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# Photocatalytic Decarboxylative Reduction of Carboxylic Acids and Its Application in Asymmetric Synthesis

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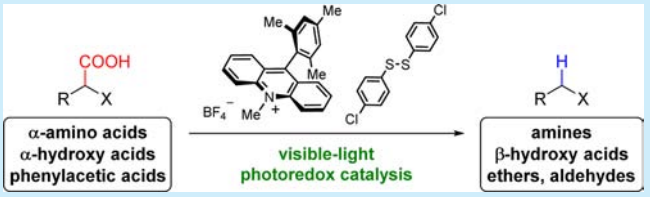
Supporting Information

**ABSTRACT:** The decarboxylative reduction of naturally abundant carboxylic acids such as α-amino acids and α-hydroxy acids has been achieved via visible-light photoredox catalysis. By using an organocatalytic photoredox system, this method offers a mild and rapid entry to a variety of high-value compounds including medicinally relevant scaffolds. Regioselective decarboxylation is achieved when differently substituted dicarboxylic acids are employed. The application of this method to the synthesis of enantioenriched 1-aryl-2,2,2-trifluoroethyl chiral amines starting from natural α-amino acids further testifies to the utility of the developed photocatalytic decarboxylative reduction protocol.




Carboxylic acids are abundant and inexpensive biomass-derived platform molecules. Their conversion into high-value chemical products such as medicinally relevant compounds and biofuels represents an important goal in organic chemistry.[1] Decarboxylation is a crucial transformation in various scientific disciplines, and several synthetic procedures to reductively remove $CO_2$ from organic molecules have thus been developed.[2] One of the most utilized is the Barton protocol which relies on the reaction of thiohydroxamic esters in the presence of a stoichiometric amount of a hydrogen atom transfer reagent.[3] Complementary photochemical protocols targeting various types of carboxylic acids have been disclosed.[4] However, they mostly rely on the use of UV-light and a stoichiometric amount of photosensitizer which represent considerable disadvantages of the procedures.

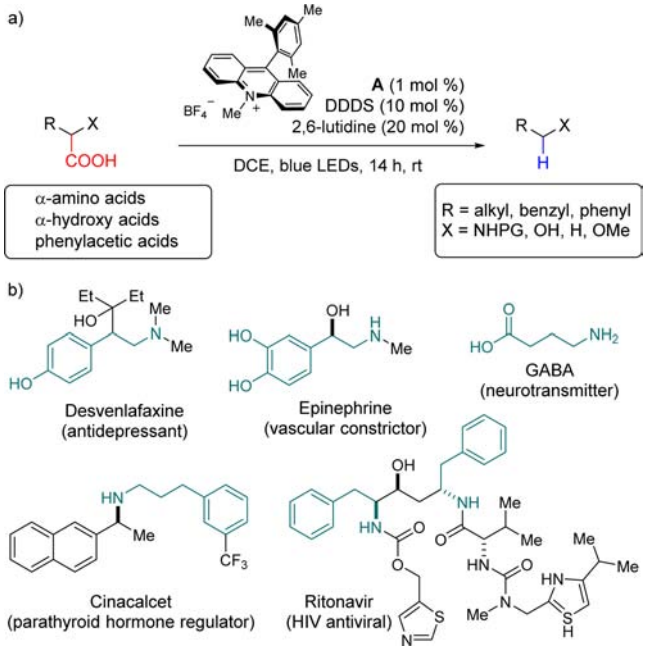
With the recent rise of visible-light photoredox catalysis,[5] reports on the use of reactive radicals generated via photocatalytic decarboxylation have been published.[6] Despite these important contributions, a discrete photocatalytic decarboxylative reduction of broadly available α-amino and α-hydroxy acids remains largely unexplored.

Herein, we describe the successful implementation of a mild organocatalytic photoredox system in an operationally simple decarboxylation reaction (Scheme 1a). By using the acridinium photoredox catalyst **A** in combination with bis(4-chlorophenyl)disulfide (DDDS) under visible-light irradiation,[7,8] the method efficiently gives access to high-value amine scaffolds which are ubiquitous in biologically active molecules (Scheme 1b).

This catalytic system also promotes the decarboxylative formation of hydrocarbons, aldehydes, ethers, and β-hydroxy acids, an ability that further expands the synthetic utility of the system.

At the onset of our investigations, we hypothesized that an initial photoinduced electron transfer (PET) should occur between the carboxylic acid and the excited state of the photocatalyst. Thus, a catalyst with a greater oxidation potential than that of carboxylic acids would be needed. We selected the

**Scheme 1. (a) Photoredox Catalyzed Reductive Decarboxylation of Biomass; (b) Examples of N-Containing Bioactive Compounds Potentially Accessible Using the Presented Decarboxylation Protocol**[a]




[a]DDDS = bis(4-chlorophenyl)disulfide. DCE = 1,2-dichloroethane. PG = protecting group.

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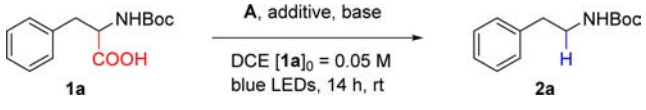
Fukuzumi acridinium **A**,[9] one of the strongest oxidizing catalysts ($E_{1/2}^{red}$ = +2.06 V vs SCE) explored within the field of photoredox catalysis, as a suitable first choice. Catalyst **A** was evaluated using Boc-Phe-OH as the model substrate under basic conditions and in the presence of a compatible hydrogen donor (Table 1).

**Table 1. Optimization of the Photocatalytic Decarboxylative Reduction**[a]




| entry | (**A** mol %) | additive (mol %) | base (mol %) | yield (%)[b] |
|---|---|---|---|---|
| 1 | 5 | thiophenol (50) | coll. (110) | 20 |
| 2 | 5 | PhSSPh (50) | coll. (110) | 75 |
| 3 | 5 | – | coll. (110) | 0 |
| 4 | – | PhSSPh (50) | coll. (110) | 0 |
| 5[c] | 5 | PhSSPh (50) | coll. (110) | 0 |
| 6 | 5 | PhSSPh (50) | – | 0 |
| 7[d] | 1 | PhSSPh (50) | coll. (110) | 79 |
| 8[d] | 1 | PhSSPh (10) | coll. (110) | 80 |
| 9[d] | 1 | PhSSPh (10) | coll. (20) | 85 |
| 10[d] | 1 | PhSSPh (10) | lut. (20) | 95 |
| 11[d] | 1 | DDDS (10) | lut. (20) | >95 |

[a]Reactions performed on 0.1 mmol scale and irradiated with 8 W blue LEDs. [b]Determined by $^1$H NMR. [c]Reaction performed in the dark. [d]$[\mathbf{1a}]_0$ = 0.025 M. Boc = *tert*-butoxycarbonyl. DCE = 1,2-dichloroethane. Coll. = 2,4,6-collidine. Lut. = 2,6-lutidine.

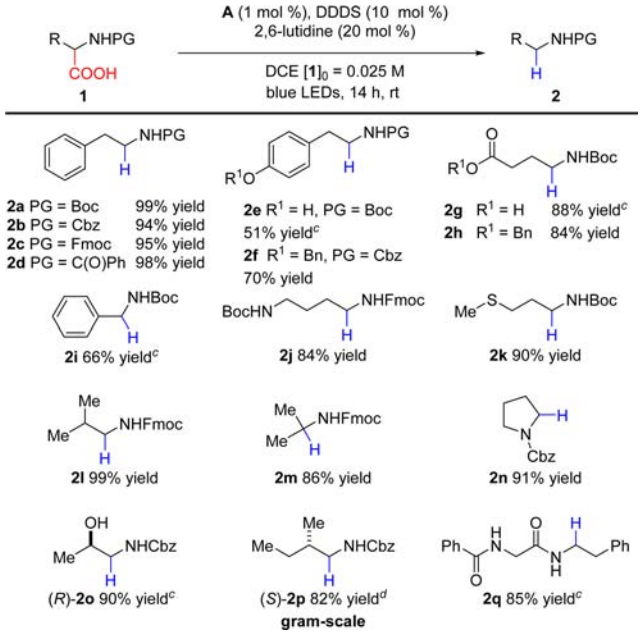
The use of thiophenol as the hydrogen atom donor provided the corresponding amine **2a** in poor yield (entry 1).[10] However, employing the less toxic phenyl disulfide, which has previously been shown to act as a phenyl thiyl radical reservoir[7] (and thus as a potential redox-coupled hydrogen shuttle), the yield of **2a** was significantly increased (entry 2). As anticipated, control experiments performed in the absence of the disulfide, the photocatalyst, or the light source completely impeded any reactivity (entries 3–5). Furthermore, it was noted that the addition of an external base was necessary to promote the reaction (entries 2 and 6). This observation is consistent with the participation of the carboxylate anion in the envisioned PET event.

Further tuning of the reaction conditions allowed us to decrease both the photocatalyst and disulfide loading to 1 and 10 mol %, respectively (entries 7–10). A final screening of various disulfides revealed that, by using the more electron-deficient DDDS, quantitative conversion could be achieved (entry 11).

With optimized conditions in hand, we investigated the scope of $\alpha$-amino acid derivatives. To our delight, the reaction proceeds in good to excellent yield with a wide range of substrates bearing different functional groups, including esters, ethers, amines, alcohols and thioethers (Scheme 2). Various *N*-protecting groups, including carbamate and benzoyl, are well-tolerated, providing the corresponding amines in excellent yield (**2a**–**2d**). Notably, 1,4-diamine **2j** equipped with two orthogonal protecting groups is conveniently obtained from the corresponding $\alpha$-amino acid.

By applying the method to substrate acids bearing an enantiopure $\beta$-stereocenter, the synthesis of (*R*)-**2o** and (*S*)-**2p** illustrates the general stereochemical compatibility of the

**Scheme 2. Scope of the Photocatalytic Decarboxylative Reduction $\alpha$-Amino Acids**[a,b]




[a]Reactions performed on 0.2 mmol scale and irradiated with 8 W blue LEDs. [b] Isolated yield. [c] Reaction performed using 5 mol % of photocatalyst **A** in combination with 1 equiv of DDDS. [d] Reaction carried out on 4 mmol (1.060 g) scale; reaction time = 36 h.

method. Moreover, it was found that dipeptides are also efficiently decarboxylated under the reaction conditions (**2q**). Importantly, *N*-protected neurotransmitters, such as phenylethylamine and GABA, could easily be accessed from the corresponding $\alpha$-amino acids (products **2a**, **2e**, and **2g**). $\alpha$-Amino acids bearing hydroxyl or $\alpha$-phenyl groups performed moderately under the optimized conditions. However, by increasing the catalyst and the DDDS loading, the corresponding products could be accessed in a more practical yield (**2e**, **2g**, **2i**, and (*R*)-**2o**). Remarkably, the optimized protocol was successfully applied to a gram-scale (4 mmol, 20-fold scale-up) reduction of Cbz-Ile-OH providing the valuable aliphatic amine (*S*)-**2p** in 82% yield.[11]

We next focused on more challenging optically active aliphatic amines, since they constitute the core unit of many pharmaceutical compounds (e.g., Cinacalcet, Scheme 1b).[12] The introduction of fluorine-containing functional groups is a chemical strategy often exploited to modulate the biological activity of drug candidates.[13] For this reason, we aimed to combine our decarboxylative protocol with the diastereoselective reductive amination of different amino acids previously described by Hughes and Devine (Table 2).[14]

Fortunately, $\alpha$-amino acids **4a**–**d** efficiently underwent decarboxylative reduction with no need for protecting groups giving access to relevant fluorine-containing amines **5a**–**d** without erosion of the enantiopurity at the benzylic stereogenic center. Thus, the carboxylic functionality on the $\alpha$-amino acid was successfully employed as a traceless chirality transfer element to access enantioenriched secondary amines.

Finally, we sought to extend the applicability of our mild protocol to other challenging classes of abundant carboxylic acids, namely phenylacetic acids (Scheme 3) and $\alpha$-hydroxy acids (Scheme 4). As shown in Scheme 3, exposing primary,


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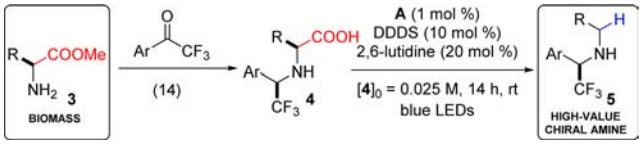
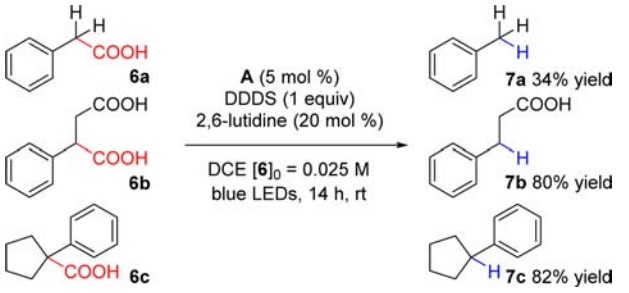
**Table 2. Visible-Light Decarboxylative Reduction of Enantioenriched 1-Aryl-2,2,2-trifluoroethyl-Substituted Amino Acids**[a]




| entry | R | Ar | 4 dr[b] (syn:anti) | 5 yield (%)[c] | ee[d] |
|---|---|---|---|---|---|
| 1 | *i*-Pr | 4F-Ph | 11:1 | (*R*)-**5a** (72) | 83 |
| 2[e] | *i*-Pr | Ph | 46:1 | (*S*)-**5b** (75) | 97 |
| 3 | $(CH_2)_2SCH_3$ | Ph | 6:1 | (*R*)-**5c** (76) | 69 |
| 4 | Bn | Ph | 18:1 | (*R*)-**5d** (37) | 88 |

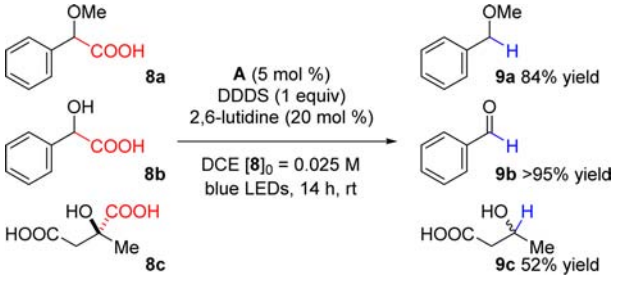
[a]Product **4** was obtained following literature procedures.[14] [b]Determined by $^{19}F$ NMR. [c]The values in parentheses refer to the isolated yields of products **5**. [d]Determined by HPLC or GC on chiral stationary phase. [e]The D-$\alpha$-amino ester was used as starting material.

**Scheme 3. Photoredox Catalyzed Decarboxylative Reduction of Phenylacetic Acids**[a]




[a]Yield of product **7a** was determined by GC analysis; yields of **7b–c** refer to the isolated compounds.

**Scheme 4. Photoredox Decarboxylation of $\alpha$-Hydroxy Acids**[a]




[a]Yields of products **9a–b** were determined by $^1H$ NMR; the yield of **9c** refers to the isolated compound.

secondary, and tertiary phenylacetic acids **6a–c** to 5 mol % of the photocatalyst **A** in the presence of 1 equiv of DDDS under visible light provided the corresponding decarboxylated products **7a–c** in moderate to good yields.

As expected, di- and trisubstituted acids **6b–c** performed better than primary phenylacetic acid **6a**. Moreover, regioselective decarboxylation at the benzylic position was observed for substrate **6b**. These results can be rationalized in terms of stability of the respective radical intermediates.

Naturally abundant $\alpha$-hydroxy carboxylic acid derivatives have also been evaluated as substrates under the present conditions. As shown in Scheme 4, $\alpha$-methoxyphenylacetic acid **8a** smoothly provided the corresponding ether with high efficiency. Notably, our photocatalytic protocol promoted the decarboxylation of the aliphatic citramalic acid **8c**, yielding the corresponding racemic $\beta$-hydroxy acid **9c** with complete regioselectively. The stereochemical outcome of this particular reaction is consistent with a radical mechanism. Interestingly, mandelic acid **8b** quantitatively furnished benzaldehyde **9b** as the product. This outcome may be rationalized by a higher oxidation potential, under basic conditions, for the $\alpha$-hydroxy radical intermediate as compared to the one derived from the $\alpha$-methoxyphenylacetic acid **8a**.

A plausible reaction mechanism (Figure 1) begins with the photoexcitation of the catalyst **A**. Single-electron oxidation of

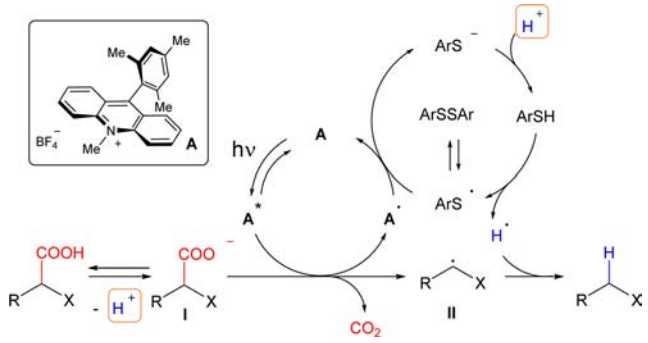



**Figure 1.** Proposed mechanism for the photocatalytic reductive decarboxylation.

carboxylate **I** by **A*** provides, after $CO_2$ extrusion, radical **II** together with $\mathbf{A}^{\bullet}$. In accordance with the mechanism recently proposed by Nicewicz and co-workers,[7] the acridine radical may be oxidized by the thiyl radical, which exists in equilibrium with the corresponding disulfide, to regenerate the ground state of photocatalyst **A**. The so-produced thiolate anion can then be protonated and act as a hydrogen-atom donor toward radical species **II** to furnish the final reduced product. Thus, the disulfide plays the role of a redox-coupled hydrogen shuttle.

In the specific case of generating **9b**, a second single-electron transfer from the radical of type **II** to the DDDS may occur producing the corresponding disulfide radical anion which is known to rapidly decay into the corresponding thiyl radical and the thiolate anion.[15,16] In this scenario, the disulfide acts not only as an indirect hydrogen donor but also as a stoichiometric oxidant. This oxidation pathway is supported by the observation of an unusually high amount of 4-chlorothiophenol in the crude reaction mixture.

In conclusion, we have developed an operationally simple visible-light photocatalytic decarboxylative reduction of biomass-derived platform compounds such as $\alpha$-amino acids and $\alpha$-hydroxy acids. The protocol presents a mild and energy-efficient system which offers a viable alternative to other classical methods often relying on stoichiometric additives and/or a high temperature. The method provides direct and easy access to hydrocarbons, $\beta$-hydroxy acids, ethers, aldehydes, and also biologically relevant enantioenriched amines. Novel photocatalytic transformations involving the decarboxylative transformation of naturally occurring platform molecules are currently under investigation in our laboratory and will be reported in due course.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## ■ ASSOCIATED CONTENT

### Supporting Information

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

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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