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Direct β-Functionalization of Cyclic Ketones with Aryl Ketones via the Merger of Photoredox and Organocatalysis

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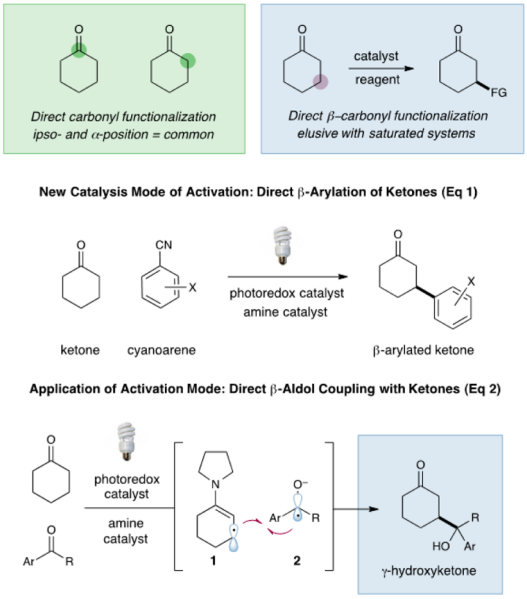
Supporting Information

ABSTRACT: The direct β-coupling of cyclic ketones with aryl ketones has been achieved via the synergistic combination of photoredox catalysis and organocatalysis. Diaryl oxymethyl or aryl−alkyl oxymethyl radicals, transiently generated via single-electron reduction of ketone precursors, readily merge with β-enaminyl radical species, generated by photon-induced enamine oxidation, to produce γ-hydroxyketone adducts. Experimental evidence indicates that two discrete reaction pathways can be operable in this process depending upon the nature of the ketyl radical precursor and the photocatalyst.

The direct β-functionalization of saturated ketones and aldehydes is an important yet elusive goal in organic chemistry.[1] While carbonyl groups are readily amenable to *ipso*- and α-carbon substitution with a range of nucleophiles and electrophiles respectively,[2,3] activation at the β-methylene position poses a significant synthetic challenge. With a few notable exceptions,[1,4] carbonyl β-functionalization has traditionally been restricted to the conjugate addition of soft nucleophiles into α,β-unsaturated carbonyl systems. As such, the development of a general catalytic platform[5] for the direct β-functionalization of saturated ketones or aldehydes would represent a conceptual and practical advance for the field. In this context, our lab has recently introduced an unprecedented 5πe$^-$carbonyl activation mode that capitalizes on the synergistic merger of photoredox catalysis and amine organocatalysis to accomplish the direct β-arylation of saturated aldehydes and ketones (eq 1).[1a] This strategy relies on the coupling of two catalytically generated radical species: a β-enaminyl radical formed via oxidation and deprotonation of a ketone-derived enamine and a radical anion generated by photocatalytic reduction of an aryl nitrile.[6] Here, we further advance this activation concept to describe the first β-functionalization of saturated cyclic ketones with aryl ketones to deliver γ-hydroxyketone motifs, a protocol that formally represents a homoenolate aldol reaction using simple carbonyl substrates, a household light source, and two commercial catalysts (eq 2).

Among the most fundamental carbonyl α-functionalization reactions in organic chemistry is the aldol coupling of nucleophilic enolates with electrophilic ketones or aldehydes to deliver valuable β-hydroxycarbonyl motifs.[7] Although the aldol reaction has been widely exploited for the α-functionalization of carbonyl substrates for over 140 years,[8] analogous "homo-aldol" transformations that allow for the direct β-functionalization of carbonyls remain elusive. Typically, homoaldol-type synthons



are accessed via carbene catalysis,[9,10] nucleophilic addition of acetal-protected Grignard reagents,[11] or stoichiometric metal-activated homoenolate equivalents.[12−16]

Drawing from the mechanistic insights gained in the course of our β-arylation program,[1a] we envisioned a direct β-coupling of saturated ketones with aryl−alkyl and diaryl ketone precursors. Specifically, we postulated that a transiently formed nucleophilic β-enaminyl 5πe$^-$ species (**1**) would be intercepted by a ketyl radical (**2**) to directly form a γ-hydroxyketone adduct (eq 2).[17] Notably, both radical species would be generated in catalytic quantities through the operation of two concurrent activation pathways: a photoredox cycle (en route to **2**) and an organocatalytic cycle (en route to **1**).

The specific mechanistic details of our proposed synergistic merger of visible-light-mediated photoredox catalysis and organocatalysis[18,19] are outlined in Scheme 1. Irradiation of tris(2-phenylpyridinato-C^2,N)iridium(III) [Ir(ppy)$_3$] (**8**) with visible light produces a long-lived (1.9 μs) photoexcited state,[20] *Ir(ppy)$_3$ (**9**), which can be readily oxidized or reduced by an appropriate substrate quencher. While *Ir(ppy)$_3$ (**9**) is a strong reductant ($E_{1/2}^{red}$ [Ir(ppy)$_3^+$/*Ir(ppy)$_3$] = −1.73 V vs SCE),[21] its capacity for single electron transfer (SET) with diarylketones such as benzophenone would be endergonic ($E_{1/2}^{red}$ = −1.83 V vs SCE).[22] However, in an acidic medium, the standard reduction

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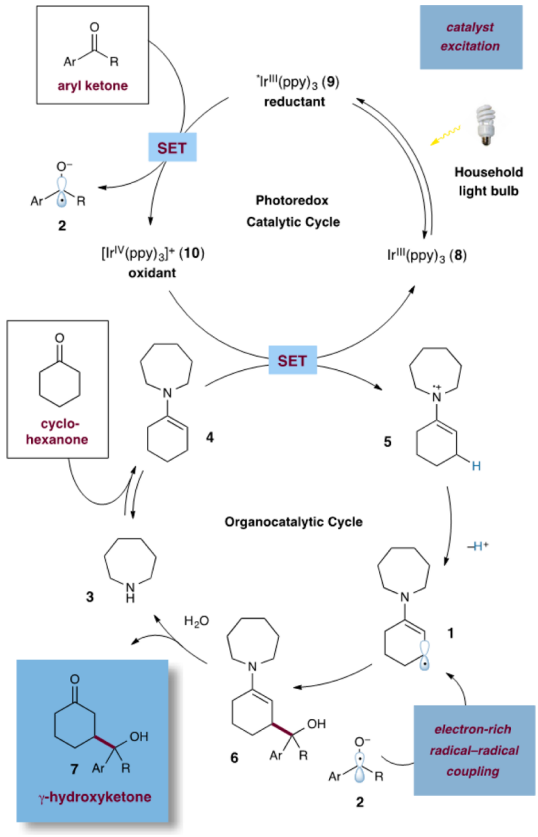
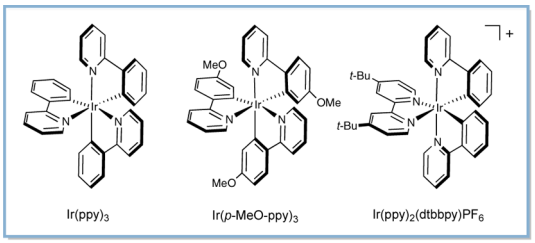
Scheme 1. Proposed Mechanism for the β-Ketone Coupling

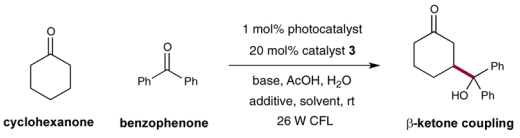


potential of the ketone is elevated and therefore it is easier to reduce, rendering this step experimentally feasible.[23] As such, electron transfer (ET) between an aryl ketone and excited state **9** would provide the oxidized $Ir^{IV}(ppy)_3$ (**10**) system along with the corresponding ketyl radical **2**. Concurrent with this photoredox cycle, we envisioned a second organocatalytic cycle, commencing with condensation of amine catalyst **3** with the ketone coupling partner (i.e., cyclohexanone) to generate an electron-rich enamine **4**. The facile oxidation of this intermediate by $Ir^{IV}(ppy)_3$ ($E_{1/2}^{red}$ $[Ir(ppy)_3^+/Ir(ppy)_3]$ = +0.77 V vs SCE; $E_{1/2}^{red}$ **4** = +0.38 V vs SCE)[24] serves to reduce the photocatalyst to its ground state, thereby completing the photocatalytic cycle. Formation of the desired enaminyl radical cation **5** would then induce an increase in the acidity of the allylic C–H bond, facilitating deprotonation at the β-position.[1a] The transiently formed $5\pi e^-$ species **1** should then readily couple with ketyl radical **2** to form the γ-hydroxyketone enamine **6**. Finally, enamine hydrolysis would serve to release the β-union product **7** and regenerate **3**, completing the organocatalytic cycle. With respect to achieving chemoselective reduction of benzophenone in the presence of cyclohexanone, it was expected that the significantly lower standard reduction potential of cyclohexanone ($E_{1/2}^{red}$ = −2.79 V vs SCE)[25] would render this substrate thermodynamically indisposed toward reduction.

We first explored the proposed direct β-carbonyl coupling reaction in the context of cyclohexanone and benzophenone (Table 1). Examination of a range of photocatalysts, amines, bases, and solvents (entries 1–6) revealed the combination of $Ir(ppy)_3$ (**8**) and 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base to be most effective. For example, when a DMPU solution[26] containing the ketone substrates, $Ir(ppy)_3$ (**8**), DABCO, and azepane organocatalyst (**3**)[27] was irradiated with 26 W

Table 1. Initial Studies towards the β-Coupling of Ketones





entry	photocatalyst	base	additive	solvent	yield[a]
1	$Ir(ppy)_3$	NaOAc	--	DMPU	52%
2	$Ir(ppy)_3$	2,6-lutidine	--	DMPU	34%
3	$Ir(ppy)_3$	DABCO	--	DMPU	67%
4	$Ir(p\text{-MeO ppy})_3$	DABCO	--	DMPU	65%
5	$Ir(ppy)_2(dtbbpy)PF_6$	DABCO	--	DMPU	59%
6	$Ir(ppy)_3$	DABCO	--	DMF	59%
7	$Ir(ppy)_3$	DABCO	$CsClO_4$	DMPU	72%
8	$Ir(ppy)_3$	DABCO	$KAsF_6$	DMPU	75%
9	$Ir(ppy)_3$	DABCO	$LiAsF_6$	DMPU	81%
10	none	DABCO	$LiAsF_6$	DMPU	0%
11	$Ir(ppy)_3$[b]	DABCO	$LiAsF_6$	DMPU	0%
12	$Ir(ppy)_3$[c]	DABCO	$LiAsF_6$	DMPU	0%

[a]Yield determined by ^1H NMR using 1,3-benzodioxole as an internal standard. [b]Reaction performed in the absence of catalyst **3**. [c]Reaction performed in the absence of light. CFL = compact fluorescent light.

fluorescent light, the γ-alkyloxy adduct was formed in 67% yield (entry 3). The desired product was accompanied by significant amounts (12%) of benzophenone dimer, which we assume arises from the combination of two molecules of ketyl radical **2**. Notably, further improvements in reaction efficiency were achieved through addition of 1 equiv of $LiAsF_6$,[28] which suppresses formation of this undesired diol, presumably via the production of a lithium alkoxide ketyl radical that is inert to dimerization (entry 9, 81% yield). The critical roles of the photocatalyst, organocatalyst, and light were demonstrated through control experiments, wherein no desired product was detected in the absence of any of these components (entries 10–12).

Having identified optimal conditions for this photocatalytic, direct β-ketone–ketone coupling reaction, we aimed to define the scope of the enaminyl radical precursor. As shown in Table 2, a series of differentially substituted cyclohexanone-derived substrates were readily coupled with benzophenone. It is of note that incorporation of both alkyl and aryl substituents at positions 3 and 4 of the cyclohexanone ring is well-tolerated (entries 2–5, 43–79% yield). As expected, the presence of groups at the ring 4-position induces higher levels of diastereoselectivity than substituents at the cyclohexanone 3-position (cf. entries 4 and 5). Interestingly, while cyclopentanone served as a suitable substrate for this reaction (entry 6, 65% yield), 7-membered ketones gave low yields of the desired β-alkyloxy product (10–20% yield; see Supporting Information).

We next sought to establish the scope of the ketyl radical substrate in this β-carbonyl functionalization reaction. As shown in Table 3, a range of substituted benzophenones can serve as

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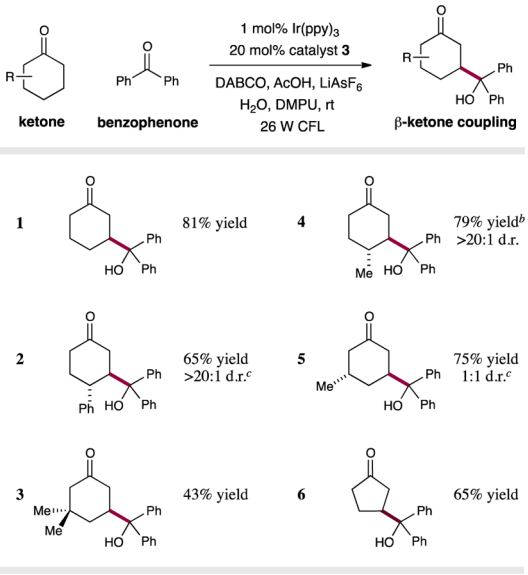
Table 2. Scope of the Ketone-Enaminyl Radical Precursor[a]

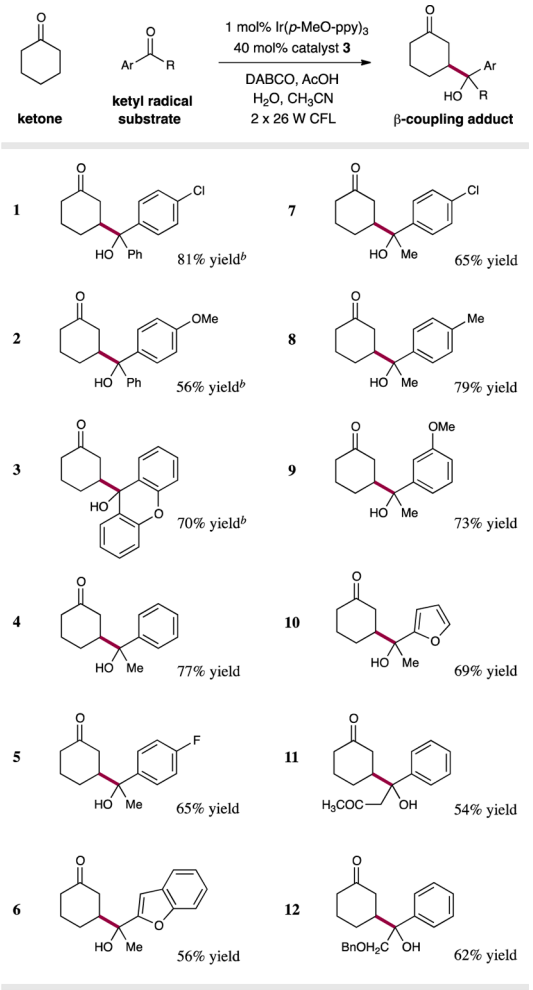


[a]Reaction typically performed with 20 mol % of amine catalyst **3**, 20 mol % of AcOH, 1 equiv of $LiAsF_6$, 2 equiv of DABCO, 2 equiv of water. [b]Reaction performed with 10 equiv of water. [c]Diastereoselectivity determined by ^1H NMR analysis.

viable coupling partners using our optimized conditions (entries 1−3, 56−81% yield) to furnish γ-hydroxyketone products with high levels of efficiency. Notably, a slightly diminished yield was obtained with 4-methoxybenzophenone (entry 2, 56% yield), likely due to the electron-donating group on the aromatic ring, which lowers the standard reduction potential of the ketone.

At this stage we turned our attention to aryl−alkyl ketone reaction partners, a more challenging substrate class given that ketyl radical formation would be thermodynamically disfavored with respect to the analogous benzophenone system. Indeed, initial efforts to achieve this photocatalytic β-heterocoupling reaction using acetophenone met with little success using our previously optimized conditions. We recognized that the excited state of the photocatalyst (**9**) is not sufficiently reducing to induce ketyl radical formation from acetophenone via ET ($E_{1/2}^{red}$ = −2.14 V vs SCE),[20] a reduction potential that is considerably lower than that of benzophenone. Fortunately, we identified Ir(p-MeO-ppy)$_3$ as an effective photocatalyst for the reduction of aryl−alkyl ketones, and indeed, this system enabled a large increase in the ketyl-radical partner scope (Table 3, entries 4−12). We initially speculated that incorporation of electron-donating substituents on the photocatalyst aryl ligand would enhance the reduction potential of the IrL_3 excited state, thereby allowing ketyl radical formation to become facile with aryl−alkyl ketones.[29] However, subsequent studies suggest that the use of Ir(p-MeO-ppy)$_3$ leads to a change in the order of ET events with enamine oxidation becoming the primary interaction for the IrL_3 excited state (*vide infra*). Using the Ir(p-MeO-ppy)$_3$ catalyst, both electron-deficient (entries 5 and 7, 65% yield) and electron-rich (entries 8 and 9, 73−79% yield) acetophenone derivatives readily coupled with cyclohexanone to generate γ-hydroxyketone adducts. Moreover, heteroaryl−methyl ketones were also suitable reaction partners in this transformation (entries 6 and 10, 56−69% yield). Although higher alkyl homologues of acetophenone failed to participate in this β-functionalization protocol, reaction efficiency was recovered via the introduction

Table 3. Scope of the Ketyl Radical Coupling Precursor[a]



[a]Diastereoselectivity, where relevant, was determined by ^1H NMR analysis to be 1−1.2:1. [b]Reaction conditions as performed in Table 2.

of electron-withdrawing groups onto the carbonyl alkyl substituent (entries 11 and 12, 54−62% yield).

To further probe the mechanistic course of this transformation and the specific utility of each photocatalyst as a function of ketyl radical subclass, we performed a series of Stern−Volmer quenching studies. As expected, these experiments revealed that benzophenone quenches the excited state of Ir(ppy)$_3$ (**9**) (Figure 1), lending support to our initial hypothesis in Scheme 1. However, similar experiments performed with acetophenone (or acetophenone in the presence of acetic acid)[30] and Ir(p-MeO-ppy)$_3$ revealed that no excited state quenching was observed with

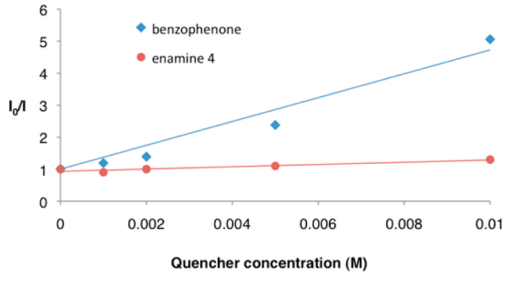


Figure 1. Ir(ppy)$_3$ emission quenching with benzophenone and enamine **4**.

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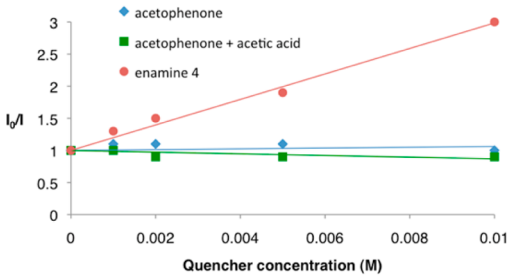

Figure 2. Ir(*p*-MeO-ppy)$_3$ emission quenching with acetophenone and enamine **4**.

this ketone class, demonstrating that an alternative mechanism is operative using aryl−alkyl ketone substrates (Figure 2). Indeed, pregenerated enamine **4** was found to quench *Ir(*p*-MeO-ppy)$_3$, providing evidence that oxidation of the enamine occurs *prior* to reduction of acetophenone when aryl−alkyl ketones are employed. This change in the sequence of the oxidation and reduction steps in the photoredox cycle is consistent with the observed requirement for a different photocatalyst depending on the ketone acceptor employed (e.g., benzophenone = Ir(ppy)$_3$ preferred, acetophenone = Ir(*p*-MeO-ppy)$_3$ preferred).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(26) The use of DMPU is related to the requirement of high-dielectric media for efficient ET processes (e.g., DMF, DMSO, etc. are also viable although slightly less effective).

(27) It is well-known that azepane and pyrrolidine amines are nucleophilic, due to the capacity to donate electrons from nitrogen to alleviate ring strain (not found to the same level with piperidine). We believe the use of an azepane catalyst leads to a more nucleophilic 5πe^- system as a result of this phenomenon.

(28) We have tried several additives such as LiCl, $LiClO_4$, $LiBF_4$, $KAsF_6$, etc.; however, slightly improved yields were obtained with $LiAsF_6$.

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(30) This experiment reveals that proton coupled electron transfer (PCET) is not operative in the reduction of acetophenone via the excited state of Ir(*p*-MeO-ppy)$_3$.