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C−H Xanthylation: A Synthetic Platform for Alkane Functionalization

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Supporting Information

ABSTRACT: Intermolecular functionalizations of aliphatic C−H bonds offer unique strategies for the synthesis and late-stage derivatization of complex molecules, but the chemical space accessible remains limited. Herein, we report a transformation significantly expanding the chemotypes accessible via C−H functionalization. The C−H xanthylation proceeds in useful chemical yields with the substrate as the limiting reagent using blue LEDs and an easily prepared *N*-xanthylamide. The late-stage functionalizations of complex molecules occur with high levels of site selectivity, and a variety of common functionality is tolerated in the reaction. This approach capitalizes on the versatility of the xanthate functional group via both polar and radical manifolds to unlock a wide array of C−H transformations previously inaccessible in synthesis.

Unactivated carbon−hydrogen (C−H) bond functionalization is a powerful tool for chemical synthesis, enabling an array of new approaches to the construction and late-stage derivatization of complex molecules.[1] In drug discovery and development, C−H functionalization offers tools to facilitate the preparation of structural analogs of targets with enhanced structure−activity relationships (SAR) or other desired physicochemical properties without *de novo* approaches.[2] Owing to the plethora of different C−H bonds present in most organic molecules, great effort has been devoted to the site-selective and predictable functionalization of C−H bonds in complex targets. Intramolecular, or substrate-directed, C−H functionalizations are widely used in chemical synthesis, as these reactions benefit from exquisite site selectivity and improved kinetics provided by the functionality present in the substrate. However, this approach is inherently limited by the requisite functionality and lacks generality in applications to diverse structures. The development of site-selective, *intermolecular* C−H functionalizations of isolated aliphatic C−H bonds is a significantly more daunting challenge, as these processes lack the advantages of intramolecular reactions.

Important recent studies have sought to address this challenge and have provided a number of practical methods for intermolecular C−H functionalizations using a substrate as the limiting reagent with good efficiency. For example, transformations achieving the oxidation,[3] azidation,[4] and halogenation[5] of isolated aliphatic C−H bonds have appeared with good site selectivities, functional group compatibilities, and notable application to the derivatization of complex molecules and natural products. However, the limited set of molecular functionality accessible via these strategies restricts the chemical space and subsequent utility of C−H functionalizations. Examples of desirable transformations with no general, practical approach include the vinylation, allylation, thiolation, hydroxylation, trifluoromethylthiolation, and deuteration of isolated aliphatic C−H bonds. The development of strategies capable of achieving these goals would greatly enhance the power of intermolecular C−H functionalization in complex synthesis and late-stage functionalization. We reasoned that the sheer number and diversity of these functional groups would render a single synthetic approach to achieve these transformations impractical. Instead, we envisioned an alternative strategy involving the development of a new intermolecular aliphatic C−H functionalization that could enable facile access to a wide array of functional groups via the established chemistry of a single intermediate.

Previous efforts from our group culminated in the development of site-selective C−H halogenations of unactivated aliphatic C−H bonds using *N*-haloamides.[6] These reactions use a bulky, electron-poor amidyl radical for site-selective C−H halogenations with the substrate as the limiting reagent, enhancing their utility in complex synthesis. We hypothesized that the combination of the efficiency and site selectivity of our approach with the transfer of a single, highly versatile functional group would generate a new, diversity-oriented approach to C−H functionalization (Figure 1).

Upon surveying functional groups for transfer to maximize molecular diversity, the xanthate (dithiocarbonate) group appeared ideally suited for this purpose. Zard and others have demonstrated the versatility of alkyl xanthates in radical-mediated synthesis to access an impressive array of valuable

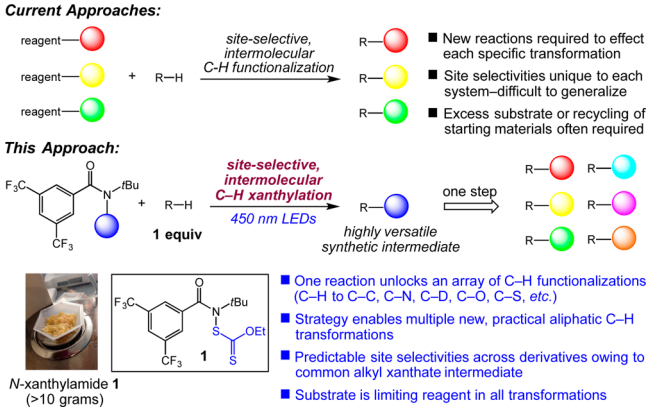

Figure 1. Approaches to site-selective, intermolecular C−H functionalization.

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functionality.[7] The diverse array of aliphatic C−H functionalizations potentially accessible via alkyl xanthates includes many unknown transformations (e.g., C−H to C−S).[8] Therefore, we hypothesized that a site-selective aliphatic C−H xanthylation would significantly increase the power of intermolecular C−H functionalization in synthesis and facilitate new late-stage modifications of complex molecules.[9]

Since the xanthate functionality participates in radical-mediated group transfer processes, we targeted the preparation of *N*-xanthylamide **1** as an initial goal. We anticipated that a successful aliphatic C−H xanthylation using **1** would display the notable site selectivity and chemoselectivity of our prior C−H halogenation, as both processes would involve similar amidyl radical intermediates. The synthesis of **1** via the direct *N*-xanthylation of amides with strong base was unsuccessful,[10] but we were able to develop a new approach that avoids the use of strongly basic conditions and is also amenable to large-scale preparation: the reaction of the parent *N*-chloroamide of **1** with inexpensive potassium ethyl xanthate provided facile access to shelf-stable *N*-xanthylamide **1** on decagram scale.[11]

With key reagent **1** in hand, we commenced our studies of the aliphatic C−H xanthylation with a number of simple hydrocarbons using the substrate as the limiting reagent to ensure reaction practicality (Figure 2).[12] Reactions of **1** with cyclo-

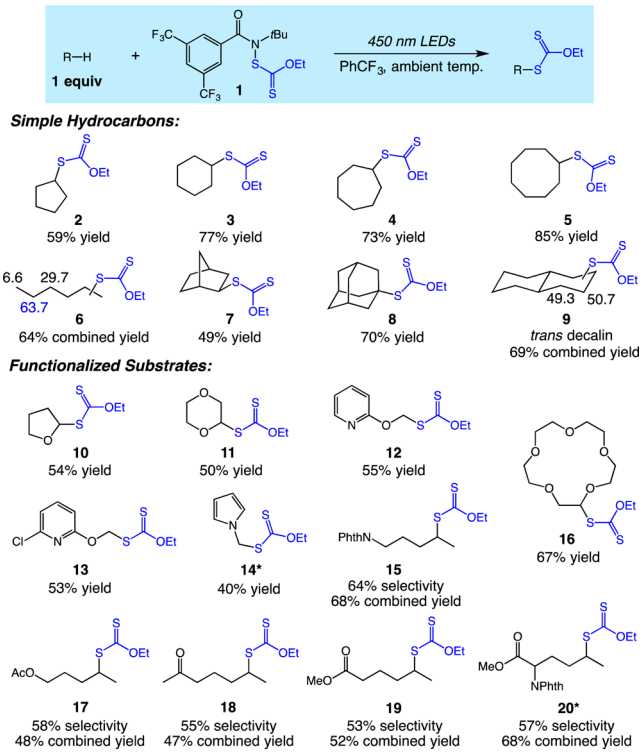

Figure 2. Products of C−H xanthylation. Yields refer to NMR yield with hexamethyldisiloxane (HMDS) as an internal standard or GC yield with dodecane as an internal standard. *Isolated yield.

alkanes in $PhCF_3$ using blue LED irradiation provided alkyl xanthates **2**−**5** in good yields (59−85%). A competition experiment between cyclohexane and d_{12}-cyclohexane indicated a kinetic isotope effect of 6.3, comparable to our C−H halogenations and consistent with irreversible C−H abstraction by an amidyl radical. The C−H xanthylation of *n*-hexane favored the methylene sites with $k_{secondary}/k_{primary}$ (k_s/k_p) ≈ 11 after correcting for the number of hydrogen atoms, with a preference for the 2-position. The xanthylation of norbornane provided **7** as the single *exo* diastereomer in 49% yield. The sterically dictated site selectivity of **1** is clear from the reactions of adamantane and *trans*-decalin: the functionalization of adamantane greatly favored the less hindered 3° C−H sites, providing xanthate **8** as a single product in 70% yield. The reaction of *trans*-decalin proceeded with a high methylene/methine site selectivity (k_s/k_t = >99).

We next surveyed a range of heterocycles and functionalized acyclic substrates to study the site selectivity and functional group compatibility of the C−H xanthylation (Figure 2). Xanthylation adjacent to heteroatoms was efficient across a number of substrates, with hyperconjugation likely assisting in the site selectivity. For example, the xanthylations of tetrahydrofuran and 1,4-dioxane delivered **10** and **11**, respectively, in useful yields. Although reagent **1** possesses similar C−H bonds adjacent to oxygen, no products resulting from such abstraction were observed. The reactions of important nitrogen heterocycles were successful, as demonstrated by the functionalizations of 2-methoxypyridines to afford **12** and **13** in addition to *N*-methyl pyrrole giving **14**. These substrates demonstrate that the system tolerates nitrogen functionality that can pose a challenge to metal-oxo catalysts. The electron-withdrawing *N*-phthalimide functionality of linear substrate **15** dictates selective functionalization of the distal methylene sites, with a δ selectivity of 64% (68% combined yield). In addition, the xanthylation of 15-crown-5 afforded **16** in good yield (67%), providing a new approach to the derivatization of crown ethers. The electronic site selectivity of the C−H xanthylation across a number of acyclic compounds (**17**−**20**) indicates a preference for reaction at the most electron-rich methylene sites, consistent with our previous studies involving amidyl radicals. These C−H xanthylations proceed in good overall yields, with site selectivities comparable (or superior) to those of most metal-catalyzed processes.

We were keenly interested in ascertaining the potential for site-selective C−H xanthylations of complex molecules owing to the range of structures accessible via the xanthate functional group. A number of diverse complex natural products and drug precursors were studied in this context (Figure 3). The C−H xanthylations

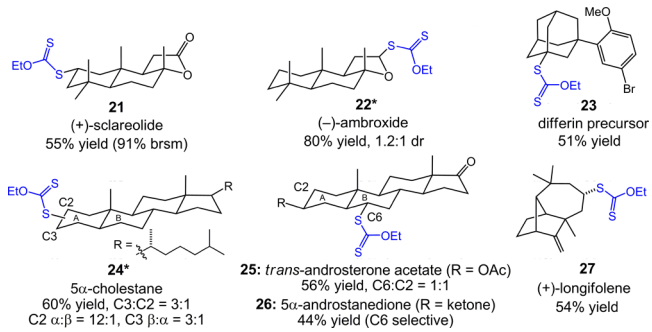

Figure 3. Aliphatic C−H xanthylations of complex molecules. Yields refer to isolated yields. *NMR yield.

of the terpenoids (+)-sclareolide and (−)-ambroxide delivered xanthates **21** and **22** in 55% and 80% yield, respectively.[13] The xanthylation reaction is amenable to scale-up, delivering xanthate **21** in 54% yield on gram scale. In both cases we observed functionalization at a single site, with (+)-sclareolide reacting at the sterically most accessible, electron-rich methylene site and (−)-ambroxide reacting at the position activated by hyper-

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conjugation. Functionalization of a precursor to the topical retinoid differin occurred at the most accessible tertiary C−H site, giving xanthate **23** in 51% yield. Notably, this xanthylation succeeds in the presence of an electron-rich aromatic ring, which would likely pose a major challenge for alternative strategies involving oxidizing intermediates. The reaction of 5α-cholestane occurred on the steroidal A-ring, with a 3:1 site selectivity favoring the C3 position to give product **24**; this selectivity is remarkable since the substrate contains seven tertiary C−H bonds and 13 methylene sites for functionalization with no inherent substrate electronic bias. Steroid *trans*-androsterone acetate underwent xanthylation to afford C6 and C2 functionalization products **25** in a 1:1 ratio as single diastereomers (56% combined yield). We next questioned whether electronic deactivation of the steroidal A-ring would enable site-selective functionalization of the B-ring. Steroid 5α-androstanedione, with ketone deactivation of the A-ring, exhibited perfect diastereoselectivity and site selectivity on the B-ring, delivering xanthate **26** as a single product in 44% yield. As a comparison, the C−H oxidation of this substrate with a number of Fe-catalysts proceeded with poor site selectivity involving several methylene and methine positions,[3e] highlighting the unique capabilities of our system in the steric and electronic differentiation of the C−H sites.[14] As a final challenge, we examined the C−H xanthylation of the terpenoid (+)−longifolene, a classic target for studies in organic synthesis. This substrate poses a significant chemoselectivity challenge for alternative C−H functionalizations involving oxidizing intermediates, as the alkene is known to undergo facile oxidation and skeletal rearrangement.[15] The xanthylation of (+)-longifolene with reagent **1** under solvent-free conditions provides xanthate **27** as a single diastereomer with excellent site selectivity. The regioselectivity of the reaction can be rationalized by selective C−H abstraction of the less hindered ring system away from the quaternary centers in the substrate, and the mild conditions of the C−H xanthylation minimize any undesired alkene functionalization.

We view the aliphatic C−H xanthylation herein as a platform technology serving to unlock an array of important C−H transformations, including many with no synthetic precedent. Our approach exploits the impressive versatility of alkyl xanthates in a broad range of radical-mediated as well as polar bond-forming reactions. An initial demonstration of this approach is outlined in Figure 4. For example, the product of C−H vinylation, **28**, is readily accessed from differin precursor xanthate **23** via radical coupling with ethyl styryl sulfone.[16] Lewis acid mediated addition of bistrimethylsilyl thymine to (−)-ambroxide xanthate **22** delivers *N*-alkyl thymine derivative **29** in high yield (87%), highlighting the utility of the xanthate group in polar reactions.[17]

The selective deuteration of aliphatic C−H bonds represents another attractive yet undeveloped transformation. Such a process would expedite the preparation of isotopically labeled compounds for mechanistic and metabolic studies and offer an attractive route to deuterated drugs with enhanced pharmacokinetic properties.[18] The reaction of amino acid derivative xanthate **20** with CD_3OD using Et_3B/O_2 initiation provides deuterated product **30** in good yield (71%, 85% deuterium incorporation).[19] Thus, the xanthylation−deuteration sequence constitutes a formal, site-selective monodeuteration of aliphatic C−H bonds, which, to our knowledge, does not exist.

Oxidations of unactivated aliphatic C−H bonds are likely the most studied intermolecular C−H transformation, but over-

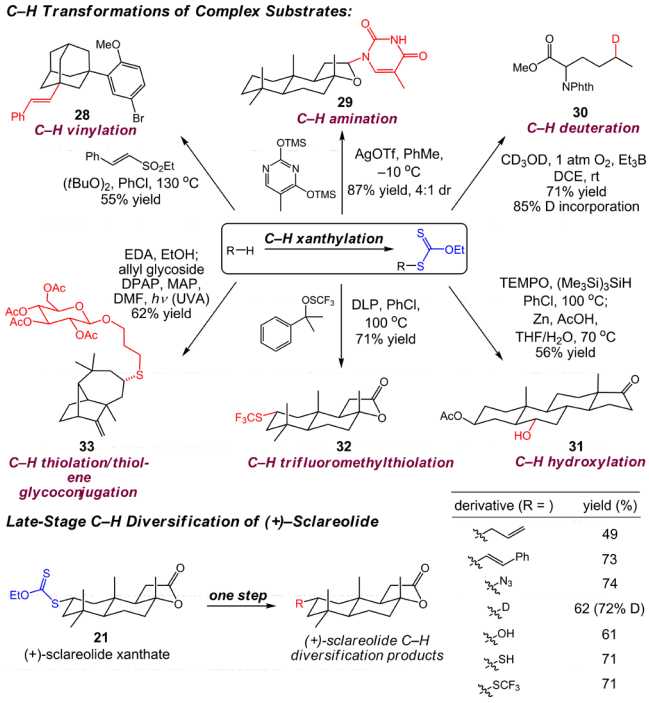

Figure 4. Aliphatic C−H transformations of complex substrates. Yields refer to isolated yields.

oxidation of alcohols to ketones is a major concern.[20] A functional group interconversion from an alkyl xanthate could enable control of the product oxidation state, and the mild conditions of our approach would allow C−H oxidation of substrates containing oxidation-sensitive functionality. We have developed a xanthate to hydroxyl group interconversion, constituting a formal C−H hydroxylation using xanthylamides. The reaction of C6-functionalized steroidal xanthate **25** with persistent radical TEMPO and tris(trimethylsilyl)silane followed by mild reduction of the intermediate alkoxyamine delivered alcohol **31** in good yield (56%).[21] Alternatively, oxidation of the alkoxyamine using *m*CPBA selectively yields a ketone product (59% yield).[22] This approach allows complete reagent control of the product oxidation state, offering an attractive solution to major challenges in aliphatic C−H oxidation.

The trifluoromethylthiol group has become invaluable in the preparation of bioactive compounds owing to its high electronegativity and ability to modulate the lipophilicity of drug molecules.[23] Recent reports of aliphatic C−H trifluoromethylthiolation using $AgSCF_3$ and persulfate oxidants have emerged, but are generally selective for tertiary C−H bonds and often require excess substrate to obtain synthetically useful yields.[24] We have developed simple conditions to introduce the trifluoromethylthiol group from alkyl xanthates using an easily accessible reagent developed by Shen, as shown in the preparation of **32**.[25] This provides a general approach to formal aliphatic C−H trifluoromethylthiolation using the substrate as the limiting reagent, appropriate for late-stage functionalizations of complex substrates.

The thiol−ene addition is useful for bioconjugation, offering a bioorthogonal alternative to azide−alkyne cycloadditions, with additional applications in polymer synthesis and materials science.[26] In this light, a site-selective, aliphatic C−H thiolation would enable a formal thiol−ene from alkane starting materials. The C−H xanthylation is ideal for such a transformation: simple workup with an amine base provides thiols in excellent yield. As a

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demonstration of this approach, we have studied the thiol−ene coupling of (+)-longifolene xanthate **27** with a glucose-derived allyl glycoside. Following quantitative conversion of **27** to its thiol derivative, photochemical thiol−ene delivered glycoconjugated (+)-longifolene adduct **33** in 62% yield. Considering the mild conditions and functional group compatibility of the C−H xanthylation and the broad utility of the thiol−ene process, we expect this tactic will offer major opportunities in the conjugation of complex molecules. We would also note that while Figure 4 offers a number of attractive avenues for molecular derivatization via C−H xanthylation, this is certainly not comprehensive. Alkylation, alkynylation,[16] and acylation reactions,[27] among others, are also possible using alkyl xanthates.

Applying different transformations to a single xanthate substrate provides facile access to a wide range of derivatives via a C−H diversification approach. As an example, (+)−sclareolide xanthate **21** is converted to seven different derivatives in a single step following the initial C−H xanthylation (Figure 4). This highlights an additional unique feature of our approach: not only does the xanthylation unlock new aliphatic C−H transformations, it also facilitates the synthesis of diverse analogs via a simple switch of reagent in the product elaboration rather than through the application of a new C−H functionalization.

The versatility of the current aliphatic C−H xanthylation, in addition to our previous efforts in C−H halogenation, clearly highlights the unique capabilities of functionalized amides in enabling a broad range of practical aliphatic C−H transformations. These studies also demonstrate the potential for enhanced site selectivity and functional group compatibility with respect to other aliphatic C−H functionalizations. We anticipate that these characteristics will lead to powerful applications in molecular derivatization for the synthesis and study of functionalized molecules in a number of contexts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09414.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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