# Acyl Radicals from Aromatic Carboxylic Acids by Means of Visible-Light Photoredox Catalysis

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Abstract: *Simple and abundant carboxylic acids have been used as acyl radical precursor by means of visible-light photoredox catalysis. By the transient generation of a reactive anhydride intermediate, this redox-neutral approach offers a mild and rapid entry to high-value heterocyclic compounds without the need of UV irradiation, high temperature, high CO pressure, tin reagents, or peroxides.*

Carboxylic acids are abundant and inexpensive starting materials readily available in great structural diversity. For this reason, continuous efforts have been made to engage this class of compounds in novel catalytic organic transformations.[1] In more recent years, visible-light photoredox catalysis has emerged as a benign and powerful tool in organic synthesis, and novel strategies targeting carboxylic acids as building blocks have been developed.[2] Those methods rely on photo-induced oxidation of carboxylates to generate, after CO_2 extrusion, reactive alkyl radical intermediates (Scheme 1a).[3] Capitalizing upon the high synthetic potential of visible-light photoredox catalysis, we questioned whether carboxylic acids might be used for the generation of acyl radicals by single-electron reduction (Scheme 1b).[4] This would offer an unprecedented synthetic method that extends beyond the existing routes to access acyl radicals, which are often characterized by harsh conditions (UV irradiation, high temperature, high CO pressure, tin reagents, or peroxides) or the need of pre-generated acyl radical precursors such as telluroesters, selenoesters, and thioesters.[3j; 5]

We envisioned that transient mixed anhydride intermediates, obtained from simple carboxylic acids in the presence of dimethyl dicarbonate (DMDC),[6] could be engaged as oxidative quenchers of a photocatalyst to generate the desired acyl radical species, along with CO_2 and methanoate as the only byproducts.[7,8] This would provide carboxylic acids with orthogonal redox reactivity under mild photocatalytic con-
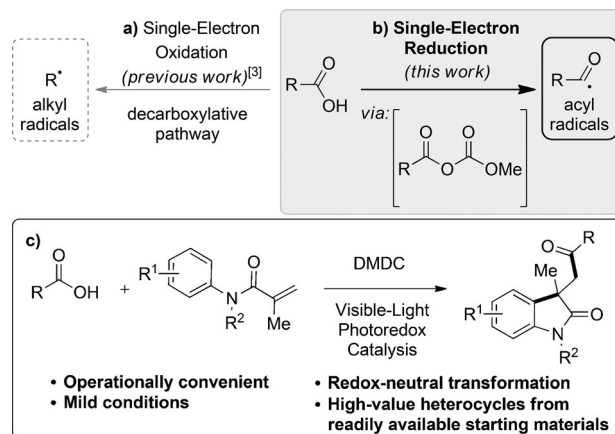
Scheme 1. a,b) Generation of reactive radical species from simple carboxylic acids by means of visible-light photoredox catalysis. c) Photocatalyzed redox-neutral acylarylation of methacrylamides using benzoic acids as starting material. DMDC = dimethyl dicarbonate.

ditions and a novel entry to a broader spectrum of accessible products.

At the onset of our investigation, we tested our idea for the formation of 3,3-disubstituted 2-oxindoles by 1,2-acylarylation of alkenes (Scheme 1c). The 3,3-disubstituted 2-oxindoles containing the carbonyl functionality are common structural motifs in pharmaceutical and bioactive natural products, and represent versatile intermediates in organic synthesis.[9]

Consequently, in the last few years, the development of efficient synthetic methods for the synthesis of 3,3-disubstituted 2-oxindoles has received increased interest. Among these, 1,2-acylarylation of methacrylamides has emerged as a particularly interesting approach.[10] However, the use of stoichiometric amounts of external oxidants, high temperature, or high-energy UV light represent considerable disadvantages of the procedures.
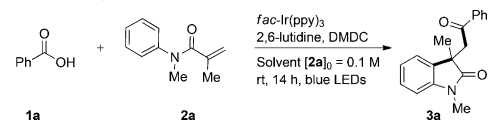
Herein we report the first redox-neutral approach for the mild visible-light-mediated tandem acylarylation of olefines using carboxylic acids as an acyl radical source. We first explored the proposed acylarylation reaction using benzoic acid **1a** and *N*-methyl-*N*-phenylmethacrylamide **2a** as the model substrates in the presence of the photocatalyst, DMDC, and 2,6-lutidine under visible-light irradiation (Table 1). We were pleased to find that the strongly reducing *fac*-Ir(ppy)$_3$ provided the desired product **3a** in excellent yield (entry 1). In contrast, much weaker reductants such as [Ir(ppy)$_2$(dtbbpy)]$^+$ and [Ru(bpy)$_3$]$^{2+}$ were unable to promote the reaction (Supporting Information, Table S1, entries 1 and

[*] Dr. G. Bergonzini,[+] Dr. C. Cassani,[+] Dr. C.-J. Wallentin
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Table 1: Selected optimization studies.[a]

Entry	fac-Ir(ppy)$_3$ [mol%]	DMDC [equiv]	2,6-lutidine [equiv]	Solvent	Yield [%][b]
1	1	4	2	DMA	>95
2[c,d]	0.5	3	0.5	DMF	>95
3[c,e]	0.5	3	0.5	DMF	<5
4[c,e,f]	0.5	3	0.5	DMF	88

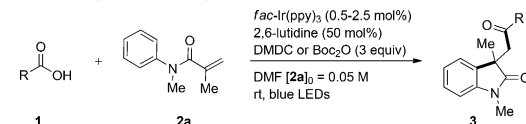[a] Reactions performed on 0.1 mmol scale using 2 equiv of **1a**.
[b] Determined by ^{1}H NMR using 2,5-dimethylfuran as internal standard.
[c] Performed with 1.5 equiv of **1a**; [**2a**]$_0$ = 0.05 м. [d] Reaction
time = 6 h; [e] Reaction performed with 3 equiv of Boc$_2$O instead of
DMDC; [f] Addition of 1 equiv of MgCl$_2$. DMA = N,N-dimethylaceta-
mide; DMF = N,N-dimethylformamide.

Table 2: Carboxylic acid scope.[a]

3a R^1 = H 97% yield[f]
3b R^1 = Cl 93% yield[b]
3c R^1 = Ph 89% yield[b]
3d R^1 = OMe 81% yield[c]
3e R^1 = Me 99% yield[d]
3f R^1 = CF$_3$ 72% yield[d]
3g R^1 = OBoc 99% yield[d,e]

3h R^1 = Cl, R^2 = H 95% yield[c]
3i R^1 = Me, R^2 = H 80% yield[c]
3j R^1 = NHCOOMe, R^2 = H 76% yield[c]
3k R^1 = Cl, R^2 = OMe 89% yield[c]

3l R^1 = Cl 84% yield[b]
3m R^1 = Me 99% yield[d]

3n R = naphthalen-2-yl 90% yield[b]
3o R = thyophen-2-yl 78% yield[d]
3p R = furan-2-yl 55% yield[d]
3q R = pyridin-3-yl 65% yield[d]
3r R = 1-methylindol-2-yl 33% yield[d]

3s 83% yield[g] (1:1 d.r.)

[a] Reactions performed on 0.2 mmol scale. Yield of isolated product.
[b] Reaction performed using 0.5 mol% of fac-Ir(ppy)$_3$ and 3 equiv of
DMDC over 6 h (Method A). [c] Method A using 2.5 mol% of fac-Ir(ppy)$_3$
over 14 h. [d] Reaction performed with 2.5 mol% of fac-Ir(ppy)$_3$, 3 equiv
of Boc$_2$O and 1 equiv of MgCl$_2$ over 48 h (Method B). [e] 4 equiv of
Boc$_2$O were used. [f] Reaction carried out with Method A on 1 mmol
scale; reaction time = 10 h. [g] See the Supporting Information for
details.

2). Control experiments performed in the absence of the
photocatalyst, the dicarbonate or the light source completely
impeded any reactivity (Supporting Information, Table S1,
entries 4–6). Fine tuning of the reaction conditions provided
the desired product quantitatively while also decreasing
reaction time and catalyst loading (Table 1, entry 2, Meth-
od A). When di-tert-butyl dicarbonate (Boc$_2$O) was used
instead of DMDC to generate the corresponding mixed
anhydride, only traces of product **3a** were found (entry 3).
However, upon Lewis acid activation of Boc$_2$O with the
addition of MgCl$_2$ the product was obtained in high yield
(entry 4).[11]

With the optimized conditions in hand (Method A), we
examined the scope of the acid component.

As shown in Table 2, the reaction proceeds in good to
excellent yield with a broad range of benzoic acids bearing
different substituents in the para-, meta-, and ortho-position
as well as carboxylic acids with extended aromatic systems
(**3a–3n**). Ortho- and para-methyl, as well as para-hydroxy and
para-trifluoromethyl benzoic acid, performed poorly under
the optimized conditions, and fast conversion of these acids
into the corresponding unreactive methyl esters was
observed.[12] However, they could be efficiently employed
(**3e–3g**, **3m**) by replacing DMDC with Boc$_2$O together with
the use of 1 equiv of MgCl$_2$ and 2.5 mol% of fac-Ir(ppy)$_3$ over
48 h (Method B).[13] Electron-rich carboxylic acids, expected
to be more difficult to reduce, can also serve to generate acyl
radicals by simply increasing catalyst loading and reaction
time (**3d**, **3i–k**). Notably, carboxylic acids bearing free
hydroxy and amino groups smoothly furnished oxindoles **3g**
and **3j** as carbonate and carbamate derivatives, providing an
efficient and mild acylarylation/protection procedure in one-
pot. Heteroaromatic substrates such as 2-thiophene, 2-furoic,
nicotinic, and 1-methylindole-2-carboxylic acid proved to be
valuable reaction partners, generating products **3o–3r** in
moderate to good yields. Isophtalic acid could also be
employed as a substrate furnishing product **3s** by a consec-
utive difunctionalization. Furthermore, the optimized method
was successfully applied to five-fold scale-up of the reaction
providing product **3a** in excellent yield (97%).[14] 2-Oxo-2-

phenylacetic acid was also tolerated as a substrate, giving **3a**
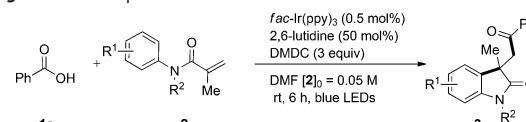in 30% yield.[15] However, when aliphatic carboxylic acids
such as 1-phenylcyclopentanecarboxylic acid, 2-methoxy-2-
phenylacetic acid, and N-Boc-glycine were employed under
the optimized conditions, no formation of the corresponding
products was observed.[16]

We next turned to evaluate the scope of the olefin
(Table 3). A range of methacrylates successfully gave access
to the corresponding products in good to excellent yields (74–
95%). Differently N-substituted phenylmethacrylamide
could be used without loss of efficiency (**3t**, **3u**).

Table 3: Olefin scope.[a,b]

3t 95% yield
3u 95% yield
3v 79% yield[c]
3w 92% yield
3x 74% yield[c]
3y 87% yield
3z 75% yield

[a] Reactions performed on 0.2 mmol using Method A. [b] Yield of
isolated product. [c] Reaction performed using 2.5 mol% of fac-Ir(ppy)$_3$
over 14 h.

Substrates bearing electron-donating groups reacted smoothly and furnished the products in excellent yields (**3w**, **3y**). Electron poor substrates reacted slower under the optimized conditions, and higher catalyst loading and reaction times were needed to obtain good yields (**3v**, **3x**).

To showcase the generality and synthetic utility of this method, we sought to employ a range of olefins beyond methacrylamides (Scheme 2).

Pleasantly, we found that the procedure can be applied to styrene-type substrates **4a–c** to readily build high molecular complexity accessing diverse heterocyclic motifs **5a–c** in promising yields (Scheme 2).
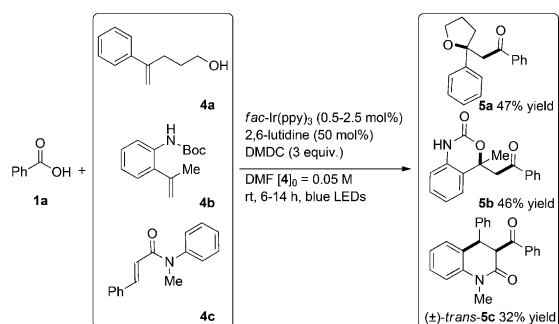
Scheme 2. Acylarylation of styrene-type olefins for the generation of diverse heterocyclic scaffolds.

A further demonstration of the synthetic value of the method is given by the straightforward preparation of compound **6**, which features the hexahydropyrrolo[2,3-b]indole unit found in many natural products (Scheme 3).[17]

A plausible reaction mechanism (Figure 1 a) begins with the photoexcitation of *fac*-Ir^{III}(ppy)$_3$ (depicted as Ir^{III} in
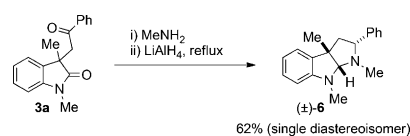
Scheme 3. Preparation of derivative **6** bearing the hexahydropyrrolo-[2,3-b]indole core.

Figure 1 a) under visible light, to generate *fac*-*Ir^{III}(ppy)$_3$, which is a strong reductant ($E_{1/2}$ [Ir^{IV}/*Ir^{III}] = −1.73 V vs SCE).[2] Single-electron reduction of mixed anhydride **I** (generated in situ from carboxylic acid **1** in the presence of DMDC under basic conditions) by *fac*-*Ir^{III}(ppy)$_3$ provides *fac*-Ir^{IV}(ppy)$_3$ and radical anion **II** that, after fragmentation, delivers acyl radical **III** along with CO$_2$ and methanoate. Subsequently, acyl radical **III** undergoes selective radical addition to olefin **2** giving radical intermediate **IV**.[10b–g] Upon intramolecular cyclization, intermediate **V** is oxidized by *fac*-Ir^{IV}(ppy)$_3$ providing final product **3** along with the ground-state of the photocatalyst. To verify the proposed role of **I** in the catalytic cycle, we reacted isolated mixed anhydride **7** ($E_{1/2}^{red}$ = −1.74 V vs SCE)[15] with olefin **2a** in the presence of the photocatalyst under visible-light (Figure 1 b) and as expected, smooth conversion into product **3a** was observed. Furthermore, a series of Stern–Volmer fluorescence quench-
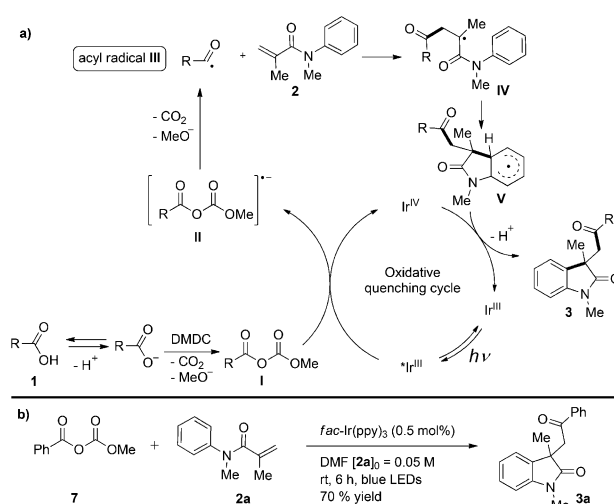
Figure 1. a) Proposed mechanism. b) Reaction performed using 0.1 mmol of **2a** and 1.5 equiv of **7**. Yield determined by ^{1}H NMR using 2,5-dimethylfuran as internal standard.

ing studies clearly revealed that **7** is the only molecular entity in the reaction mixture that efficiently quenches *fac*-*Ir^{III}-(ppy)$_3$.[15] Together, these experiments strongly support the proposed mechanism delineated in Figure 1 a.

In conclusion, we have developed an operationally convenient visible-light photocatalytic tandem acylarylation of olefins using available aromatic carboxylic acids as starting material. The protocol presents a mild and energy-efficient system which offers a viable method for the generation of acyl radicals and their employment in C−C bonding reactions.

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