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# Selective Reduction of Carboxylic Acids to Aldehydes with Hydrosilane *via* Photoredox Catalysis

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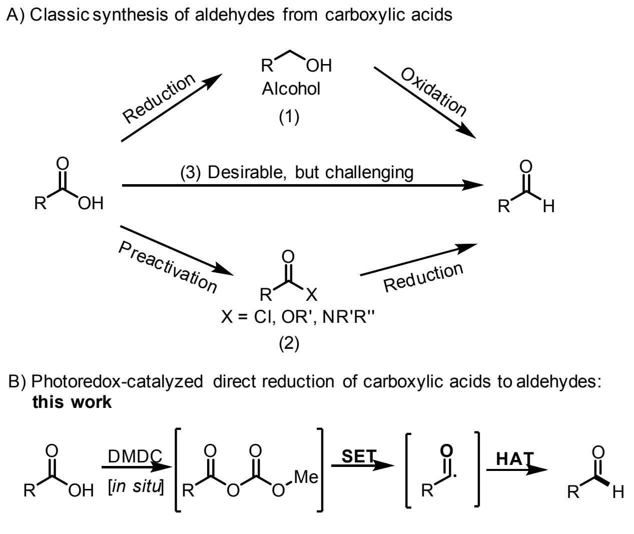
**The direct reduction of carboxylic acids to aldehydes with hydrosilane was achieved through visible light photoredox catalysis. The combination of both single electron transfer and hydrogen atom transfer steps offer a novel and convenient approach to selective reduction of carboxylic acids to aldehydes. The method also features mild conditions, high yields, broad substrate scope, and good functional group tolerance, such as alkyne, ester, ketone, amide and amine groups.**

The reduction of carboxylic acids to aldehydes is one of the most important functional group transformations, which is frequently encountered in organic synthesis.[1] As is known, a two-step procedure is often empolyed for the preparation of aldehydes, involving either full formation to alcohol prior to re-oxidation to aldehyde (Scheme 1A, path 1),[2] or the transformation of carboxylic acids to more reactive acyl halides,[3] acid anhydrides,[4] amides [5] and activated esters,[6] which are followed by hydrogenation or hydride reduction to aldehydes (Scheme 1A, path 2). While direct reductions by strong reductants, such as lithium in methylamine,[7] alane,[8] thexylborane[9] are classic means for effecting the reaction, it is still a great challenge to selectively control the chemoselectivity due to the ready reduction of aldehydes to alcohols (Scheme 1A, path 3).[10] In addition, these reductants are often incompatible with many sensitive functional groups. In this context, the availability of a simple and chemoselective strategy for the direct reduction of carboxylic acids to aldehydes will continue to have a significant impact on chemical synthesis.



Scheme 1 Reduction of carboxylic acids to aldehydes

Recently, visible light-induced photoredox catalysis has emerged as a powerful protocol for activating carboxylic acids, which could be easily converted into many valuable chemical products.[11] These methods most depend on photo-induced single electron oxidation of carboxylates, leading to the formation of reactive radical intermediates after $CO_2$ extrusion. Consequently, a great number of radical transformations have been developed using this oxidative mode under mild conditions.[12] In addition, there are few reports that carboxylic acids are used for the generation of acyl radicals by single electron transfer (SET) reductive process. The Wallentin group reported a redox-neutral approach for the visible-light-mediated tandem acyl arylation of olefins and multicomponent 1,2-acylalkylation of alkenes.[13] Very recently, our group achieved hydroacylation of olefins employing carboxylic acids and hydrosilanes via photoredox catalysis.[14] However, current applications of visible light-induced acyl radical reactions are only limited to radical addition onto carbon-carbon multiple bonds. Seeking to develop more conversions for carboxylic acids, we continued our further

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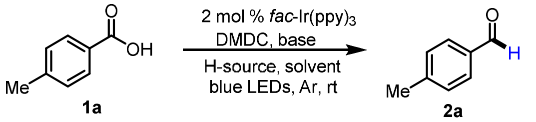
study on acyl radical intermediates produced by a SET reductive process. To the best of our knowledge, no direct reduction of carboxylic acids to aldehydes *via* photoredox catalysis has been reported. We wondered whether acyl radicals generated by SET would rapidly undergo hydrogen atom transfer (HAT) from a suitable source of hydrogen in the system, which lead to direct formation of aldehydes (Scheme 1 B). We herein present a practical and simple process for the challenging transformation of carboxylic acids into aldehydes *via* photoredox catalysis.

Table 1 Optimization of the Reaction Conditions[a]

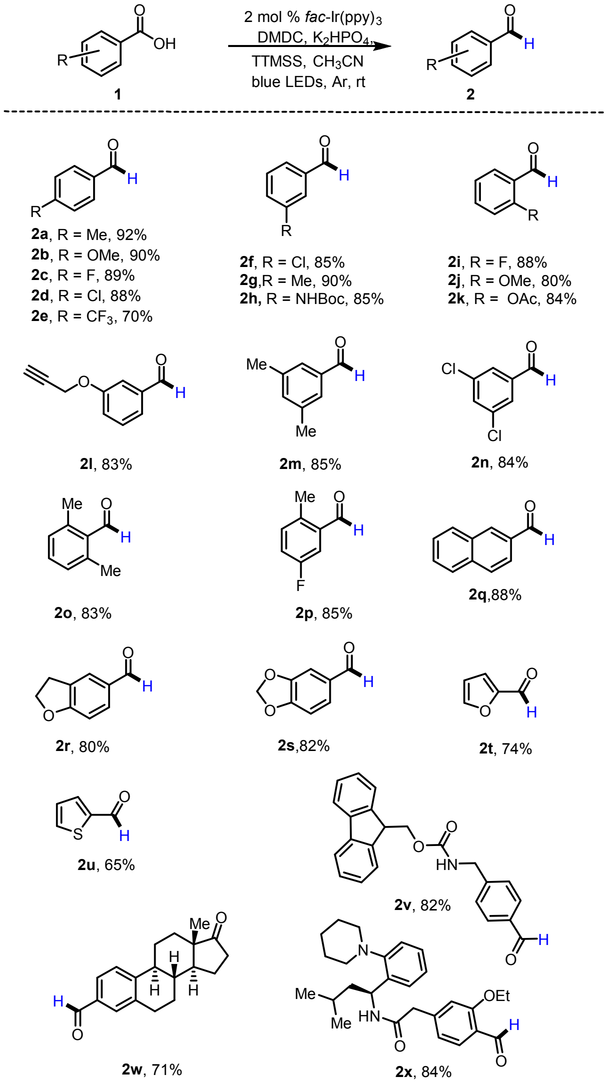


| entry | photo. | base | H source | solvent | yield[b] |
|---|---|---|---|---|---|
| 1 | *fac*-Ir(ppy)$_3$ | $K_2CO_3$ | DIPEA-HE | DMF | 12 |
| 2 | *fac*-Ir(ppy)$_3$ | $K_2CO_3$ | DIPEA-HE | dioxane | -- |
| 3 | *fac*-Ir(ppy)$_3$ | $K_2CO_3$ | DIPEA-HE | DMSO | 10 |
| 4 | *fac*-Ir(ppy)$_3$ | $K_2CO_3$ | DIPEA-HE | DCE | -- |
| 5 | *fac*-Ir(ppy)$_3$ | $K_2CO_3$ | DIPEA-HE | $CH_3CN$ | 18 |
| 6 | *fac*-Ir(ppy)$_3$ | $K_2CO_3$ | DIPEA | $CH_3CN$ | -- |
| 7 | *fac*-Ir(ppy)$_3$ | $K_2CO_3$ | HE | $CH_3CN$ | 8 |
| 8 | *fac*-Ir(ppy)$_3$ | $K_2CO_3$ | TTMSS | $CH_3CN$ | 80 |
| **9** | ***fac*-Ir(ppy)$_3$** | **$K_2HPO_4$** | **TTMSS** | **$CH_3CN$** | **92** |
| 10 | *fac*-Ir(ppy)$_3$ | 2,6-Lutidine | TTMSS | $CH_3CN$ | 15 |
| 11 | *fac*-Ir(ppy)$_3$ | $Cs_2CO_3$ | TTMSS | $CH_3CN$ | -- |
| 12 | -- | $K_2HPO_4$ | TTMSS | $CH_3CN$ | -- |
| 13[c] | *fac*-Ir(ppy)$_3$ | $K_2HPO_4$ | TTMSS | $CH_3CN$ | -- |

[a]The reactions were carried out with **1a** (0.1 mmol), DMDC (0.3 mmol, 3.0 equiv), base (0.2 mmol, 2.0 equiv), photocatalyst (0.002 mmol, 2 mol %), solvent (2 mL), TTMSS (0.2 mmol, 2.0 equiv), at room temperature, 5 W blue LEDs, 6 h. [b]Isolated yields. [c]Reaction performed in the absence of light.

To assess the feasibility of our catalytic strategy, we began our investigation with 4-methylbenzoic acid **1a** in the presence of dimethyl dicarbonate (DMDC), which made mixed anhydride intermediates obtained as oxidative quenchers of a photocatalyst. As shown in Table 1, different solvents were examined using *fac*-Ir(ppy)$_3$ as the photoredox catalyst, *N,N*-diisopropylethylamine (DIPEA) and Hantzsch ester (HE) as hydrogen sources, in the presence of $K_2CO_3$ under argon atmosphere. Although the carboxylic acid could be directly reduced to produce aldehyde, the yield was quite low (entries 1-7). The most compound we isolated was the mixed anhydrides produced in the reaction solution. We speculated that the reductive efficiency of the acyl radical by the hydrogen source was not very good in the system, which resulted in the vast majority of raw materials not reacting. As is known, tris(trimethylsilyl)silane (TTMSS) is also a potent hydrogen atom donor, representing a substitute for tin hydride. We posited that the reductive efficiency of acyl radicals could be improved by the presence of TTMSS. Using this protocol, an 80% yield of the aldehyde product was actually obtained, when DIPEA-HE was replaced by TTMSS (entry 8). Then, examination of a range of bases revealed that two equivalents of $K_2HPO_4$ was superior (92% yield) and the organic base was not conducive to the reaction (entries 9-11). Finally, control experiments confirmed the requirement of a photocatalyst, and a light source in this new selective reduction reaction of carboxylic acids (entries 12 and 13).

Scheme 2 Scope of Carboxylic Acids in Reduction to Aldehyde Reaction[a]



[a]Reaction conditions: **1** (0.1 mmol), DMDC (0.3 mmol, 3.0 equiv), TTMSS (0.2 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (0.002 mmol, 2 mol %), $K_2HPO_4$ (0.2 mmol, 2.0 equiv), $CH_3CN$ (2 mL), at room temperature, 5 W blue LEDs, 6 - 24 h.

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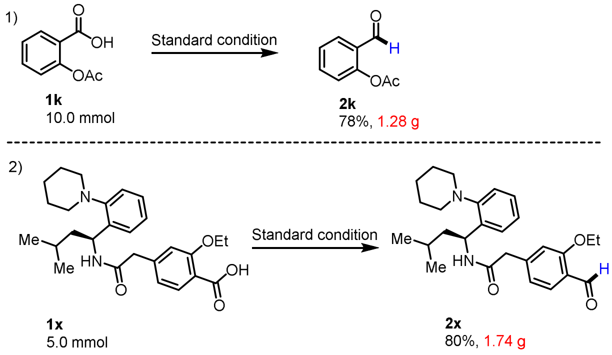
With the optimized reaction conditions above, we examined a variety of functionalised carboxylic acids (Scheme 2), and were pleased to find effective reduction of carboxylic acids to aldehydes for a wide substrate range. Most of the carboxylic acids bearing electron-donating (methyl, methoxyl) or electron- withdrawing (fluoro, chloro) groups provided the corresponding aldehydes (**2a**-**2d**) in high yields under standard conditions, whereas the yield declined to 70% (**2e**) for the carboxylic acid with strong electron-withdrawing trifluoromethyl group. The position of the substituents on the aromatic ring does not significantly affect the reaction. *Meta*-(methyl, chloro, amide) and *ortho*-(fluoro, methoxy, acetoxy) acids were found to be suitable substrates for this transformation (**2f**-**2h**, **2i**-**2k**). Moreover, free alkynyl, amide and ester groups were well tolerated in this reaction system. Multiply substituted aldehydes (**2m**-**2p**) could also be easily produced in good yields from the corresponding acids. Heteroaromatic acids including thiophenes and furans reacted smoothly to give aldehydes (**2t**-**2u**). This visible light photocatalytic single-electron reduction process allows the application of complex molecules under our standard reaction conditions. Some biologically important molecule-derived carboxylic acids, such as estrone and prandin, could undergo this single-electron reduction reaction to give the corresponding aldehyde product (**2w**, **2x**). The presence of an amine or ketone did not inhibit the reaction. However, aliphatic carboxylic acids such as 3-phenylpropanoic acid, cyclohexanecarboxylic acid, and *N*-Boc-glycine were used as substrates, and no formation of the corresponding aldehydes were observed. Aliphatic acids possessing electron-withdrawing groups such as benzoyl, trifluoromethyl, were subjected to the standard condition, the only mixed anhydride of aliphatic acids were also isolated.

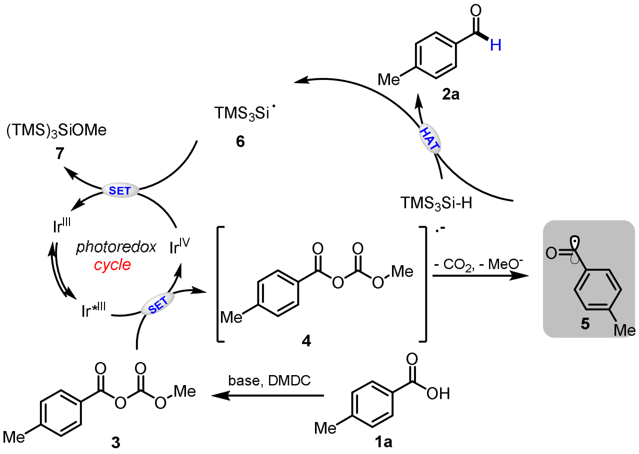
In addition, demonstrations of the synthetic utility of our selective reductive catalytic strategy for carboxylic acids with HAT have been performed. A gram-scale carboxylic acid reduction reaction was carried out under standard conditions, which afforded the desired aldehyde products **2k** and **2x** in good yield (Scheme 3).



Scheme 3 Gram Scale Reduction

The fluorescence quenching experiments were performed and the results of a series of Stern–Volmer quenching studies revealed that mixed anhydride of aromatic acid efficiently quenched the excited state of the photocatalyst, (see: supporting information). Based on experimental results and our previous research work,[14] a proposed mechanism for single electron reduction reaction of carboxylic acids is depicted in Scheme 4. The anhydride intermediate **3** is quickly produced from aromatic carboxylic acid **1a** and DMDC in the presence of base. Under visible-light irradiation, the photocatalyst *fac*-Ir(ppy)$_3$ leads to the generation of a long-lived excited state $Ir^{*III}$, undergoing a metal to ligand charge-transfer (MLCT) pathway. Then a SET process from this strongly reducing excited state species $Ir^{*III}$ to **3** will generate acyl radical precursor **4** and $Ir^{IV}$. **4** delivers acyl radical **5** along with CO$_2$ and methoxide after fragmentation. At this time, acyl radical **5** rapidly undergoes hydrogen atom transfer from H source TTMSS, delivering the aldehyde product **2a** and silyl radical **6**. Finally, another SET step can occur between **6** and Ir, regenerating the ground state photocatalyst, and (TMS)$_3$SiOMe **7** is detected in the reaction mixture by GC–MS.

Scheme 4 Proposed Mechanism



## Conclusions

In summary, we have successfully designed a simple catalytic system to reduce carboxylic acids based on the photoinduced electron transfer processes. The disclosed photoredox-catalyzed selective reduction of carboxylic acids with hydrosilanes represents a mild and novel method for aldehyde synthesis. Attractive features of this process include use of hydrosilanes, which effectively intercept acyl radical through a HAT process. The reaction also has good substrate suitability and functional group tolerance, and high yield, making it a valuable alternative to the existing protocols. In addition, we will continue working on new visible light photoredox-catalyzed transformation involving carboxylic acids.

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