Communication

Israel Journal of Chemistry

DOI: 10.1002/ijch.201900130

Decarboxylative Oxygenation via Photoredox Catalysis

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Dedicated to 2019 Wolf Prize Awardees Professor Stephen L. Buchwald and Professor John F. Hartwig.

Abstract: The direct conversion of aliphatic carboxylic acids to their dehomologated carbonyl analogues has been accomplished through photocatalytic decarboxylative oxygenation. This transformation is applicable to an array of carboxylic acid motifs, producing ketones, aldehydes, and amides in excellent yields. Preliminary results demonstrate that this methodology is further amenable to aldehyde substrates via *in situ* oxidation to the corresponding acid and subsequent decarboxylative oxygenation. We have exploited this strategy for the sequential oxidative dehomologation of linear aliphatic chains.

Keywords: photoredox catalysis · oxygenation · carbonyl synthesis · decarboxylation

The ubiquitous nature of carboxylic acids in biomass sources and synthetic products makes them highly attractive functional handles in organic synthesis, and their activation to organic transformations through decarboxylation has been a long-standing area of research in organic synthesis.[1] Recently, our lab and others have developed a suite of value-adding photoredox-catalyzed decarboxylative protocols, including Michael addition, fluorination, vinylation, and nickel-mediated cross-couplings.[2] To date, the primary focus of decarboxylative methodologies has been on the formation of carbon-carbon bonds; in contrast, the use of photoredox-mediated decarboxylation for the formation of carbon-oxygen bonds has not been extensively explored, despite the ubiquity of structures containing a carbonyl moiety within the field of organic chemistry. The synthetic versatility of carbonyl-based functionalities allows for a wide range of direct and proximal transformations including Wittig olefinations, Grignard additions, and reductive aminations directly at the carbonyl group, as well as arylations and alkylations at the α- and β-positions (Scheme 1).[3] In addition to their prevalence as intermediates for bond construction, these moieties are also a common functional motif in natural products, pharmaceuticals, and agrochemicals. Thus, the development of novel synthetic strategies towards the preparation of carbonyl-containing compounds is an area of great interest to organic chemists.

Among the stoichiometric oxidants used for oxidative transformations, molecular oxygen is generally recognized as ideal due to its abundance, non-toxicity, and benign byproducts.[4] However, direct reactions between closed-shell, ground-state organic molecules and triplet oxygen are not kinetically facile; therefore either oxygen or the substrate must be activated for a reaction to proceed. On the other hand, the conversion of radical intermediates into oxidized functionality such as alcohols or ketones is known to occur via combination with molecular oxygen.[5] Existing methods for incorporating molecular oxygen into organic molecules frequently rely on the generation of open-shell species from olefins or C–H bonds, with control of the regioselectivity of radical formation posing a considerable challenge.[6]

Given the ability of photocatalytic decarboxylation to generate radicals under mild conditions in a regiospecific fashion, we envisioned that visible light photoredox catalysis could mediate the formation of dehomologated carbonyl compounds from inexpensive building blocks through an oxygen-trapping mechanism. Seminal studies from the Barton group have demonstrated that decarboxylative oxygenation is feasible, with pre-functionalized carboxylic acid derivatives delivering alcohol products upon reduction of the intermediate peroxide.[7,8] In addition, Song *et al.* have shown that secondary benzylic alcohols can be generated via radical decarboxylative oxygenation, followed by reductive work up.[9] Despite these advances, a general method for decarboxylative oxygenation, which is selective for the carbonyl product, has not yet been described. Herein, we present a broadly applicable decarboxylative oxygenation protocol, enabling the synthesis of ketones, aldehydes, and amides directly from a diverse range of aliphatic carboxylic acids.

Design Plan. The proposed catalytic cycle for this decarboxylative oxygenation is shown in Scheme 2. This cycle is initiated by visible light excitation of the iridium(III) photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**1**) to its long-lived triplet excited state (**2**). Single-electron reduction of molecular oxygen by **2** ($E_{1/2}^{red}[Ir^{IV/III*}] = -0.89$ V vs. the saturated calomel electrode (SCE) in MeCN) gives superoxide anion and highly oxidizing Ir(IV) complex **3** ($E_{1/2}^{red}[Ir^{IV/III}] = +$

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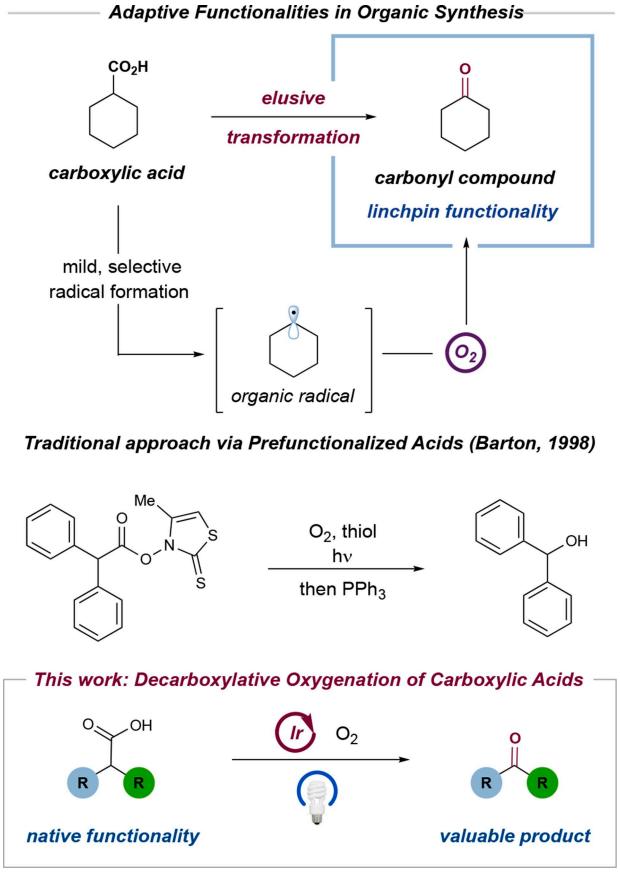
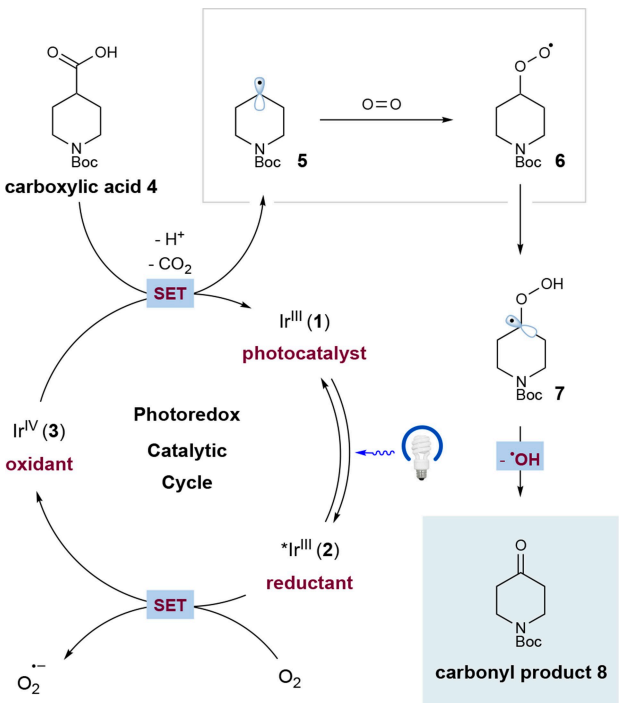
Supporting information for this article is available on the WWW under https://doi.org/10.1002/ijch.201900130

Israel Journal of Chemistry



Scheme 1. Photocatalytic Decarboxylative Oxygenation.

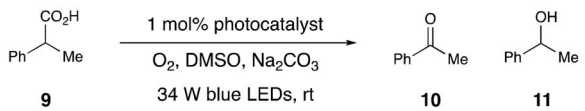


Scheme 2. Proposed Mechanism of Oxygenation Reaction.

1.69 V vs. SCE in MeCN). Complex **3** subsequently oxidizes the carboxylate anion (formed *in situ* under basic conditions from **4**) to a carboxyl radical ($E_{pa}[RCO_2^-/RCO_2^\bullet] = +1.16$ V vs. SCE in MeCN for cesium hexanoate),[1b] regenerating the ground state Ir(III) catalyst (**1**). The carboxyl radical undergoes rapid decarboxylation to give open-shell alkyl species **5**. This carbon-centered radical traps oxygen to give an alkyl peroxyl radical **6**,[10] which then collapses to give the desired carbonyl product **8**.[11] The most likely pathway for this collapse involves an intermediate α-hydroperoxyl radical (i.e., **7**), which is known to form carbonyl groups via extrusion of hydroxyl radical.[12]

We conducted initial studies with 2-phenylpropanoic acid (**9**) as the model substrate, reasoning that the stabilized benzylic radical should readily trap oxygen. We were pleased to find that under air (in DME with sodium carbonate as base), acetophenone (**10**) and 1-phenylethanol (**11**) were obtained in 18% and 17% yield, respectively, upon irradiation with visible light (Table 1, entry 1). Upon evaluation of reaction parameters, DMSO was observed to give a high degree of selectivity for the carbonyl product when used as the reaction solvent. This solvent potentially promotes ketone formation by known quenching of the hydroxyl radical species formed by the collapse of intermediate **7**, forming sulfinic acid and methyl radical via a characteristic C–S bond cleavage.[13] As expected an atmosphere of oxygen delivered a higher yield (entries 2 and 3). Intriguingly, an evaluation of multiple photocatalysts found that the significantly less oxidizing photocatalyst [Ir(F(Me)ppy)$_2$(bpy)]PF$_6$ (**12**) ($E_{1/2}^{red}$ [$Ir^{III*/II}$] = +0.82 V vs. SCE,

Table 1. Initial Optimization of Oxygenation Reaction.



9 **10** **11**

Entry	O_2 Source	Photocatalyst	Yield **10**[a]	Yield **11**[a]
1[b]	air	[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$	18%	17%
2	air	[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$	42%	0%
3	O_2	[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$	67%	0%
4	O_2	[Ir(F(Me)ppy)$_2$(bpy)]PF$_6$	87%	0%
5[c]	O_2	[Ir(F(Me)ppy)$_2$(bpy)]PF$_6$	90%	0%
6	none[d]	[Ir(F(Me)ppy)$_2$(bpy)]PF$_6$	0%	0%
7	O_2	none	0%	0%
8[e]	O_2	[Ir(F(Me)ppy)$_2$(bpy)]PF$_6$	0%	0%

[a] Yields determined via ^{1}H NMR vs. mesitylene as an internal standard, see Supporting Information for experimental details. [b] DME as solvent. [c] 5 mol% ethyl viologen diperchlorate as additive, reaction time 3 hours as opposed to 6 hours without additive. [d] Reaction performed under an atmosphere of nitrogen. [e] Reaction performed in the absence of visible light.

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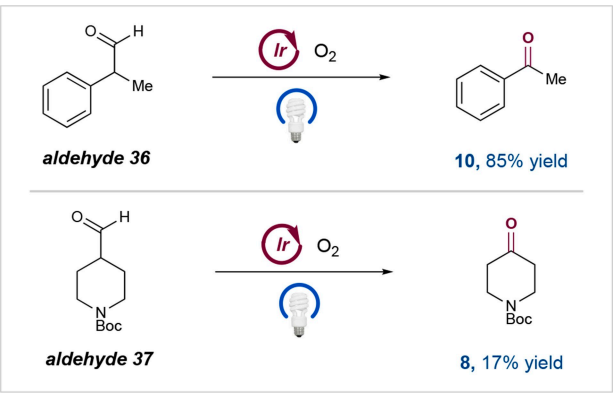
$E_{1/2}^{red}$ [$Ir^{IV/III}$] = +1.39 V vs. SCE in MeCN) was the most effective catalyst for this reaction (entry 4, 87% yield). This phenomenon can potentially be attributed to more efficient singlet oxygen sensitization by [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6.[14] This process is detrimental to our reaction as the excited *Ir(III) state of the catalyst is quenched without net electron transfer, regenerating the Ir(III) ground state. To facilitate generation of the more oxidizing Ir(IV) state, we evaluated a range of oxidizing co-catalysts, and were pleased to find that addition of 5 mol% ethyl viologen diperchlorate (**13**) doubled the rate of the reaction (see Supporting Information). Viologen catalysts are known to act as electron shuttles in photochemical reactions,[15] and in addition their reduced forms can readily reduce oxygen to the superoxide anion.[16] We hypothesize that **13** can thus act as an electron shuttle between the photocatalyst and molecular oxygen, compensating for the low solubility of oxygen in our reaction solvent.[10b] These combined changes to the reaction conditions led to a 90% yield of acetophenone, with no 1-phenylethanol observed, offering complete selectivity for ketone **10** over the alcohol product (entry 5, 90% yield). Finally, control experiments demonstrated that photocatalyst, visible light, and an atmosphere of oxygen were all necessary for the reaction (entries 6–8).

With the optimized conditions in hand, we investigated the scope of the decarboxylative oxygenation (Table 2). A range of secondary benzylic carboxylic acids were converted to their ketone analogues in high efficiency (**10**, **14**, **15** and **16**, 75–86% yield). The reaction can also generate fused bicyclic fused bicyclic ketones, including tetrahydronaphthyl and indanyl scaffolds (**17** and **18**, both 77% yield). Notably, the drug molecules flurbiprofen, ketoprofen, and naproxen were converted to the corresponding ketones in excellent yields (**19**, **20**, and **21** respectively, 80–90% yield), highlighting the application of this method to biologically-relevant molecules. In addition to benzylic substrates, we were pleased to find that aliphatic ketones were also generated in good levels of efficiency (**8**, **25**–**29**, 59–82% yield). The reaction was amenable to acids containing a wide variety of aliphatic structures, including acyclic (**27** and **29**), cyclic (**8**, **25**, and **26**), and bicyclic (**28**) scaffolds. In these cases, the viologen co-catalyst proved vital for achieving high levels of efficiency and selectivity for the ketone product over the reduced alcohol byproduct. For example, in the case of product **8**, we observed a 40% yield of ketone **8** and 13% of the corresponding secondary alcohol in the absence of the viologen co-catalyst. However, upon addition of viologen co-catalyst **13**, 67% of the ketone and 5% of the alcohol byproduct were obtained (see Supporting Information). As formation of the alcohol product likely arises via photocatalyst-mediated reduction of the hydroperoxide intermediate, we hypothesize that the viologen co-catalyst helps favor the ketone product by accelerating oxidative quenching of the *Ir(III) excited state. The fact that no reaction is observed without photocatalyst when viologen is present, as well as the fact that the viologen salts absorb minimally in the blue region of the spectrum either in the ground state or reduced form makes it unlikely that excitation of the viologen co-catalyst plays a part in the reaction mechanism.[17,18] α-Amino acids could also be readily converted to their amide analogues in good efficiency (**30**–**35**, 45–85% yield), with both benzylic (**30** and **31**) and non-benzylic (**33**–**35**) amino acids being well tolerated. The transformation was amenable to a variety of ring sizes (**33**–**34**), as well as acyclic variants (**35**). This methodology thus provides a unique and facile means for the synthesis of amides and lactams from amino acid precursors. Finally, we sought to investigate the use of primary benzylic acids in this catalytic protocol. We anticipated that primary acids would be challenging substrates due to the known tendency for aldehydes to undergo aerobic oxidation to the corresponding carboxylic acids under an atmosphere of oxygen. However, we were pleased to find that under our optimized conditions arylacetic acids could be converted to the corresponding substituted benzaldehydes in excellent yields (**22**–**24**, 71–79% yield).

We then sought to explore whether other abundant functional groups could also undergo oxidative dehomologation to yield carbonyl products. Since the autoxidation of aldehydes to their carboxylic acid analogues is a well-established process,[19] we hypothesized that simple aldehydes would also be amenable as substrates via a putative carboxylic acid intermediate.

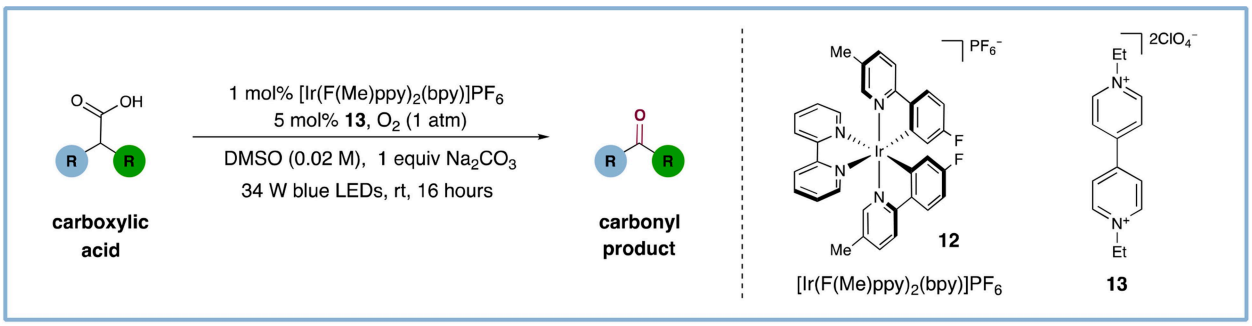
Although minimal overoxidation of benzylic aldehydes was previously observed, we hypothesized that longer reaction times would enable the formation of the requisite acid intermediate, which could then subsequently undergo decarboxylative oxygenation. We examined this oxidation-decarboxylation strategy in the context of both a benzylic and non-benzylic aldehyde (**36** and **37**), and were pleased to observe formation of ketones **10** and **8** in 85% and 17% yield, respectively (Scheme 3, see Supporting Information).

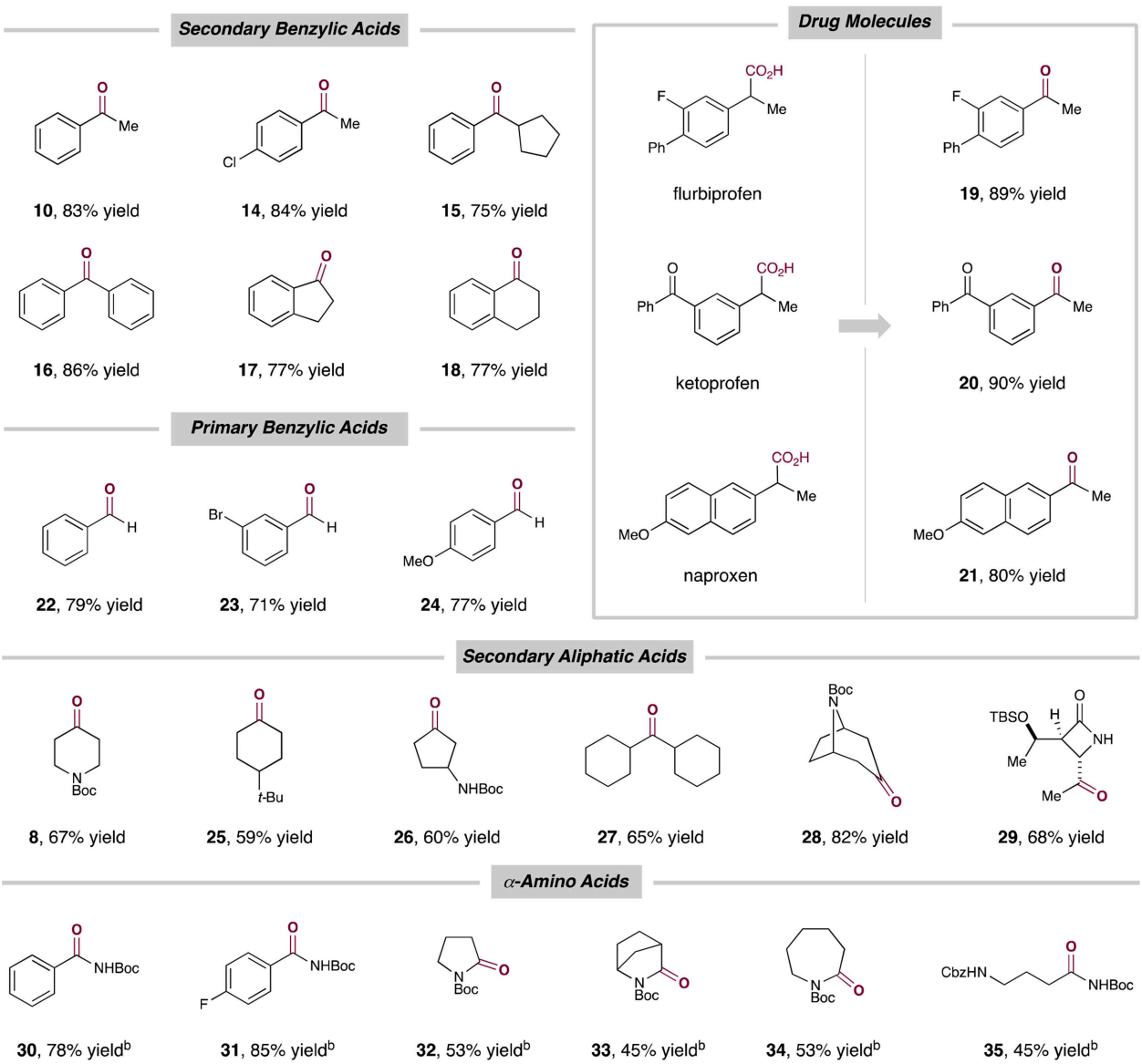
Finally, we examined the possibility of using our decarboxylative oxygenation strategy as a method for the oxidative degradation of linear aliphatic chains. Such dehomologations have previously been explored for the depolymerization of lignin into simple aromatic molecules[20] and have also found



Scheme 3. Decarboxylative Oxygenation of Aldehydes.

Table 2. Substrate Scope of Decarboxylative Oxygenation.[a]

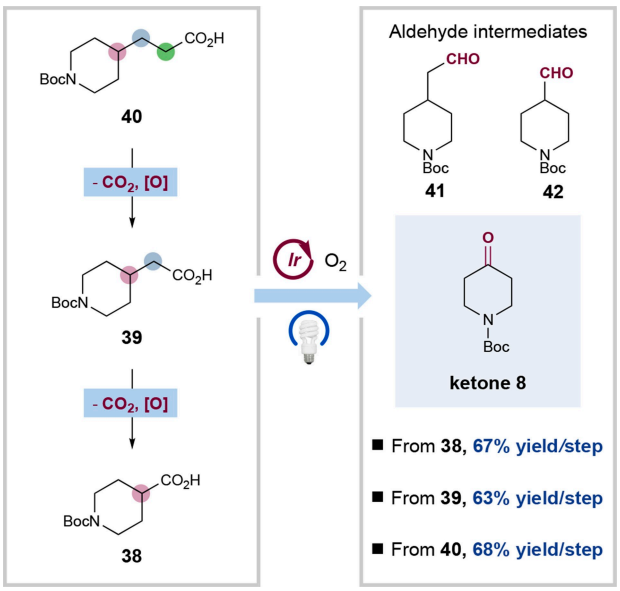




[a] Isolated yields, reaction performed with 0.5 mmol of carboxylic acid, see Supporting Information for experimental details. [b] Ethyl acetate used as solvent and cesium fluoride as base.

application in the synthesis of drugs and natural products.[21,22] As noted above, aliphatic aldehydes can undergo *in situ* autoxidation to the corresponding carboxylic acids and subsequent decarboxylative oxygenation to give ketone products. For longer alkyl chains, this decarboxylation-oxidation sequence could be continued until a product which could not undergo further oxidation was formed (Scheme 4). As such, we subjected primary acid **39** to our reaction conditions, and were pleased to find the reaction yielded ketone **8** over a sequence of three oxidation and decarboxylation steps, with an average yield of 63% yield per step and an overall yield of 26%. Notably, we also observed aldehyde **42** by ^{1}H NMR, supporting the hypothesis that this reaction proceeds via aldehyde oxidation and subsequent decarboxylation. Primary acid **40**, with a further extended alkyl chain, was also amenable a six-step oxidation-decarboxylation sequence, giving ketone **8** in an average of 68% yield per step and an overall yield of 10%, with both **41** and **42** observed as intermediates. This sequence demonstrates the potential of this oxidative strategy as a means for the degradation of aliphatic side chains (see Supporting Information for experimental details).

In summary, we have developed a broadly applicable photoredox-catalyzed decarboxylative oxygenation protocol that generates dehomologated carbonyl compounds, and demonstrated its applicability to a wide range of carboxylic acids, including a number of drug molecules. Extension of this protocol to aldehyde substrates has facilitated the development of a strategy for the oxidative degradation of linear aliphatic chains through a putative sequential oxidation-decarboxylation mechanism, providing a route for the excision of methylene units. We anticipate that this oxygenation protocol will find broad applicability in the pharmaceutical industry and could potentially have applications in biomass derivatization.



Scheme 4. Aliphatic Chain Oxidative Degradation Strategy.

Acknowledgements

Financial support was provided by the National Institute of General Medical Sciences (NIGMS), R01 GM078201-05, the Princeton Catalysis Initiative, and kind gifts from MSD, Abbvie, Pfizer, Celgene, Genentech, and Janssen.

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Manuscript received: October 18, 2019
Revised manuscript received: November 24, 2019
Version of record online: December 13, 2019