A general deoxygenation approach for synthesis of ketones from aromatic carboxylic acids and alkenes

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The construction of an aryl ketone structural unit by means of catalytic carbon–carbon coupling reactions represents the state-of-the-art in organic chemistry. Herein we achieved the direct deoxygenative ketone synthesis in aqueous solution from readily available aromatic carboxylic acids and alkenes, affording structurally diverse ketones in moderate to good yields. Visible-light photoredox catalysis enables the direct deoxygenation of acids as acyl sources with triphenylphosphine and represents a distinct perspective on activation. The synthetic robustness is supported by the late-stage modification of several pharmaceutical compounds and complex molecules. This ketone synthetic strategy is further applied to the synthesis of the drug zolpidem in three steps with 50% total yield and a concise construction of cyclophane-braced 18–20 membered macrocyclolketones. It represents not only the advancement for the streamlined synthesis of aromatic ketones from feedstock chemicals, but also a photoredox radical activation mode beyond the redox potential of carboxylic acids.
Aromatic carboxylic acids are extremely promising feedstock chemicals, which can be used to rapidly populate libraries of complex small molecules. To date, transition metal-catalyzed decarboxylative coupling enables aromatic carboxylic acids as an alternative source of aryl substructures. Examination of thermodynamic data indicates that direct deoxygenative functionalization of aromatic carboxylic acid by activation of C–O bonds remains a serious challenge owing to the similar bond dissociation energies of C–C and C–O bonds (103 vs 102 kcal mol⁻¹; Fig. 1a)²⁻⁶.

The concise forging of aryl ketone structural unit by means of carbon–carbon coupling represents the state of the art in synthetic chemistry as they are versatile building blocks for the construction of complex natural products and pharmaceuticals. In order to streamline the synthesis of aryl ketones from aromatic carboxylic acids, certain activating steps are usually necessary to generate acid chlorides from carboxylic acids, certain activating steps are usually necessary to generate acid chlorides from carboxylic acids, certain activating steps are usually necessary to generate acid chlorides from carboxylic acids, certain activating steps are usually necessary to generate acid chlorides from carboxylic acids, certain activating steps are usually necessary to generate acid chlorides from carboxylic acids, certain activating steps are usually necessary to generate acid chlorides from carboxylic acids, certain activating steps are usually necessary to generate acid chlorides from carboxylic acids, certain activating steps are usually necessary to generate acid chlorides from carboxylic acids, certain activating steps are usually necessary to generate acid chlorides from carboxylic acids.

However, the requirement of cautious operations and the preformation of intermediates compromises the functional group tolerance and synthetic flexibility together with the increasing demand of late-stage modification of complex target molecules in proteins or living cells under mild conditions. Therefore, the exploration of a practical and sustainable strategy for direct deoxygenative synthesis of ketones in aqueous solution from carboxylic acids is still very desirable but highly challenging.

Although an indirect deoxygenation coupling of acids with a few simple styrenes has been reported via the preformation of reactive arhydride intermediates, a large excess of moisture-sensitive dimethylcarbonates and (TMS)₂SiH reagents were required to initiate the photoredox catalytic cycle. To overcome the mechanistically intrinsic drawbacks, we realized that the diversification of deoxygenation means would potentially offer a conceptually distinct activation mode of carboxylic acids for reaction development. An insight into the classical Wittig reaction inspries us to enquire if the strong P–O affinity between a Ph₃P radical cation and a carbonylate anion could facilitate homolytic C–O bond cleavage of carboxylic acids. If feasible, such deoxygenative functionalization of aromatic acids would be independent of the oxidation potential of acids, and thus would significantly expand the synthetic applications. From our continuing efforts in photocatalysis, we report herein a visible-light-mediated direct deoxygenation activation mechanism of carboxylic acids with cheap triphenylphosphine, which powers deoxygenative C–C coupling of aromatic carboxylic acids with a wide range of alkenes in aqueous solution in the absence of external anhydrides and hydroxilanes additives.

**Results**

**Reaction optimization.** Initially, the direct deoxygenative C–C coupling of 4-methylbenzoic acid (1a) and 2-vinylpyridine (2a) was chosen as the model reaction that could be used to optimize the reaction conditions (Table 1 and also Supplementary Table 1). The optimized reaction conditions include 1 mol% of [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (I) as a photocatalyst, 20 mol% K₂HPO₄ as a base, and 1.2 equiv. Ph₃P as an O-transfer reagent in dichloromethane (DCM)/H₂O (4:1, v/v) (Table 1, entry 1). Under the standard conditions, the corresponding ketone (3a) was obtained in 72% yield. When DCM was employed in place of DCM/H₂O, the yield declined significantly, from 72 to 40% (Table 1, entry 2). It was interesting to find that the O-transfer reagent triphenylphosphine was essential for a successful deoxygenative transformation (Table 1, entry 3). Other photocatalysts such as fac-Ir(ppy)₃ (II), Ru(bpy)₃(PF₆)₂ (III), eosin Y (IV), and Acr⁷⁺–Mes (V) were proved ineffective for this transformation (Table 1, entries 4–7). Control experiments also demonstrated that the reaction could not occur in the absence of either the photocatalyst or light (Table 1, entries 8 and 9).

**Substrate scope of aromatic acids.** With the optimized reaction conditions (Table 1, entry 1) in hand, we investigated the scope of the carboxylic acid substrates (Fig. 2). It was found that acyl radicals generated directly from carboxylic acids could site-selectively add to the β-position of the pyridyl ring with no detectable branched α-position selectivity. In general, aromatic carboxylic acids bearing both electron-donating (e.g., –Me, –Ph, –RnO) and electron-withdrawing groups (e.g., –F and –Cl) at the para-position could react smoothly to produce linear ketones in good yields (3a–h). It is noteworthy that 4-bromo (3g) and 4-iodo (3h) benzoic acids tolerate the conditions well, and this provides an extremely important choice for downstream C–C coupling via palladium catalysis. The substrates on para-, meta-, and ortho-positions of aromatic rings had little influence on the reaction efficiency (3a–r). Significantly, carboxylic acids bearing versatile functional groups, such as –NHBoc, –CHO, –COOMe, –OAc, –OH, alkynyl, alkenyl, and acetal are competent reaction partners (3j–l, 3n–t). Terminal alkene and alkyne structural motifs are compatible with this radical transformation (3q and 3r). Heteroaromatic acids, including furan-, thiophene-, quinoline-, and indole-based acids uniformly underwent deoxygenative C–C coupling, furnishing the desired ketones (3u–x) in moderate

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**Fig. 1** Applications of aromatic carboxylic acids in organic synthesis. **a** The nature choice of aromatic carboxylic acid. **b** Known ketone synthesis from acids (indirect strategies). **c** This work: direct deoxygenative C–C coupling by visible light.
yields. Besides aromatic acids, other kinds of carboxylic acids, including aliphatic carboxylic acids and \( \alpha,\beta \)-unsaturated carboxylic acids however failed in this reaction.

**Substrate scope of alkenes.** Subsequently, many alkenes were examined, giving the results shown in Fig. 3. In view of the prevalence of the pyridine moiety in natural products, pharmaceuticals, and chiral ligands\(^{29,30} \), a wide range of structurally diverse 2-vinylpyridines possessing different kinds of functional groups were subjected to this protocol. Both electron-rich and electron-poor substituents, including Me, –Cl, –CHO, –COOEt, –CF\(_3\), –Br, and –OMe at different positions of the pyridyl ring were well tolerated (3a, 3y–3gg). The benign compatibility of halogen substituents further emphasized the potential synthetic applications (3z, 3ee, and 3gg). 4-Vinylpyridines could be converted into the corresponding linear pyridine-based ketones (3hh) in 68% yields. Other heteroaromatic styrenes were also efficient substrates (3ii–kk). When a variety of 1,1-disubstituted vinylpyridines were employed, the desired products (3ll–rr) were obtained in 43–89% yields. Notably, the electron-rich indole and benzofuran could survive this radical process, indicative of good chemoselectivity (3pp and 3qq). Beside terminal alkenes, \( \alpha,\beta \)-disubstituted alkenylpyridines successfully delivered the products (3ss–uu) in practically useful yields and with moderate diastereoselectivity. A gram-scale experiment demonstrated that this protocol could be easily scaled up (3cc, 5 mmol scale).

To highlight the structural diversification of ketones, other kinds of styrenes were investigated and it was found that they could uniformly react with an aromatic carboxylic acid (1a) to give the desired ketone products (3vv–jy) in moderate to good yields under the optimized conditions. Its synthetic potential is distinguished by excellent and important functional group compatibility as ketone, thioether, terminal olefin/alkyne, and ester are tolerated. Due to the ubiquity of 1,1-diarylalkanes in pharmaceuticals and natural products\(^{31} \), representative 1,1-diaryl olefins were used and they were found to deliver 3,3-diaryl-propanones (3ll–rr and 3cC–jy) in 43–89% yields.

The \( \gamma \)-carbonyl ester and \( \gamma \)-diketones are significant raw materials for the construction of five-membered heterocycle frameworks but their efficient and general accessibility in contemporary synthetic chemistry remains highly challenging\(^{32,33} \). As illustrated in Fig. 3 (lower part), the direct deoxygenative C–C bond formation of carboxylic acids (1a) with varied electron-deficient alkenes allows for modular synthesis of a diverse array of important \( \gamma \)-carbonyl esters, \( \gamma \)-carbonyl aldehydes, and \( \gamma \)-diketones (3kk–vv) in 51–86% yields. Its success arguably could complement the classical Weinreb ketone syntheses from Weinreb amides and Grignard reagents\(^{34} \).

**Examining functional group compatibility.** After observation of the broad substrate scope, we turned our attention upon examining the functional group compatibility, with addition of a wide array of biomolecules, including natural amino acids, nucleic acids, and proteins into the reaction mixture. To avoid the use of inorganic bases, a neutral phosphate saline buffer (pH 7.4) was used. We found that the deoxygenative ketone synthesis occurred smoothly in neutral buffer–DCM solvent without any compromise of the synthetic efficiency in the presence of stoichiometric amounts of unprotected biomolecules such as L-cysteine, L-tyrosine, L-methionine, guanosine, naringin, DNA, miRNA, and bovine serum albumin (Fig. 4). In comparison with our previous deoxygenative coupling using stoichiometric

| Entry | Variation of conditions | Yield\(^a\) |
|-------|-------------------------|-------------|
| 1     | None                    | 72%         |
| 2     | Without H\(_2\)O        | 40%         |
| 3     | No Ph\(_3\)P            | nd          |
| 4     | 1 mol% cat-\( \text{I} \) instead of cat-\( \text{I} \) | nd          |
| 5     | 2 mol% cat-\( \text{II} \) instead of cat-\( \text{I} \) | nd          |
| 6     | 2 mol% cat-\( \text{IV} \) instead of cat-\( \text{I} \) | nd          |
| 7     | 2 mol% cat-\( \text{V} \) instead of cat-\( \text{I} \) | nd          |
| 8     | No photocatalyst         | nd          |
| 9     | No light                | nd          |

Standard conditions: photocatalyst \( \text{I} (1 \text{ mol\%}) \), 1a (0.2 mmol), 2a (1.5 equiv.), Ph\(_3\)P (1.2 equiv.), K\(_2\)HPO\(_4\) (20 mol%), DCM/H\(_2\)O (2.0 mL, v/v = 4:1), rt, 5 W blue light-emitting diodes (LEDs), 48 h

\(^a\)isolated yield

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Table 1 Optimization of reaction conditions
dimethyldicarbonates and (TMS)$_3$SiH$_2$, this clearly demonstrates that the deoxygenative ketone synthesis strategy has an excellent functional group compatibility. Significantly, the selective deoxygenation of only aromatic carboxylic acids in the presence of natural amino acids further underscores its synthetic advantages as amino acids are known to tend to undergo photoredox decarboxylative coupling.

Closed captions for Figures 2, 3, and 4.

**Synthetic application.** The late-stage modification of complex molecules is a basis for the evaluation of a practical protocol. In this context, several biologically important natural products, pharmaceuticals, and agrochemicals were successfully used in this reaction and are shown in Fig. 5a. Three pharmaceuticals with an aromatic acid unit, telmisartan (4), hiestrone (5), and adapalene (6) readily underwent this deoxygenative ketone synthesis. Moreover, 11 complex alkene substrates bearing varying functional groups could be employed, affording the desired products (7–17) in moderate yields in aqueous solution. Interestingly, when two competing electron-deficient alkenes were assembled into one molecule, site-specific hydroacylation occurred at the less sterically hindered site (15). These examples clearly suggest that this strategy represents a promising late-stage application of both carboxylic acids and alkenes, and has the potential to rapidly convert two widely available starting materials into complex ketone molecules.

To underline its synthetic potential, we have applied this deoxygenative coupling protocol to synthesize the drug zolpidem, which ranks 28 in the 200 top-selling drugs (https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/2016Top200PharmaceuticalPrescriptionSalesPosterLowResV2.pdf). As illustrated in Fig. 5b, six steps are usually required for the synthesis of zolpidem from air-sensitive 2-bromo-1-(p-tolyl)ethan-1-one with 19% total yield, but we achieved a concise three-step synthesis of zolpidem with 50% total yield. First, application of deoxygenative C–C coupling of para-methylbenzoic acid (1a) with the electron-deficient alkene (18) successfully produced a γ-carbonyl amide (19) and a subsequent cyclization revealed a simple strategy for the synthesis of zolpidem from commercially abundant para-methylbenzoic acids.

**Intramolecular macrocyclization.** Macroyclic ketones are used widely as fragrances, such as musk and zibeton. To date, the macrocyclization remains a robust but highly challenging synthetic strategy, which usually calls for very low concentrations to avoid intermolecular polymerization. To further demonstrate the practicality of our method, we adapted the visible-light-mediated direct deoxygenation C–C coupling to an elegant macrocyclization under optimized conditions in aqueous solution. As shown in Fig. 6,18–20 membered cyclophane-braced cycloketones (21a–c) have been successfully constructed in...
Fig. 3 Alkene scope
the proposed radical deoxygenation. The resulting radical the triphenylphosphine radical cation (3a).

The intramolecular hydroacylation of 2-allylbenzoic acid (Fig. 8b) and the deuterium-labeling experiments demonstrated further exempli ed the intermediacy of the acyl radical species. The corresponding Stern-Volmer studies further revealed that the photoexcited *Ir(dF(CF3)ppy)2(dbbpy)PF6 was quenched by triphenylphosphine (see Supplementary Information).

A possible mechanism is proposed in Fig. 8f. The photoexcited *Ir(dF(CF3)ppy)2(dbbpy)PF6 [E1/2,red (*IrIII/IrII) = +1.21 V vs SCE; τ = 2.3 μs] is able to undergo single-electron transfer (SET) oxidation with Ph3P (E1/2,red = +0.98 V vs SCE) to form the triphenylphosphine radical cation (31), which could trigger the proposed radical deoxygenation. The resulting radical cation (31) reacts with carboxylic anion to generate the phosphoryl radical (32). This is followed by β-selective C(acyl)–O bond cleavage with thermodynamic impetus for the formation of Ph3P–O. The acyl radical (33) generated in this way then selectively attacks the alkene to form the radical species (34), which is capable of undergoing an SET with reductive Ir3+ species to afford the corresponding ketone in the presence of water. Alternatively, the homocoupling of acyl radicals (33) can afford a little amount of 1,2-diketones as byproducts.

**Three-component reductive coupling.** Based on this reductive quenching mechanism, we extended this deoxygenative catalytic system to an attractive three-component reductive coupling reaction of carboxylic acids (1), primary amines (36), and aromatic aldehydes (37). To our delight, the resulting valuable α-amino ketone products (38) were obtained in moderate yields (Fig. 9).

**Discussion**

In summary, a deoxygenative ketone synthesis from aromatic carboxylic acids and alkenes has been developed in aqueous solution enabled by visible-light photoredox catalysis with commercially cheap triphenylphosphine as an oxygen transfer reagent. This catalytic system enables direct deoxygenation of aromatic acids to generate acyl radical in the presence of a broad variety of biomolecules. This ketone synthesis strategy allows practical and friendly reaction conditions, which significantly broadens the substrate scope, improves the functional group compatibility, and emphasizes the synthetic application in complex molecules. Based on the direct deoxygenative mechanism, a reductive three-component coupling reaction of amines, aldehydes and acids has been achieved. It offers not only a strategy for the streamlined synthesis of structurally diverse ketones from abundant carboxylic acids, but also a photoredox radical activation mode beyond the redox potential of carboxylic acids.

**Methods**

General methods. See Supplementary Methods for further details.

**General procedure for the synthesis of 3.** To a 10 mL Schlenk tube equipped with a magnetic stir bar was added aromatic carboxylic acid 1 (0.2 mmol, 1.0 equiv.), photocatalyst Ir[CF(CF3)ppy]2(dbbpy)PF6 (2.3 mg, 1 mol%), K3PO4 (7.0 mg, 20 mol%), and Ph3P (62.9 mg, 0.24 mmol, 1.2 equiv.) and the tube was evacuated and backfitted with argon for three times. For the alkenes 2 (0.3 mmol, 1.5 equiv.) in DCM/H2O (2.0 mL, 4:1 v/v) were added by syringe under argon. After completion, the mixture was quenched with water and extracted with DCM (3 × 10 mL). The organic layer was dried over anhydrous Na2SO4, then the solvent was removed under vacuo. The residue is subjected to chromatography column on silica gel (eluents: petroleum ether/ethyl acetate) to give the corresponding ketone products 3.

**General procedure for the synthesis of 4–8.** To a 10 mL Schlenk tube equipped with a magnetic stir bar was added aromatic carboxylic acid 1 (0.1 mmol, 1.0 equiv.), photocatalyst Ir[CF(CF3)ppy]2(dbbpy)PF6 (2.3 mg, 2 mol%), K3PO4 (3.5 mg, 20 mol%), and Ph3P (31.5 mg, 0.12 mmol, 1.2 equiv.) and the tube was evacuated and backfilled with argon for three times. The alkenes 2 (0.15 mmol, 1.5 equiv.) in DCM/H2O (2.0 mL, 4:1 v/v) were added by syringe under argon. The tube was then sealed and was placed at a distance (app. 5 cm) from 5 W blue light-emitting diode (LED) lamp, and the mixture was stirred for 36–60 h at room temperature. After completion, the mixture was quenched with water and extracted with DCM (3 × 10 mL). The combined organic layer was dried over anhydrous Na2SO4, then the solvent was removed under vacuo. The residue was subjected to chromatography column on silica gel (eluents: petroleum ether/ethyl acetate) to give the corresponding ketone products 4–8.

**General procedure for the synthesis of 9–17.** To a 10 mL Schlenk tube equipped with a magnetic stir bar was added aromatic carboxylic acid 1 (0.015 mmol,
1.5 equiv.), photocatalyst Ir[dpF(CF3)ppy]2(dtbbpy)PF6 (2.3 mg, 2 mol%), K2HPO4 (7.0 mg, 40 mol%), and Ph3P (31.5 mg, 0.12 mmol, 1.2 equiv.) and the tube was evacuated and backfilled with argon for three times. The alkenes (0.1 mmol, 1.0 equiv.) in DCM/H2O (2.0 mL, 4:1 v/v) were added by syringe under argon. The tube was then sealed and was placed at a distance (approx. 5 cm) from 5 W blue LED lamp, and the mixture was stirred for 48 h at room temperature. After completion, the mixture was quenched with water and extracted with DCM (3 × 10 mL). The combined organic layer was dried over anhydrous Na2SO4, then the solvent was removed under reduced pressure.

Fig. 5 Synthetic application. a Late-stage application in the complex molecules. b Synthesis of zolpidem.
removed under vacuo. The residue was purified with chromatography column on silica gel (eluent: petroleum ether/ethyl acetate) to give the corresponding ketone products 9–17.

**General procedure for the synthesis of 21.** To a 10 mL Schlenk tube equipped with a magnetic stir bar was added aromatic carboxylic acid (36.2 mg, 0.1 mmol, 1.0 equiv.), photocatalyst Ir[dF(CF3)ppy]2(dtbbpy)PF6 (2.3 mg, 2 mol%), K2HPO4 (40 mol%), DCM/H2O, hv. The tube was evacuated and back filled with argon for three times. The amine 3a (0.15 mmol, 1.5 equiv.) and aldehydes 27 (0.15 mmol, 1.5 equiv.) in DCM (2.0 mL) were added by syringe under argon. The tube was then sealed and was placed at a distance (app. 5 cm) from 5 W blue LED lamp, and the mixture was stirred under room temperature for 48 h. After completion, the mixture was quenched with water and extracted with DCM (3 × 10 mL). The combined organic layer was dried over anhydrous Na2SO4, then the solvent was removed under vacuo.

**General procedure for the synthesis of 38.** To a 10 mL Schlenk tube equipped with a magnetic stir bar was added aromatic carboxylic acid 1 (0.15 mmol, 1.5 equiv.), photocatalyst Ir[dF(CF3)ppy]2(dtbbpy)PF6 (1.2 mg, 1 mol%), K2HPO4 (28.1 mg, 1.5 equiv.), and Ph3P (31.5 mg, 0.12 mmol, 1.2 equiv.) and the tube was evacuated and backfilled with argon for three times. The amines 36 (0.1 mmol, 1.0 equiv.) and aldehydes 37 (0.15 mmol, 1.5 equiv.) in DCM (2.0 mL) were added by syringe under argon. The tube was then sealed and was placed at a distance (app. 5 cm) from 5 W blue LED lamp, and the mixture was stirred at room temperature for 48 h. After completion, the solvent was removed under vacuo. The residue was purified with chromatography column on silica gel (eluent: petroleum ether/ethyl acetate) to give the corresponding macrocyclic products 21.

**Fig. 6** Deoxygenative macrocyclization in the synthesis of cyclophane-braced cycloketones

**Fig. 7** Downstream transformations

**Fig. 8** Mechanistic studies. a Control experiments with additives. b Radical cyclization experiment. c Deuteron-labeling experiments. d 18O-labeling experiments. e Aromatic carboxylic anion as substrate. f Proposed mechanism

**Fig. 9** A three-component reductive coupling reaction
under vacuo. The resulting residue was subjected to chromatography column on silica gel (eluents: petroleum ether/ethyl acetate) to give the corresponding α-amino ketone products.

**Data availability**

The authors declare that all other data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon reasonable request.

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Author contributions
M.Z. performed and analyzed the experiments. M.Z., J.X. and C.Z. co-wrote and discussed the manuscript. J.X. conceived and directed the whole project. All authors commented on the final manuscript and contributed to the analysis and interpretation of the results.

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