Synthesis of γ-Oxo-α-amino Acids via Radical Acylation with Carboxylic Acids

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ABSTRACT: Herein we present a highly efficient, light-mediated, deoxygenative protocol to access γ-oxo-α-amino acid derivatives. This radical methodology employs photoredox catalysis, in combination with triphenylphosphine, to generate acyl radicals from readily available (hetero)aromatic and vinylic carboxylic acids. This approach allows for the straightforward synthesis of γ-oxo-α-amino acids bearing a wide range of functional groups (*e.g.* Cl, CN, furan, thiophene, Bpin) in synthetically useful yields (~ 60% average yield). To further highlight the utility of the methodology, several deprotection and derivatization reactions were carried out.

γ-Oxo-α-amino acids are highly versatile building blocks in organic synthesis, as well as key components in biologically active molecules. They can be used as precursors for homophenylalanine derivatives,[1] γ-hydroxy-α-amino acids,[2] γ-valerolactones[3] or γ-valerolactames, for example. As it is often the case in synthetic chemistry, one of the main challenges associated with this interesting class of amino acids is their stereoselective synthesis. There are three main retrosynthetic pathways to achieve this goal: a) via acylation reactions, starting from *L*-or *D*-aspartic acid,[4] b) via asymmetric or diastereoselective Mannich reactions,[5] or c) via asymmetric Stetter reactions (Scheme 1A).[6] While powerful, these methodologies present limitations regarding the scope of nucleophiles, or require the use of chiral catalysts.

Radical chemistry offers exciting and highly attractive approaches to access new chemical space in a rapid fashion.[7] As such, it has been exploited for the synthesis and derivatization of amino acids and peptides.[8] We recently contributed to this area with the development of a decarboxylative protocol for the diastereoselective synthesis of a wide range of unnatural amino acids (UAAs) using the Beckwith-Karady alkene **I**[9] as radical acceptor.[10] Although this methodology granted access to γ-oxo-α-amino acids derivatives (**II**) when using α-keto acids as acylating reagents (Scheme 1B), it afforded diminished yields with electron deficient or (hetero)aromatic systems. In addition, α-keto acids are not readily available and their synthesis often requires the use of hazardous reagents, such SeO_2. Since **II** is a highly versatile species, we became interested in developing alternative methodologies for its synthesis using more readily available starting materials.

Recently, the development of deoxygenative radical strategies to access acyl radicals has attracted increased attention.[11] Seminal independent studies by Rovis and Doyle,[11e] and Zhu[11d] described the use photoredox catalysis to generate phosphine radical cations that swiftly react with carboxylates to generate acyl radicals and phosphine oxide after β-scission (*vide infra*).[12] Encouraged by these reports, we envisioned that it might be possible to develop a diastereoselective synthesis of γ-oxo-α-amino acids using **I** and readily available carboxylic acids as acyl radical sources (Scheme 1C).

Herein we present a highly efficient, light-mediated deoxygenative protocol to access products **II** from readily and commercially available (hetero)aromatic and vinylic carboxylic acids.

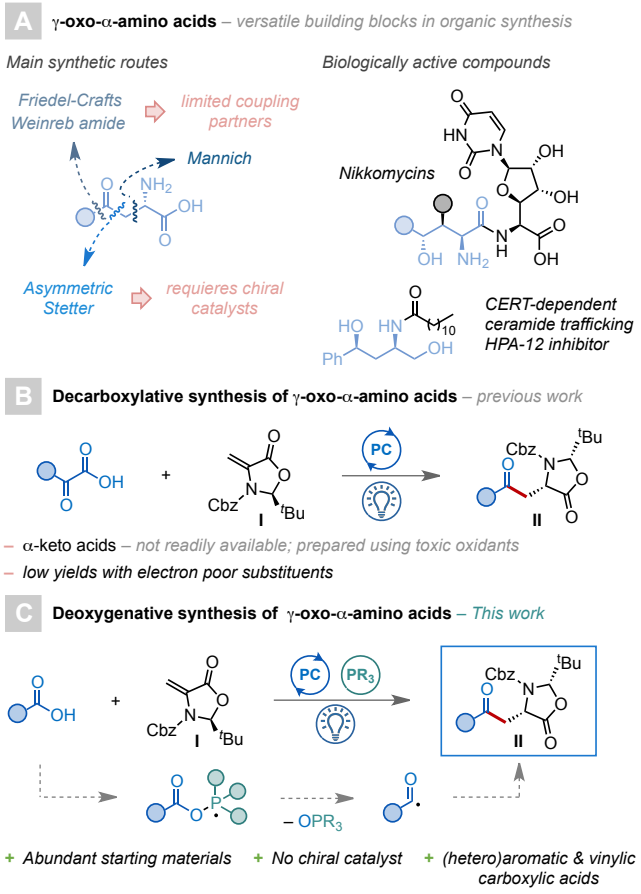


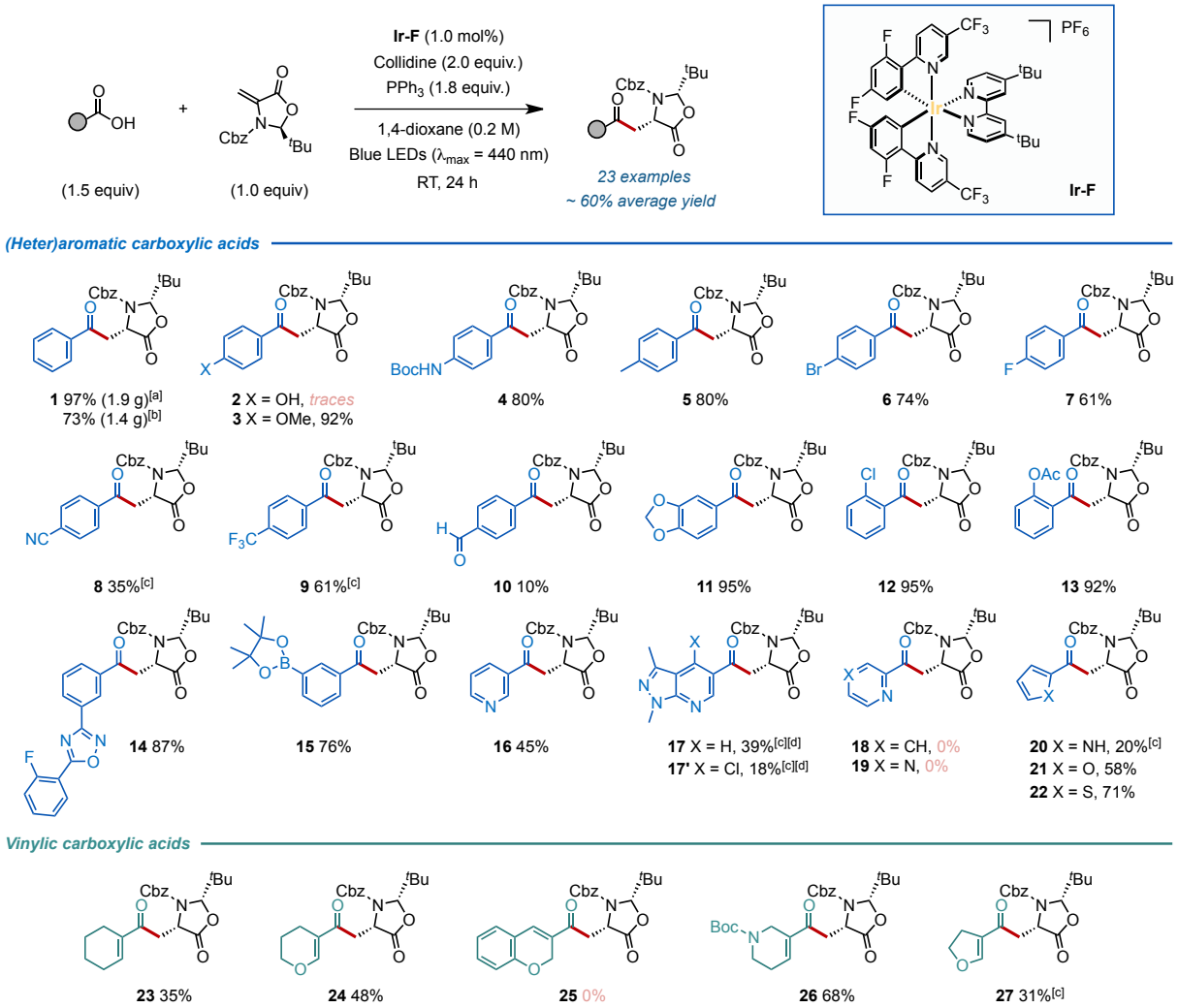
Figure 1. Synthetic strategies towards γ-oxo-α-amino acids

In addition, the utility of this methodology is further highlighted by several derivatizations and deprotections of product **II**.

Initial optimisation studies were carried out using benzoic acid as the acylating reagent.[13] The targeted product (**1**) could be isolated in 95% yield and excellent diastereoselectivity (d.r. >20:1) using 1.0 equiv. of **I**, 1.5 equiv. of benzoic acid, 1.8 equiv. of PPh_3, 2.0 equiv. of 2,4,6-collidine and 1.0 mol% $[Ir(dFCF_3ppy)_2(dtbbpy)][PF_6]$ (**Ir-F**) in 1,4-dioxane (0.2 M) while irradiating with 32W blue LEDs (λ_{max} = 440 nm) for 24 h at room temperature. Control experiments showed that the reaction needs both light and a photocatalyst to proceed, and that the reaction does not proceed when using 4CzIPN,[14] an organophotocatalyst possessing similar redox potentials to **Ir-F**.

With the optimized conditions in hand, the scope and limitations, as well as the scalability of the methodology, were explored (Scheme 1). The standard reaction with benzoic acid was scaled up to 5.0 mmol (1.4 g of **II**), affording **1** in 95% (1.9 g) and 73% (1.4 g) yield using 0.5 mol% and 0.25 mol% of **Ir-F**, respectively. This highlights the high catalytic efficiency of the methodology, affording TON up to 288. Regarding the scope, aromatic carboxylic acids were first tested (**2-15**). Both electron rich and poor *para*-substituents on the aromatic ring were tolerated (**2-10**), although the latter afforded diminished yields. However, this represents a significant improvement compared to our previous methodology employing α-keto acids as acylating reagents, *e.g.* compound **9** was isolated in 61% yield *vs* 31% yield using α-keto acids.[10] Free nucleophilic motifs, such as hydroxy groups, were not tolerated (**2**), however this limitation could be circumvented by the use of protecting groups (**3** and **4**). Challenging substrates bearing sensitive functional groups, such as nitriles (**8**) or aldehydes (**10**) afforded the desired products in moderate to poor yields, while compound **15,** bearing a *meta*-boronic ester substituent, was obtained in 76% yield. Gratifyingly, *ortho*-substituents were well tolerated (**12** and **13**), and salicylic acid derived **13** was obtained in an excellent 92% yield. More complex aromatic carboxylic acids bearing multiple functional groups (**14**), afforded the targeted γ-oxo-α-amino acid derivative in excellent yield.

Scheme 1. Scope & limitations of the methodology



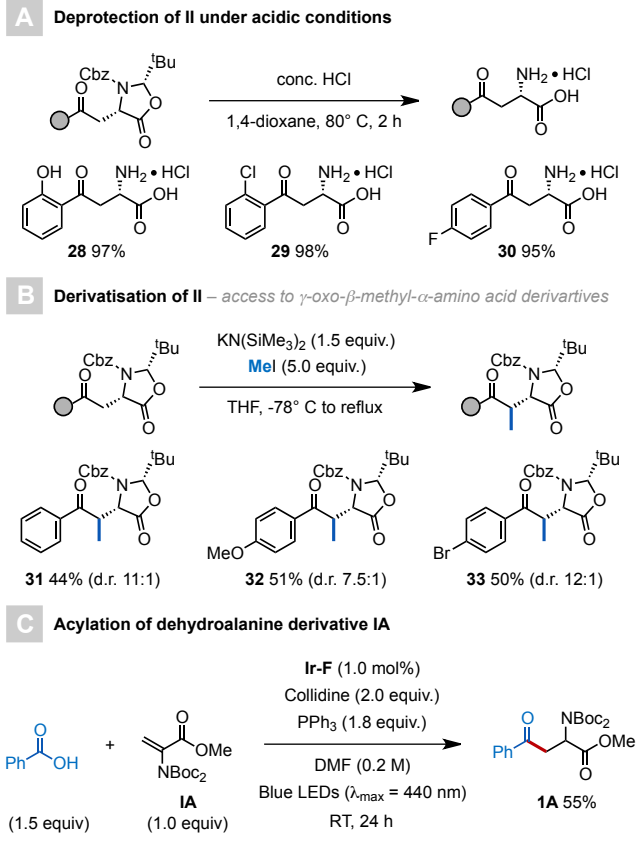
Reaction conditions: Acid (0.75 mmol, 1.5 equiv.), **I** (0.50 mmol, 1.0 equiv.), **Ir-F** (1.0 mol%), 2,4,6-collidine (0.9 mmol, 1.8 equiv.), 1,4-dioxane (0.2 M), RT, 24 h; [a] 5.0 mmol scale, **Ir-F** 0.5 mol%; [b] 5.0 mmol scale, **Ir-F** 0.25 mol%, 72 h; [c] 48 h; [d] DMF (0.2 M); unless otherwise noted d.r. > 20:1.

The use of heteroaromatic carboxylic acids was also investigated (**16-23**). While nicotinic acid afforded the desired product in moderate yields (**16**), no product was observed with picolinic or pyrazinoic acids (**18-19**). Surprisingly, when the reaction was carried out using 4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridine-5-carboxylic acid, the main product was the dechlorinated species **17** (39%), while the expected product **17'** was isolated in 18% yield. The use of 5-membered heterocycles **(20-22)**, such as unprotected pyrroles (**20**), furans (**21**) and thiophenes (**22**) afforded the desired products in variable yields (21-71%). Overall, our new methodology presents a broad functional group tolerance, where compounds bearing several vectors for further functionalization, such as halides, boronic esters or amines, can be readily obtained.

To further challenge the limits of our methodology, the use of aliphatic, cinnamic and vinylic carboxylic acids as acylating reagents was evaluated. While hydrocinnamic acid failed to afford the desired product,[13] cinnamic acid delivered a complex mixture, from where the targeted product could not be isolated.[15] However, the use of cyclic, vinylic carboxylic acids afforded interesting γ-oxo-α-amino acid derivatives bearing 5- and 6-membered heterocycles, such dihydrofuranes **(24)**, tetrahydropyrines **(26)**, and tetrahydropyrans **(27)**. To the best of our knowledge, this is the first time that vinylic carboxylic acids have been directly used as acyl radical precursors.

To highlight the utility of our methodology, a series of derivatization reactions were carried out. Acidic deprotection of **II** using concentrated HCl in 1,4-dioxane, afforded γ-oxo-α-amino acid salts **28-30** in quantitative yields (Scheme 2A). Moreover, by exploiting the carbonyl motif in **II** to access the corresponding enolate, it was possible to access γ-oxo-β-methyl-α-amino acid derivatives (**31-33**) in good yields and diastereoselectivities (Scheme 2B). Moreover, this methodology can also be applied for the acylation of dehydroalanine derivative **IA**, affording the corresponding product **1A** in 55% yield (Scheme 2C).

Scheme 2. Deprotection & derivatisation reactions



Finally, a plausible reaction mechanism for this transformation is shown in Figure 2. First, the excited photocatalyst (***Ir**^{III}, $*E_{1/2}$ = +1.21 V versus SCE)[16] undergoes reductive quenching by PPh_3 ($E_{1/2}$ = +0.98 V versus SCE)[17] to generate triphenylphosphine radical cation **III** and a **Ir**^{II} species. **III** reacts with the corresponding carboxylic acid to afford phosphoranyl radical **IV**, which readily undergoes β-scission to deliver $OPPh_3$ and the key acyl radical **V**. Subsequent radical addition of the latter to **I** affords α-amino radical **VI**, which after reduction by the reduced **Ir**^{II} ($E_{1/2}$ = −1.37 V vs SCE)[16] and protonation delivers the desired product **II**. This mechanism is in accordance with previous proposals for acylation reactions using photoredox catalysis to access phosphoranyl radicals.[11-12] Quantum yield determinations suggest that there is also a significant contribution from a radical-chain pathway (Φ = 13.5).[13] Based on further experiments, 2,4,6-collidine seems to play a crucial role in the chain process. However, at this point, the nature of the chain carrier remains elusive.[13]

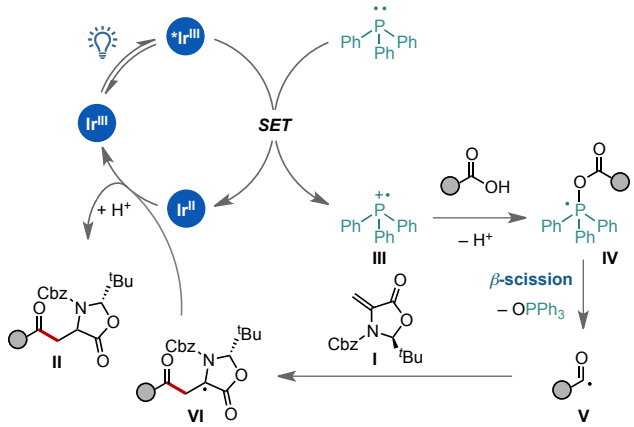


Figure 2. Plausible reaction mechanism

In conclusion, we have developed a highly efficient, light-mediated, deoxygenative strategy for the synthesis of γ-oxo-α-amino acid derivatives. This radical methodology exploits the addition of acyl radicals, generated from readily available carboxylic acids, to Beckwith-Karady alkene **I,** allowing for the straightforward synthesis of a wide range of γ-oxo-α-amino acid derivatives in excellent diastereoselectivities and synthetically useful yields (~ 60% average yield). Furthermore, the synthetic utility of this protocol was highlighted by a series of derivatization reactions, granting access to γ-oxo-β-methyl-α-amino acids in good yields and diastereoselectivities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures & characterization data (PDF)

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