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Radical Hydrocarboxylation of Unactivated Alkenes via Photocatalytic Formate Activation

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Abstract

Herein we disclose a strategy to promote the hydrocarboxylation of unactivated alkenes using photochemical activation of formate salts. We illustrate that an alternative initiation mechanism circumvents the limitations of prior approaches and enables hydrocarboxylation of this challenging substrate class. Specifically, we found that accessing the requisite thiyl radical initiator without an exogenous chromophore eliminates major byproducts that have plagued attempts to exploit similar reactivity for unactivated alkene substrates. This redox-neutral method is technically simple to execute and effective across a broad range of alkene substrates. Feedstocks alkenes, such as ethylene, are hydrocarboxylated at ambient temperature and pressure. A series of radical cyclization experiments indicate how the reactivity described in this report can be diverted by more complex radical processes.

Alkene hydrofunctionalization methods that exploit radical intermediates are a fundamental class of synthetic reactions. Radical reactivity offers a complementary regio- and chemoselectivity profile relative to polar pathways.[1,2] Despite anti-Markovnikov hydrobromination dating back a century,[3,4] the development of radical hydrofunctionalization reactions remains a contemporary area of investigation.[5-17] Our group has a particular interest in alkene hydrocarboxylation using radical intermediates.[18,19] Carboxylic acids are a readily diversifiable functional handle[20-24] and are themselves a common motif found in natural products, pharmaceuticals, and commodity chemicals.[25-28] We envision that a broad and general radical hydrocarboxylation reaction would offer a powerful complement to transition-metal-catalyzed methods, such as the numerous established CO-based approaches[29-32] and the emerging alternative technologies that proceed through migratory insertion into CO_2.[33-39] However, established approaches to

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radical hydrocarboxylation have remained largely limited to activated alkenes (Figure 1A).[18,19,40-46] Unactivated aliphatic alkenes are an abundant and important substrate class but remain more challenging to engage due to their attenuated reactivity. Indeed, in the past year, Yu and coworkers reported the first and only synthetic methodology that engages unactivated alkenes with $CO_2^{\bullet-}$.[47] While this pioneering report was a substantial step for unactivated alkene hydrocarboxylation, this strategy nonetheless relies on highly reducing and basic conditions alongside stoichiometric reductants. More broadly, unactivated alkenes remain a challenging substrate class to engage not only for radical strategies but also across a broader sampling of hydrocarboxylation methods.

We questioned whether the limitations encountered with radical hydrocarboxylation of unactivated alkene substrates are tied to the reliance on single-electron reduction of CO_2. In principle, $CO_2^{\bullet-}$ should be sufficiently reactive to undergo radical addition with unactivated aliphatic alkene substrates.[48-50] However, despite numerous successful examples with activated alkene substrates,[42-46] the comparatively slower rates of $CO_2^{\bullet-}$ addition to unconjugated π-systems expose numerous liabilities for these net-reductive transformations. For example, oxalate formation becomes a competitive pathway that parasitically consumes stoichiometric reducing equivalents. Furthermore, many strategies rely on highly reducing photocatalytic or electrochemical systems that become more susceptible to deactivation for slower reactions. We envisioned that an approach to generate the key $CO_2^{\bullet-}$ intermediate without relying on CO_2 reduction might circumvent each of these challenges.

Our group[51] and others[52,53] have recently reported a strategy that generates $CO_2^{\bullet-}$ from inexpensive formate salts via hydrogen atom abstraction (formate C(sp^2)—H BDE = 86 kcal/mol).[54] This approach has been applied to activated alkene hydrocarboxylation; however, attempts to expand the scope of this process to unactivated alkenes have been categorically unsuccessful.[18,19,40,41] Nonetheless, we recognized that, in principle, this formate-based mechanistic manifold should be uniquely well matched to address the specific challenges encountered by other approaches to unactivated alkene hydrocarboxylation. Based on our working mechanistic model, $CO_2^{\bullet-}$ generation is coupled to its consumption, which maintains a low steady-state concentration of the reactive radical intermediate (Figure 1B). This should minimize the deleterious pathways available to $CO_2^{\bullet-}$, such as dimerization. This redox-neutral process also bypasses the potent reductants demanded by the thermodynamically challenging reduction of CO_2 (E_{red} ($CO_2/CO_2^{\bullet-}$) = −2.2 V vs. SCE).[55] This presents an opportunity to generate $CO_2^{\bullet-}$ under exceptionally mild conditions with perfect atom[56] and redox[57] economy. We envisioned that a deeper investigation into the reactivity of unactivated alkene substrates using this formate-based approach could reveal the origin of its previously encountered limitations. These findings would then guide the development of a new catalytic system capable of engaging this challenging substrate class. Herein, we report the outcome of these studies, which produced a new approach to initiation that enables the hydrocarboxylation of unactivated alkenes (Figure 1C). The high atom economy, operational simplicity, and mild reaction conditions of this process render it an appealing complement to all alternative hydrocarboxylation approaches.

We initiated our investigations with model unactivated alkene **1**. Under our previously developed alkene hydrocarboxylation conditions, acid product **2** was formed in 18% yield

alongside 10% of a solvent-derived thioether side product (**3**).[58] Further interrogation of the reaction parameters modestly improved the yield relative to this initial lead result; however, the process remained unselective for the desired product (Scheme 1A, entry 1). These observations suggested that fine-tuning of reaction parameters was unlikely to lead to a synthetically useful protocol. With this in mind, we aimed to diagnose the factors stymying our attempts at reaction optimization. To this end, we monitored the reaction progress as a function of time. These experiments revealed that the conversion of the alkene substrate is preceded by a brief induction period. Parallel monitoring of the reaction by UV-Vis spectroscopy indicated that the photocatalyst, **4DPAIPN**, is consumed during this induction period. Overlaying these two datasets illustrated that product formation begins after the majority of the catalyst absorption features have been lost. These data suggest that **4DPAIPN** is not responsible for hydrocarboxylation reactivity under these modified conditions. We next ran the reaction in the absence of **4DPAIPN** and found that product **2** is formed despite omission of the exogeneous dye although an induction period was still observed. While the yield of the desired acid product, **2**, under these conditions was attenuated, the previously problematic byproduct, **3**, was not observed (entry 2). Additional control experiments revealed that both thiol and light remained necessary reaction components (see SI for details). Taken together, these data suggest that $CO_2^{\bullet-}$ addition into unactivated alkenes is slower than photocatalyst decomposition, which potentially occurs via radical attack on the isophthalonitrile core.[59-64] In contrast, we suspect that $CO_2^{\bullet-}$ addition into activated alkenes (*e.g.* vinylarenes) outcompetes this pathway given that the dye was necessary under those conditions and that no catalyst bleaching was observed.[65]

These mechanistic investigations provided a new foundation from which to continue our reaction development efforts. In the absence of an exogeneous chromophore, we envisioned that thiol identity and irradiation wavelength would have a significant impact on reaction efficiency. A collection of thiols with varying steric and electronic profiles were evaluated as potential catalysts for this transformation (Scheme 1B, see Table S5 for details regarding the thiols and wavelengths examined). Varying the ortho-substituent from an ester (S1) to other electron-withdrawing groups, such as nitrile (S2), had minimal impact. In contrast, trace product was formed with electronically neutral (S3) and electron-rich (S4) analogs. We next questioned whether reducing the steric encumbrance proximal to the thiyl radical would improve the reaction efficiency. Minimal change in reactivity was observed for the nitrile (S6) and methoxy (S7) substituted thiols. However, the para-ester thiol S5 increased reactivity and furnished the desired product in 75% yield.

We next investigated the origin of reactivity with unactivated alkenes in the absence of an exogeneous photocatalyst. In our previous studies the proposed role of **4DPAIPN** was to initiate the reaction by generating a thiyl radical intermediate. We suspected that an alternative mechanism still generated an analogous thiyl radical species under these modified conditions. To evaluate if S5 was oxidized under the reaction conditions, we monitored disulfide formation in the absence of other reactants (Scheme 1C).[66] Indeed, disulfide was formed over the course of a few hours. Next, we examined whether the disulfide is a competent pre-catalyst for formate activation via S—S homolysis.[67]

Replacement of thiol (S5) with the corresponding disulfide (S8), under otherwise identical conditions, resulted in similar yield of the desired product (Table S8). These data provide a plausible rationale for the observed induction period for the purely thiol-catalyzed hydrocarboxylation process.

We next examined the scope of alkene substrates that undergo the hydrocarboxylation reaction (Table 1). An array of linear aliphatic alkenes bearing a variety of functional groups were smoothly converted to the desired carboxylic acid in moderate to high yields (**2–8**). Of note, reductively sensitive aryl chlorides (**8**) were tolerated without any measurable dehalogenation despite the established examples of their reduction with $CO_2^{\bullet-}$.[51-53] Indeed, similar yield of the hydrocarboxylation product was observed from an analogous deschloro alkene substrate (**9**). The reaction tolerates diverse protic functional groups, including ureas (**10**), unprotected alcohols (**11**, **12**), carboxylic acids (**13**), carbamates (**13**), and amides (**4, 7**). Of particular note, an α-amino acid derivative was found to be compatible under the reaction conditions and could be transformed into the linear diacid product in high yield (**13**). Substrates bearing a variety of pendant heterocycles, including oxetanes (**12**), γ-lactones (**14**), piperidines (**15, 16**), pyrans (**17**), andimidazoles (**18**), each underwent the desired transformation. Hydrocarboxylation proceeds smoothly across a series of sterically hindered substrates (**11, 12, 14–17, 19**), which included fully substituted carbon centers in both cyclic (**12**) and acyclic systems (**19**). Moderate to high yields of the linear carboxylic acid products were obtained across a series of exocyclic and acyclic 1,1-disubstituted alkene substrates upon gentle heating (**20–22**). Under these conditions, internal alkenes still produce the corresponding carboxylic acid albeit in diminished yield (21% yield, see SI for details).

We next evaluated this new hydrocarboxylation methodology on a preparative scale (Scheme 2). With modified conditions that reduced the thiol catalyst loading (5 mol%) and employed a less expensive formate salt (potassium formate), carboxylic acid **4** was prepared on decagram scale in 95% yield (10.6 g, 48 mmol). While photochemical reactions often require specialized equipment to be scaled,[68,69] we found that this preparative reaction could be conducted in a simple batch setup despite relying on a poorly absorbing chromophore.[70] Furthermore, no precautions to exclude air were required and the product could be purified by aqueous extraction without the need for chromatography. Overall, these results illustrate the operational simplicity and immediate utility of this formate-based hydrocarboxylation approach in fine chemical synthesis.

We next evaluated whether this hydrocarboxylation reaction is amenable to the functionalization of commodity feedstock alkenes derived from steam cracking (Scheme 3).[71] Previous work by du Pont engaged formic acid and feedstock alkenes to generate carboxylic acid products; however, energy-intensive pyrolysis conditions at elevated pressures (*e.g.* 325 °C at 700 atm) were required to circumvent the high kinetic barrier associated with this thermal process.[72] In stark contrast, room temperature irradiation of a mixture of potassium formate and catalytic thiol under an atmosphere (1 atm) of ethylene resulted in high yield of the desired acid product relative to formate (Scheme 4). These results underscore the exquisite selectivity these conditions provide for hydrocarboxylation over $CO_2^{\bullet-}$ dimerization to form oxalate salts. We suspect dimerization is avoided because

a low steady state concentration of $CO_2^{\bullet-}$ is maintained throughout the reaction by coupling $CO_2^{\bullet-}$ generation to product formation through the putative chain mechanism. Additionally, the thiol catalyst remains intact after the reaction and could, in principle, be recovered and recycled. These data outline that this catalytic system may ultimately unlock an attractive new approach for the conversion of feedstock alkenes to value-added commodity acid products with an inexpensive thiol organophotocatalyst.

We next questioned whether this methodology could provide a new route to synthesize saturated rings via carboxylation-induced radical cyclization. Specifically, we envisioned that unconjugated diene substrates might undergo cyclization to forge a new $C(sp^3)$—$C(sp^3)$ bond. Subsequently, the nascent $C(sp^3)$ radical intermediate could be intercepted by a hydrogen atom to propagate the chain mechanism. Successful implementation of this idea would require that radical cyclization is substantially faster than hydrogen atom transfer (HAT) to the alkyl radical formed following $CO_2^{\bullet-}$ addition.[73] We found that a collection of model unconjugated dienes underwent the desired carboxylation-cyclization reaction, forming tetrahydrofurans, pyrrolidines, and cyclopentanes with modest cis-selectivity (Scheme 4).[74] These results illustrate the potential utility of this catalytic engine beyond hydrocarboxylation processes, given that these simple carboxylic acid building blocks either required multistep sequences using previous approaches or had not been previously reported.

Overall, we have identified a new photocatalytic system that enables the direct synthesis of linear carboxylic acids from unactivated alkenes and formate salts. We identified a more efficient thiol catalyst that undergoes spontaneous oxidation to the requisite thiyl radical *in situ*. This new approach to initiation circumvented the fundamental challenges that have stymied previous attempts to engage unactivated alkenes in such reactions. These studies have introduced a practical alkene hydrocarboxylation protocol that proceeds under mild conditions, tolerates a wide array of functional groups, and is readily scaled in batch. Proof-of-concept experiments further illustrated that this new technology is amenable to the preparation of commodity chemicals as well as saturated rings. This study fundamentally expands the scope of formate-based radical hydrocarboxylation and, more broadly, introduces a new catalytic system for HAT-based formate activation with diverse potential applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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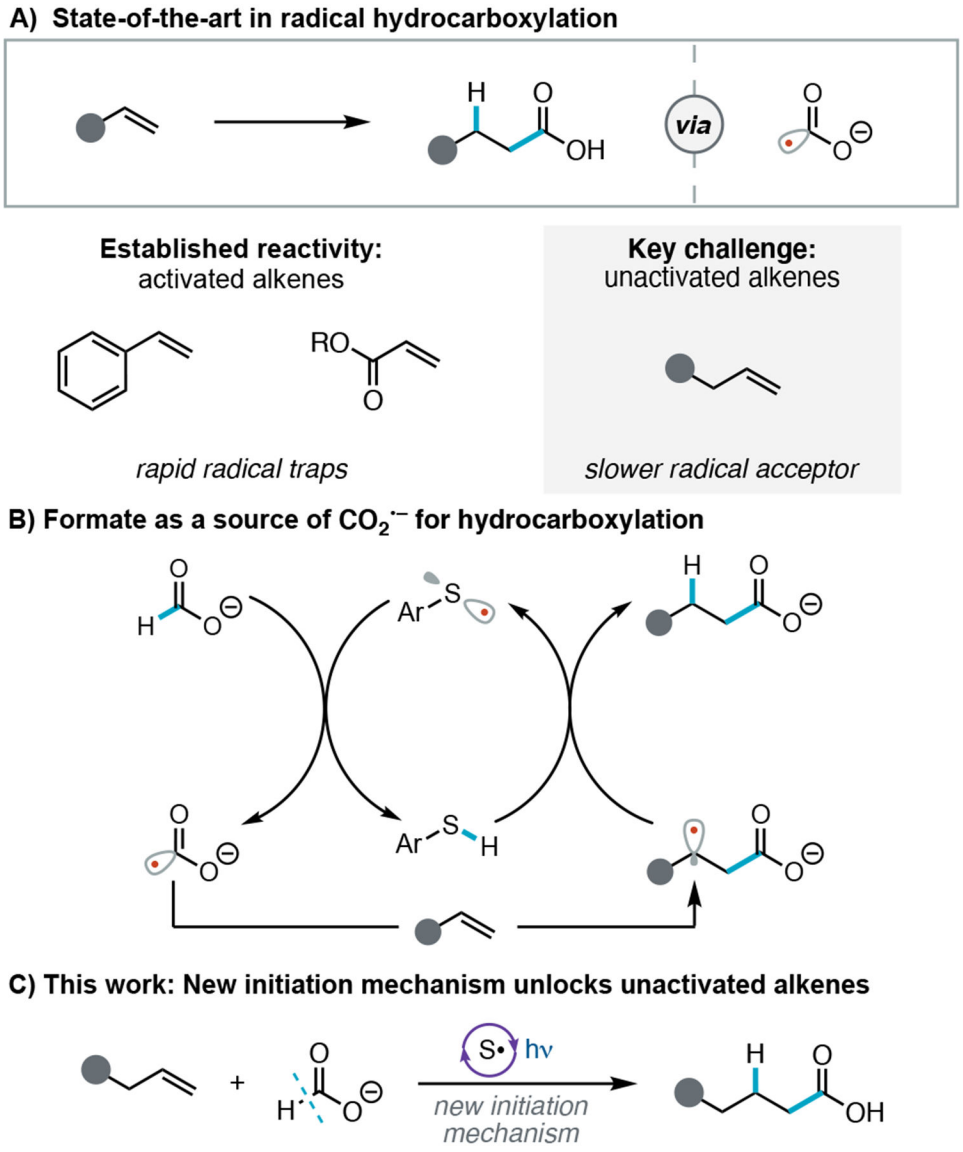
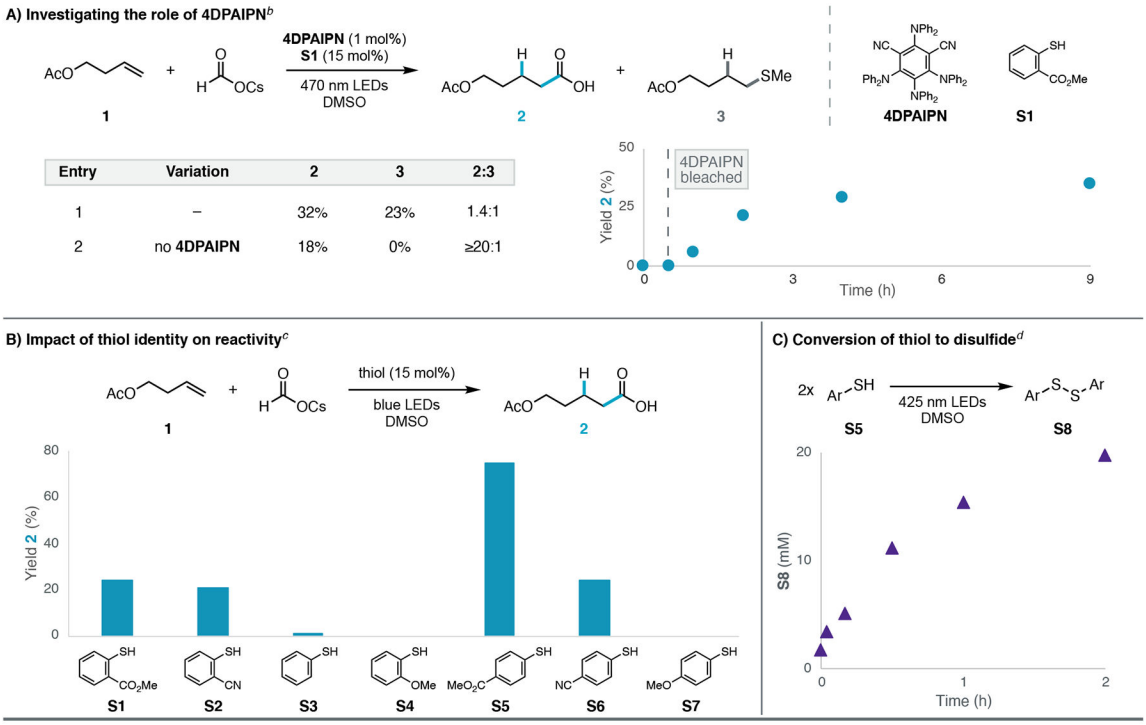


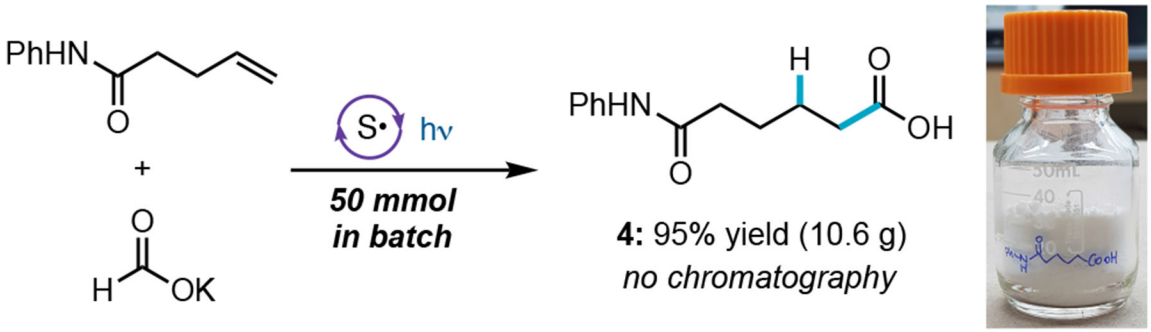
Figure 1.
Project overview



Scheme 1.

Optimization of formate-based conditions for unactivated alkenes[a]

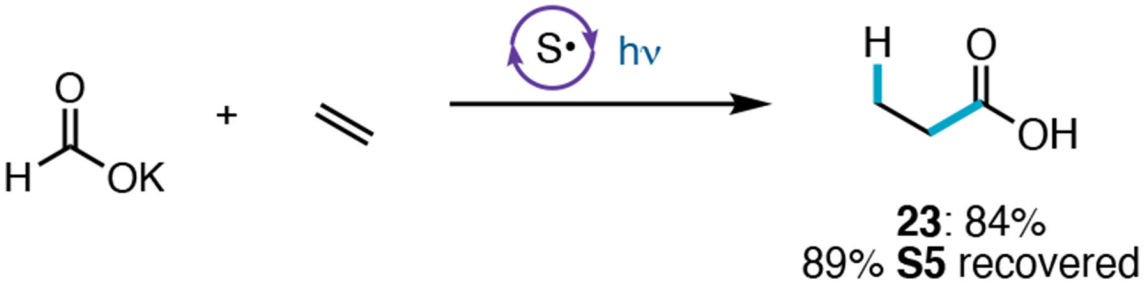
[a]Reactions were conducted under air on a 0.05 mmol scale with 2 equiv $CsCHO_2$ at 24 °C unless otherwise noted. The yield of **2**, **3**, and S8 were determined via ^{1}H NMR. See the SI for further details. [b]Reactions were run for 24 h and yields are an average of 4 runs. [c]Reactions were run for 5 h. [d]Reactions were run on 0.03 mmol scale.



Scheme 2.

Multigram-scale hydrocarboxylation for fine chemical synthesis[a]

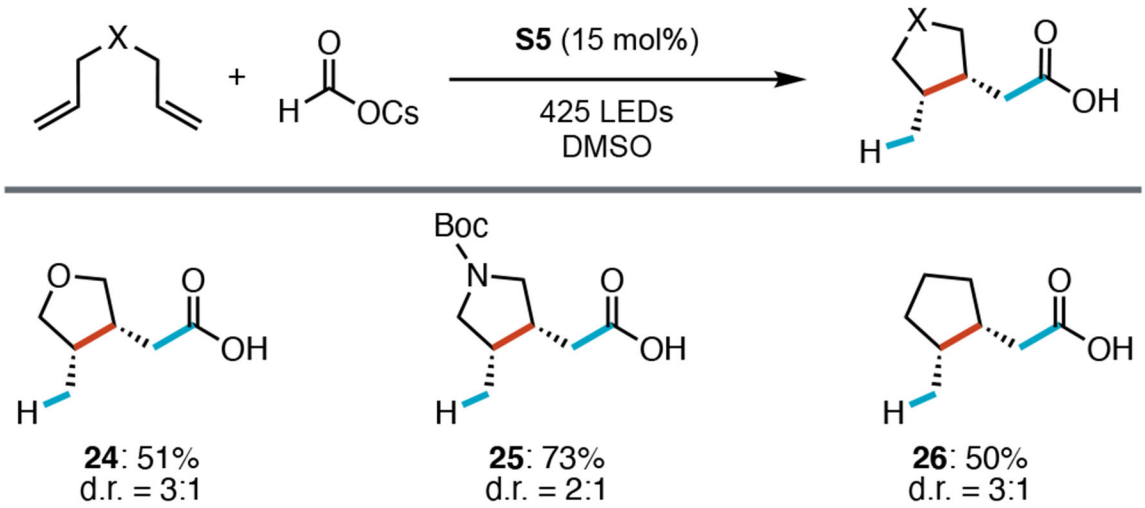
[a]The reaction was conducted under air on a 50 mmol scale with 2 equiv $KCHO_2$ and 5 mol% S5 for 24 h at 24 °C. See the SI for further details.



Scheme 3.

Hydrocarboxylation for bulk chemical synthesis[a]

[a]Reaction was conducted under air at 1 atm on a 1 mmol scale with 5 mol% S5 and limiting $KCHO_2$ for 6 h at 24 °C. Yields were determined via 1H NMR. See the SI for further details.



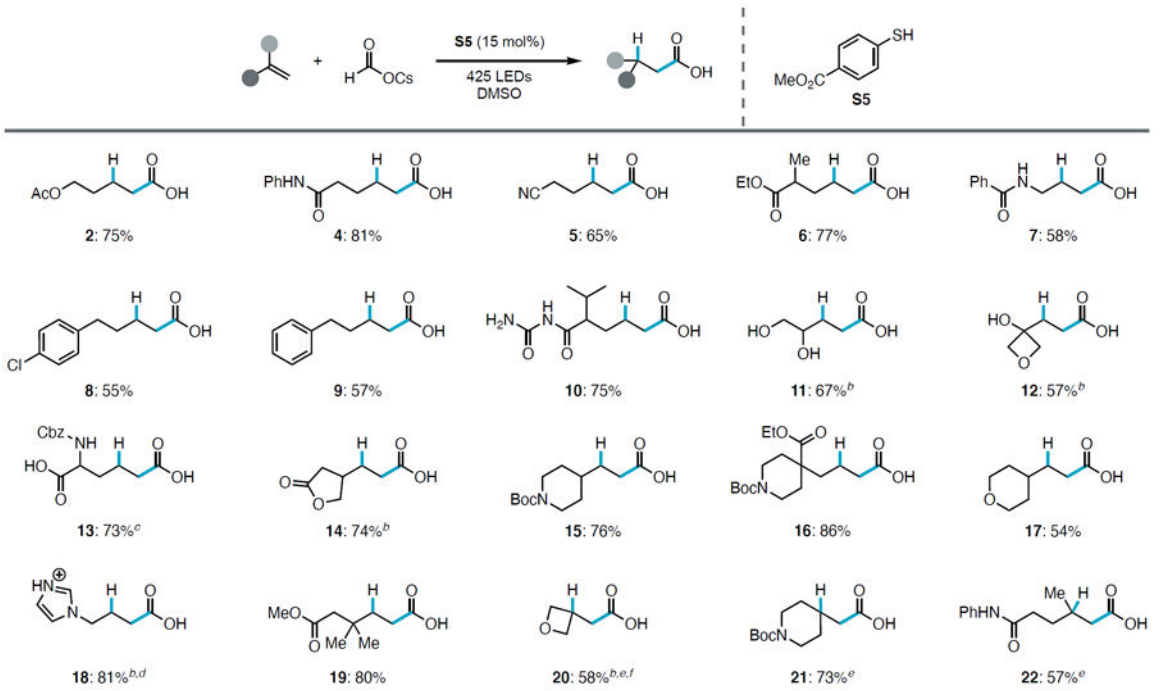
Scheme 4.

Carboxylation–induced radical cyclization[a]

[a]Reaction were conducted under air on a 1 mmol scale with 2 equiv $CsCHO_2$ for 24 h at 24 °C, and yields are of purified product unless otherwise noted. See the SI for further details.

Table 1.

Scope of Unactivated Alkene Substrates[a]



[a]Reactions were conducted under air on a 1 mmol scale with 2 equiv of $CsCHO_2$ for 24 h at 24 °C, and yields are of the purified product unless otherwise noted. See the SI for further details. [b]Yield was determined via 1H NMR analysis. [c]10 equiv $CsCHO_2$ was used. [d]The reaction was run on 0.05 mmol scale in DMSO-d_6 and measured as the yield of the trifluoroacetate salt. [e]The reaction was heated to 50 °C. [f]The substrate was used as a THF solution.