CHEMISTRY
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To be cited as: *Chem. Eur. J.* 10.1002/chem.201701589

Link to VoR: http://dx.doi.org/10.1002/chem.201701589

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Chemistry - A European Journal
10.1002/chem.201701589

Photoredox Catalysis

Redox Neutral Dual Functionalization of Electron Deficient Alkenes

*Fredrik Pettersson, Giulia Bergonzini, Carlo Cassani, and Carl-Johan Wallentin**

Abstract: *Visible-light photoredox catalysis has been utilized in a novel multicomponent reaction forming β-functionalized δ-diketones under mild conditions in an operationally convenient manner. Single-electron reduction of* in situ *generated carboxylic acid derivatives forms acyl radicals that react further via 1,2-acylalkylation of olefins in an intermolecular, three components cascade reaction, yielding valuable synthetic entities from readily available starting materials. A diverse set of substrates have been used, demonstrating robust methodology with broad substrate scope.*

In recent years synthetic chemistry has evolved at such a pace that molecular complexity can be rapidly achieved with high selectivity. One of the most efficient methods to construct molecular complexity is by utilizing multicomponent reactions (MCRs) and cascade type transformations.[1] MCRs are convergent reactions in which three or more starting materials are reacted together to form a single product with high atom efficiency.[1a] As opposed to the classical sequential synthetic approach to construct complex molecules, MCRs enable the assembly of complex molecules in a single operation. The product is formed via a cascade of elementary chemical reactions through a series of reaction equilibria, ideally ending in an irreversible step to afford the desired product. MCRs have become a very popular tool in many areas of applied chemistry due to its labor efficient way to access a vast array of structural space. [1e, f]

Recently, visible-light mediated photoredox catalysis has emerged as a competitive method for functional group interconversions generating reactive radical intermediates under mild and environmentally benign conditions.[2] Contributions to this field from our group include the formation of acyl radicals via single-electron reduction of aromatic carboxylic acid derivatives (Figure 1b).[3] This approach combines the benefits of using readily available and inexpensive starting materials with a synthetic method that extends beyond the existing routes to access acyl radicals.[4] Mixed anhydride intermediates, formed *in situ* from simple carboxylic acids by reaction with dimethyl dicarbonate (DMDC) have proven to be efficient oxidative quenchers of the excited state of the photocatalyst *fac*-Ir(ppy)$_3$ to generate the desired acyl radical species, along with CO$_2$ and methanoate as the only byproducts.[3b]
Capitalizing on this mild way to access acyl radical intermediates, we envisioned that MCRs could be engaged in a radical context under redox neutral conditions.

Electron rich acyl radicals have a pronounced reactivity preference towards electron-deficient alkenes, a property that can be exploited in a multicomponent setting by achieving selectivity towards electron-poor coupling partners in the presence of electron-rich olefins. Strategically, such a combination of coupling partners would provide access to the synthetically challenging 1,2-dicarbofunctionalization of alkenes (Figure 1c).

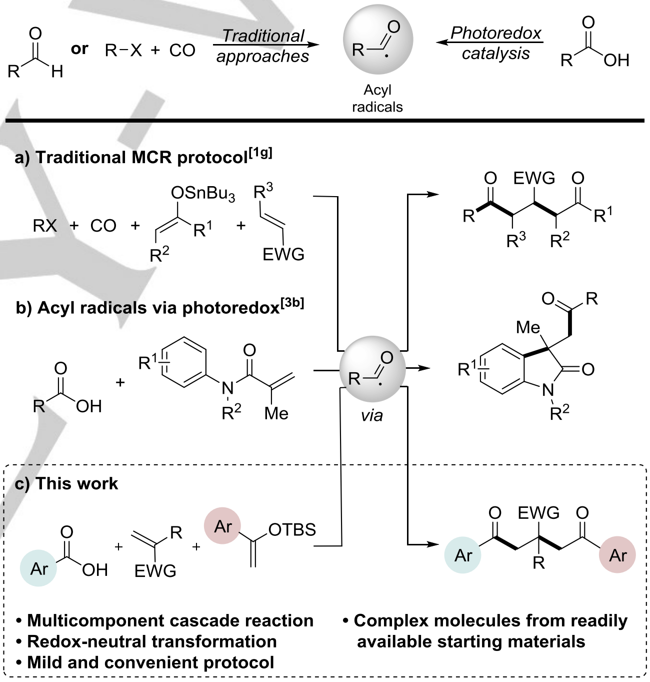

Figure 1. a) Tin enolate mediated carbonylative coupling reaction. b) Acylarylation of *N*-aryl acrylamides by means of visible-light photoredox catalysis. c) Photoredox-catalyzed intermolecular three component synthesis of β-functionalized δ-diketones.

The majority of published photoredox mediated MCRs rely on radical polar crossover transformations in which free radical-based bond formations are combined with nucleophilic trapping of an intermediate carbocation, typically by a solvent or co-solvent.[5] Photoredox mediated MCRs where two or more C–C bonds are formed in a pure radical fashion remain relatively unexplored.[6] Moreover, MCRs based on classical free radical chemistry are typically characterized by the need of external oxidants, UV irradiation, high CO pressure, high temperature or tin-, borane or lead-based reagents as well as stannylated and silylated phosphanes as precursors.[7] Herein, we report the first redox-neutral approach for the mild visible-light mediated

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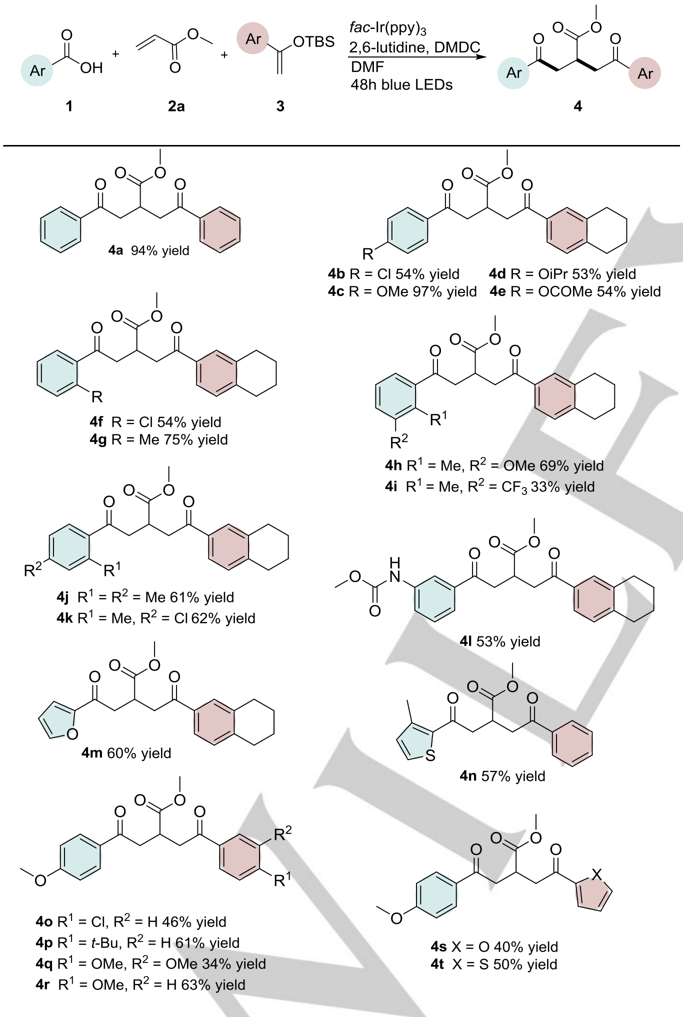
Supporting information for this article is given via a link at the end of the document multicomponent 1,2-acylalkylation of alkenes giving convenient access to β-functionalized δ-diketones (Figure 1c).

Preliminary studies of the three component reaction were investigated using benzoic acid **1a**, methyl acrylate **2a** and *tert*-butyldimethyl((1-phenylvinyl)oxy)silane **3a** as the acyl radical precursor, electron-deficient and electron-rich coupling partners, respectively. In addition to the specified substrates, *fac*-Ir(ppy)$_3$, DMDC, and 2,6-lutidine were added to the protocol and the reaction was conducted under visible-light irradiation (Table S1, Supporting Information). The choice of the photocatalyst was based on previous studies which demonstrated that *fac*-Ir(ppy)$_3$ is capable of reducing mixed anhydride **I** to the corresponding acyl radical species **III** as depicted in Figure 2.[3b] To our delight, initial experiments validated our approach and provided the corresponding product **4a** in a modest yield (Table S1, Supporting Information). Subsequent optimizations revealed that employing **3** as the limiting reagent in combination with a catalyst loading of 2-5 mol % provided robust and optimal conditions for the transformation.

Table 1. Scope of the carboxylic acids **1** and electron-rich olefins **3**[a]



4a 94% yield

4b R = Cl 54% yield
4c R = OMe 97% yield
4d R = OiPr 53% yield
4e R = OCOMe 54% yield

4f R = Cl 54% yield
4g R = Me 75% yield

4h R^1 = Me, R^2 = OMe 69% yield
4i R^1 = Me, R^2 = CF_3 33% yield

4j R^1 = R^2 = Me 61% yield
4k R^1 = Me, R^2 = Cl 62% yield

4l 53% yield

4m 60% yield

4n 57% yield

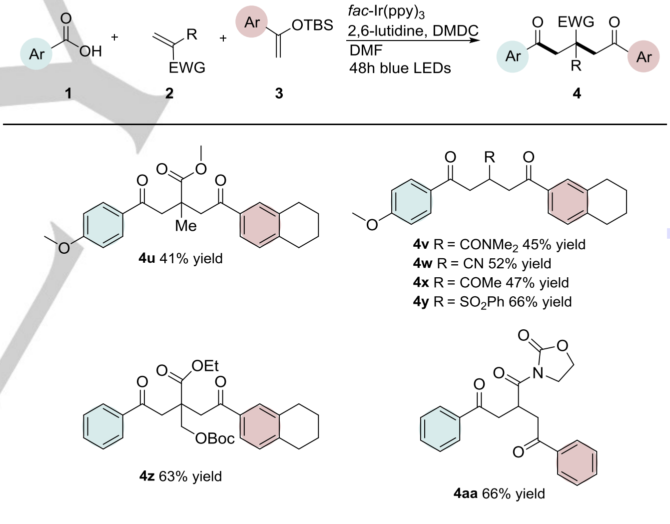
4o R^1 = Cl, R^2 = H 46% yield
4p R^1 = *t*-Bu, R^2 = H 61% yield
4q R^1 = OMe, R^2 = OMe 34% yield
4r R^1 = OMe, R^2 = H 63% yield

4s X = O 40% yield
4t X = S 50% yield

[a] Reaction performed using 2-5 mol% of *fac*-Ir(ppy)$_3$, 0.5 equiv of 2,6-lutidine, 3 equiv of DMDC, 2 equiv of **1**, 2 equiv of **2a** and 1 equiv of **3** on a 0.2 mmol scale (detailed description in the Supporting Information). Isolated yields.

Control experiments performed in the absence of the photocatalyst, DMDC or light irradiation did not result in the formation of the desired product (Entries 14-16 in Table S1, Supporting Information), observations that validated our mechanistic rational. With optimized reaction conditions in hands, the scope of the reaction in terms of structural diversity of all components was examined. As shown in Table 1, the reaction proceeds in modest to excellent yields (**4a-n**, Table 1) for a wide range of mono- or disubstituted benzoic acids (**1a**-**l**, Table S2, Supporting Information) as well heteroaromatic substrates such as 5-methylthiophene-2-carboxylic acid and 2-furoic acid (**1m-n**, Table S2, Supporting Information). In general, unfunctionalized and electron-rich carboxylic acids provided higher yields as compared to their electron-deficient counterparts (*e.g.* **4a** and **4c**). However, the inclusion of strongly electron-withdrawing groups, such as trifluoromethyl or nitro moieties, at the *para*-position of the carboxylic acid resulted in very low yields (≤10%). For these substrates the background reaction (*i.e.* the conversion of the acid into the corresponding unreactive methyl esters) was evidently faster than the redox chemistry (Table S2 and NMR spectra, Supporting Information).[8] Notably, carboxylic acids bearing free hydroxy or amino groups (**1e** and **1l**, Table S2 Supporting Information) smoothly furnished the corresponding carbonate and carbamate derivatives without affecting the yields in a deleterious way (**4e** and **4l**, Table 1).

Table 2. Scope of the electron-poor olefins **2**[a]



4u 41% yield

4v R = $CONMe_2$ 45% yield
4w R = CN 52% yield
4x R = COMe 47% yield
4y R = SO_2Ph 66% yield

4z 63% yield

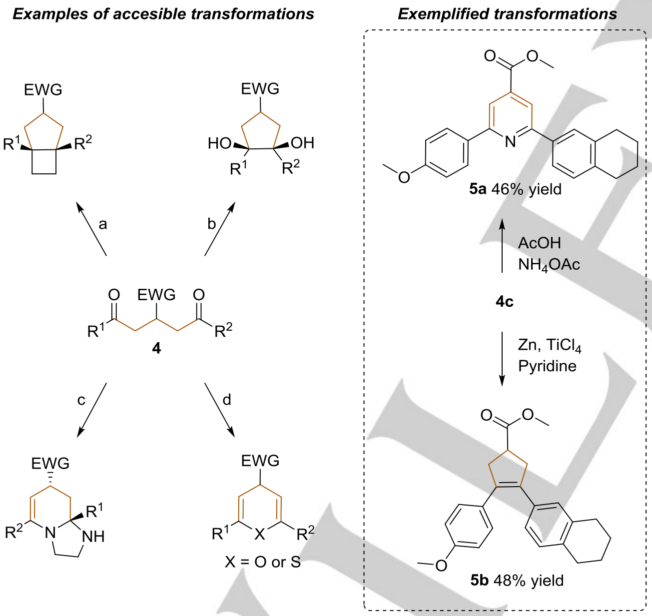
4aa 66% yield

[a] Reaction performed using 2-5 mol% of *fac*-Ir(ppy)$_3$, 0.5 equiv of 2,6-lutidine, 3 equiv of DMDC, 2 equiv of **1**, 2 equiv of **2** and 1 equiv of **3** on a 0.2 mmol scale (detailed description in Supporting Information). Isolated yields.

The scope of the reaction was further explored with regards to the olefin substrates **2** and **3** (Table 1 and 2). *p*-Anisic acid (**1c**) and methyl acrylate (**2a**) together with various electron-rich olefins (**3c-f**, Table S3, Supporting Information), yielded the desired products in generally good yields (**4o-t**, Table 1). The reaction appears to tolerate both mono- and disubstituted aryls as well as heteroaromatic derivates of the silylenolether **3**, while possible limitations include strongly electron deficient aryl groups (trifluromethyl (**4ad**), Table S3, Supporting Information) or non-aromatic silylenolethers (*t*-butyl (**4ae**), Table S3, Supporting Information). In a similar manner, different electron-poor olefins with a number of electron-withdrawing groups (**2b-h**, Table S4 Supporting Information) were evaluated as coupling partners together with benzoic acid (**1a**) or *p*-anisic acid (**1c**) and silylenolethers **3a** or **3b**. Common acrylic derivatives were compatible with the optimized conditions providing the corresponding products in fair yields (**4u**-**aa**, Table 2). Taken together, the protocol provides a novel entry to 1,2-acylalkylated alkenes in the form of β-functionalized δ-diketones. The protocol demonstrates a relatively broad scope with respect to the different substrates, with yields ranging from 58% to 99% for each individual C–C bond forming reaction.

In order to demonstrate the robustness and thus synthetic value of this photoredox-mediated multicomponent reaction, its scalability was evaluated. Satisfyingly, the reaction was successfully scaled-up to 1 mmol scale using *p*-anisic acid (**1c**), methyl acrylate (**2a**) and *tert*-butyldimethyl((1-(5,6,7,8-tetrahydronaphthalen-2-yl)vinyl)oxy)silane (3b), providing 4c in very good yield (87 %). Furthermore, to illustrate the diverseness of δ-diketones in synthetic elaborations, **4c** was converted to a trisubstituted pyridine and a trisubstituted cyclopentene derivative in 46% and 48% yield, respectively, following published literature procedures (Scheme 1).[9] It is worth noting that these compounds were accordingly synthesized in two steps from commercially available and structurally simple starting materials.

A plausible catalytic cycle for the presented transformation is proposed in Figure 2. Photoexcitation of *fac*-Ir^{III}(ppy)$_3$ (depicted as Ir^{III}) under visible light, generates the strong reductant *fac*-*Ir^{III}(ppy)$_3$.



Scheme 1. Examples of accessible transformations of 1,5-diones: a) Mojr *et al.*[10] b) Foster *et al.*[11] c) Wang *et al.*[12] d) Padmavathi *et al.*[13] Transformations of **4c** into cyclized compounds **5a** and **5b** following published literature procedures.[9]

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 the electron-poor olefin **2** affording radical intermediate **IV**.

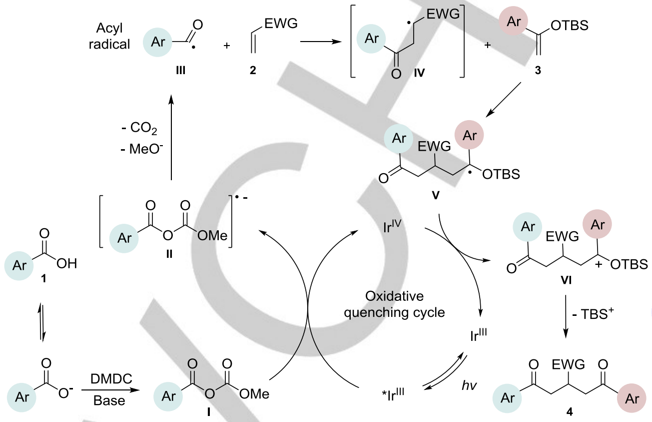


Figure 2. Proposed mechanism.

Next, **IV** reacts selectively with the silylenolether **3** forming intermediate **V**, which in turn is oxidized by *fac*-Ir^{IV}(ppy)$_3$ to provide intermediate **VI** while regenerating the ground-state of the catalyst. Finally the elimination of TBS$^+$ from **VI** forms the desired product in an irreversible step.

In conclusion, a novel photoredox catalyzed multicomponent reaction for the formation of variously β-functionalized δ-diketones under mild visible-light conditions is presented. The use of simple carboxylic acids as acyl radical precursors promoted by visible light, allowed the development of this intermolecular cascade reaction, which combines three compounds in a radical process. The overall reaction proceeds in a redox neutral fashion avoiding the need for stoichiometric amounts of external electron donors or oxidants. Furthermore, the possibility of accessing a large variety of structures by the straightforward derivatization of compound **4c** showcases the synthetic utility of the presented method. Exploration of the reactivity of acyl radicals under photoredox catalyzed conditions and exploitation of this chemistry in unprecedented multicomponent reactions are currently under investigation in our laboratory.

Acknowledgements

The authors thank the Olle Engkvist Byggmästare foundation, the Wilhelm and Martina Lundgren research foundation, the Ollie and Elof foundation, the Magnus Bergvall foundation, the Adlerbertska foundation and the Swedish Research Council. C.C. is grateful to the European Commission for a Marie Skłodowska-Curie fellowship (H2020-MSCA-IF-2014 n: 660668). We would also like to thank Dr. Cassandra L. Fleming for proof reading the manuscript.

Keywords: *photoredox catalysis • multicomponent reactions • acyl radicals • carboxylic acids • cascade transformation*

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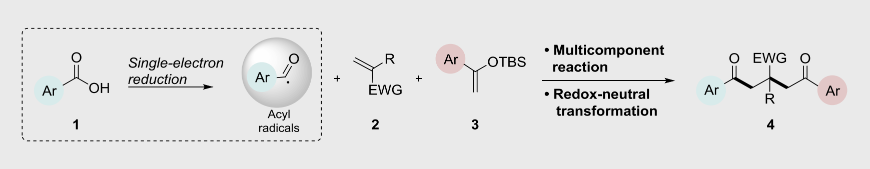

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Redox neutral dual functionalization of electron deficient alkenes

A mild method for C–C bond formation in multicomponent cascade type reactions: Acyl radicals have been accessed from simple aromatic carboxylic acids under visible-light photoredox catalysis. The method offers an atom efficient entry to valuable synthetic entities from readily available starting materials without the need of high-energy UV irradiation, stoichiometric oxidants, high CO pressure, or high temperature.