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Direct Decarboxylative Functionalization of Carboxylic Acids via O—H Hydrogen Atom Transfer

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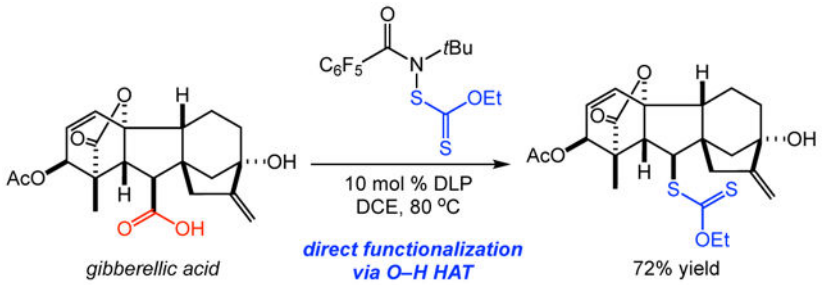
Abstract

Decarboxylative functionalization via hydrogen-atom transfer offers an attractive alternative to standard redox approaches to this important class of transformations. Herein, we report a direct decarboxylative functionalization of aliphatic carboxylic acids using *N*-xanthylamides. The unique reactivity of amidyl radicals in hydrogen-atom transfer enables decarboxylative xanthylation under redox-neutral conditions. This platform provides expedient access to a range of derivatives through subsequent elaboration of the xanthate group.

Graphical Abstract



Decarboxylative functionalizations constitute a diverse class of synthetic transformations that leverage the wide availability of carboxylic acids as substrates to deliver a variety of useful products.[1] For example, the classic Barton decarboxylation via thiohydroxamate esters is a powerful approach to the modification of carboxylic acids.[2] Oxidative processes are also featured in many reactions, from the Kolbe electrolysis to an array of Ag(II)-mediated transformations. Recently, photoredox catalysis has significantly expanded the breadth of decarboxylative transformations. These typically involve either oxidations of carboxylate salts,[3] or reductions of activated carboxylate derivatives (Figure 1).[4] *N*-hydroxyphthalimide esters have found much use in this reductive platform.[5]

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Supporting Information. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

A complementary approach to decarboxylative functionalization would involve O—H hydrogen-atom transfer (HAT) of a carboxylic acid to generate a carboxyl radical under neutral conditions. Such a process presents a significant challenge, however: the O—H bond dissociation energy is approximately 112 kcal/mol, providing a large barrier to reaction.[6] Unsurprisingly, a ground state O—H HAT of a carboxylic acid is unknown and would require a highly reactive species to occur.[7]

We have demonstrated previously that *N*-functionalized amides can serve as precursors of amidyl radicals for achieving a range of intermolecular, site-selective aliphatic C—H bond functionalizations.[8] The key thermodynamic driving force for these reactions is the formation of a strong amide N—H bond (BDE ~ 111 kcal/mol) from an unactivated aliphatic C—H bond (BDE = 96–101 kcal/mol).[9] Considering that the range of BDEs for carboxylic acid O—H bonds (BDE ~ 112 kcal/mol) is similar to that of an amide N—H bond, we hypothesized that amidyl radicals could engage carboxylic acids directly via O—H HAT to facilitate decarboxylative transformations. Herein, we report a direct, decarboxylative xanthylation of carboxylic acids as a representative reaction of this type, demonstrating the unique ability of amidyl radicals to perform O—H HAT.[10]

Our studies commenced with hexanoic acid as substrate using 440 nm blue LED photoinitiation and our previously reported *N*-xanthylamide **1**.[8c] We found that under these conditions, alkyl xanthate **3** was formed in moderate yield (59%, Table 1, entry 1). The use of dilauroyl peroxide (DLP) as initiator provided **3** with similar efficiency (entry 2). Switching to the use of a pentafluorophenyl-substituted *N*-xanthylamide (**2**) significantly increased the reaction yield (entries 3 and 4).

Chemical initiation of the xanthylation using reagent **2** was also successful, albeit with slightly decreased efficiency (entries 5 and 6). The reaction of a carboxylate salt using Cs_2CO_3 as base (entry 7) or performing a reaction in the absence of initiator (entry 8) led to no conversion of the carboxylic acid. We continued our studies using reagent **2** owing to its superior performance and ease of large-scale reagent preparation.

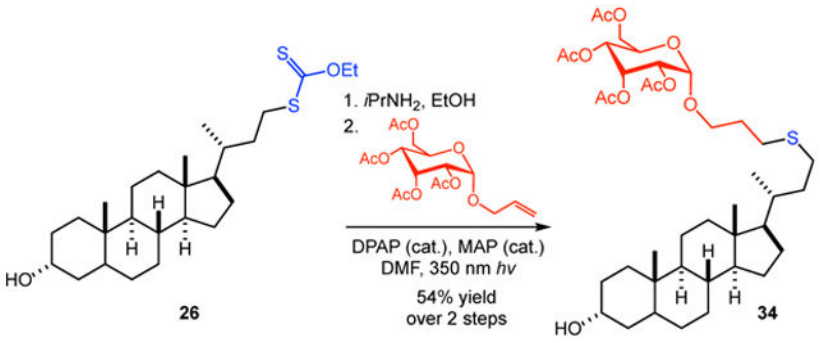
Figure 2 details our studies demonstrating the considerable scope of the decarboxylative xanthylation. Both chemical (10 mol % DLP) and photochemical (440 nm LEDs) modes of initiation were successful with virtually all of the substrates shown. The highest reaction yield of the two methods is provided in Figure 2; all yields and the corresponding conditions are provided in the Supporting Information. Primary carboxylic acids were converted to alkyl xanthates **3-8** in good yields. Alkyl bromides are tolerated (**4**), which is notable considering that substitution of alkyl halides is the most common method for the preparation of alkyl xanthates and thiols.[11] The presence of aryl, ester, ketone, or alkene functionalities was also permitted (**5-8**). The functionalization of an *N*-Boc indole-substituted primary carboxylic acid delivered xanthate **9** in 62% yield.

Secondary carboxylic acids were also excellent substrates (Figure 2). The xanthylation of endo-norbornane-2-carboxylic acid provided solely the exo diastereomer of xanthate **12** in 92% yield. The reaction of 1,4-cyclohexanedicarboxylic acid with 2 equiv of **2** provided dixanthate **13** in excellent yield (94%) as a mixture of diastereomers. Decarboxylative

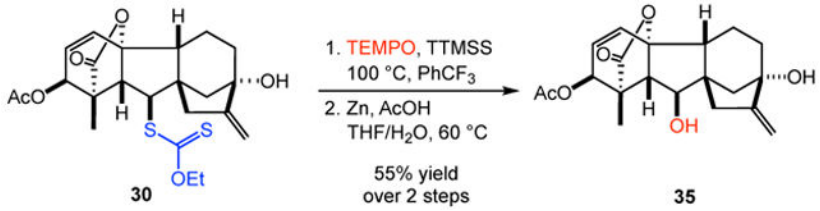
xanthylation of 3-oxocyclobutanecarboxylic acid delivered bifunctional cyclobutane **14** (85% yield), which is an attractive derivative for medicinal chemistry applications.[12] Transformations of 4-substituted tetrahydropyran and piperidine carboxylic acids were also efficient, providing **15** and **16** in 73 and 69% yield, respectively. Tertiary carboxylic acids were likewise excellent substrates, providing xanthates **17-20** in nearly quantitative yield. Ketopinic acid yielded xanthate **21** in 67% yield, which is notable considering that decarboxylation of this substrate is known to be challenging.[13]

We next applied the decarboxylative xanthylation as a tool for late-stage modification of a range of natural products and drug derivatives (Figure 2). Xanthylation of clotting agent tranexamic acid provided **22** in 90% yield as a mixture of diastereomers. Reactions of the nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen and indomethacin delivered xanthates **23** and **24**, respectively. We hypothesize that the decreased efficiency of these reactions is due to the increased stability of the intermediate conjugated radicals, which may lead to reversible xanthate transfer.[14] Interestingly, ibuprofen was the sole substrate which we examined that gave a higher yield using xanthylamide **1**. A number of complex terpenoids and steroids were also good substrates for the xanthylation (**25-29**), indicating compatibility with unprotected alcohol, ketone, and enone functionalities.[15] The plant hormone gibberellic acid efficiently provided xanthate **30** in 72% yield as a single diastereomer. In addition, protected amino acids provided decarboxylative functionalization products **31** and **32** in good yields. Notably, glutamic acid provides opportunities for both unnatural amino acid synthesis and late-stage functionalization of peptides via the carboxylic acid side chain. As a representative example, we performed the decarboxylative xanthylation on a tripeptide to deliver an analogue of the antioxidant glutathione xanthate **33** in moderate yield, albeit with good recovery of the remaining starting material. In light of the importance of cysteine-containing peptides in maintaining regulatory and metabolic functions in plants, animals, fungi and bacteria, we view the decarboxylative xanthylation as an attractive method for peptide modification in future biological studies.[16]

The xanthate functional group is readily elaborated to a wide range of derivatives.[8c,17] For example, aminolysis of lithocholic acid-derived xanthate **26** with isopropylamine provided the corresponding thiol in excellent yield.[18] Subsequent photochemical thiol-ene coupling with a glucose-derived allyl glycoside produced the conjugation product **34** in 54% yield over two steps. In addition, hydroxylation of gibberellic acid-derived xanthate **30** proceeded in 55% yield using conditions we previously developed for accessing hydroxyl or ketone functionality from alkyl xanthates via an alkoxyamine intermediate.[8c] Alternative approaches to accessing the products of a formal decarboxylative oxidation include the Barton decarboxylation via thiohydroxamate esters and decarboxylative borylation using *N*-hydroxyphthalimide esters.[19,20]



(1)



(2)

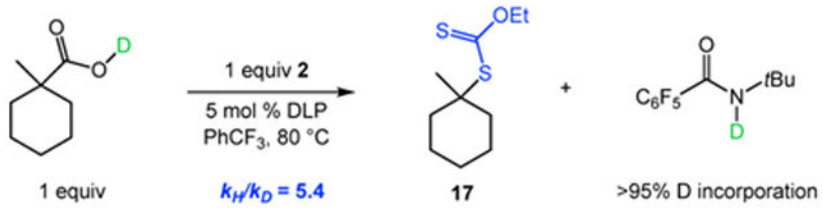
We envision the decarboxylative xanthylation herein to significantly expand the synthetic capabilities in decarboxylative functionalization via the versatile alkyl xanthate products.

In order to assess the unique reactivity of the amidyl radical in the O—H HAT process, we analyzed the reactivity of related xanthylsulfonamide **36** (Figure 3). The parent sulfonamide has a calculated N—H bond strength of 104 kcal/mol,[9] which is somewhat lower than that of alkyl carboxylic acid O—H bonds. Indeed, in an attempted xanthylation of hexanoic acid using **36**, no decarboxylative products were observed–a mixture of C—H functionalization products was formed instead.[21] Furthermore, in an intermolecular competition between hexanoic acid and cyclohexane, xanthylsulfonamide **36** provided only cyclohexyl xanthate **10** (Figure 3A). In contrast, the same experiments using xanthylamides were selective for decarboxylative xanthylation with a selectivity ($k_{O—H}/k_{C—H}$) of 10 and 24 for reagents **1** and **2**, respectively, correcting for the number of hydrogen atoms. This marked difference in reactivity profile between the amide and sulfonamide reagents offers opportunities for multi-site xanthylations of carboxylic acids. As an example, adamantane carboxylic acid was transformed to either the decarboxylative xanthylation product **18** or the C—H xanthylation product **37** simply by selecting the appropriate reagent (Figure 3B).

While our results are consistent with a reaction mechanism involving direct O—H HAT, other potential mechanisms were considered, such as oxidation of a carboxylate salt by the xanthylamide reagent. No reaction was observed in the presence of a non-coordinating base (Table 1, entry 7) or with a cesium carboxylate salt as substrate, which is inconsistent with an oxidative pathway. Furthermore, no reaction was observed upon heating hexanoic acid

and xanthylamide **2** in the dark with no initiator. As further evidence for the intermediacy of carbon-centered radicals, an enantioenriched carboxylic acid provided the corresponding xanthate as a racemate (see Supporting Information for details).

With respect to the O—H HAT step, a primary kinetic isotope effect (KIE) of 5.4 was determined from a comparison of the initial rates of decarboxylative xanthylation between O—H and O—D forms of 1-methyl-1-cyclohexanecarboxylic acid, consistent with an irreversible O—H HAT (eq 3). The present study clearly indicates the possibility for HAT of a stronger O—H bond in the presence of weaker C—H bonds, such as activated benzylic, allylic, and α-heteroatom positions. We hypothesize that this chemoselectivity stems from the kinetic facility of HAT between heteroatoms.[22]



(3)

We additionally undertook a computational analysis of a model O—H HAT process involving the relevant nitrogen-centered radicals to support the proposed pathway. As depicted in Figure 4A, we evaluated the O—H HAT of *n*-propanoic acid by the pentafluorophenyl-substituted amidyl radical **2'** (from reagent **2**) and the 3,5-bis(trifluoromethyl)phenyl-substituted sulfonamidyl radical **36'** (from reagent **36**). We optimized the transition state structures **38** (see Figure 4B) and **39**, and tracked the evolution of the systems along the corresponding intrinsic reaction coordinates (IRC; see Figures S7 and S8). We also determined the associated Gibbs free energy barriers ($\Delta G^{\ddagger}$) and changes (ΔG).[23]

Our calculations suggested that the O—H HAT involving **2'** is slightly exergonic (ΔG = −1.68 kcal•mol^{-1}), while that of **36'** is endergonic (ΔG = +5.90 kcal•mol^{-1}). Similarly, the reaction of **2'** proceeds with a lower energy barrier ($\Delta G^{\ddagger}$ = +20.04 kcal•mol^{-1}) than that promoted by **36'** ($\Delta G^{\ddagger}$ = +25.39 kcal•mol^{-1}), with a $\Delta\Delta G^{\ddagger}$ value of 5.35 kcal•mol^{-1}. Overall, these computational data support a facile O—H HAT by amidyl radical **2'**, with a somewhat larger barrier for the reaction of **36'**. We also speculate that hydrogen bonding to the carboxylic acid may play a role in facilitating the O—H HAT step. Investigations targeting these mechanistic details are underway.[24]

In conclusion, we have developed a direct decarboxylative xanthylation of aliphatic carboxylic acids using *N*-xanthylamides. This transformation exhibits a broad substrate scope, excellent functional group tolerance, and serves as a general platform for decarboxylative functionalization via the synthetic versatility of alkyl xanthates. Mechanistic data support a pathway involving direct O—H HAT, which complements standard redox-

based approaches to decarboxylative chemistry. We anticipate that this unique mode of direct hydrogen-atom transfer will prove valuable in a variety of synthetic contexts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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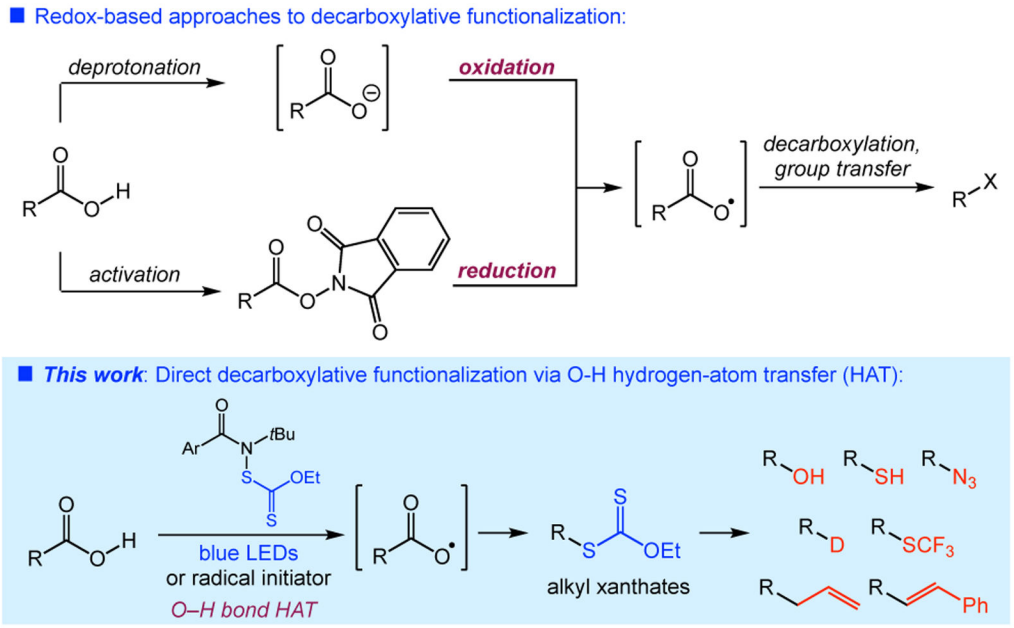


Figure 1.
Decarboxylative functionalizations of carboxylic acids.

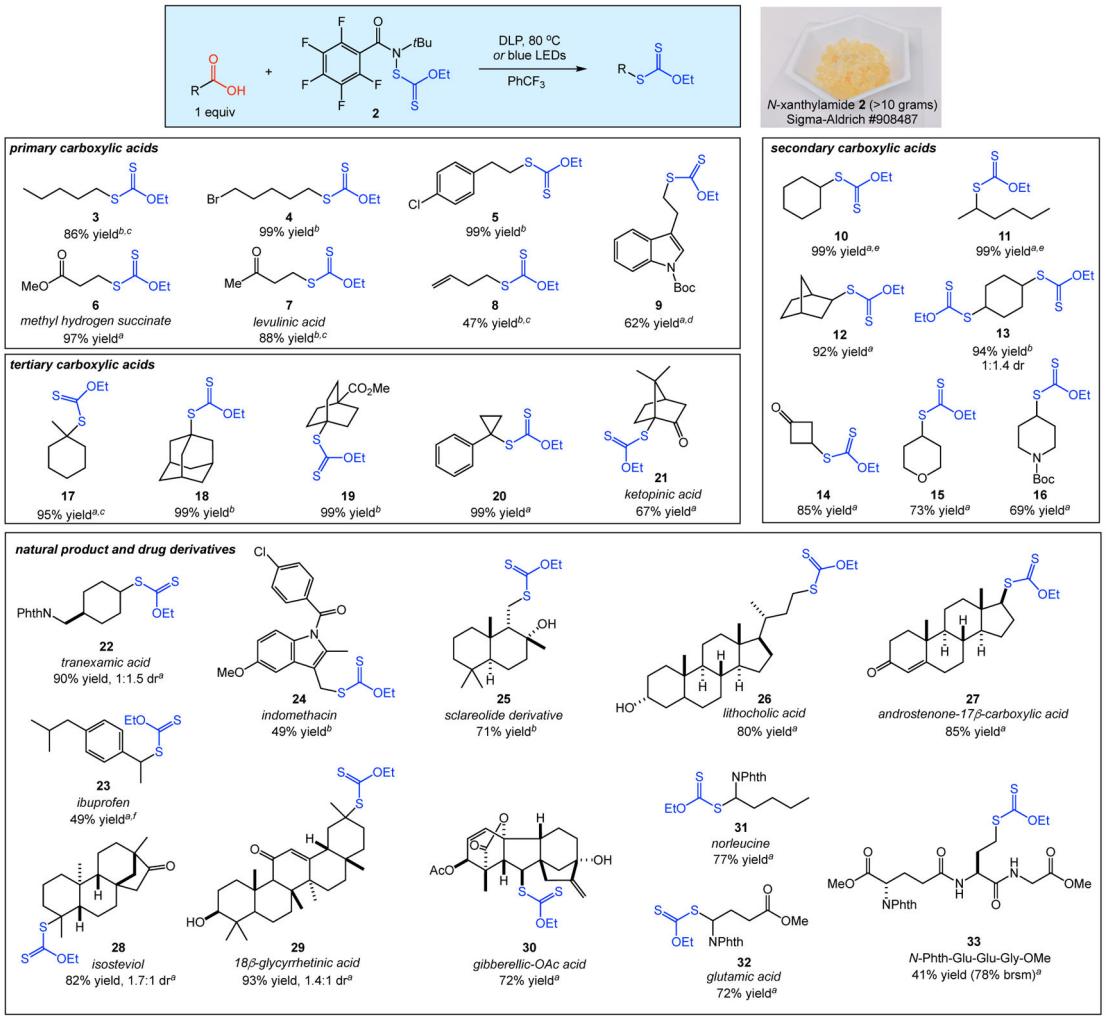


Figure 2.

Decarboxylative xanthylation of diverse substrates. [a]10 mol % DLP used as initiator. [b]440 nm LEDs used as initiator. [c]Yield refers to NMR yield with hexamethyldisiloxane as an internal standard. [d]50 mol % DLP used as initiator. [e]GC yield using dodecane as an internal standard. [f]Reaction performed using reagent **1**.

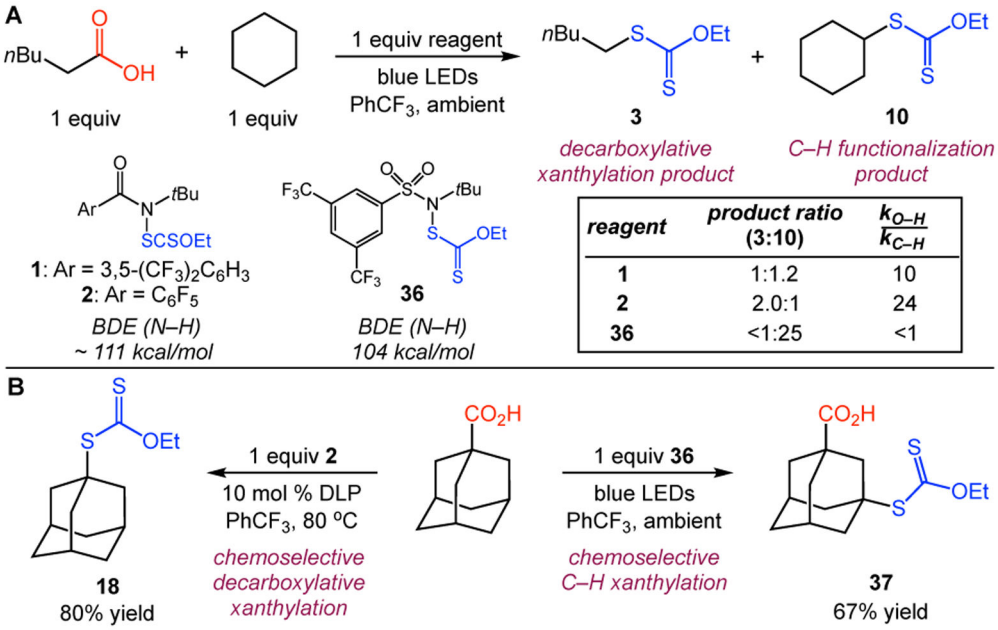


Figure 3.
Chemoselective O—H versus C—H HAT studies.

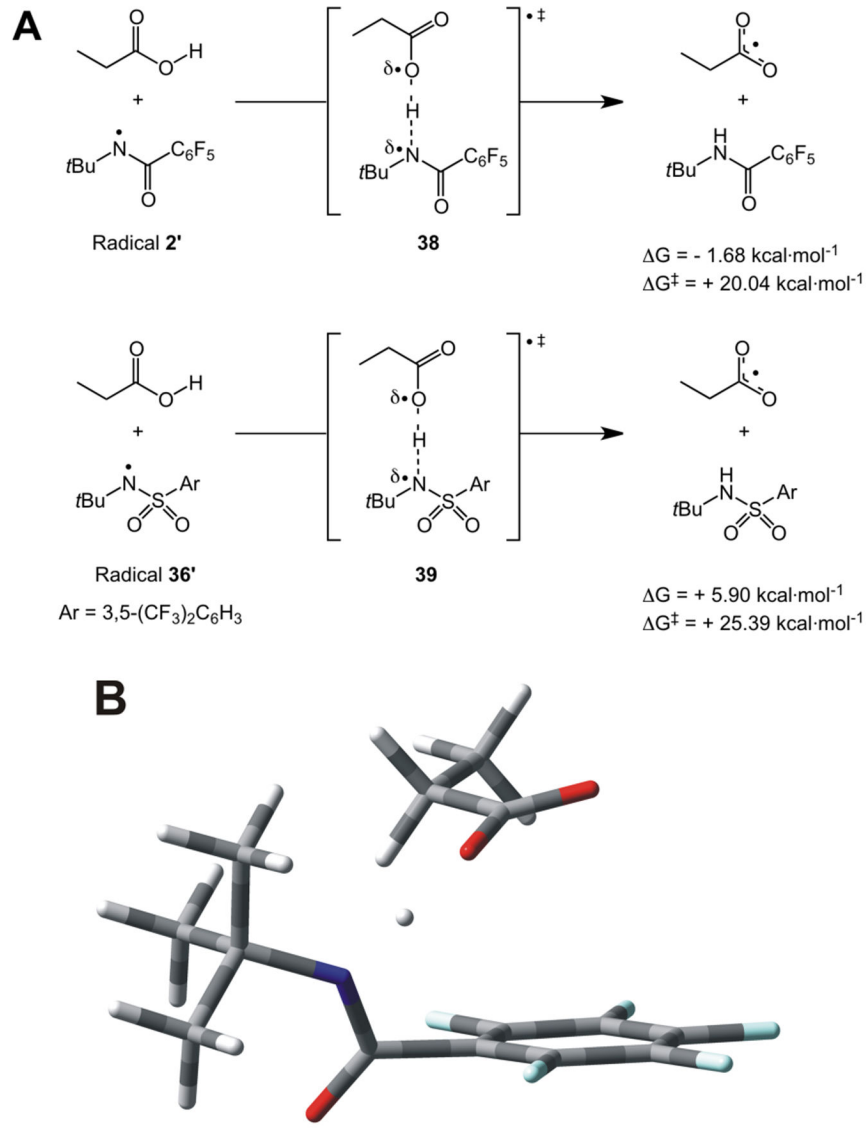
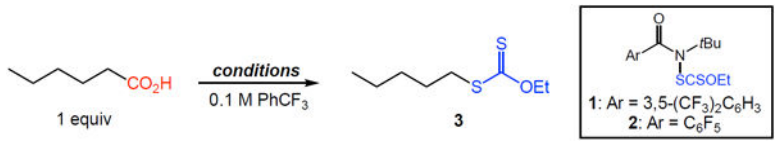


Figure 4.

A) O—H HAT processes modeled by computational means; the reported ΔG and $\Delta G^{‡}$ values were obtained at the SMD(CH_2Cl_2)-UωB97XD/def2TZVP//UωB97XD/def2TZVP level of theory (see SI for further details). B) Optimized structure of transition state **38** at the UωB97XD/def2TZVP level of theory (gas phase optimization).

Table 1.

Decarboxylative xanthylation of hexanoic acid.



entry	xanthylamide reagent	initiation	% yield[a]
1	**1** (1 equiv)	440 nm LED	59
2	**1** (1 equiv)	10 mol % DLP	49
3	**2** (1 equiv)	440 nm LED	81
4	**2** (1.2 equiv)	440 nm LED	86
5	**2** (1 equiv)	10 mol % DLP	55
6	**2** (2 equiv)	10 mol % DLP	70
7[b]	**2** (1 equiv)	10 mol % DLP	<2
8	**2** (1 equiv)	-	<2

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixtures using hexamethyldisiloxane as an internal standard.

[b] Reaction was performed in the presence of 1 equiv Cs_2CO_3.