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β -Selective Aroylation of Activated Alkenes by Photoredox Catalysis

Zhen Lei^[a], Arghya Banerjee^[a], Elena Kusevska^[b], Eric Rizzo^[a], Peng Liu^[b], and Ming-Yu Ngai^[a]

^[a]Department of Chemistry and Institute of Chemical Biology and Drug Discovery, the State University of New York at Stony Brook, Stony Brook, New York 11794 (USA)

^[b]Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260 (USA)

Abstract

Late-stage synthesis of α,β -unsaturated aryl ketones remains an unmet challenge in organic synthesis. Herein, we report a photocatalytic non-chain radical aroyl-chlorination of alkenes *via* 1,3-chlorine atom shift to form β -chloroketones as masked enones that liberate the desired enones upon workup. This strategy suppresses side reactions of enone products such as double aroylation, E/Z isomerization, [2+2]-dimerization, and cross-[2+2]-cycloaddition under photoredox-catalysed conditions. The reaction tolerates a wide array of functional groups and complex molecules including derivatives of peptides, sugars, natural products, nucleosides, and marketed drugs, and offers a potential application in modern drug discovery programs. Notably, addition of 2,6-di-*tert*-butyl-4-methyl-pyridine enhances the quantum yield and efficiency of the cross-coupling reaction. Experimental and computational studies suggest a mechanism involving PCET, formation and reaction of α -chloro- α -hydroxy benzyl radical, and 1,3-chlorine atom shift. These discoveries and mechanistic insights are useful in the development of new photocatalytic reactions.

Graphical Abstract

A photocatalytic β -selective alkene aroylation using readily available aroyl chlorides and activated alkenes is developed. The synthetic utility of the reaction is highlighted by its broad functional group compatibility and high levels of chemo- and regioselectivity. The reaction is amenable to late-stage functionalization of complex molecules including derivatives of sugars, peptides, natural products, nucleosides, and commercially available drugs.

Keywords

photoredox; enones; radical; arylation; aroyl chlorides

Late-stage C–H functionalization of biorelevant molecules is a powerful strategy for the discovery of novel functional molecules, because it avoids laborious *de novo* synthesis of new analogues, increases the efficiency of structure-activity relationship studies, and produces promising new candidates that might have never been evaluated otherwise.^[1] Thus, establishment of new methodologies that introduce useful pharmacophores such as α,β -unsaturated aryl ketones at late-stages of a synthesis is highly desirable. Aryl vinyl ketones are key components of synthetic building blocks, natural products, and pharmaceuticals and have important anticancer, antimicrobial, anti-inflammatory, and immunosuppressive activities.^[2] Consequently, in addition to the conventional stoichiometric reactions,^[3] a range of catalytic intermolecular strategies for the preparation of aryl enones, such as cross-metathesis reactions,^[4] transition metal-catalyzed hydroacylation of alkynes,^[5] copper-catalyzed dehydrogenative cross-coupling reactions,^[6] palladium-catalyzed carbonylation reactions,^[7] NHC-catalyzed (NHC: *N*-heterocyclic carbene) olefination of aldehydes using vinylidonium salts,^[8] and photocatalytic coupling reactions of α -keto-carboxylic acids and styrenes in the presence of a stoichiometric amount of SelectFluor™, a strong oxidant,^[9] have been developed in recent years.^[10] Although these elegant approaches have provided access to a range of simple α,β -unsaturated aryl ketones, the development of mild and general catalytic methods for late-stage synthesis of this important pharmacophore remains a significant challenge in organic synthesis. To address this unmet need, we examined photoredox-catalyzed acyl radical chemistry,^{[11],[12],[13]} in which photo-catalytically generated aroyl radicals can react with olefins to form a $C(sp^2)$ - $C(sp^3)$ bond and alkyl radical intermediates.^[14] Direct oxidation of these alkyl radicals by photoredox catalysts to the corresponding cations followed by deprotonation to afford α,β -unsaturated carbonyls is feasible in view of their electrochemical character.^[15] However, both the efficiency and generality of such an approach are limited because (i) the enone products, especially the β -mono-substituted enones, are susceptible to a second radical addition of nucleophilic aroyl radicals, forming doubly aroylated side products, and (ii) the α,β -unsaturated carbonyl products can undergo *E/Z*-isomerization,^[16] [2+2]-dimerization, and cross [2+2]-

cycloaddition with alkenes^[17] *via* a photocatalytic energy transfer mechanism. We questioned whether these challenges could be addressed by minimizing the amount of enones generated in the reaction mixture through producing masked enones, for example, β -chloroketones (Scheme 1).^[18] We envisioned that direct aroyl-chlorination of alkenes using readily available aroyl chlorides^[19] should give the desired masked enones, which then would undergo HCl elimination upon workup to liberate α,β -unsaturated aryl ketone products.^[20] This formal β -selective alkenyl C–H aroylation strategy is appealing because it obviates the use of stoichiometric quantities of strong oxidants such as SelectFluorTM^[9] and eliminates the need for pre-functionalization of the alkenes. As a result, it will allow direct incorporation of the aroyl group at any time towards the target synthesis. Herein, we report (i) the successful development of a mild photocatalytic protocol that enables late-stage synthesis of α,β -unsaturated aryl ketones from aroyl chlorides and alkenes, (ii) unprecedented effects of 2,6-di-*tert*-butyl-4-methyl-pyridine additive on the reaction efficiency and quantum yield, and (iii) a novel reaction mechanism of aroyl-chlorination of alkenes.

After a systematic variation of different reaction parameters, such as additives, solvents, photoredox catalysts, concentrations, and stoichiometries, we were pleased to identify optimal reaction conditions in which a mixture of 4-fluorobenzoyl chloride (**1b**, 1.50 equiv), 1,1-diphenyl-ethylene (**2am**, 1.00 equiv), *fac*-Ir(ppy)₃ { *fac* tris[2-phenylpyridinato-C²,N]iridium(III), 1.00 mol% }, and 2,6-di-*tert*-butyl-4-methyl-pyridine (1.20 equiv) in CHCl₃ (0.100 M) at 23 °C with irradiation by a blue LED light for 16 h afforded the desired product **3b** in 85% isolated yield.^[21] Although aliphatic acyl chlorides failed to react under these conditions, a diverse set of aroyl chlorides was successfully coupled to afford the desired enone products (Table 1a). For example, electron-neutral (**1a**, **1r-1s**), electron-rich (**1i-1m**), and electron poor (**1n-1q**) aroyl chlorides reacted well under these reaction conditions affording the desired enones in 46–96% isolated yields. Different halogen functionalities (**1b-1h**), in particular, Br and I, survived the reaction, and provided synthetic handles for further structural elaboration through metal-catalyzed coupling reactions. The reaction tolerated *o*-, *m*-, and *p*-substituted aroyl chlorides (**1d-1f**). Substrates bearing extended π -system (**1r**, **1s**) and heteroarenes such as thiophene (**1t**) and furan (**1u**) reacted smoothly, providing the desired products in 55–89% yields.

We next directed our attention to examine the scope of alkenes and found that a wide range of mono- and di-substituted alkenes participate in this coupling reaction, affording the desired enones in modest to good yields (Table 1b). For example, various styrenes regardless of their electronics (**2a-2h**, **2m-2t**, **2v**, **2x**, **2aa**) were viable substrates. Alkenes substituted with biologically important heteroarenes such as thiophene (**2i**), thiazole (**2j**), quinoline (**2k**), furan (**2l**), pyridine (**2r-2s**), benzofuran (**2r**), and indole (**2s**) were compatible under the optimized reaction conditions. Both 1,2- and 1,1-disubstituted (hetero)aryl alkenes (**2m-2t**, **2v**) reacted to give the desired trisubstituted enones in yields of 51–82%. The *E* and *Z* diastereoselectivity of the resulting enones is determined by the sterics of alkene substituents. While alkenes with sterically distinct substituents afforded one diastereomer (**2n**, **2t**) exclusively, alkenes with substituents of similar sizes gave a mixture of diastereomers (1–1.3:1, **2o-2s**). Most of the mono-substituted alkenes afforded the desired

products as a single diastereomer. Although aliphatic alkenes afforded only trace amount of the desired products, our method was successfully applied to other alkene derivatives such as an enyne (**2u**), a diene (**2v**), mono- and di-substituted α,β -unsaturated esters (**2w-2aa**), acyclic (**2ab**) and cyclic (**2ac**) enones, and acrylonitrile (**2ad**) to furnish the corresponding products in 43–89% yields. More importantly, the protocol allows a straightforward and selective synthesis of molecular scaffolds (*e.g.*, **4m**, **4n**, **4t**, **4v**, **4ac**) that are otherwise difficult to access.

To demonstrate the amenability of the photocatalytic alkene arylation process to late-stage synthetic applications, drug-like molecules were subjected to the standard reaction conditions (Table 1c). For example, derivatives of peptides, sugars, natural products, nucleosides, and marketed drugs bearing functional groups such as free hydroxyl groups, tertiary amines, alkyl alkenes, acetal and triethylsilyl protecting groups, oxetane, ketones, and heteroaromatics were successfully arylated to afford the desired products (**4ae-4al**) in 48–80% yields and with excellent levels of chemo-, regio-, and diastereoselectivity. It is noteworthy that preparation of these complex aryl enones via the cross-metathesis protocol is challenging due to (i) the instability and limited availability of aryl vinyl ketones and (ii) the difficulty in distinguishing between two different terminal alkenes (**4ak**). Thus, our strategy is complementary to the cross-metathesis.

To illustrate the synthetic utility of the enone products for preparation of useful molecular scaffolds, we derivatized the products under various reaction conditions (Scheme 2). Treatment of **4t**, an enone derivative that is difficult to prepare otherwise, with the Febuxostat-derivative **5** under Suzuki coupling reaction conditions afforded the desired product **6** in 43% yield with 2:1 *E:Z*-ratio. Under redox annulation reaction conditions, the chalcone **4a'** coupled with pyrrolidine and tetrahydroisoquinoline, forming the cyclic amines **7** and **8**, respectively, in modest yields.^[22] The enone **4m** underwent epoxidation smoothly to afford the desired product in 78% yield.

It is noteworthy that 2,6-di-*tert*-butyl-4-methyl-pyridine additive is critical for the success of the reaction. We conducted a series of experiments to understand the role of 2,6-di-*tert*-butyl-4-methyl-pyridine additive. First, Stern-Volmer experiments revealed that aryl chlorides quench excited $\text{fac-}^*\text{Ir(ppy)}_3$ photocatalysts but alkenes and 2,6-di-*tert*-butyl-4-methyl-pyridine do not. Interestingly, the presence of 2,6-di-*tert*-butyl-4-methyl-pyridine enhanced the quenching constant of aryl chlorides from $9.89 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ to $1.29 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$ (Figure S1). In addition, TEMPO [(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl] trapping experiments demonstrated that 2,6-di-*tert*-butyl-4-methyl-pyridine additive increased the yield of the benzoyl-TEMPO adduct from 53% to 96%. These observations suggested that the reaction proceeds through a radical mechanism and the additive promotes the formation of the aryl radicals (Scheme 3a). We also noticed that the steric bulk at the 2,6-position of pyridine is crucial in obtaining high yields and no desired product was observed by using 4-methylpyridine as the additive (Scheme 3b). ¹H-NMR studies showed a significant downfield shift of 4-methylpyridine protons after the addition of aryl chloride **1q**, indicating the formation of aryl-pyridinium salt **10** (Figure S3). Once **10** was formed, the ¹H-NMR of the reaction mixture remained unchanged even after irradiation with blue LEDs for 16 hours. Thus, these results rule out the aryl chloride activation via the formation of

aroyl-pyridinium salts. Notably, the addition of 2,6-di-*tert*-butyl-4-methyl-pyridine increased both the product yield (**4d'** and **4d**) and the ratio of product distribution (Scheme 3c, entries 1 and 2), favouring the formation of the chloro-product **4d'**. These observations implied that 2,6-di-*tert*-butyl-4-methyl-pyridine (*Py) additive serves more than just a base. Although the exact role of the 2,6-di-*tert*-butyl-4-methyl-pyridine requires further studies, we speculated that a small amount of HCl formed in the reaction mixture protonates the pyridine additive to give the corresponding *Py-HCl salt.^[23] This salt may act as a Brønsted acid catalyst and facilitate the generation of the α -chloro- α -hydroxybenzyl radical *via* the proton-coupled electron transfer (PCET) mechanism.^[24] Indeed, the addition of 0.05 equivalents of *Py-HCl salt and a mixture of *Py/*Py-HCl (1.15/0.05 equiv) improved the product yield from 42% to 70% and 94% (entries 1, 3, and 4), respectively,^[25] demonstrating the feasibility of the PCET reaction pathway. Furthermore, the quantum yield of the reaction was increased from 0.19 to 0.66 by the addition of 2,6-di-*tert*-butyl-4-methyl-pyridine additive (Scheme 3d).^[11d, 26] Since the quantum yield is lower than 1, an extended radical chain reaction mechanism is unlikely, which corroborates with Light ON/OFF experiments (Figure S6).

Detailed DFT calculations provided additional insights into the reaction mechanism (Scheme 3e). First of all, the proposed PCET step to form α -chloro- α -hydroxybenzyl radical **1b** is thermodynamically favourable.^[27] Notably, instead of undergoing HCl elimination to give the benzoyl radical **1c'**, the radical **1b** reacts with styrene to form benzyl radical **1c**. In addition, while an intermolecular oxidation of **1c** by Ir(ppy)₃⁺ to form benzylic cation **1d'** is an endergonic process, an intramolecular 1,3-chlorine atom shift^[28] to produce radical **1d** is an exergonic reaction. Subsequent single electron oxidation of **1d** by Ir(ppy)₃⁺ and deprotonation of **1e** are both highly exothermic.

Based on these experimental and computational studies, a plausible reaction mechanism is depicted in Scheme 4. Photoexcitation of the photocatalyst Ir(ppy)₃ produces the long-lived excited *Ir(ppy)₃ ($t_{1/2}$ = 1.9 μ s, $E_{1/2}^{IV/III*}$ = -1.73 V vs SCE).^[29] In the presence of 2,6-di-*tert*-butyl-4-methyl-pyridinium species, aroyl chloride **IIa** (E_p of benzoyl chloride = -1.02 V vs SCE)^[19b] undergoes a proton couple electron transfer (PCET) process with *Ir(ppy)₃ to liberate 2,6-di-*tert*-butyl-4-methyl-pyridine and α -chloro- α -hydroxy benzyl radical **IIb**. This nucleophilic radical adds to an alkene to give intermediate **IIc** followed by 1,3-chlorine atom shift to afford α -hydroxy radical **IIId**. Single electron oxidation of **IIId** by Ir(ppy)₃⁺ followed by deprotonation regenerates the ground state Ir(ppy)₃ and affords the desired β -chloro-ketone **IIe**, which delivers the final enone upon workup.

In conclusion, we have developed a photocatalytic β -selective alkene aroylation using readily available aroyl chlorides and activated alkenes. The synthetic utility of the reaction is highlighted by its broad functional group compatibility and high levels of chemo- and regioselectivity. The reaction is amenable to late-stage functionalization of complex molecules including derivatives of sugars, peptides, natural products, nucleosides, and commercially available drugs. Notably, 2,6-di-*tert*-butyl-4-methyl-pyridine additive serves more than a base, it also promotes electron transfer, increases quantum yields, and enhances the reaction efficiency. DFT calculations suggests that a reaction mechanism involving PCET, formation and reaction of α -chloro- α -hydroxy benzyl radical, and 1,3-chlorine atom shift is operable. We anticipate that these new mechanistic insights will be useful in the

development of photocatalytic reactions and that this mild, versatile reaction will find applications in modern drug discovery and development programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Scheme 1.

Photocatalytic β -arylation of alkenes. BT = Baccatin

Scheme 2.
Synthetic utility of the enone products.

Scheme 3. Mechanistic studies.

All energies are Gibbs free energies in kcal/mol computed at the M06-2X/6-311+G(d,p)/SMD(CHCl₃)/M06-2X/6-31+G(d)/SMD(CHCl₃) level of theory using benzoyl chloride and styrene as substrates. [a] Cited yields in the parenthesis are of amount of the corresponding enone formed in the reaction mixture. See SI for details.

Scheme 4.
Proposed reaction mechanism.

Table 1

Selected examples of the coupling reaction between aroyl chlorides and alkenes.^[a]

^[a] Cited yields and E/Z ratio. in the parenthesis are of isolated material. DE = 1,1-diphenylethylenyl, B¹ = 2-trifluorobenzoyl, B² = 4-chlorobenzoyl, Bz = benzoyl, Ac = acetyl, Py = pyridyl, TES = triethylsilyl, Boc = *tert*-butoxycarbonyl, Pr = *n*-propyl, 2,6-di^tBu-4-MePy = 2,6-di-*tert*-butyl-4-methyl-pyridine