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Visible-Light-Promoted Activation of Unactivated C(sp^3)–H Bonds and Their Selective Trifluoromethylthiolation

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Supporting Information

ABSTRACT: Selective functionalization of ubiquitous C(sp^3)–H bonds using visible light is a highly challenging yet desirable goal in organic synthesis. The development of such processes relies on both rational design and serendipitous discoveries from innovative tools such as screening technologies. Applying a mechanism-based screening strategy, we herein report photoredox-mediated hydrogen atom transfer catalysis for the selective activation of otherwise unactivated C(sp^3)–H bonds, followed by their trifluoromethylthiolation, which has high potential as a late-stage functionalization tool. The generality of this method is exhibited through incorporation of the trifluoromethylthio group in a large number of C(sp^3)–H bonds with high selectivity without the need for an excess of valuable substrate.

The functionalization of abundant C–H bonds in chemical synthesis is an attractive concept because of its inherent economic and environmentally benign nature. However, controlling the site selectivity, as most organic molecules contain a large number of methyl, methylene, and methine groups, represents perhaps the biggest challenge in the development of such processes. Enzymes have evolved to selectively oxidize these inert C–H bonds by their inherited protein-embedded active core.[1] Chemists on the other hand have utilized either a directing group[2] or the electronic properties of the molecule for selective oxidation of C(sp^3)–H bonds.[3] In this regard, for use in visible-light photoredox catalysis, small-molecule hydrogen atom transfer (HAT) catalysts were developed to selectively activate weak allylic (bond dissociation energy (BDE) = 88.8 kcal/mol), benzylic (BDE = 89.7 kcal/mol), and α-heteroatom (BDE ~ 92 kcal/mol) C–H bonds under mild reaction conditions.[4] We recently became interested in utilizing HAT catalysis for the activation of more challenging unactivated C(sp^3)–H bonds (BDE for $(CH_3)_2CH$–H = 98.6 kcal/mol and for $(CH_3)_3C$–H = 96.5 kcal/mol).[5] In particular, in line with our current research, we focused on the direct C(sp^3)–H trifluoromethylthiolation reaction employing visible light as the energy source.[6] It was envisioned that the key to success would be the identification of a highly hydridophilic small-molecule organocatalyst to selectively activate an electron-rich C(sp^3)–H bond of an organic substrate (Figure 1A).

The trifluoromethylthio (SCF_3) group is under investigation because of its potential in modern drug design.[7] By protecting against in vivo enzymatic metabolism, it can improve the pharmacokinetics and efficiency of a drug candidate because of its high electron-withdrawing power (Hammett constants σ_p = 0.50, σ_m = 0.40) and lipophilicity (Hansch parameter π = 1.43).[8] However, the growth of trifluoromethylthiolated drugs and lead compounds is hampered by the lack of synthetic tools, especially ones that can be applied under mild conditions with broad functional group tolerance.[9] Traditionally, SCF_3 groups were

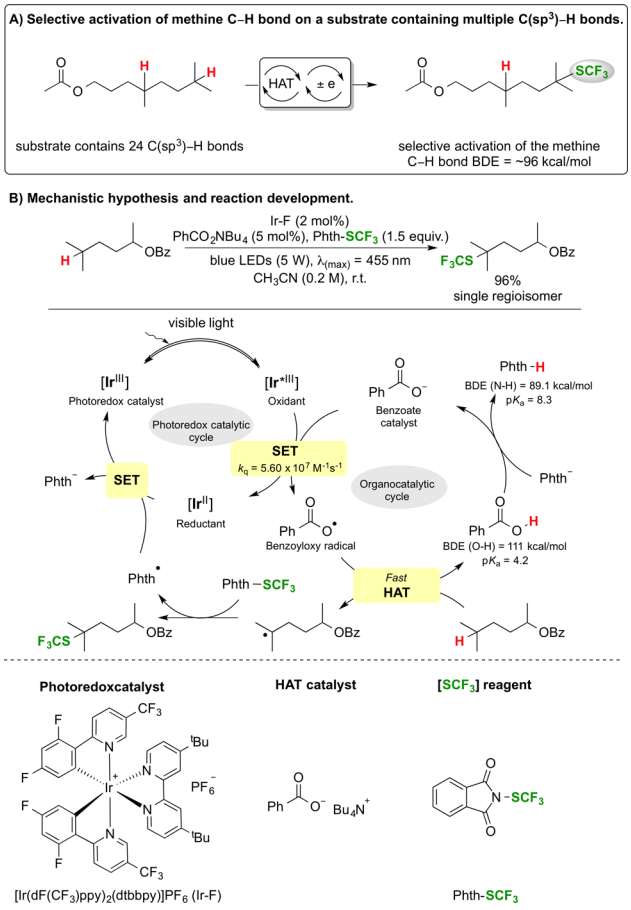

Figure 1. Photoredox-mediated HAT catalysis enables highly selective trifluoromethylthiolation of C(sp^3)–H bonds. (A) Selective activation of a methine C–H bond on a substrate containing multiple C(sp^3)–H bonds. (B) Mechanistic hypothesis and reaction development. HAT, hydrogen atom transfer; SET, single-electron transfer; BDE, bond dissociation energy; LED, light-emitting diode; Bz, benzoyl; Phth, phthalimidyl.

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introduced by halogen−fluorine exchange reactions or trifluoromethylation of disulfides and thiols.[10] Recently, a number of electrophilic SCF_3-containing reagents were introduced for the functionalization of C−H bonds.[11] Impressive trifluoromethylthiolations of benzylic and nonactivated C(sp^3)−H bonds were achieved using $AgSCF_3$ as a reagent.[12] However, these methods require either a large excess of starting material or superstoichiometric amounts of oxidant. Moreover, use of a strong oxidant often deflates the selective functionalization when the molecule contains several C−H bonds with comparable electronic properties. We reasoned that the direct and selective functionalization of C(sp^3)−H bonds on a target molecule under mild redox-neutral conditions without using an excess of valuable substrate would obviate the need for prefunctionalization steps, and we anticipated that this would create the opportunity to modify natural and bioactive molecules amenable for further drug discovery.

Visible-light-promoted photoredox catalysis has recently emerged as a powerful tool to generate highly reactive open-shell species under mild and controlled conditions.[13] We recently reported a novel mechanism-based screening method for accelerated reaction discovery.[14] This approach focused on the luminescence quenching step in a photocatalytic cycle and proved to be a useful tool to facilitate the development of new reactions. Building on this concept, we found that the strongly oxidizing excited state of the iridium-based photoredox catalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (Ir−F); ($dF(CF_3)ppy$) = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) was quenched by tetrabutylammonium benzoate ($Bu_4N^+PhCO_2^-$) in acetonitrile solution at room temperature. Further investigation revealed a Stern−Volmer constant of 128 M^{-1}, corresponding to a quenching rate constant (k_q) of 5.60×10^7 M^{-1} s^{-1} (see Figure S2).[15] On the basis of this analysis, we hypothesized that under catalytic conditions the benzoyloxy radical ($PhCO_2\cdot$) could be generated upon reductive quenching of Ir−F by $PhCO_2^-$ (Figure 1B).[16,17] We envisioned that at room temperature the electrophilic $PhCO_2\cdot$ radical could perform fast yet selective hydrogen atom abstraction from electron-rich hydridic C(sp^3)−H bonds of an alkane substrate R−H.[18] The generated nucleophilic alkyl radical R· would then react with the shelf-stable electrophilic trifluoromethylthiolating reagent Phth−SCF_3[19] to form the product R−SCF_3 along with the phthalimide radical (Phth·). Oxidation of the reduced photoredoxcatalyst with Phth· via single-electron transfer would regenerate the photocatalyst and $Phth^-$. The latter then readily deprotonates benzoic acid (pK_a = 8.3 for phthalimide against 4.2 for benzoic acid in water) to regenerate the HAT catalyst and complete the catalytic cycle (Figure 1B).

On the basis of our mechanistic hypothesis, we performed the direct trifluoromethylthiolation of 5-methylhexan-2-yl benzoate (1 equiv) using Ir−F (2 mol %) as the photocatalyst, tetrabutylammonium benzoate (5 mol %) as the HAT catalyst, and Phth−SCF_3 (1.5 equiv) in acetonitrile under irradiation with 5 W blue light-emitting diodes (LEDs) (λ_{max} = 455 nm) at room temperature (Figure 1B). To our delight, we observed the formation of the desired trifluoromethylthiolated product in 96% isolated yield with very high selectivity (>20:1) for the tertiary C−H bond over several secondary and primary C(sp^3)−H bonds present in the molecule. We found that reducing the photocatalyst loading to 1 mol % and changing the HAT catalyst to more convenient sodium benzoate did not change the outcome of the reaction. A series of control experiments were then performed to confirm the absolute necessity of each reaction component (light, photocatalyst, and HAT catalyst). As expected, no product was formed in the absence of any of these components (see Table S1).

With these conditions in hand, we explored the scope of this direct trifluoromethylthiolation reaction. As shown in Figure 2A,

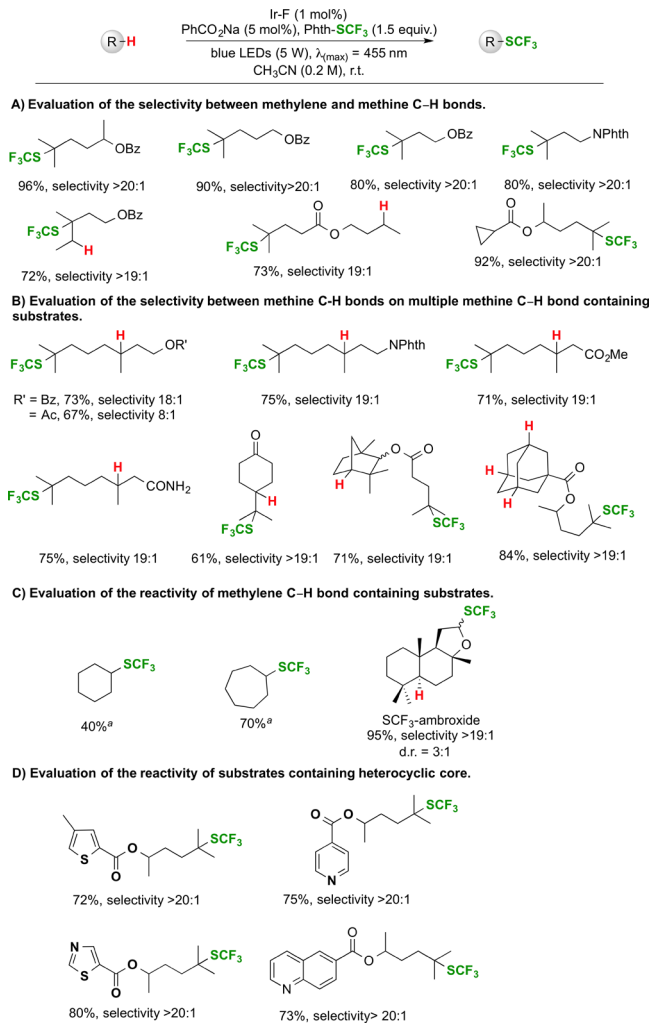

Figure 2. Scope of the photoredox-mediated HAT-catalyzed direct C(sp^3)−H bond trifluoromethylthiolation. (A) Evaluation of the selectivity between methylene and methine C−H bonds. (B) Evaluation of the selectivity between methine C−H bonds on substrates containing multiple methine C−H bonds. (C) Evaluation of the reactivities of substrates containing methylene C−H bonds. (D) Evaluation of the reactivities of substrates containing a heterocyclic core. Isolated yields are given. See the Supporting Information for experimental details. The site selectivities for reaction at two or multiple C−H bonds were determined by ^{19}F NMR analyses of the crude reaction mixtures. [a]Substrate (2 equiv); ^1H NMR yield.

a range of functionalized hydrocarbons were trifluoromethylthiolated in high yields with high selectivities for the electron-rich tertiary C−H bonds over secondary and primary ones. The reaction was also found to tolerate the strained cyclopropyl ring. We then evaluated the inherent reactivity and selectivity of this C−S bond-forming reaction in substrates with multiple tertiary C−H bonds. Dihydrocitronellol derivatives, having two electronically comparable tertiary C−H bonds and many secondary C−H bonds, were chosen as model substrates for

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this purpose. As shown in Figure 2B, the C−H trifluoromethylthiolation takes place at the distal C−H bond with high selectivity while tolerating a range of functional groups such as protected alcohols, amines, esters, and amides, and the major products were isolated in good yields (67−75%).[20] The trifluoromethylthiolation of 4-isopropylcyclohexanone also took place selectively at the remote C−H bond. High selectivity of the trifluoromethylthiolation reaction for the most hydridic C−H bonds was also observed for the more complex fenchyl ester and the adamantanecarboxylate substrate with multiple tertiary C−H bonds, where the trifluoromethylthiolated products were isolated in 71% and 84% yield, respectively.

Substrates with secondary C−H bonds generally reacted only sluggishly. Nevertheless, cyclohexane and cycloheptane were trifluoromethylthiolated in 40% and 70% yield, respectively, with 2 equiv of the substrate (Figure 2C). On the other hand, methylene C−H bonds adjacent to heteroatoms were easily functionalized. For example, ambroxide, a naturally occurring terpenoid responsible for the odor of Ambergris, was selectively trifluoromethylthiolated in high yield.[21]

Heterocycles are prevalent units in a vast majority of marketed drugs. We therefore wanted to test the tolerance of such motifs under our reaction conditions. To our delight, we found that substrates containing thiophene, pyridine, thiazole, and quinoline cores smoothly gave the corresponding trifluoromethylthiolated derivatives with high selectivity in good isolated yields of 72−80% (Figure 2D).

The reaction was not compatible with benzylic C−H trifluoromethylthiolation, and a complex reaction mixture was formed.[22]

To demonstrate the amenability of this mild trifluoromethylthiolation strategy for late-stage synthetic applications, we subjected bioactive molecules to our protocol to prepare their SCF_3 analogues (Figure 3). In all cases, the SCF_3 group was

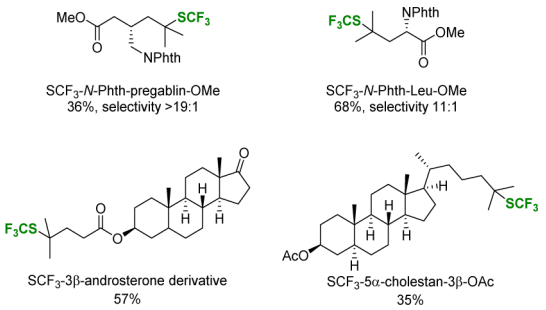

Figure 3. Direct trifluoromethylthiolation of biologically active molecules. Reaction conditions are as shown in Figure 2. Isolated yields are given. See Supporting Information for experimental details. The site selectivities for reaction at two or multiple C−H bonds were determined by ^{19}F NMR analyses of the crude reaction mixtures.

introduced selectively at the most electron-rich hydridic C−H bond, which is generally more susceptible to metabolic degradation. Pregabalin, a drug marketed as Lyrica, is used to treat epilepsy, neuropathic pain, fibromyalgia, and generalized anxiety disorder.[23] Steroid derivatives were trifluoromethylthiolated using our reaction conditions. A derivative of the steroid hormone 3β-androsterone was trifluoromethylthiolated at the methine position of the side chain. Similarly, SCF_3-modified 3α-cholestan-3β-acetate was synthesized with very high selectivity. We further applied this method to modify amino acids, demonstrating its potential for late-stage peptide functionalization. When the protected leucine *N*-Phth-L-Leu-OMe was subjected to the C−S bond-forming reaction conditions, the SCF_3-modified leucine was isolated in 68% yield. At present, further research is ongoing in our group to selectively put the SCF_3 group into long-chain peptides and protein molecules.

Finally, our mechanistic hypothesis was supported by quenching studies in which no significant quenching interactions between the excited state of the photocatalyst and either the substrate or the SCF_3 reagent were observed (see Figure S2). Further, considering that a radical chain is involved in many photochemical processes,[15,24] one can assume that phthalimidyl radical is a potential chain carrier in a chain propagation step by HAT from either benzoic acid or the substrate. The first scenario can be ruled out by taking into account the BDEs (Figure 1B).[5,25] The second possibility cannot unambiguously be ruled out. However, it is less likely to contribute substantially because of the observed high selectivities for tertiary C−H bonds over secondary ones in this reaction (vide supra). The >20:1 selectivity for methine C−H bonds over methylene ones implies that the majority of the hydrogen atoms are abstracted by BzO·[26] rather than Phth·, which is known to be less selective [3°/2° ≈ 4].[18a,27] This can further be supported by the low quantum yield measured by chemical actinometry at 415 nm under the reaction conditions (Φ = 1.76). Moreover, determination of the quenching fraction (Q) revealed that 86% of the photons absorbed by Ir−F participate in productive electron transfer processes.[15] Therefore, considering a radical chain proceeding in this reaction, we calculated the average chain length as Φ/Q = 2.[15] This suggests a very little contribution of the radical chain processes to the overall product formation.

Visible-light-promoted photoredox catalysis has recently emerged as a tool to accomplish various otherwise synthetically challenging transformations. Herein we have reported its first use in the direct catalytic activation of otherwise unactivated C(sp^3)−H bonds followed by their trifluoromethylthiolation. We could envision its potential to accomplish other direct unactivated C(sp^3)−H functionalizations in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09970.

Experimental procedures and additional data (PDF)

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Notes

The authors declare no competing financial interest.

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