OL Organic Letters

pubs.acs.org/OrgLett

Letter

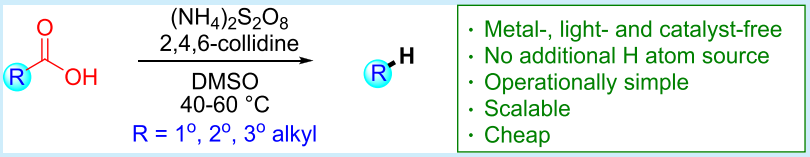
Direct Hydrodecarboxylation of Aliphatic Carboxylic Acids: Metal- and Light-Free

Euan B. McLean, David T. Mooney, David J. Burns, and Ai-Lan Lee*

Cite This: *Org. Lett.* 2022, 24, 686–691

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

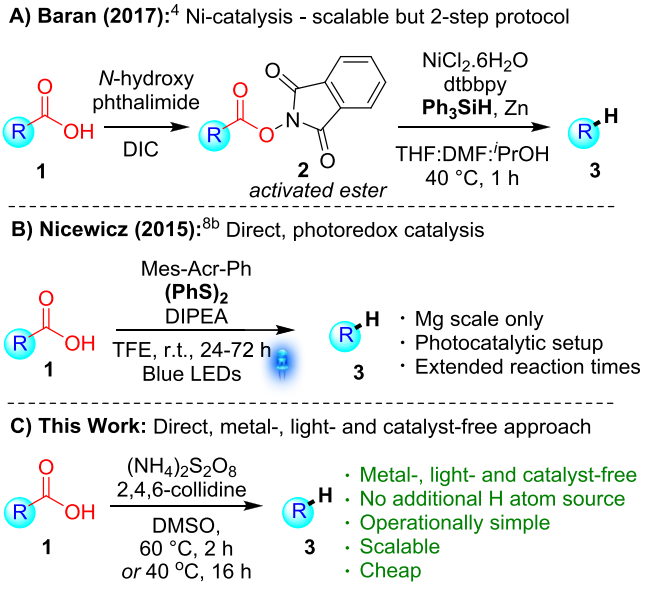


ABSTRACT: A mild and inexpensive method for direct hydrodecarboxylation of aliphatic carboxylic acids has been developed. The reaction does not require metals, light, or catalysts, rendering the protocol operationally simple, easy to scale, and more sustainable. Crucially, no additional H atom source is required in most cases, while a broad substrate scope and functional group tolerance are observed.

The carboxylic acid moiety, and its derivatives, is one of the most abundant and synthetically versatile functional groups that is present in many naturally occurring compounds.[1] The ability of carboxylic acids to promote a range of different chemical transformations, particularly C−C bond-forming reactions, makes these compounds highly valuable starting materials for organic synthesis.[2] However, the carboxylic acid functionality is often unwanted in later synthetic intermediates, so methods for removing the carboxylic acid functionality via hydrodecarboxylation are highly sought after.

The most famous of these is the Barton decarboxylation,[3] but the reaction suffers from several notable drawbacks. The reaction requires two steps (via activated ester), harsh reaction conditions, and the use of notoriously noxious H atom donors [(^{n}Bu)$_3$SnH]. In recent years, progress has been made to render hydrodecarboxylations of aliphatic carboxylic acids more palatable to modern synthetic chemists. For example, less toxic hydrogen atom donors have been used (e.g., Scheme 1A), such as silanes,[4] thiols,[5] and chloroform;[6] however, drawbacks such as harsh reaction conditions, the use of toxic or unsustainable transition metals, complex reaction mixtures, two-step protocols, and poor atom economy remain.[7] Meanwhile, milder reactions were also developed by harnessing visible light through the use of photocatalysis[8] and electron−donor−acceptor complexes,[9] although these still mainly proceed via activated esters. A notable and seminal example of direct decarboxylation is that of Nicewicz (Scheme 1B);[8b] however, it requires a photocatalytic setup with associated scalability issues,[10] use of a glovebox, extended reaction times, and odorous thiols (formed *in situ*) as the H atom source. A significant advancement in the field would therefore be a direct hydrodecarboxylation that addresses all of the limitations of the original Barton decarboxylation, while also being operationally simple, scalable, and more sustainable. We herein describe the first metal-, catalyst-, and light-free direct hydrodecarboxylation procedure for aliphatic carboxylic

Scheme 1. Notable Developments in Hydrodecarboxylations



Received: December 7, 2021
Published: January 7, 2022

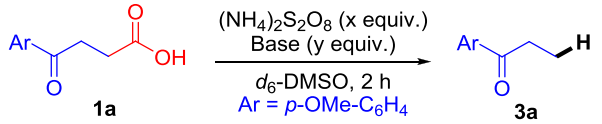
https://doi.org/10.1021/acs.orglett.1c04079
Org. Lett. 2022, 24, 686−691

acids that not only fits all of the criteria mentioned above but also crucially does not require an additional H atom source (Scheme 1C).[11]

The inspiration for our work was our recent discovery that Minisci-type reactions can proceed under mild conditions without any metal, photocatalyst, or light.[12] The use of DMSO as solvent was thought to allow for the breakdown of $S_2O_8^{2-}$ to the active $SO_4^{-\bullet}$ under mild conditions, without the need for the previously used metal mediation or photolysis.[13] We were also inspired by the original Kochi hydrodecarboxylation [Ag(II), $S_2O_8^{2-}$, and heat], although low yields, poor selectivity, a limited substrate scope, and expensive/unsustainable use of silver have so far limited any widespread utility in synthetic applications.[14]

We commenced our investigations with substrate **1a**, using conditions based on our previously reported Minisci-type alkylation,[12a] but in the absence of the heterocycle radical acceptor. Disappointingly, these initial conditions failed to produce the desired **3a** (Table 1, entry 1). To our delight, the

Table 1. Selected Optimization and Control Studies



entry	base[a]	notes	T (°C)	x	y	1a[d] (%)	3a[d] (%)
1[b,c]	–		40	2	–	nd	0
2[b,c]	collidine		40	2	3	<5	22
3[b,c]	Na_2CO_3		40	2	3	5	11
4	lutidine		60	2	3	27	22
5	pyridine		60	2	3	<5	5
6[b,c]	collidine		40	2	2	nd	13
7[b,c]	collidine		40	2	5	nd	24
8[e]	collidine		60	2	3	25	57
9	collidine	anhydrous	60	2	3	23	56
10	collidine		60	2	3	30	60
11	collidine		60	3	3	16	68
12	collidine	$Na_2S_2O_8$	60	3	3	23	27
13	collidine	$K_2S_2O_8$	60	3	3	31	21
14	collidine	in the dark	60	3	3	25	67
15	–	no base	60	3	–	95	<5
16	collidine	no $S_2O_8^{2-}$	60	–	3	100	<5
17	collidine	under air	60	3	3	25	46

[a]Collidine = 2,4,6-collidine; lutidine = 2,6-lutidine. [b]DMSO/H_2O (600:1) as the solvent. [c]For 16 h. [d]Yields determined by ^1H NMR analysis using dimethylsulfone or 1,3,5-trimethoxybenzene as an internal standard. [e]d_6-DMSO/H_2O (600:1).

inclusion of 2,4,6-collidine allowed us to observe **3a** in a moderate yield of 22% (entry 2). The desired reactivity could be obtained from other basic additives (see the Supporting Information for the full study), indicating that 2,4,6-collidine is acting as a base to promote the reaction (entries 3−5). Changes to the stoichiometry of 2,4,6-collidine did not have a positive impact (entries 6 and 7). Increasing the temperature to 60 °C proved to be beneficial, increasing the yield of **3a** to 57% [entry 8 (see the Supporting Information for rates at different temperatures)]. The water content had no appreciable impact (entries 8−10). Pleasingly, the yield increased to 68% with 3 equiv of $(NH_4)_2S_2O_8$ (entry 11). Other persulfates also promote the transformation (entries 12 and 13), with $(NH_4)_2S_2O_8$ giving the best performance presumably due to increased solubility. Control reactions show that the reaction performs equally well in the dark (entry 14) and that both 2,4,6-collidine and $(NH_4)_2S_2O_8$ are crucial (entries 15 and 16, respectively). Running the reaction under air also forms desired **3a**, albeit with a decrease in yield from 68% to 46% (entry 17). It should be noted that d_6-DMSO was used solely for ease of ^1H NMR analysis; the reaction performs just as well in nondeuterated DMSO.

With the optimized reaction conditions in hand, we began to investigate the substrate scope (Scheme 2). Primary carboxylic acids are tolerated, with model substrate **1a** forming **3a** in 68% yield. 1,3-Ketoacids were shown to be excellent substrates (73% **3b**). In contrast, long chain fatty acid **1c** reacted more sluggishly and provided **3c** in a modest 35% yield. These results indicate that for primary carboxylic acids, having a polar withdrawing group (e.g., carbonyl) in the proximity of the carboxylic acid helps to promote radical formation. Substrate **1d** corroborates our theory, as moving the carbonyl one carbon away (vs **1a**) substantially decreases the reactivity and yield (68% **3a** vs 11% **3d**).[15] Pleasingly, amino acid derivatives were compatible substrates, with protected glutamic acid **1e** providing the desired **3e** in 59% yield.

Secondary carboxylic acids were good substrates with **3h** obtained in good yield (65%). Protected amines, esters, and Cl groups were all shown to be compatible, furnishing products **3i**−**3k**, respectively, in good yields (60−72%). Contracting the ring size of the substrate initially proved to be problematic, with substrate **1l** performing poorly under the standard conditions due to high reactivity. Nevertheless, these problems could be mitigated by decreasing the temperature to 40 °C to produce **3l** in 50% yield. Cyclic carboxylic acids with four- and seven-membered rings (**1m** and **1n**, respectively) required similar treatment to access desired products **3m** and **3n**, albeit in reduced yields (31% and 28%, respectively).[16] While the reaction exhibits a high degree of functional group tolerance, substrates in which the acid functionality is α to nitrogen, such as in L-proline (**1o**), gave a complex mixture of products with no desired **3o** observed.

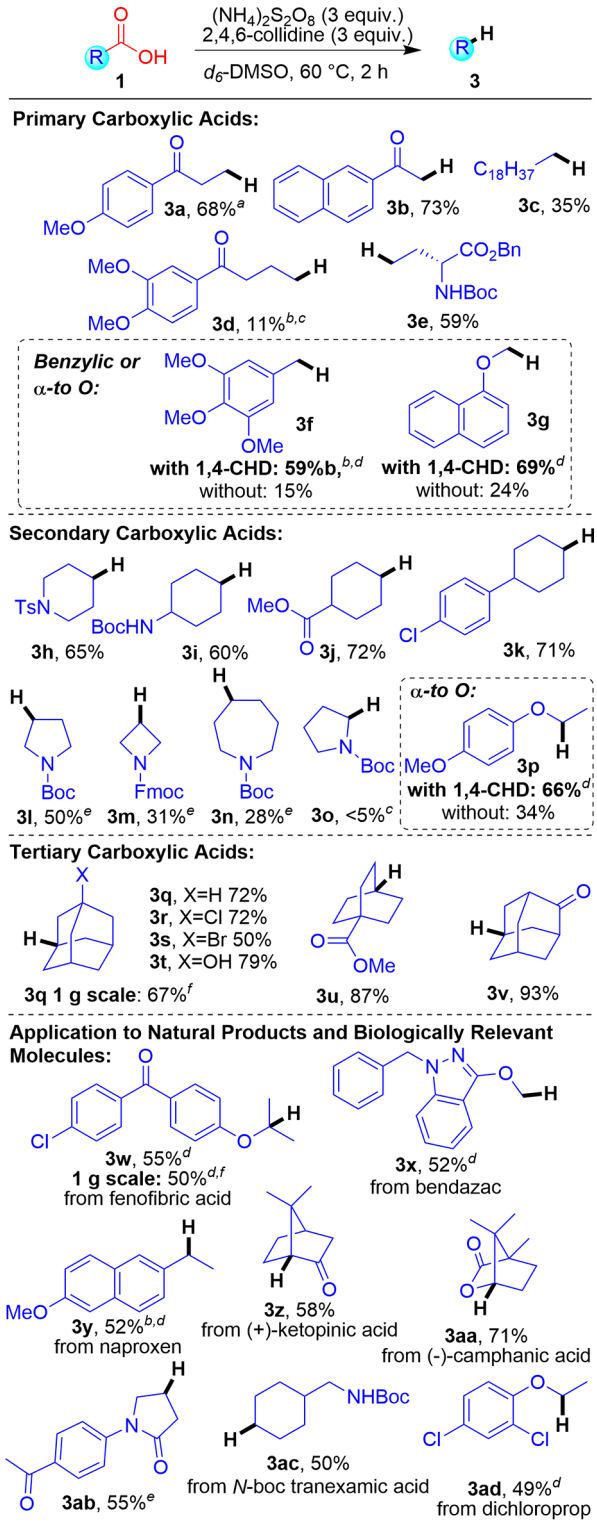
Tertiary carboxylic acids proved to be excellent substrates. Adamantane (**3q**) could be obtained in a good yield of 72%. Halogenated substrates (**1r** and **1s**) and free hydroxyl-containing **1t** were all tolerated, providing **3r**−**3t** in moderate to good yields (50−79%). The performance of bromine-containing substrate **1s** was particularly pleasing as this functional group can be susceptible to transformations of a radical nature. Strained ring system **1u** was also compatible, furnishing **3u** in 87% yield. Cyclic ketone **1v** performed well, producing **3v** in an excellent 93% yield.

The reaction is very readily scalable under our operationally simple and inexpensive conditions, as exemplified by the gram scale reaction on **1q** to produce **3q** in 67% yield.

Studies using our initial standard conditions demonstrated a wide substrate scope encompassing primary, secondary, and tertiary carboxylic acids, and excellent functional group compatibility. Nevertheless, we identified certain classes of carboxylic acids **1** that were too reactive for our initial standard conditions. In particular, benzylic or α to O substrates (e.g., **1f**, **1g**, and **1p**) were prone to forming homocoupling products [e.g., **4f** (Scheme 3)], which resulted in low yields of **3**. Gratifyingly, adding 1,4-CHD (1,4-cyclohexadiene) as a more reactive hydrogen atom source significantly improved the yield of **3f** from 15% to 59% and decreased the level of competitive

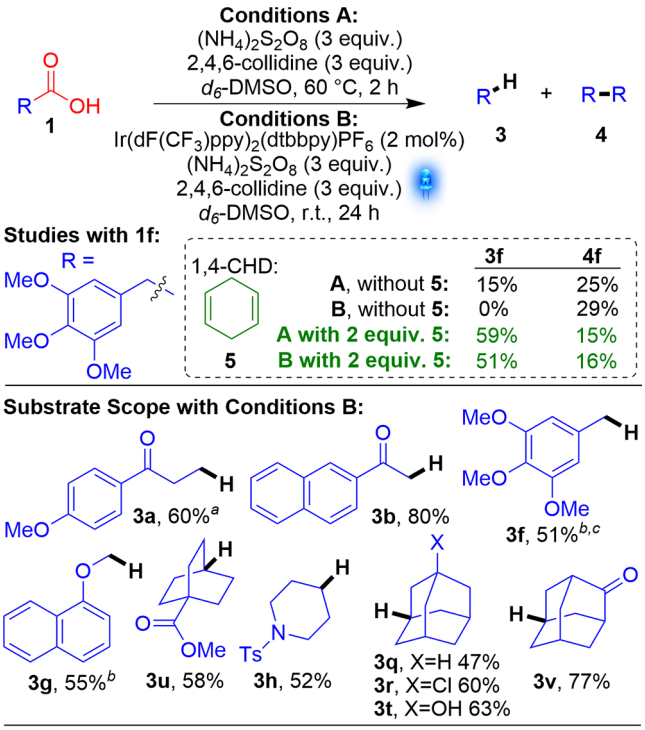
https://doi.org/10.1021/acs.orglett.1c04079
Org. Lett. 2022, 24, 686−691

Scheme 2. Substrate Scope Studies



0.375 mmol scale (0.5 M), under Ar unless otherwise stated. [a]Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard due to volatility of product. [b]Yield determined by ^{1}H NMR analysis using dimethylsulfone as an internal standard. [c]With or without 1,4-CHD. [d]With 1,4-CHD (2 equiv.). [e]40 °C for 16 h. [f]Non-deuterated DMSO used.

Scheme 3. Studies using Photocatalytic Conditions



0.375 mmol scale (0.5 M), under Ar unless otherwise stated. [a]Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]2 equiv. of **5**. [c]Yield determined by ^{1}H NMR analysis using dimethylsulfone as an internal standard.

homocoupling (Scheme 2). Addition of **5** similarly improved the yields for α to O substrates [**3g** and **3p** (Scheme 2)]. However, 1,4-CHD does not help substrates with low reactivity (e.g., unchanged yield of 11% for **3d**) or ones that usually form a complex mixture of side products (e.g., no conversion for **3o**).

To further highlight the utility of our reaction, we applied it to a range of natural products, pharmaceuticals, and other biologically relevant molecules (Scheme 2). Fenofibric acid[17] performs well to give 55% **3w** and was readily scaled to 1 g (50%). NSAIDs bendazac **1x** and naproxen **1y** both formed the desired **3x** and **3y** in 52% yield. Natural products **1z** and **1aa** performed well (58% **3z**, 71% **3aa**). Compound **3ab** formed smoothly from β-lacatmase docking fragment[18] **1ab** in 55% yield, whereas N-protected tranexamic acid[19] **1ac** decarboxylated smoothly to **3ac** in 50% yield. Finally, herbicide dichloroprop[20] **1ad** provided access to **3ad** in a reasonable yield of 49%.

During our attempts to improve the yields for benzylic or α to O substrates, we initially also developed a visible-light photocatalytic reaction (see the Supporting Information), as it was hoped that the milder reaction conditions (rt) would suppress the formation of homocoupling product **4f** (Scheme 3, conditions B). Unfortunately, the use of photocatalytic conditions B gave 0% **3f**. However, as with conditions A, adding 1,4-CHD significantly improved the yield of **3f** to 51%.

At this stage, we thought it prudent to perform a smaller substrate scope study using the photocatalytic conditions (Scheme 3). The yields from photocatalytic conditions, although decent to good (51−80%), were often significantly lower than for the corresponding thermal reactions (Scheme 2). Further investigation determined that this was due to conversions being limited by changes in homogeneity over the course of the reaction. This was confirmed by quantum yield measurements. The average quantum yield (ϕ) was 0.035; however, the ϕ for each reaction varied significantly and

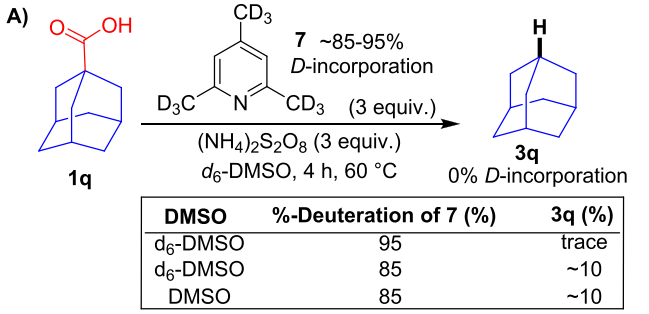
https://doi.org/10.1021/acs.orglett.1c04079
Org. Lett. 2022, 24, 686−691

decreased with reaction time (see the Supporting Information). Therefore, the original thermal reaction (still mild at 40−60 °C) was deemed to have significant advantages over the photocatalytic reaction: better yields, metal- and light-free, operationally simple, and scalable.

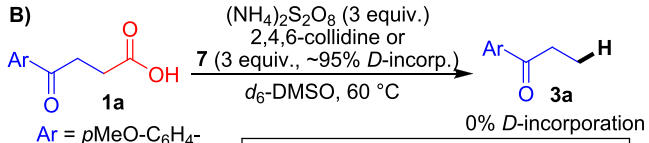
Next, radical trapping experiments were conducted using **1a**. The desired hydrodecarboxylation reaction was totally inhibited in the presence of TEMPO and BHT (see the Supporting Information), indicating a radical-based mechanism.

Because no additional H atom source is required (except for benzylic and α to O substrates), we set out to elucidate the source of the H atoms in **3**. Initially, we investigated the potential of the various exchangeable protons within the reaction mixture to act as H atom sources; however, this possibility was quickly ruled out when hydrodecarboxylation still occurred smoothly with deuterated acid *d*-**1q** (see the Supporting Information). Next, investigations using d_9-2,4,6-collidine **7** were carried out (Scheme 4A). In the presence of

Scheme 4. Deuterium Labeling Experiments



DMSO	%-Deuteration of 7 (%)	3q (%)
d_6-DMSO	95	trace
d_6-DMSO	85	~10
DMSO	85	~10

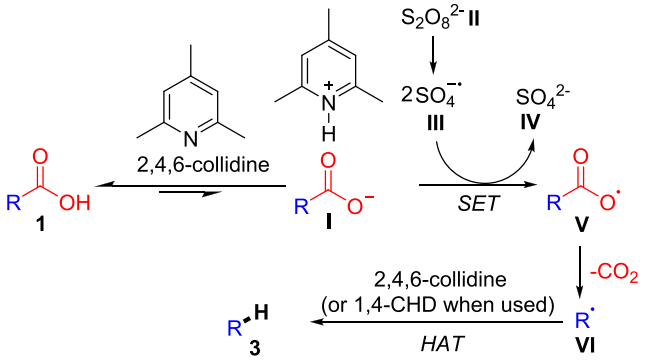


Time (h)	Conversion with 2,4,6-collidine (%)	Conversion with 7 (%)
0.25	38	21
0.5	48	32
1	66	32
2	81	32

95% deuterated **7**, only trace amounts of desired **3q** were observed with no D incorporation. In the presence of 85% deuterated **7**, the yield of **3q** correspondingly increased to ~10%, again with no D incorporation. Examination of the bond dissociation energies (BDEs) would suggest that the benzylic C−H bonds of 2,4,6-collidine[21] are the most likely to be abstracted by alkyl radical **VI**,[22] although it is close to the limit. The inhibitory effect of **7** can be attributed to the increased strength of a C−D bond versus a C−H bond,[23] suggesting that 2,4,6-collidine is the source of the H atoms. A similar inhibitory effect was observed with substrate **1a** (Scheme 4B). Finally, the reaction in Scheme 4A gives the same low yield of **3q** in nondeuterated DMSO, thus ruling out DMSO as the H atom source.

On the basis of the results presented above and the literature,[12a,b,18] we propose the following mechanism (Scheme 5). The reaction is initiated by formation of **I**. Meanwhile, persulfate anion **II** decomposes, in a process accelerated by the

Scheme 5. Proposed Mechanism



DMSO solvent,[13] to give persulfate radical anion **III** (E_{ox} = +2.5−3.1 V vs SHE).[24] **III** can then carry out a single-electron oxidation of **I** (E_{ox} ≈ +1.25−1.31 V vs SCE)[8b] to generate **V**, which quickly decomposes to release CO_2 as well as alkyl radical **VI**. **VI** then undergoes HAT from 2,4,6-collidine to form product **3**. In cases in which the addition of 1,4-CHD is required, 1,4-CHD is the H atom source. In these cases, the improvement in yield can be rationalized as the C−H bond strengths in 1,4-cyclohexadiene[25] are much weaker than those estimated for 2,4,6-collidine, allowing for competitive HAT versus undesired homocoupling.

In conclusion, we have successfully developed a cheap, operationally simple, and scalable method for the hydrodecarboxylation of alkylcarboxylic acids, without the need for any metals or light. The reaction benefits from a broad functional group tolerance, crucially without the addition of an additional noxious or toxic hydrogen atom source. Mechanistic studies indicate that the intermediate radical abstracts H from the base (2,4,6-collidine) for normal substrates. Addition of 1,4-CHD is required only when more reactive radicals are formed, such as benzylic or α to O radicals, to reduce the level of competitive homocoupling.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c04079.

Optimization studies, all of the experimental details, characterization, and copies of NMR data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Ai-Lan Lee − *Institute of Chemical Sciences, Heriot-Watt University, Edinburgh EH14 4AS Scotland, United Kingdom*; orcid.org/0000-0001-9067-8664; Email: A.Lee@hw.ac.uk

Authors

Euan B. McLean − *Institute of Chemical Sciences, Heriot-Watt University, Edinburgh EH14 4AS Scotland, United Kingdom*

David T. Mooney − *Institute of Chemical Sciences, Heriot-Watt University, Edinburgh EH14 4AS Scotland, United Kingdom*

David J. Burns − *Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, United Kingdom*

https://doi.org/10.1021/acs.orglett.1c04079
Org. Lett. 2022, 24, 686−691

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.1c04079

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Engineering and Physical Sciences Research Council, Heriot-Watt University, and CRITICAT Centre for Doctoral Training and Syngenta (Ph.D. studentship to E.B.M., Grant EP/L016419/1) and the Engineering and Physical Sciences Research Council and AstraZeneca for financial support (Industrial CASE Ph.D. studentship to D.T.M., Grant EP/V519522/1).

■ REFERENCES

(1) (a) Schwarz, J.; König, B. Decarboxylative Reactions with and without Light − a Comparison. *Green Chem.* **2018**, *20*, 323−361. (b) Dawes, G. J. S.; Scott, E. L.; Le Nôtre, J.; Sanders, J. P. M.; Bitter, J. H. Deoxygenation of Biobased Molecules by Decarboxylation and Decarbonylation − a Review on the Role of Heterogeneous, Homogeneous and Bio-catalysis. *Green Chem.* **2015**, *17*, 3231−3250.

(2) For example, see: (a) Rossiter, B. E.; Swingle, N. M. Asymmetric Conjugate Sddition. *Chem. Rev.* **1992**, *92*, 771−806. (b) Kagan, H. B.; Riant, O. Catalytic asymmetric Diels Alder reactions. *Chem. Rev.* **1992**, *92*, 1007−1019. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. Enantioselective Copper-Catalyzed Conjugate Addition and Allylic Substitution Reactions. *Chem. Rev.* **2008**, *108*, 2796−2823. (d) Daugulis, O.; Do, H.-Q.; Shabashov, D. Palladium- and Copper-Catalyzed Arylation of Carbon−Hydrogen Bonds. *Acc. Chem. Res.* **2009**, *42*, 1074−1086.

(3) (a) Barton, D. H. R.; Dowlatshahi, H. A.; Motherwell, W. B.; Villemin, D. A New Radical Decarboxylation Reaction for the Conversion of Carboxylic Acids into Hydrocarbons. *J. Chem. Soc., Chem. Commun.* **1980**, 732−733. (b) Barton, D. H. R.; Crich, D.; Motherwell, W. B. New and Improved Methods for the Radical Decarboxylation of Acids. *J. Chem. Soc., Chem. Commun.* **1983**, 939−941. (c) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. Reductive Radical Decarboxylation of Amino-acids and Peptides. *J. Chem. Soc., Chem. Commun.* **1984**, *0*, 1298−1299.

(4) Qin, T.; Malins, L. R.; Edwards, J. T.; Merchant, R. R.; Novak, A. J. E.; Zhong, J. Z.; Mills, R. B.; Yan, M.; Yuan, C.; Eastgate, M. D.; Baran, P. S. Nickel-Catalyzed Barton Decarboxylation and Giese Reactions: A Practical Take on Classic Transforms. *Angew. Chem., Int. Ed.* **2017**, *56*, 260−265.

(5) (a) Itou, T.; Yoshimi, Y.; Nishikawa, K.; Morita, T.; Okada, Y.; Ichinose, N.; Hatanaka, M. A Mild Deuterium Exchange Reaction of Free Carboxylic Acids by Photochemical Decarboxylation. *Chem. Commun.* **2010**, *46*, 6177−6179. (b) Yoshimi, Y.; Itou, T.; Hatanaka, M. Decarboxylative Reduction of Free Aliphatic Carboxylic Acids by Photogenerated Cation Radical. *Chem. Commun.* **2007**, 5244−5246.

(6) (a) Ko, E. J.; Savage, G. P.; Williams, C. M.; Tsanaktsidis, J. Reducing the Cost, Smell, and Toxicity of the Barton Reductive Decarboxylation: Chloroform as the Hydrogen Atom Source. *Org. Lett.* **2011**, *13*, 1944−1947. (b) Ho, J.; Zheng, J.; Meana-Pañeda, R.; Truhlar, D. G.; Ko, E. J.; Savage, G. P.; Williams, C. M.; Coote, M. L.; Tsanaktsidis, J. Chloroform as a Hydrogen Atom Donor in Barton Reductive Decarboxylation Reactions. *J. Org. Chem.* **2013**, *78*, 6677−6687.

(7) (a) Bazyar, Z.; Hosseini-Sarvari, M. On/Off O_2 Switchable Photocatalytic Oxidative and Protodecarboxylation of Carboxylic Acids. *J. Org. Chem.* **2019**, *84*, 13503−13515. (b) Billingham, N. C.; Jackson, R. A.; Malek, F. Free Radical Reactions in Solution. Part 4. Radical-initiated Reduction of Acid Chlorides to Alkanes by Tri-n-propylsilane: Removal of Unwanted Carboxy-groups from Organic Molecules. *J. Chem. Soc., Perkin Trans.* **1979**, *1*, 1137−1141. (c) Hasebe, M.; Tsuchiya, T. Photoreductive Decarboxylation of Carboxylic Acids via their Benzophenone Oxime Esters. *Tetrahedron Lett.* **1987**, *28*, 6207−6210.

(8) (a) Cassani, C.; Bergonzini, G.; Wallentin, C.-J. Photocatalytic Decarboxylative Reduction of Carboxylic Acids and Its Application in Asymmetric Synthesis. *Org. Lett.* **2014**, *16*, 4228−4231. (b) Griffin, J. D.; Zeller, M. A.; Nicewicz, D. A. Hydrodecarboxylation of Carboxylic and Malonic Acid Derivatives via Organic Photoredox Catalysis: Substrate Scope and Mechanistic Insight. *J. Am. Chem. Soc.* **2015**, *137*, 11340−11348. (c) Patra, T.; Mukherjee, S.; Ma, J.; Strieth-Kalthoff, F.; Glorius, F. Visible-Light-Photosensitized Aryl and Alkyl Decarboxylative Functionalization Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 10514−10520. (d) Huang, Z.; Zhao, Z.; Zhang, C.; Lu, J.; Liu, H.; Luo, N.; Zhang, J.; Wang, F. Enhanced Photocatalytic Alkane Production from Fatty Acid Decarboxylation via Inhibition of Radical Oligomerization. *Nature Catal.* **2020**, *3*, 170−178.

(9) (a) Zheng, C.; Wang, G.-Z.; Shang, R. Catalyst-free Decarboxylation and Decarboxylative Giese Additions of Alkyl Carboxylates through Photoactivation of Electron Donor-Acceptor Complex. *Adv. Synth. Catal.* **2019**, *361*, 4500−4505. (b) Bosque, I.; Bach, T. 3-Acetoxyquinuclidine as Catalyst in Electron Donor−Acceptor Complex-Mediated Reactions Triggered by Visible Light. *ACS Catal.* **2019**, *9*, 9103−9109.

(10) (a) Davidson, R. S.; Steiner, P. R. The Photosensitized Decarboxylation of Carboxylic Acids by Benzophenone and Quinones. *J. Chem. Soc. C* **1971**, 1682−1689. (b) Libman, J. Light Induced Charge Transfer Processes. Photochemical Behavior of 1-Cyanonaphthalene in the Presence of Phenylacetic Acid Derivatives. *J. Am. Chem. Soc.* **1975**, *97*, 4139−4141. (c) Okada, K.; Okamoto, K.; Oda, M. A New and Practical Method of Decarboxylation: Photosensitized Decarboxylation of N-Acyloxyphthalimides via Electron-transfer Mechanism. *J. Am. Chem. Soc.* **1988**, *110*, 8736−8738.

(11) Metal-free hydrodecarboxylation of unsaturated carboxylic acids, such as electron-rich aryl carboxylic acids and alkynoic carboxylic acids, however, is known. For examples, see: (a) Fang, J.; Wang, D.; Deng, G.-J.; Gong, H. Transition Metal-Free Protodecarboxylation Of Electron Rich Aromatic Acids Under Mild Conditions. *Tetrahedron Lett.* **2017**, *58*, 4503−4506. (b) Seo, E.; Oh, J.; Lee, S. Metal-Free Decarboxylation of Alkynoic Acids for the Synthesis of Terminal Alkynes. *Asian J. Org. Chem.* **2020**, *9*, 1774−1777.

(12) (a) Sutherland, D. R.; Veguillas, M.; Oates, C. L.; Lee, A.-L. Metal-, Photocatalyst-, and Light-Free, Late-Stage C−H Alkylation of Heteroarenes and 1,4-Quinones Using Carboxylic Acids. *Org. Lett.* **2018**, *20*, 6863−6867. (b) Westwood, M. T.; Lamb, C. J. C.; Sutherland, D. R.; Lee, A.-L. Metal-, Photocatalyst-, and Light-Free Direct C−H Acylation and Carbamoylation of Heterocycles. *Org. Lett.* **2019**, *21*, 7119−7123. (c) Mooney, D. T.; Donkin, B. D. T.; Demirel, N.; Moore, P. R.; Lee, A.-L. Direct C−H Functionalization of Phenanthrolines: Metal- and Light-Free Dicarbamoylations. *J. Org. Chem.* **2021**, *86*, 17282−17293.

(13) Zil'berman, E. N.; Krasavina, N. B.; Navolokina, R. A.; Kharitonova, O. A. Potassium Persulfate Decomposition in Organic Solvents. *Zh. Obshch. Khim.* **1986**, *56*, 937−940.

(14) (a) Anderson, J. M.; Kochi, J. K. Silver(I)-catalyzed Oxidative Decarboxylation of Acids by Peroxydisulfate. Role of Silver(II). *J. Am. Chem. Soc.* **1970**, *92*, 1651−1659. (b) Anderson, J. M.; Kochi, J. K. Silver(II) Complexes in Oxidative Decarboxylation of Acids. *J. Org. Chem.* **1970**, *35*, 986−989. (c) Fristad, W. E.; Fry, M. A.; Klang, J. A. Persulfate/silver Ion Decarboxylation of Carboxylic Acids. Preparation of Alkanes, Alkenes, and Alcohols. *J. Org. Chem.* **1983**, *48*, 3575−3577. (d) Zhan, K.; Li, Y. Microwave-Assisted Silver-Catalyzed Protodecarboxylation and Decarboxylative Iodination of Aromatic Carboxylic Acids. *Catalysts* **2017**, *7*, 314−322. (e) Khotavivattana, T.; Calderwood, S.; Verhoog, S.; Pfeifer, L.; Preshlock, S.; Vasdev, N.; Collier, T. L.; Gouverneur, V. Synthesis and Reactivity of ^{18}F-Labeled α,α-Difluoro-α-(aryloxy)acetic Acids. *Org. Lett.* **2017**, *19*, 568−571.

(15) The low yields with **3c** and **3d** (via unstabilized primary radicals) are due to low reactivity: unreacted starting materials are fully recovered.
(16) The rest of the mass balance for **3l−n** was a complex mixture of products that could not be identified.
(17) Guay, D. R. P. Update on Fenofibrate. *Cardiovasc. Drug Rev.* **2002**, *20*, 281−302.
(18) Teotico, D. G.; Babaoglu, K.; Rocklin, G. J.; Ferreira, R. S.; Giannetti, A. M.; Shoichet, B. K. Docking for Fragment Inhibitors of AmpC β-Lactamase. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 7455−7460.
(19) McCormack, P. L. Tranexamic Acid. *Drugs* **2012**, *72*, 585−617.
(20) Lewis, D. L.; Garrison, A. W.; Wommack, K. E.; Whittemore, A.; Steudler, P.; Melillo, J. Influence of Environmental Changes on Degradation of Chiral Pollutants in Soils. *Nature* **1999**, *401*, 898−901.
(21) The BDEs of the benzylic C−H in 2-methylpyridine and 4-methylpyridine are estimated to be 87.2 and 86.5 kcal mol^{-1}, respectively; the BDE of the benzylic C−H in toluene is 89.8 ± 1.2 kcal mol^{-1}, thereby approximately placing the BDE for benzylic C−H of 2,4,6-collidine within this region: Denisov, E. T.; Tumanov, V. E. Estimation of the bond dissociation energies from the kinetic characteristics of liquid-phase radical reactions. *Russ. Chem. Rev.* **2005**, *74*, 825−858. Also see ref 22.
(22) Alkyl C−H BDE ≈ 95−105 kcal mol^{-1}; BDE of C−H in DMSO = 94.0 kcal mol^{-1}: Luo, Y. *Comprehensive Handbook of Chemical Bond Energies*, 1st ed.; CRC Press: Boca Raton, FL, 2007.
(23) Wiberg, K. B. The Deuterium Isotope Effect. *Chem. Rev.* **1955**, *55*, 713−743.
(24) Liang, C.; Lee, I. L.; Hsu, I. Y.; Liang, C.-P.; Lin, Y.-L. Persulfate Oxidation of Trichloroethylene with and without Iron Activation in Porous Media. *Chemosphere* **2008**, *70*, 426−435.
(25) 1,4-CHD C(sp^3)−H BDE = 74.8 kcal mol^{-1}: Agapito, F.; Nunes, P. M.; Costa Cabral, B. J.; Borges dos Santos, R. M.; Martinho Simões, J. A. Energetic Differences between the Five- and Six-Membered Ring Hydrocarbons: Strain Energies in the Parent and Radical Molecules. *J. Org. Chem.* **2008**, *73*, 6213−6223.

https://doi.org/10.1021/acs.orglett.1c04079
Org. Lett. 2022, 24, 686−691