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Visible-Light-Mediated Photocatalytic Difunctionalization of Olefins by Radical Acylarylation and Tandem Acylation/ Semipinacol Rearrangement

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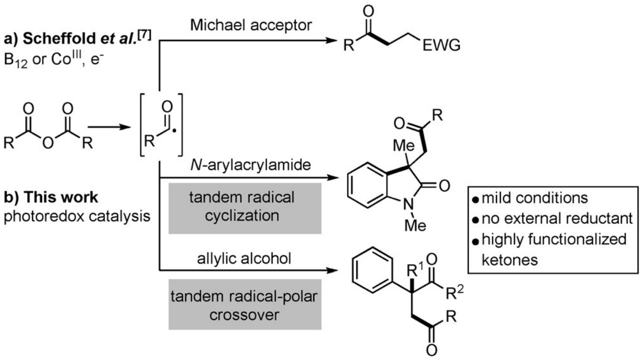
Abstract: A novel method for the mild photoredox-mediated tandem radical acylarylation and tandem acylation/semipinacol rearrangement has been developed. The synthesis of highly functionalized ketones bearing all-carbon α- or β-quaternary centers has been achieved using easily available symmetric aromatic carboxylic anhydrides as the acyl radical source. The method allows for a straightforward introduction of the keto functionality and concomitant construction of molecular complexity in a single operation.

The development of novel catalytic, mild, and efficient generation of acyl radicals and their application in C–C bond forming reactions represents a fundamental goal in organic synthesis.[1,2] A variety of procedures have been achieved to access such radical species.[3] Despite the remarkable advances (typically involving UV irradiation, high temperature, high CO pressure, tin reagents or peroxides), the development of novel catalytic protocols to access acyl radicals for further transformations under environmentally friendly and sustainable conditions have proven to be challenging.

In the last decade, visible-light photoredox catalysis has emerged as a powerful entry to highly reactive radical intermediates under very mild and operationally accessible conditions.[4] In this context, we became interested in the activation of aromatic carboxylic acids and their use as acyl radical precursors under visible-light photoredox-catalyzed conditions.[5] Further exploring complementary methods towards acyl radicals generation, we sought to employ easily available symmetric carboxylic anhydrides as the acyl radical source. In radical chemistry, symmetric anhydrides have been utilized as acyl radical source for spectroscopic and mechanistic studies.[6] In 1983, Scheffold and Orlinski reported on the cobalt-catalyzed addition of acyl radicals generated from the electrochemical or chemical reduction of anhydrides to activated olefins (Scheme 1 a).[7] However, the need for controlled potential electrolysis or stoichiometric amount of activated zinc dust as electron source represent major drawbacks of these protocols. Herein, we describe a novel, mild, and efficient method for the synthesis of high-value 3,3-disubstituted 2-oxindoles and 1,4-diketones initiated by a single-electron reduction of symmetric aromatic carboxylic anhydrides by means of photoredox catalysis (Scheme 1 b).



Scheme 1. Symmetric carboxylic anhydrides as acyl radical precursors: a) Cobalt-catalyzed hydrocarbonylation of activated olefins; b) acylarylation of *N*-arylacrylamides and acylation/semipicanol rearrangement by visible-light photoredox catalysis.

The 3,3-disubstituted 2-oxindole framework containing the carbonyl functionality is a privileged heterocyclic motif found in many pharmaceutical and bioactive natural products.[8] Moreover, due to the innate reactivity of the carbonyl functional group, 3,3-disubstituted 2-oxindoles represent versatile intermediates in organic synthesis. Owing to the importance and versatility of this class of compounds, much effort has gone into the development of novel approaches for their preparation.[8c,9] Among these, the tandem radical acylarylation of *N*-arylacrylamides has recently emerged as a powerful approach.[10] However, new strategies to provide access to valuable carbonyl containing 3,3-disubstituted 2-oxindoles that proceed under mild conditions without the requirement for external oxidants, high temperature, or high-energy UV light still remains elusive. Here we report an operationally simple redox-neutral protocol for the mild visible-light-mediated tandem radical acylarylation and tandem acylation/semipinacol rearrangement of olefins

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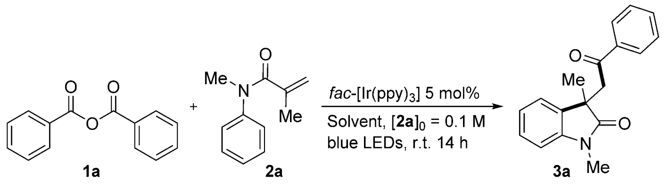
Table 1. Selected optimization studies.[a]



Entry	Photocatalyst	Solvent	Yield **3 a** [%][b]
1	$[Ir(ppy)_2(dtbbpy)]BF_4$	CH_3CN	0
2	$[Ru(bpy)_3]Cl_2$	CH_3CN	0
3	*fac*-$[Ir(ppy)_3]$	CH_3CN	38
4	*fac*-$[Ir(ppy)_3]$	DMA	>95
5[c]	*fac*-$[Ir(ppy)_3]$	DMA	>95 (94)[d]
6	–	DMA	0
7[c,e]	*fac*-$[Ir(ppy)_3]$	DMA	0

[a] Reactions performed on 0.1 mmol scale using 2 equiv of **1 a**. [b] Determined by ^{1}H NMR using 2,5-dimethylfuran as internal standard. [c] Performed with 1 mol% of *fac*-$[Ir(ppy)_3]$. [d] Isolated yield. [e] Reaction carried out in the dark. DMA = *N*,*N*-dimethylacetamide.

using readily available and inexpensive carboxylic anhydrides as acyl radical source.

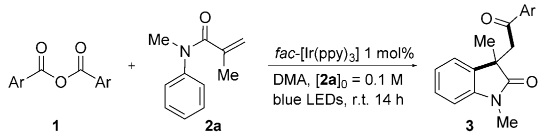
We began our investigation using benzoic anhydride (**1 a**) and *N*-methyl-*N*-phenylmethacrylamide (**2 a**) as the model substrates in the presence of a photocatalyst under visible-light irradiation at room temperature in acetonitrile (Table 1). The evaluation of different photocatalysts showed that although no product was observed using $[Ir(ppy)_2(dtbbpy)]^+$ and $[Ru(bpy)_3]^{2+}$ (entries 1 and 2), strongly reducing *fac*-$[Ir(ppy)_3]$ was able to promote the desired acylarylation reaction (entry 3). When *N*,*N*-dimethylacetamide (DMA) was used as solvent, **3 a** was obtained in quantitative yield (entry 4). Moreover, it was possible to lower the catalyst loading to 1 mol% without affecting the reaction efficiency (entry 5). Control experiments indicated that both the photocatalyst and visible light were essential in this acylarylation protocol (entries 6 and 7).

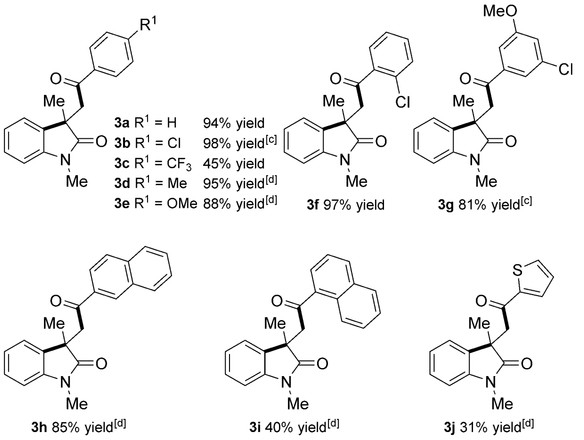
Having identified the optimal reaction conditions, we next turned our attention to the scope of the symmetric carboxylic anhydride (Table 2). As shown, differently substituted aromatic as well as heteroaromatic carboxylic anhydrides were applicable to this transformation. Anhydrides bearing electron-deficient arenes could be readily employed, providing the corresponding products in good to excellent yields (**3 a**–**c** and **3 f**). Pleasingly, the Lewis acid activation of more challenging electron-rich aromatic and heteroaromatic carboxylic anhydrides allowed for the generation of the corresponding carbonyl radicals and the efficient synthesis of products **3 d**, **3 e** and **3 g**–**j**.[11,12] As a limitation, hydrocinnamic anhydride was found to be unreactive under these conditions.

With respect to the olefin reaction partner (Table 3), the protocol could be applied to differently substituted *N*-phenylacrylamides, obtaining products **3 k** and **3 l** in excellent yields. Moreover, olefins bearing electron-withdrawing as well as -donating groups on the phenyl ring were highly compatible with the optimized conditions (**3 m**–**o**).

To further extend the utility of this visible-light-mediated method for the introduction of the carbonyl functionality while building structural diversity, we next turned to the synthesis of versatile 1,4-diketones and 1,4-ketoaldehydes by a tandem acylation/semipinacol rearrangement of allylic alcohol derivatives (Scheme 2). The semipinacol rearrangement of allylic alcohols is of high importance in natural product synthesis for the formation of α-quaternary carbonyl structures.[13] Taking advantage of the ability of photoredox catalysis to facilitate radical–polar crossover reactions,[14] we envisioned that after the addition of the photogenerated acyl radical and subsequent single-electron oxidation, the resulting carbocation would undergo 1,2-migration (Scheme 2 a).[15] This transformation would constitute the first visible-light photoredox-catalyzed tandem acylation/semipinacol rearrangement initiated by acyl radicals.

Table 2. Tandem radical cyclization: carboxylic anhydride scope.[a,b]



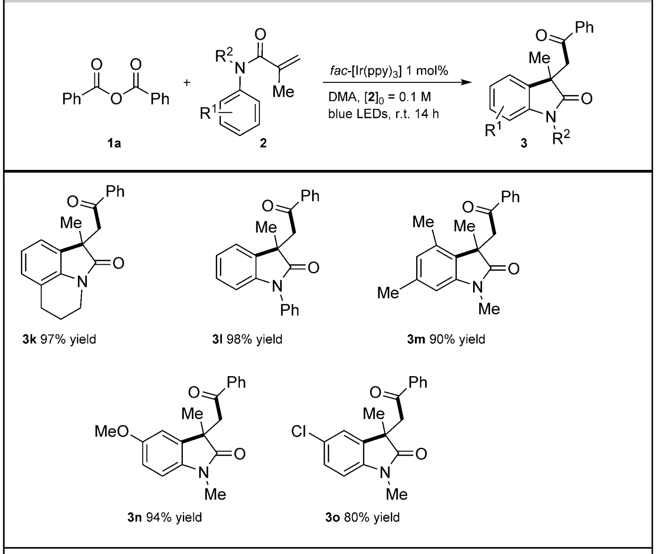


3a R^1 = H 94% yield
3b R^1 = Cl 98% yield[c]
3c R^1 = CF$_3$ 45% yield
3d R^1 = Me 95% yield[d]
3e R^1 = OMe 88% yield[d]
3f 97% yield
3g 81% yield[c]
3h 85% yield[d]
3i 40% yield[d]
3j 31% yield[d]

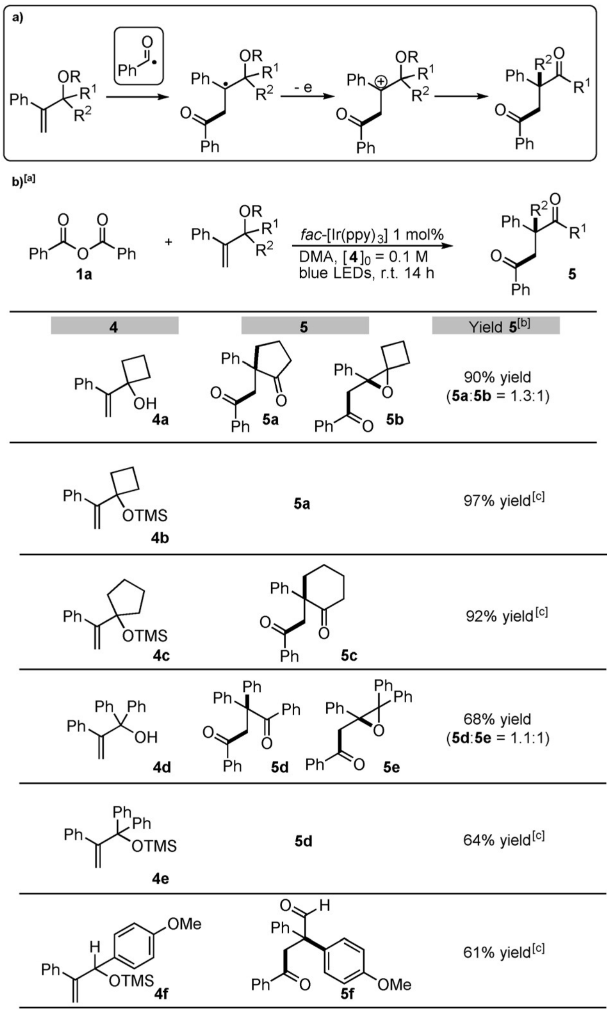
[a] Reactions performed on 0.1 mmol scale using 2 equiv of **1**. [b] Isolated yield. [c] $[\mathbf{2a}]_0 = 0.05$ M. [d] Reaction performed by adding 1 equiv of $MgCl_2$; reaction time = 60 h. [e] Photocatalyst loading = 2.5 mol%.

As shown in Scheme 2b, subjecting olefin **4 a** to our optimized conditions, ring expanded product **5 a** was obtained as the major product together with epoxide **5 b**. Upon trimethylsilyl (TMS) protection of the hydroxyl group, we were pleased to find that compound **5 a** could be generated as the exclusive reaction product in excellent yield. Furthermore, the less strained five-membered carbacycle derivative **4 c** also provided the corresponding ring expanded cyclohexanone **5 c** in almost quantitative yield. Acylation/aryl 1,2-migration was achieved utilizing 1,1,2-triphenylprop-2-en-1-ol (**4 d**). Also in this case, the rearranged product **5 d** was obtained along with epoxide **5 e**. Decreasing the nucleophilicity of the hydroxyl group through TMS protection (**4 e**) allowed for the formation of **5 d** as the sole reaction product. Remarkably, when TMS-protected secondary allylic alcohol **4 f** was used as reaction partner, good yield of densely functionalized aldehyde **5 f** was obtained. This

Table 3. Tandem radical cyclization: olefin scope.[a,b]



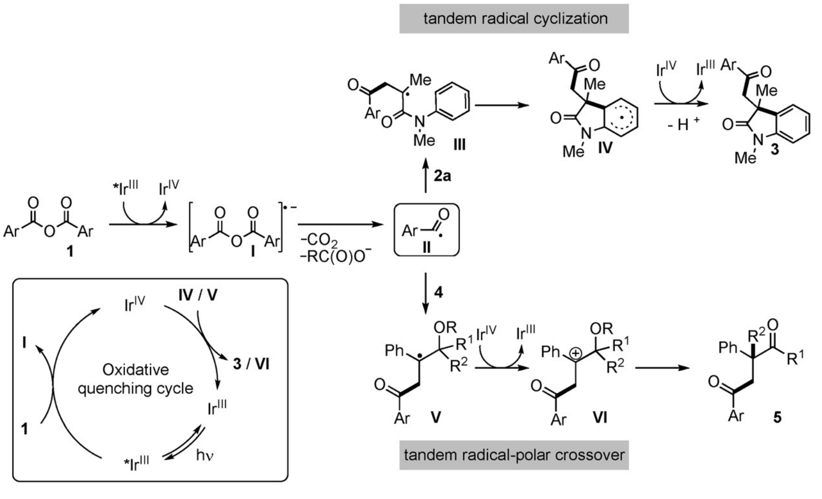
[a] Reactions performed on 0.1 mmol scale using 2 equiv of **1**. [b] Isolated yield.



Scheme 2. a) Visible-light-mediated tandem acylation/semipinacol rearrangement of allylic alcohols by a radical–polar crossover mechanism; b) scope of the reaction. [a] Reactions performed on 0.1 mmol scale using 2 equiv of **1 a**; [b] isolated Yield; [c] reaction time = 60 h. TMS = trimethylsilyl.

example illustrates that the protocol is competent for the formation of both diketones and ketoaldehydes.

A plausible reaction mechanism for the tandem radical acylarylation reaction and the tandem acylation/semipinacol rearrangement is shown in Scheme 3. Photoexcitation of *fac*-[$\mathrm{Ir^{III}(ppy)_3}$] (depicted as $\mathrm{Ir^{III}}$) under visible light generates *fac*-[$\mathrm{{}^*Ir^{III}(ppy)_3}$], which is a strong reductant ($E_{1/2}$ [$\mathrm{Ir^{IV}/{}^*Ir^{III}}$] = −1.73 V versus SCE).[4] Thermodynamically favorable single-electron reduction of symmetric carboxylic anhydride **1** (benzoic anhydride **1 a**, $E_{1/2}^{\mathrm{red}}$ = −1.13 V versus SCE)[6b] by *fac*-[$\mathrm{{}^*Ir^{III}(ppy)_3}$] would generate *fac*-[$\mathrm{Ir^{IV}(ppy)_3}$] and radical anion **I**, which after fragmentation delivers acyl radical **II**. At this stage, acyl radical **II** might undergo a selective radical addition to olefin **2**, giving radical intermediate **III**.[10] Upon intramolecular cyclization, the oxidation of intermediate **IV** by *fac*-[$\mathrm{Ir^{IV}(ppy)_3}$] would provide final product **3** along with the ground state of the photocatalyst. In the presence of protected allylic alcohols **4**, acyl radical **II** may undergo a radical addition to generate benzylic radical **V**. Single-electron transfer (SET) from **V** to *fac*-[$\mathrm{Ir^{IV}(ppy)_3}$] regen-



Scheme 3. Proposed mechanism.

erates the photocatalyst and delivers carbocation **VI**.[16] A 1,2-alkyl or -aryl migration would form product **5** upon loss of the silyl protecting group.[15] As a support for the proposed initial SET event between the photocatalyst and the symmetric anhydride **1**, Stern–Volmer fluorescence quenching studies showed that the emission intensity of the excited state of *fac*-[Ir(ppy)$_3$] was significantly quenched by symmetric benzoic anhydride **1 a**.[17]

In conclusion, we have developed a photoredox-mediated method for the tandem radical acylarylation and tandem acylation/semipinacol rearrangement of olefins. The method represents a mild and powerful entry to the synthesis of highly functionalized carbonyl compounds bearing all-carbon α- or β-quaternary centers using easily available symmetric aromatic carboxylic anhydrides as the acyl radical source. The method allows for the sustainable, mild, and straightforward introduction of the keto functionality and concomitant construction of molecular complexity in a single operation.

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[16] This step could also proceed by SET from radical **V** to anhydride **1** as part of a radical chain propagation.

[17] See the Supporting Information for details on fluorescence quenching studies.

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