids

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ABSTRACT: Intermolecular functionalization of C(sp^3)-H bonds and aliphatic carboxylic acids enables the efficient synthesis of high value-added organic compounds from readily available starting materials. Although methods involving hydrogen atom transfer have been developed for such functionalization, these methods either work for only activated C(sp^3)-H bonds, or bring in a narrow set of functional groups. Here we describe a Cu-catalyzed process for the diverse functionalization of both unactivated C(sp^3)-H bonds and aliphatic carboxylic acids. The process is enabled by the trapping of alkyl radicals generated through hydrogen atom abstraction by arylsulfonyl-based SOMO-philes, which introduces a large array of C, N, S, Se, and halide-based functional groups. The chemoselectivity can be switched from C-H functionalization to decarboxylative functionalization by matching the bond dissociation energy of the hydrogen atom transfer reagent with that of the target C-H or O-H bond.

1. Introduction.

Alkanes and aliphatic carboxylic acids are appealing raw materials for chemical transformation given their widespread natural and synthetic occurrence.[1-2] Direct C-H and decarboxylative functionalization can be of great value in drug discovery. C-H functionalization facilitates the preparation of structural analogs of targets with enhanced structure-activity relationships (SAR) and other desired physicochemical properties without resorting to de novo synthesis.[3-6] Likewise, decarboxylative functionalization is amenable for late-stage modifications due to the broad availability of carboxylic acids in natural products and drugs.[2] Although many methods for C-H and decarboxylative functionalization have been developed in the past decades, most of them require prefunctionalization such as the introduction of a directing group,[1] pre-activation of aliphatic carboxylic acids,[7] to ensure reactivity and site-selectivity. Most methods can only perform either C-H functionalization or decarboxylative functionalization, but not both. While intramolecular C(sp^3)-H[8-14] and intermolecular activated C(sp^3)-H functionalization,[15-19] as well as decarboxylative reaction of redox-active esters[20-28] have been extensively studied, intermolecular functionalization of unactivated C(sp^3)-H[29-34] and aliphatic acids remains a challenge. The latter is due to several factors: (i) unactivated C(sp^3)-H bonds and a carboxylic acid O-H bond have high bond dissociation energies (BDEs), the former being about 96-101 kcal/mol and the latter being up to 112 kcal/mol.[35] (ii) Intermolecular reactions are both thermodynamically and kinetically less favorable than intramolecular reactions, subjecting to more side reactions.

Activation of strong C-H and O-H bonds might be achieved by a hydrogen atom transfer (HAT) reagent.[35-39] The groups of Zhang,[15] Liu[17] and Stahl[18-19] have reported copper-catalyzed intermolecular functionalization of benzylic C-H bonds using *N*-fluorobenzenesulfonimide (NFSI) (Figure 1A), a strong oxidant and a precursor of a hydrogen-atom transfer reagent. Reduction of NFSI by a Cu^I species generates a *N*-centered imidyl radical, which abstracts a hydrogen atom from a benzyl C-H bond (BDE < 90 kcal/mol) to form a dibenzenesulfonimide and a benzylic radical.[40] The latter participates in copper-catalyzed coupling reactions to form various new chemical bonds (Figure 1A). These methods are only suitable for the activation of activated C(sp^3)-H bonds[15-19] because the two phenyl sulfonyl groups attached to the nitrogen atom in NFSI largely disperses the spin density of the *N*-centered imidyl radical and reduces the percentage of σ character of its orbital, leading to lower activity. By introducing *N*-radicals with *N*-tert-butyl amidyl or *N*-tert-butyl sulfonamidyl backbones, Alexanian and coworkers have achieved functionalization of unactivated C(sp^3)-H bonds [36-38, 41] and aliphatic carboxylic acids (Figure 1B),[35] typically using light initiation. However, the newly introduced functional groups are limited to the leaving groups in the precursors to the amidyl radicals, namely, Br, Cl, and xanthyl groups. Here we describe Cu-catalyzed diverse intermolecular functionalization of unactivated alkanes and aliphatic acids. Essential to our method is an appropriate *N*-amidyl radical precursor and a suitable SOMO-phile. Our method is developed based on an initial design outlined in Figure 1C.

Reduction of an N-F reagent **I** by a ligated Cu^I complex **II** via single electron transfer (SET) would generate an *N*-centered radical **IV** and a Cu^{II}-F complex **III**. The *N*-centered radical abstracts a hydrogen atom from an alkane (C-H) or a carboxylic acid (O-H) to give an alkyl radical **VI** (directly from the alkane and after decarboxylation from carboxylic acid) and the parent N-H bond **V**. The alkyl radical would be

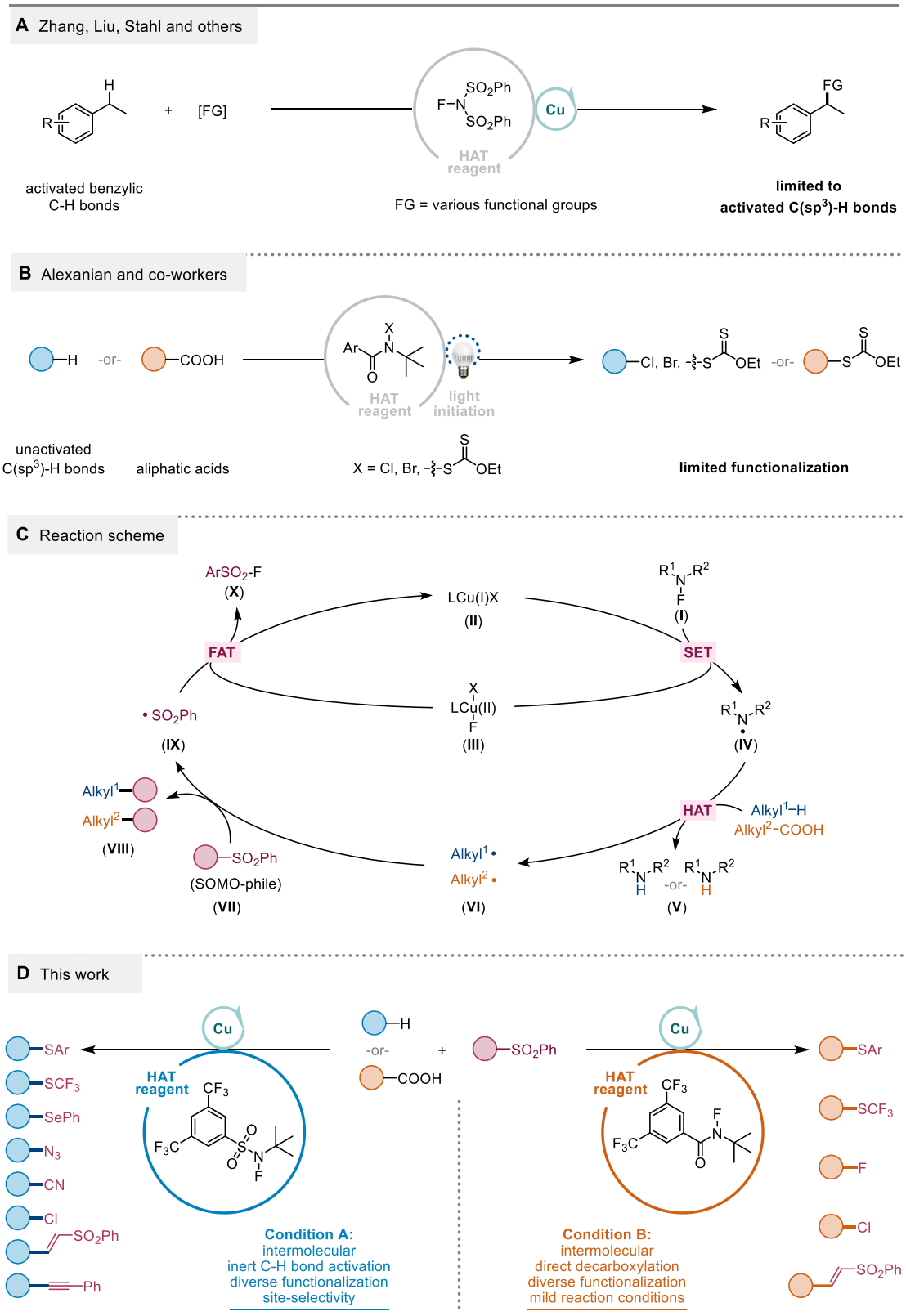
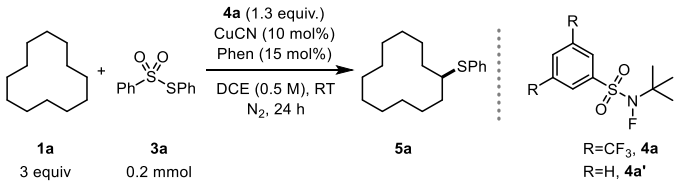


Figure 1. (A) A previous method for the copper-catalyzed intermolecular functionalization of benzylic C-H bonds by *N*-fluorobenzenesulfonimide (NFSI); (B) A previous method for the intermolecular chlorination, bromination, and xanthylation of alkanes and aliphatic acids; (C) Reaction scheme; (D) This work: copper-catalyzed functionalization of alkanes and aliphatic acids.

trapped by an arylsulfonyl-based SOMO-phile **VII** to furnish the functionalized product **VIII** along with an arylsulfonyl radical **IX**. The latter would abstract an F atom from the Cu^{II}-F complex **III**, via fluorine-atom transfer (FAT),[42] to form a stable sulfonyl fluoride byproduct and regenerate the Cu^{I} catalyst.[42] By matching the BDEs of the parent amide of the

Table 1. Summary of the effects of reaction parameters and conditions on the reaction efficiency of C-H thiolation[a]



entry	variation	yield (%)[a]
1	no ligand	5
2[b]	no variation	46
3	BC (15 mol%)	44
4	CuCl (10 mol%)	37
5	$Fe(OTf)_2$ (10 mol%)	trace
6	60 °C	78
7	no CuCN	0
8	no **4a**	0
9	60 °C, **4a'** (1.3 equiv.)	38

[a]Corrected GC yield using *n*-dodecane as an internal standard. [b]Reaction was carried out with **1a** (3 equiv.), **3a** (0.2 mmol), **4a** (1.3 equiv.), CuCN (10 mol%), Phen (15 mol%) in DCE (0.5 M) under a N_2 atmosphere at room temperature. DCE = 1,2-dichloroethane, RT = room temperature, Phen = 1,10- phenanthroline, BC = bathocuproine

amidyl radical with those of the substrates, we are able to control the selectivity between C-H and decarboxylative functionalization using two novel HAT reagents (Figure 1D). By using electron-deficient SOMO-philes where a functional group is attached to an aryl sulfonyl group, which were previously used in radical-mediated C-C and C-heteroatom functionalization,[43-45] we are able to introduce a large array of C, N, S, Se, and halide-based functional groups (Figure 1D).

2. Results and discussion

2.1. Reaction development of C-H thiolation

We commenced our investigations by screening conditions for direct C-H thiolation (Table 1). To abstract H atom from an unactivated alkane, we chose the N-F reagent *N*-(tert-butyl)-*N*-fluoro-3,5-bis(trifluoromethyl)benzenesulfonamide (**4a**) which has a BDE of 104 kcal/mol for the parent N-H[35]. Inspired by the analogous N-X (X = Cl, xanthyl group)[35, 41] and Ph-$S(O)_2NF(t$Bu)[46] compounds, we designed and synthesized the N-F reagent **4a**, which serve as a HAT precursor and release HAT reagent under reducing conditions (see cyclic voltammogram of **4a** in Figure S60, SI) for C-H thiolation. The reaction of cyclododecane **1a** (3 equiv.) with *S*-phenyl benzenethiosulfonate **3a** (0.2 mmol) in the presence of 10 mol % of CuCN in 1,2-dichloroethane (DCE, 0.5 M) at 25 °C under N_2 provided a small amount of the thiolated product **5a** (5%) after 24 h (Table 1, entry 1). Previous reports showed that phenanthroline-type ligand promoted Cu^I-mediated reduction of NFSI and other N−F reagents to generate *N*-centered radicals.[12, 47] Thus, we added 1,10-phenanthroline (15 mol%; premixed with CuCN (10 mol%) for 15 minutes) to the reaction mixture. The yield of **5a** was increased to 46% (Table 1, entry 2). Other phenanthroline ligands were screened but the yields were inferior (Table 1, entry 3 for bathocuproine and SI, Table S1, entries 2-10 for others). Other metal salts were less efficient than CuCN (e.g., Table 1, entries 2, 4−5 and SI, Table S1, entries 2, 11-17). Increasing the temperature to 60 °C increased the yield of **5a** to 78% (Table 1, entry 6). We found that the conversion of **4a** was higher at 60 °C than at room temperature (100% vs 71%), suggesting that a higher temperature increases the reactivity. Control experiments showed that both a copper catalyst and N-F reagent **4a** were essential (Table1, entries 7-8). When **4a'** was used under the optimal reaction condition (entry 9, Table1), the yield decreased significantly, indicating the importance of the electron-withdrawing CF_3 group on the aryl moiety for this reaction.

The optimal conditions in Table 1 were applied to explore the scope of C-H thiolation (Table 2). The method is general for aryl thiolation of cycloalkanes, yielding a wide range of alkyl aryl sulfides **5a**-**5o** in 50−90% yields (Table 2). Various substituted aryl thiolate and even heteroaryl thiolate groups were installed. Thiolation of *n*-pentane gave **5p** in a combined yield of 61%. The reaction favors the methylene sites with $k_{secondary}/k_{primary}$ (k_s/k_p) > 99. Among methylene sites, the 2-position was favored likely due to a steric factor. For norbornane, the thiolation yielded exclusively 2-*exo*-norbornyl phenyl sulfide **5q** (54%). Likewise, the thiolation of adamantane gave exclusively the thiolated product **5r** (90%). The thiolation of *trans*-decalin occurred with a high methylene/methine site selectivity (**5s**, $k_{secondary}/k_{tertiary}$ > 99). These examples further highlight the steric origin of the observed site-selectivity. The direct C-H thiolation also worked for a range of heterocycles and functionalized substrates (**6a**-**6g**). α-Thiolation was successful on tetrahydrofuran(**6a**), 1-Boc-pyrrolidine (**6b**), and 1-Boc-piperidine (**6c**). The reaction of 2-heptanone gave **6d** where only methylene sites were thiolated (combined yield: 55%). The 6-position was preferentially thiolated (65% selectivity) due to both electronic and steric factors. The thiolation of 1-acetamidoadamantane, adamantanone and 1-chloroadamantane gave **6e**, **6f** and **6g** in good yields (66%, 70% and 76%, respectively) and a complete site selectivity for the less-hindered tertiary C−H sites. Selective C(sp^3)-H thiolation of 1-adamantanecarboxylic acid was also obtained, albeit in a decreased yield (**S1**, SI).

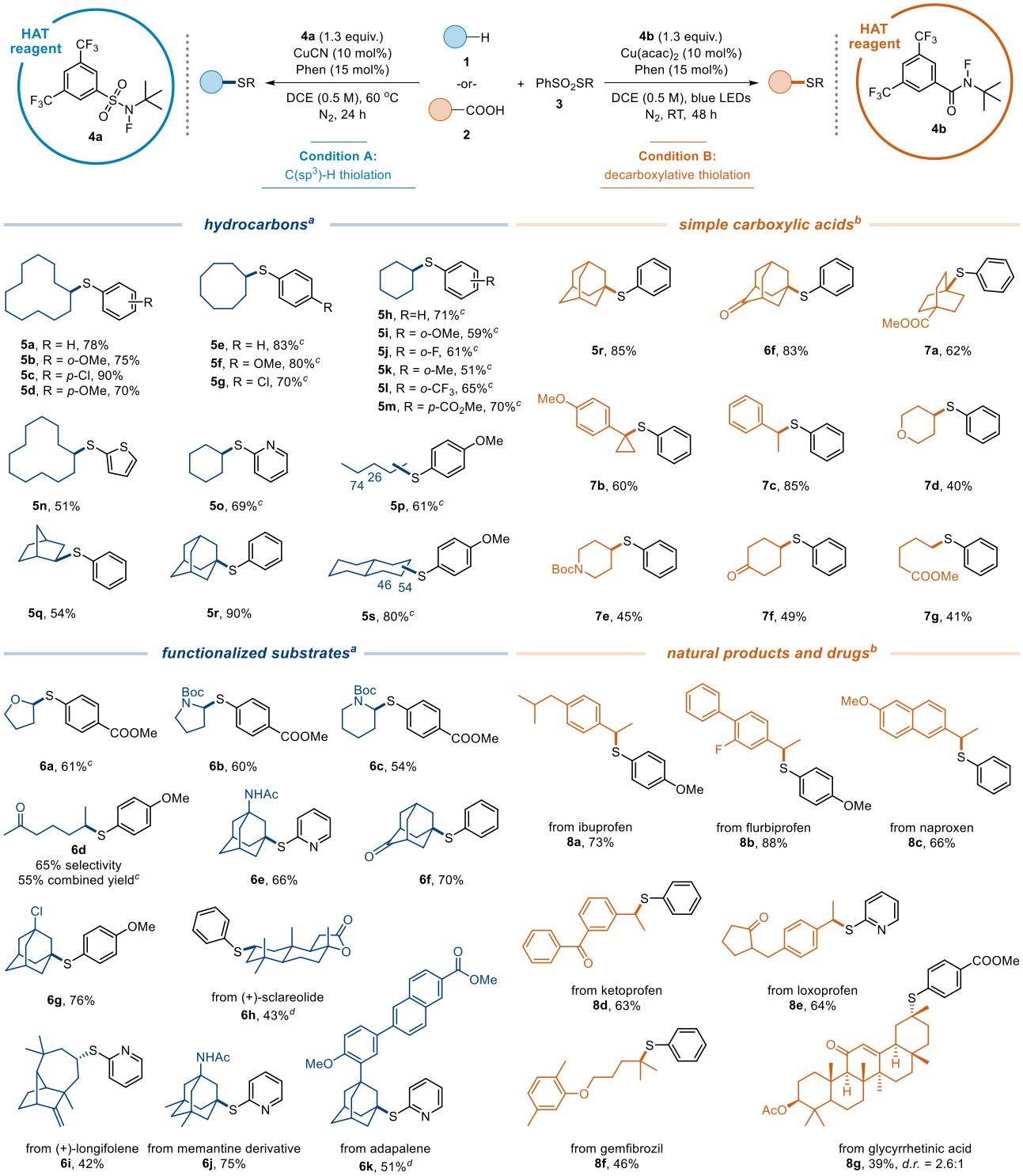
Site selective C−H thiolation of complex molecules is highly relevant to late-stage functionalization in drug discovery and total synthesis. A number of complex natural products and drug precursors were studied in this context (**6h**-**6k**). In all these examples single-site selectivity and synthetically useful yields were obtained. For (+)-sclareolide, thiolation occurred at the sterically most accessible and most electron-rich C2 position in 43% yield (**6h**). For (+)-longifolene, the thiolated product **6i** was obtained as a single diastereomer. For the memantine derivative and adapalene, thiolation occurred at the most accessible tertiary C−H site, giving **6j** and **6k** in 75% and 51% yields, respectively. Overall, the method has good functional group tolerance.

2.2. Reaction development of decarboxylative thiolation

Decarboxylative functionalization enables the efficient use of widely available carboxylic acids in organic synthesis.[2] Nearly all decarboxylative reactions require either (i) deprotonation

followed by oxidative decarboxylation;[48-49] or (ii) conversion to redox-active esters followed by decarboxylation.[7, 20] There are only a few reports of direct decarboxylation under neutral conditions[35, 39] due to the high BDE

Table 2. Scope of Cu-catalyzed intermolecular C-H thiolation and decarboxylative thiolation



[a]General conditions for C(sp^3)-H thiolation: **1** (3 equiv.), **3** (0.2 mmol), **4a** (1.3 equiv.), CuCN (10 mol%), 1,10- phenanthroline (15 mol%) and DCE (0.5 M), 60 °C, N_2, 24 h; [b]General conditions for decarboxylative thiolation: **2** (3 equiv.), **3** (0.1 mmol), **4b** (1.3 equiv.), $Cu(acac)_2$ (10 mol%), 1,10- phenanthroline (15 mol%) and DCE (0.5 M), irradiated at room temperature under N_2 atmosphere for 48 h; [c]1 (10 equiv.); [d]1 (1 equiv.).

of the O-H bond (BDE ≈ 112 kcal/ mol) in carboxylic acids. This BDE is higher than that of the N-H bond of the parent sulfonamide of **4a** (BDE = 104 kcal/ mol). To adapt the thiolation method for decarboxylation, we replaced **4a** with **4b** whose parent amide has a N-H BDE of about 111 kcal/ mol).[35] Compound **4b** was previously used as a fluorination reagent,[46] but it had not been used as a HAT reagent.

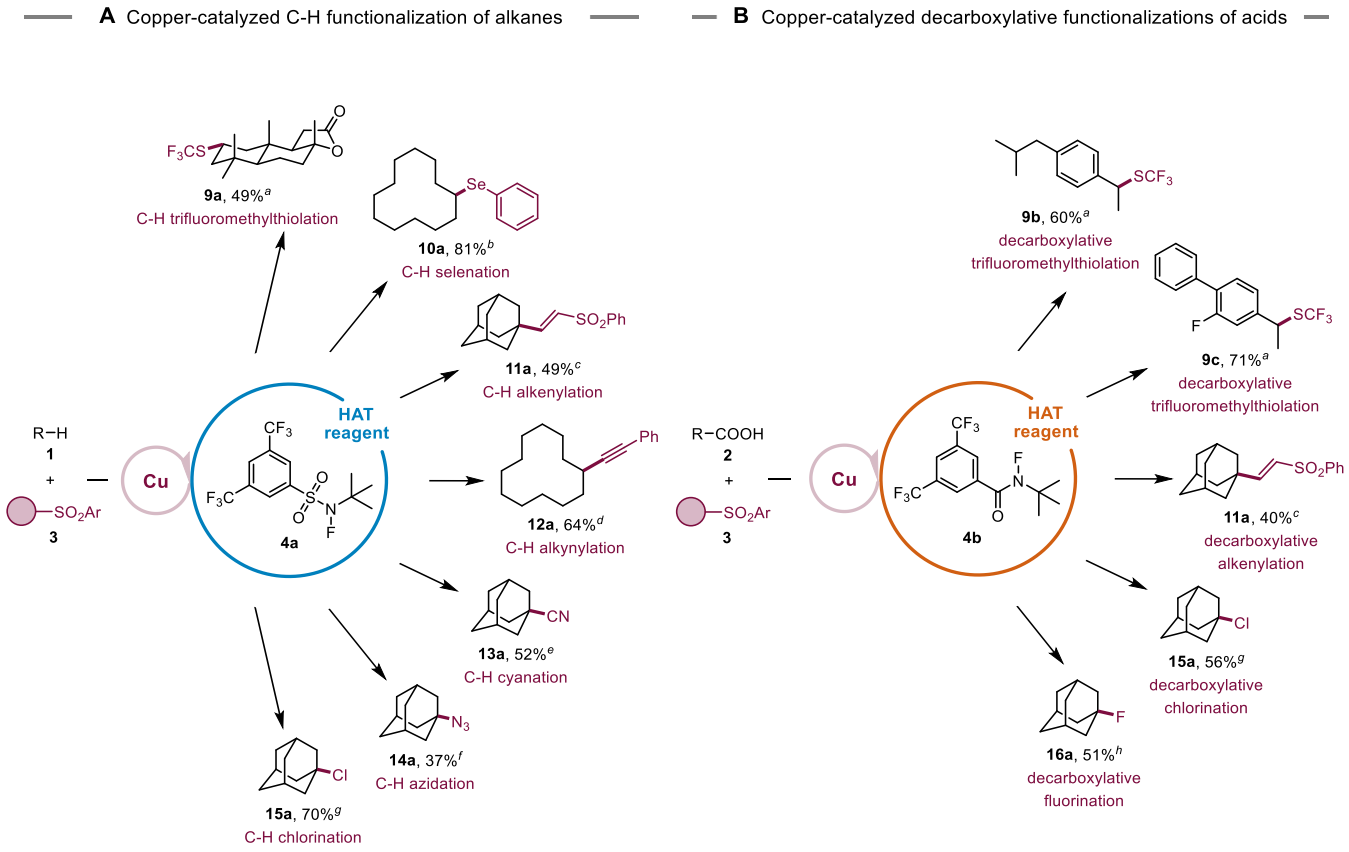


Figure 2. (A) General conditions for C-H functionalization: alkane (**1**, 3 equiv.), R-SO_2Ar (**3**, 0.2 mmol), **4a** (1.3 equiv.), CuCN (10 mol%), 1,10- phenanthroline (15 mol%) and DCE (0.5 M), 60 °C, N_2, 48 h; (B) General conditions for decarboxylative functionalization: carboxylic acid (3 equiv.), R-SO_2Ar (0.2 mmol), **4b** (1.3 equiv.), Cu(acac)$_2$ (10 mol%), 1,10- phenanthroline (15 mol%) and DCE (0.5 M), irradiated at room temperature under N_2 atmosphere for 48 h; [a]*S*-(trifluoromethyl) benzenesulfonothioate (**3j**, 0.2 mmol); [b]*Se*-phenyl benzenesulfonoselenoate (**3k**, 0.2 mmol); [c]*trans*-1,2-Bis(phenylsulfonyl)ethylene (**3l**, 0.2 mmol); [d]((phenylethynyl)sulfonyl)benzene (**3m**, 0.2 mmol); [e]*p*-toluenesulfonyl cyanide (**3n**, 0.2 mmol); [f]4-acetamidobenzenesulfonyl azide (**3o**, 0.2 mmol); [g]benzenesulfonyl chloride (**3p**, 0.2 mmol); [g]without **3**.

As expected, the desired decarboxylative thiolation of 1-adamantanecarboxylic acid **2a** with **3a** under the conditions of C-H thiolation was not observed (SI, Table S2, entry 1). However, replacing **4a** with **4b** gave the thiolated product **5r** in a low but promising yield of 8% (SI, Table S2, entry 2). Using different copper sources had small effects on the reaction efficiency (SI, Table S2, entries 2-5). The conversion of the N-F reagent **4b** was very low (< 40%) under these conditions (SI, Table S2, entries 1-5), suggesting that the SET process from the Cu(I) catalyst to **4b** was not efficient. Alexanian and coworkers reported that illumination by blue LEDs promoted the N-X (X=Cl, Br) homolysis of *N*-chloroamide[37] and *N*-bromoamide[36] analogs of **4b**. We thought illumination might promote the SET process from Cu(I) to **4b** as well (see cyclic voltammogram of **4b** in Figure S61, SI),. Indeed, when running the reaction under illumination from a blue LED for 24 h, the reaction yield was boosted to 64% (SI, Table S2, entry 6). The role of light might be to reduce Cu(II) complexes to Cu(I) species, as reported previously.[50-51] According to UV-vis spectroscopy, copper(II) acetylacetonate complexes have absorption in the visible region (xxx, SI), consistent with this hypothesis. Extension of the reaction time further improved the yield to 85% (SI, Table S2, entry 7).

The decarboxylative thiolation has broad scope (Table 2). Many simple acids, including tertiary, secondary, and primary alkyl carboxylic acids, were converted to alkyl aryl sulfides (**5r**, **6f**, **7a**-**7g**) in moderate to good yields. The preparation of tertiary alkyl aryl sulfides (**5r**, **6f**, **7a**-**7b**) by this method is noteworthy because such compounds are difficult to obtain by nucleophilic substitution. The decarboxylative thiolation of 4-substituted tetrahydropyran and piperidine carboxylic acids gave **7d** and **7e** in 40% and 45% yield, respectively. These reactions were chemoselective for decarboxylative thiolation over C-H thiolation, as no thiolation at the α-position of O, N atoms was observed. We propose that when the BDE of the N-H bond of the parent amide of **4b** makes it sufficient to activate both the C(sp^3)-H and O-H bonds on a carboxylic acid, the bond strength will no longer be the sole determinant of the HAT reactivity. Instead, from a kinetic point of view, HAT occurs more rapidly for O-H bonds than for C-H bonds,[52] thus the HAT for O-H bonds in carboxylic acids will dominate. The latter leads to high

chemoselectivity for decarboxylative functionalization. The decarboxylative thiolation could be applied to the late-stage modification of a range of natural products and drug derivatives as well. Reactions of the nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen, flurbiprofen, naproxen, ketoprofen, and loxoprofen[53] delivered the corresponding alkyl aryl sulfides **8a**-**8e** in moderate to good yields. In all these cases, no C-H thiolation products were observed, even for ibuprofen and loxoprofen which contain one or more benzylic C-H bonds. Decarboxylative thiolation of gemfibrozil,[54] a prescription medication used to lower triglycerides, provided **8f** in 46% yield. Decarboxylative thiolation of AcO-derivative of glycyrrhetinic acid, which is effective in the treatment of peptic ulcer and also has expectorant (antitussive) properties,[55] delivered **8g** in 39% yield.

2.3. Other functionalization reactions

The thiolation method could be easily adapted into analogous functionalization methods by using other aryl sulfonyl based SOMO-philes (Figure 2). The incorporation of the trifluoromethylthio group (SCF_3) into new drugs and agrochemicals has attracted much attention owing to its strongly electron - withdrawing nature and high lipophilicity.[56] The C-H trifluoromethylthiolation of (+)-sclareolide could be performed by using *S*-(trifluoromethyl) benzenesulfonothioate **3b** as a SOMO-phile under otherwise standard conditions of C-H thiolation (Table 1, entry 6), giving **9a** in 49% yield. Decarboxylative trifluoromethylthiolation was successful for ibuprofen and flurbiprofen under the standard conditions of decarboxylative thiolation, delivering **9b** and **9c** in 60% and 71% yields, respectively. Similarly, C-H selenation of cyclododecane gave **10a** in 81% yield by using *Se*-phenyl benzenesulfonoselenoate as the coupling partner (Figure 2). Renaud and co-workers previously demonstrated alkyl radical addition to the carbon atom of a multiple (double or triple) bond bearing an arene sulfonyl group.[44] Using such compounds as SOMO-philes, we achieved direct C-H or decarboxylative vinylation (**11a**), alkynylation (**12a**), and cyanation (**13a**). Azides are important intermediates in organic syntheses. While the group of Stahl reported copper-catalyzed intermolecular azidation of benzylic C–H Bonds,[19] intermolecular azidation of unactivated C(sp^3)-H is still challenging.[57-61] Using a sulfonyl azide as the SOMO-phile, we were able to perform unactivated C(sp^3)-H azidation (**14a**). Following the same protocol, C-H and decarboxylative chlorination and fluorination reactions were successful (**15a** and **16a**).

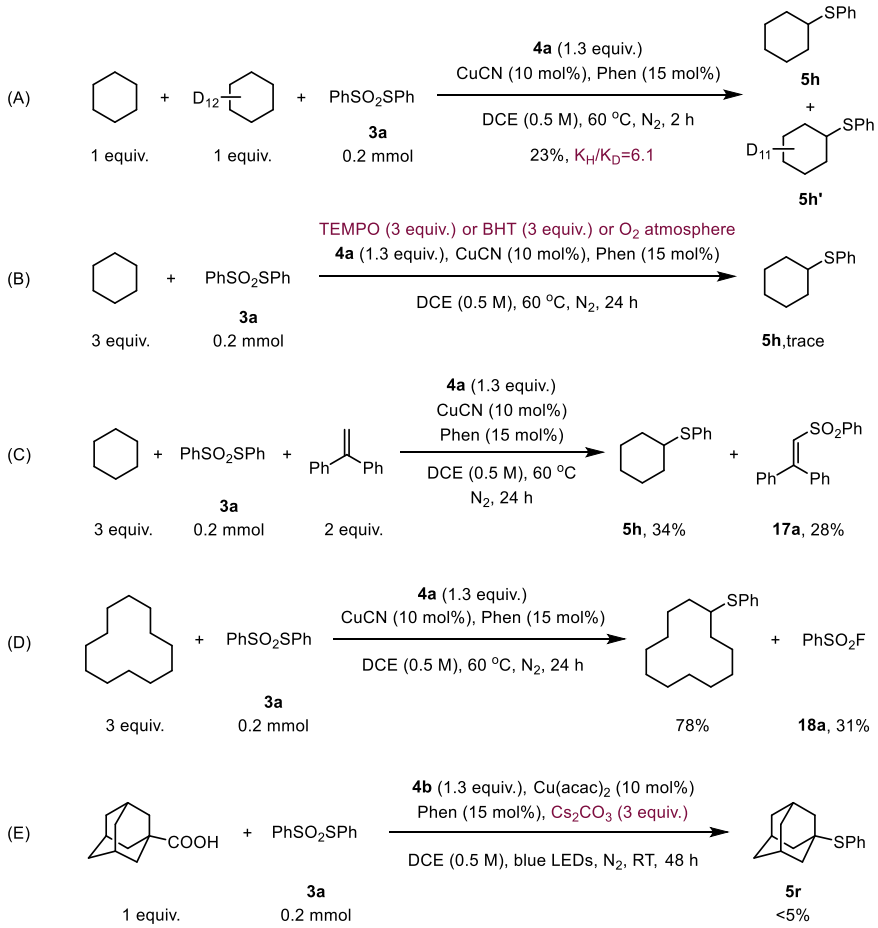


Figure 3. Results of mechanistic experiments.

2.4. Mechanistic investigation

Several experiments were conducted to obtain insight into the mechanism. A competition deuterium kinetic isotope effect (KIE) study, employing a mixture of cyclohexane and cyclohexane-d12, revealed a KIE of 6.1 (Figure 3A). In the presence of 3 equiv. of 2,2,6,6- tetramethyl-1-piperidinyloxy (TEMPO) or 3 equiv. of 2,6-di-tert-butyl-4-methylphenol (BHT), C-H thiolation was completely inhibited under the standard reaction conditions (Figure 3B). Additionally, no product was observed when the reaction was run under O_2 atmosphere (Figure 3B). These results are consistent with the involvement of various

radical species as proposed in Figure 1C. When 2 equiv of ethene-1,1- diyldibenzene was added to a reaction mixture, the desired thiolation product **5h** was only obtained in 34% yield (vs. 62% without the scavenger), along with **17a** (28%) which originated from the addition of a benzenesulfonyl radical to the scavenger (Figure 3C). This result supports the proposed PhS group transfer from *S*-phenyl benzenethiosulfonate to the alkyl radical to give the thiolation product and a benzenesulfonyl radical.[9] In the thiolation of cyclododecane, besides the thiolated **5a** (78%), we obtained the benzenesulfonyl fluoride **18a** (31%) (Figure 3D). This result is consistent with our proposed reaction of benzenesulfonyl radical with a Cu^{II}-F to give benzenesulfonyl fluoride through FAT and regenerate the Cu^{I} catalyst (Figure 1C). Given the importance of sulfonyl fluoride compounds,[62] we attempted to recover these products from the reactions mixture. We found in most cases, benzenesulfonyl fluorides could be isolated with ease. When running the decarboxylative thiolation reaction of 1-adamantanecarboxylic acid with **3a** in the presence of 3 equiv. Cs_2CO_3, less than 5% of thiolated product **5r** was detected (Figure 3E). This result indicates that deprotonation of the carboxylic acid inhibits the reaction. The result agrees with HAT being the initiation step of decarboxylative functionalization (Figure 1C),[35] but is inconsistent with oxidation of carboxylic acid as the initiation step which should work under basic conditions.[63]

The group of Faust demonstrated that Cu^{I} species can be generated from Cu^{II} carboxylate species under irradiation.[64] It is possible that light facilitates the regeneration of Cu^{I} species from Cu^{II} species in our reactions, ensuring a high concentration of Cu^{I} catalyst. Recently, Ritter and co-workers reported a ligand-to-metal charge transfer (LMCT)-enabled radical decarboxylative carbometalation strategy for Cu-catalyzed aromatic decarboxylative fluorination.[65] Currently, we cannot exclude an similar LMCT process in our reactions. However, the unique reactivity of **4b**, compared to **4a**, is inconsistent with an LMCT process, which should occur regardless of the HAT reagent (SI, Table S2, entries 7-8). The mechanism of the reactions, including the role of the light in the decarboxylative functionalization, warrants a further study.

3. Conclusion

In summary, using Cu catalysis in combination with an N-F-based HAT reagent and an arenesulfonyl-based SOMO-phile, we have developed a general method for unactivated C(sp^3)-H functionalization and decarboxylative functionalization of aliphatic carboxylic acids. A series of C–X (S, SCF_3, Se, N_3, CN, Cl, F) and C–C (Csp^3-Csp^2 and Csp^3-Csp) bonds can be constructed under simple and mild reaction conditions using abundant and readily available alkanes and carboxylic acids as starting materials. The chemoselectivity can be switched from C-H functionalization to decarboxylative functionalization by judicious choice of HAT reagents. The method has demonstrated utility in the late-stage modification of natural products and drugs.

ASSOCIATED CONTENT

All data supporting the findings of this study, including experimental procedures and compound characterization, are available within the Article and its Supporting Information. The supporting information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing interests.

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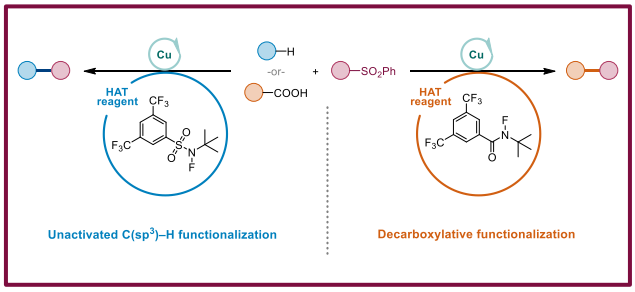
Cu
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Unactivated C(sp3)–H functionalization
Decarboxylative functionalization