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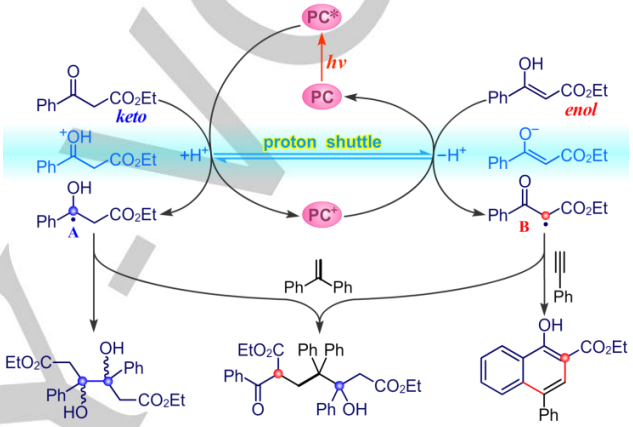
Photoredox Catalysis of Aromatic β-Ketoester *in Situ* toward Transient and Persistent Radicals for Organic Transformation

Xiu-Long Yang, Jia-Dong Guo, Hongyan Xiao, Ke Feng, Bin Chen, Chen-Ho Tung, and Li-Zhu Wu*

Abstract: Radical formation is an initial step for conventional radical chemistry. Reported herein is a unified strategy to generate radicals *in situ* from aromatic β-ketoester only by a photocatalyst. Under visible light irradiation, a small amount of photocatalyst *fac*-Ir(ppy)$_3$ succeeds in the generation of transient α-carbonyl radical and persistent ketyl radical *in situ*, for the first time. In contrast to the well-established approaches, neither stoichiometric external oxidant nor reductant is required for this reaction. The synthetic utility is demonstrated by pinacol-coupling of ketyl radicals and benzannulation of α-carbonyl radicals with alkynes to give a series of highly substituted 1-naphthols in good to excellent yields. Provided the readily available photocatalyst, extremely mild reaction condition, broad substrate scope and functionality tolerance offer a unique perspective in synthetic planning and implementation.

Development of atom- and step-economic approaches to make useful molecular structures is always an important concern of organic synthesis.[1] Recent blooming of visible light catalysis becomes sought after to success of this easy manipulation and environmental benign transformation.[2] In terms of a photocatalyst either reductive-quenching by electron donor (reductant) or oxidative-quenching by electron acceptor (oxidant), the generated reactive open-shell radical cations ($D^{\bullet+}$) and radical anions ($A^{\bullet-}$) exhibit rich synthetic reactivity for subsequent reactions.[3] Over the past decade, these photocatalytic designs have spurred tremendous research interest and there have been numerous advances in an array of photoredox catalytic reactions, for example, cross-coupling reactions,[4] α-amino/oxy/carbonyl C(sp^3)−H bond functionalization,[5] cycloadditions,[6] reductive umpolung of carbonyl derivatives[7] and dehalogenation reactions.[8] In these reactions, however, stoichiometric external oxidant or reductant is often required for subsequent oxidative or reductive reactions. In light of the fact that a photocatalyst in its excited state is a stronger oxidant and a stronger reductant than in its ground state,[3] we wondered whether one could make full use of a photocatalyst to form radicals without any aid of external oxidant and reductant in one pot reaction.[9] Toward this goal, one needs not only to satisfy the thermodynamical requirement for radical generation but also to keep the kinetic reactivity of the generation radicals for following transformation. What's more, the intermediates generated *in situ* with different lifetime under neutral condition seems even more difficult to couple for subsequent product formation.



Scheme 1. Photoredox catalysis of aromatic β-ketoester *in situ* toward transient and persistent radicals for organic transformation.

With this in mind, we initiated the study to generate radicals *in situ* by a photocatalyst under redox-neutral condition. Herein, 1,3-dicarbonyl compound, aromatic β-ketoester, is selected due to the fact that the activation of its unique molecular skeleton is difficult to access without the aid of external oxidant or reductant. It was expected that both electrophilic and nucleophilic functional groups by keto−enol tautomerism[10] of aromatic β-ketoester is able to interact with photoexcited photocatalyst (**PC***) to afford ketyl radical **A**[7, 11] and photocatalyst radical cation (**PC**$^{\bullet+}$).[12] The higher electron affinity and lower LUMO energy level of aromatic β-ketoesters[13] render the keto form rather than the enol form of aromatic β-ketoester to act as electron acceptor (Table S4, supported by the results of the DFT calculation in the Supporting Information) (Scheme 1). Although photocatalyst **fac*-Ir(ppy)$_3$ ($E_{1/2}^{ox}$ $^+$Ir(ppy)$_3$/*Ir(ppy)$_3$ = −1.73 V *vs*. SCE)[2a] is not able to take place single electron transfer (SET) with aromatic β-ketoester **1a** (E^{red} < −1.90 V *vs*. SCE, E^{ox} > +1.90 V *vs*. SCE in CH_3CN, Figures S4 and S6), the anion **1a**$^-$ ($E_{1/2}^{ox}$ **1a**$^{\bullet}$/**1a**$^-$ = +0.66 V *vs*. SCE in DMF, Figure S5)[14] resulted from partially deprotonated **1a** would be oxidized by $^+$*fac*-Ir(ppy)$_3$ species ($E_{1/2}^{red}$ $^+$Ir(ppy)$_3$/Ir(ppy)$_3$ = +0.77 V *vs*. SCE) to have photocatalyst *fac*-Ir(ppy)$_3$ regenerated and simultaneously transient α-carbonyl radical **B** produced.[13] The striking feature of aromatic β-ketoester is that the enol form enables to eliminate proton to form its anion, and at the same time, the eliminated proton can activate keto form to significantly decrease the reduction potential of **1a**. As a result, the persistent ketyl radical **A** and transient α-carbonyl radical **B** are produced only by

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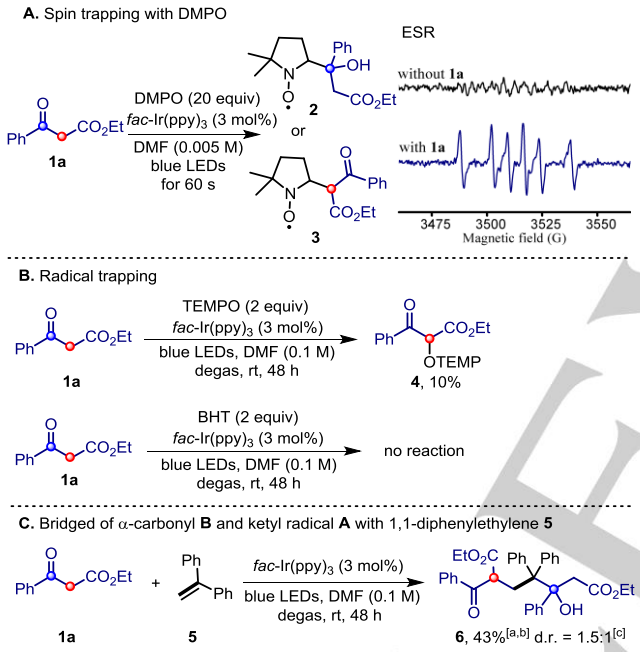
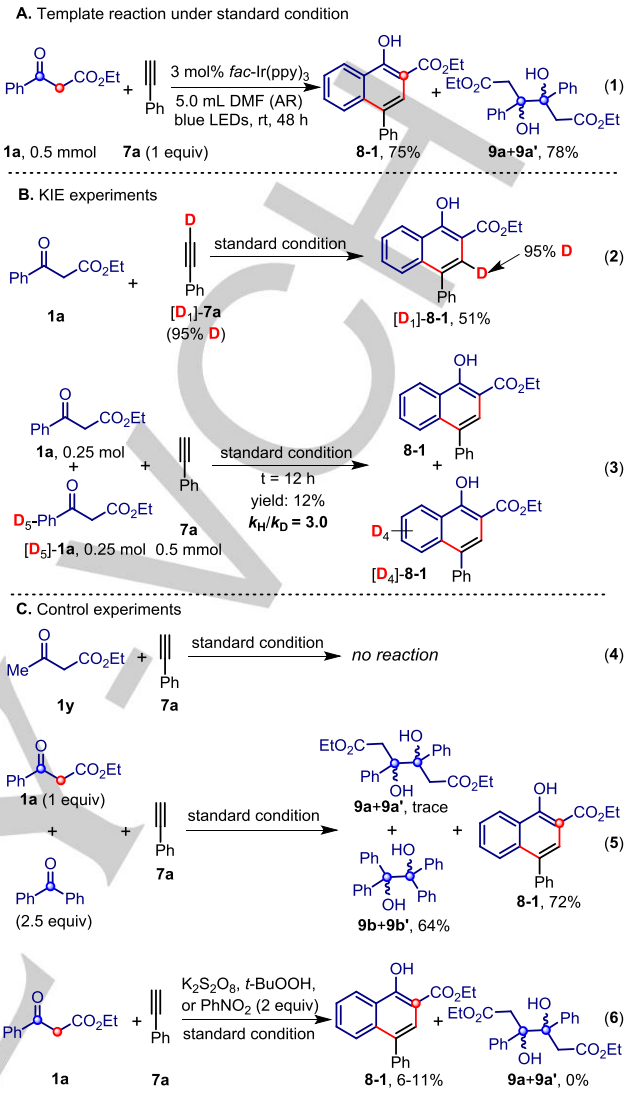
photocatalyst *fac*-Ir(ppy)$_3$ under visible light irradiation without any stoichiometric external oxidant and reductant, which is unprecedented in the photoredox catalysis.

Indeed, after irradiation of aromatic *β*-ketoester **1a**, 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) and *fac*-Ir(ppy)$_3$ in *N,N*-dimethylformamide (DMF) for 60 seconds, a characteristic signal **2** or **3** of ketyl radical **A** or *α*-carbonyl radical **B** were detected by electron spin resonance (ESR) (Scheme 2A). The two radical inhibitors, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) greatly suppressed the reaction with the formation of alkoxyamine **4** in about 10% yield (Scheme 2B).[14-15] Importantly, visible light irradiation of aromatic *β*-ketoester **1a** to generate persistent ketyl radical **A**[7, 11] and transient *α*-carbonyl radical **B**[16] can couple with 1,1-diphenylethylene **5** to afford bridged diethyl heptanedioate **6** with the persistent radical effect (PRE) principle[17] (Scheme 2C).



Scheme 2. Radical capture experiments in support of generation of *α*-carbonyl **B** or ketyl radical **A**. [a] Reaction conditions: **1a** (0.5 mmol) or **5** (0.5 mmol), *fac*-Ir(ppy)$_3$ (3 mol%, 0.015 mmol), DMF (5.0 mL, AR), in the argon under blue LEDs irradiation at room temperature for 48 h. [b] Isolated yield based on 0.25 mmol **1a**. [c] The configuration of the diastereomer was determined by ^{1}H NMR.

Given the difference in reactivity, an alkyne was selected to intercept the transient *α*-carbonyl radical **B**, while the accumulated persistent ketyl radical **A** was found to undergo the pinacol-coupling along with the consumption of transient *α*-carbonyl radical **B**. As shown in Scheme 3, when aromatic *β*-ketoester **1a** and phenylacetylene **7a** were mixed with 3 mol% *fac*-Ir(ppy)$_3$ in 5.0 mL DMF for visible light irradiation, the annulation product **8-1** and pinacol-coupling products **9a/9a'** were obtained in a ratio of 1 : 1 with 75% and 78% yields (based on the consumption of **1a**) in one reaction [Eq. (1)]. Among the investigated photocatalysts (Table S3, entries 1−11), strongly



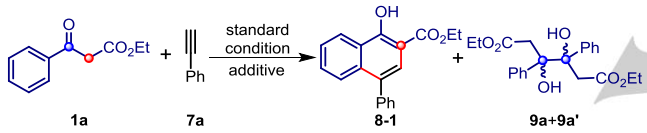
Scheme 3. Kinetic isotope effect (KIE) and control experiments.

reducing **fac*-Ir(ppy)$_3$ displayed the best photocatalytic activity. When ethyny-*d*-benzene ([D$_1$]-**7a**) was employed as a substrate, the fully retained deuteration ratio of the desired product [D$_1$]-**8-1** suggested that the C–H bond of alkyne was not cleaved in this reaction [Eq. (2)]. Intermolecular kinetic isotope effect (KIE) of k_H/k_D = 3.0 further ascertained the C−H bond cleavage for the generation of persistent ketyl radical **A** and transient *α*-carbonyl radical **B** [Eq. (3)]. All of the results demonstrated the keto form and enol form of aromatic *β*-ketoester were activated by the photocatalyst under visible light irradiation. When the framework of phenyl group of substrate **1a** was changed to methyl substituted **1y**, no any product was observed, suggesting the redox potential and equilibrium of keto and enol form are critical for these radical generation [Eq. (4)]. Interestingly, when benzophenone,[18] a well-known hydrogen and electron acceptor were added under the standard conditions, another ketyl radical suppressed the formation of ketyl radical **A**, leading to the pinacol coupling of benzophenone **9b**+**9b'** in 64% yield and

benzannulation product **8-1** in 72% yield [Eq. (5)]. In contrast to those reported methods for synthesis of 1-naphthols scaffold[19] and pinacols,[20] neither excess of external oxidant ($Mn(OAc)_3$,[21] $Pd(OAc)_2/Cu(OAc)_2$,[22] Ag salt/$Na_2S_2O_8$,[23] Br source/TBHP[24]) nor reductant (tertiary amines,[25] Hantzsch esters[26]) were employed. The reaction occurred through photoredox catalysis to generate *α*-carbonyl radical **B** and ketyl radical **A** for the formation of 1-naphthols and pinacols in one reaction. Moreover, the presence of commonly used oxidants ($K_2S_2O_8$, *t*-BuOOH and $PhNO_2$) almost inhibited the reaction completely [Eq. (6)] (Table S3, entries 23−25).

In the course of investigations, we noted that photocatalyst, light and DMF (≥ 99.5%, analytical reagent) are essential. A set of control experiments with water, formic acid, dimethylamine and other organic or inorganic bases (DABCO (1,4-Diazabicyclo[2.2.2]octane), DMAP (4-dimethylaminopyridine), Et_3N, K_2CO_3 and K_3PO_4) shown in Table 1 revealed that the small amount of dimethylamine (~ 170 ppm, ~ 3.8 mol% in 5.0 mL DMF based on 0.5 mmol **1a**, Table S6) decomposed from DMF promoted this redox-neutral reaction (Table S5 and Scheme S1).[27] On the basis aforementioned observation, we proposed that the formation of persistent ketyl radical **A** and transient *α*-carbonyl radical **B** is very dependent on the form of aromatic *β*-ketoester (Scheme 1). The anion enol by eliminating proton from enol form can be oxidized to produce *α*-carbonyl radical **B**, and the eliminated proton can activate keto form to generate ketyl radical **A**. Remarkably, cyclic voltammetry measurements showed that the reduction of enol form of **1a** was shifted to lower potentials upon addition of 5 mol% dimethylamine (E^{red} = −1.05 V *vs*. SCE, E^{ox} = +0.32 V *vs*. SCE in CH_3CN, Figures S6 and S7). Simultaneously, the eliminated proton from the enol form could activate the keto form of **1a** by generated Lewis acid ($^{+}NH_2(Me)_2$). Here, the subtle proton transfer shuttle[28] of dimethylamine facilitated the formation of the persistent ketyl radical **A** and transient *α*-carbonyl radical **B** by *fac*-Ir(ppy)$_3$ under visible light irradiation. As a result, the transient *α*-carbonyl radical **B** could be selectively intercepted by alkynes to synthesize 1-naphthols **8-1** and the persistent ketyl radical **A** followed dimerization to pinacols **9a**+**9a'**, respectively.

Table 1: Control experiments.[a]



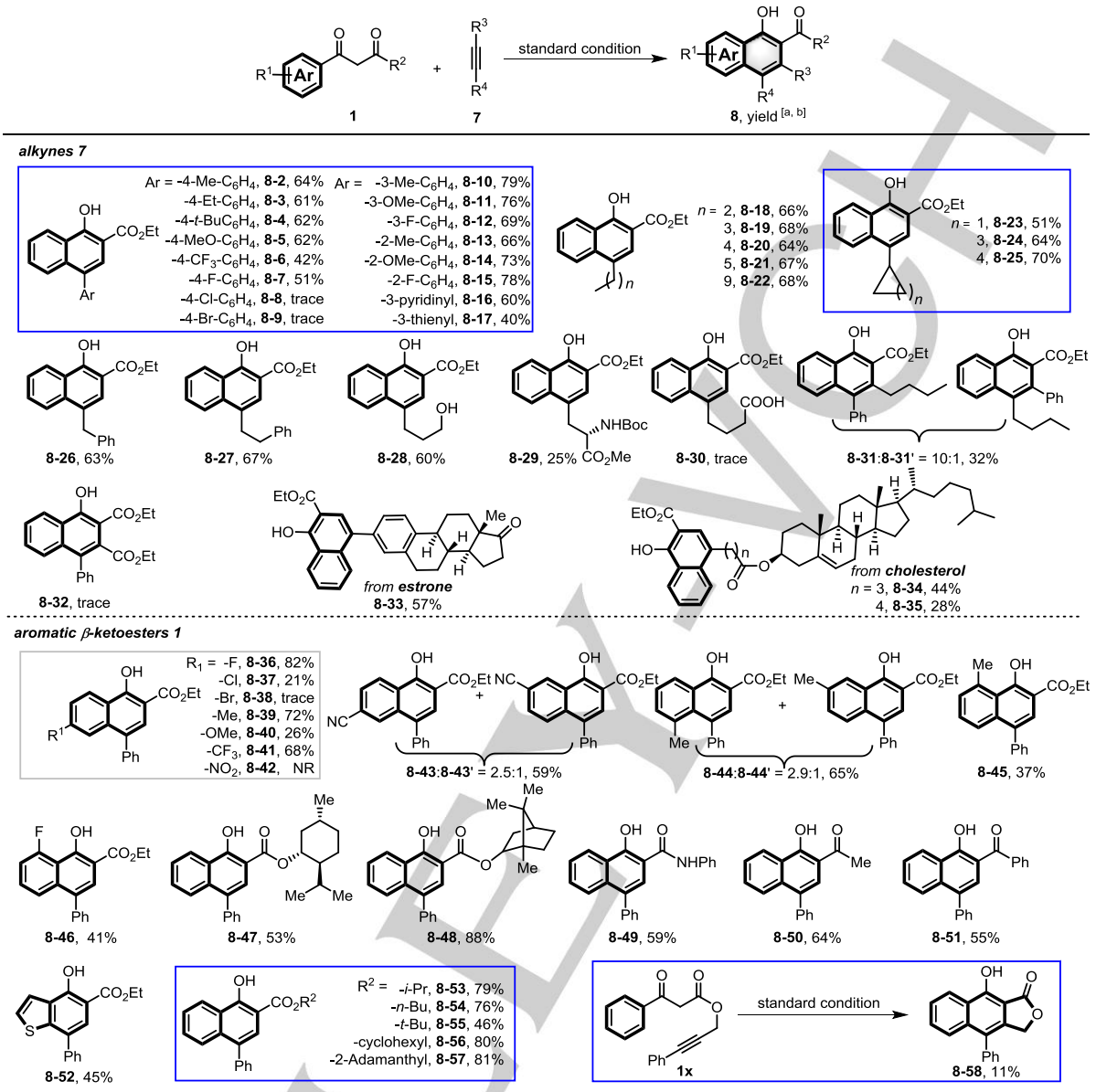
1a **7a** **8-1** **9a+9a'**

Entry	Variation from the standard condition	Yield [%]	
		8-1[b]	**9a+9a'**[c]
1	DMF (99.8%, extra dry, acroseal)	trace	trace
2[d]	**DMF (≥ 99.5%, analytical reagent)**	**75**	**78**
3[e]	H_2O (5.0/50 μL)	trace	trace
4[e]	HCOOH (0.5/5.0 μL)	trace	trace
5[e,f]	$NH(Me)_2$ (1.0 μL, 40% wt, aq.)	72	75
6[e,f]	$NH(Me)_2$ (2.5 μL, 40% wt, aq.)	53	56
7[e,f]	$NH(Me)_2$ (5.0 μL, 40% wt, aq.)	46	48
8[g]	No photocatalyst	0	0
9[g]	In dark	0	0
10	Other solvent	trace	trace
11[h]	DMF (99.8%, extra dry)	60	61

[a] Reaction conditions: **1a** (0.5 mmol), **7a** (0.5 mmol), *fac*-Ir(ppy)$_3$ (3 mol%, 0.015 mmol) and additive in 5.0 mL DMF under argon and irradiation of 3 W blue LEDs for 48 h at rt. [b] Isolated yield based on 0.167 mmol **1a**. [c] ^{1}H NMR yields based on 0.167 mmol **1a** using benzhydrol as internal standard. [d] >95% conversion of **1a**. [e] DMF (99.8%, extra dry, acroseal). [f] $NH(Me)_2$ (40 wt. % in H_2O). [g] DMF (≥ 99.5%, analytical reagent). [h] DMF (99.8%, extra dry, acroseal) was used after sealed heating for 1 h at 140 °C.

To illustrate the generality of the redox-neutral reaction established, we examined the cyclization of a wide range of alkynes **7** and aromatic *β*-ketoesters **1**. As shown in Scheme 4, both electron-donating and electron-withdrawing substituents were well tolerated. *Para*-, *meta*-, and *ortho*-substituted arylacetylenes underwent smoothly in the benzannulation to generate **8-1**–**8-7** and **8-10**–**8-15** as single regioisomers in 40–79% yields. Trace amounts of dimethylamine might generate $NH(Me)_2$•HX by dehalogenation of 4-Cl and 4-Br substituted phenylacetylenes, thus resulting in trace desired products formation. Treatment of **1a** with 3-ethynylpyridine and 3-thienylacetylene furnished the naphthols **8-16** and **8-17** in the yield of 66% and 40%, respectively. Linear, cyclic and functionalised aliphatic alkynes also performed well to afford the corresponding products (**8-18**–**8-31**) in 25–70% yields. Due to the lack of enol anion formation, the alkynic acid bearing an acidic group -COOH **7ad** did not produce any of the desired product. Internal alkynes, such as 1-phenyl-1-hexyne and ethyl phenylpropiolate were subjected to the reaction conditions, albeit with moderate yields (**8-31**/**8-31'** and **8-32**). Estrone and cholesterol derivatives were also achieved, highlighting the good functional group tolerance and potential applications for the late-stage modification of complex molecules (**8-33**−**8-35**).

Having achieved the reaction with various alkynes **7**, we shifted our attention to the scope of aromatic *β*-ketoesters **1** by reacting with phenylacetylene **7a** (Scheme 4). The reaction tolerated various functional groups including -X, -Me, and -OMe on the aromatic ring of aromatic *β*-ketoesters **1** except aromatic *β*-ketoesters containing 4-Cl, 4-Br and 4-NO_2 because of dehalogenation and reduction of nitrobenzene, providing the corresponding products in poor yields (**8-37**, **8-38** and **8-42**).[29] The aromatic *β*-ketoesters **1i** bearing a strong electron-withdrawing group 4-CN produced a mixture of regioisomers **8-43** and **8-43'** in a ratio of 2.5:1 and 59% combined yield, suggesting a radical mechanism involving *ipso* cyclization followed by rearrangement through the C–C bond cleavage in the spirocyclohexadienyl radical.[30] When a methyl group was introduced to the *meta*-position of phenyl ring, a mixture of regioisomers **8-44** and **8-44'** were obtained in a ratio of 2.9:1 and 65% combined yield. Remarkably, (+)-borneol and isobornyl substituted aromatic *β*-ketoesters delivered **8-47** and **8-48** in 53% and 88% yields. In addition to the COOEt-substituted **1**,



Scheme 4. Scope of alkynes **7** and aromatic *β*-ketoesters **1**. [a] Reaction conditions: **1** (0.5 mmol), **7** (0.5 mmol), *fac*-Ir(ppy)$_3$ (3 mol%, 0.015 mmol), DMF (5.0 mL, AR), in the argon under blue LEDs irradiation at room temperature for 48 h. [b] Isolated yield based on 0.167 mmol **1** (average of two trials).

substrates bearing *N*-phenylamide, -Me and -C_6H_5 group formed 1-naphthols **8-49**−**8-51** in 55%–64% yields. The benzannulation is not limited to the formation of naphthol, as exemplified by using 2-thienyl *β*-ketoester **1r** to generate 7-hydroxyl-benzothiophene **8-52**, albeit only in the yield of 45%. The ethyl ester of aromatic *β*-ketoesters could be replaced by *i*-propyl, *n*-butyl, *tert*-butyl, cyclohexyl and 2-adamantine esters, which could proceed smoothly in this transformation delivering the corresponding products (**8-53**−**8-57**) in moderate to excellent yields. In addition, the reaction was adapted for the intramolecular benzannulation of **1x** leading to products **8-58**.

In summary, we have designed a new strategy to generate a persistent ketyl radical **A** and a transient *α*-carbonyl radical **B** from aromatic *β*-ketoester *in situ* by photoredox catalysis. A trace amount of dimethylamine is able to facilitate the radical formation, and then the persistent ketyl radical **A** can undergo the pinacol-coupling, while the transient *α*-carbonyl radical **B** can be intercepted by alkyne to afford 1-naphthols. Remarkably, this photocatalytic method overcomes the most fundamental difficulty in the presence of stoichiometric external oxidant and reductant in one reaction vessel for a redox-neutral reaction, and utilizes commercially available substrates to produce the desired 1-naphthols in good to excellent yields under mild conditions. The simple generation of radicals to directly synthesize valuable products provided here opens up new avenues for the utilization of a catalytic amount of photocatalyst other than stoichiometric external oxidant or reductant for redox-neutral organic transformation in atom- and step-economic manner.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: photoredox catalysis • proton shuttle • aromatic *β*-ketoester • 1-naphthol • pinacol

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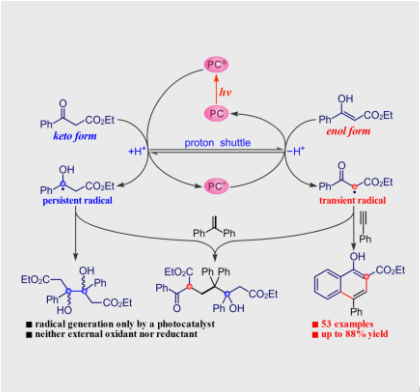
All-in-one: A photocatalyst succeeds in the generation of transient *α*-carbonyl radical and persistent ketyl radical from aromatic *β*-ketoester *in situ* for the first time, which realizes straightforward synthesis of pinacol and highly substituted 1-naphthol as well as diethyl heptanedioate in an atom- and step-economic manner under extremely mild condition.



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Photoredox Catalysis of Aromatic *β*-Ketoester *in Situ* toward Transient and Persistent Radicals for Organic Transformation