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Iodoarene-directed photoredox β-C(sp^3)–H arylation of 1-(*o*-iodoaryl)alkan-1-ones with cyanoarenes *via* halogen atom transfer and hydrogen atom transfer†

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Site selective functionalization of inert remote C(sp^3)–H bonds to increase molecular complexity offers vital potential for chemical synthesis and new drug development, thus it has been attracting ongoing research interest. In particular, typical β-C(sp^3)–H arylation methods using chelation-assisted metal catalysis or metal-catalyzed oxidative/photochemical *in situ* generated allyl C(sp^3)–H bond processes have been well developed. However, radical-mediated direct β-C(sp^3)–H arylation of carbonyls remains elusive. Herein, we describe an iodoarene-directed photoredox β-C(sp^3)–H arylation of 1-(*o*-iodoaryl)alkan-1-ones with cyanoarenes *via* halogen atom transfer (XAT) and hydrogen atom transfer (HAT). The method involves diethylaminoethyl radical-mediated generation of an aryl radical intermediate *via* XAT, then directed 1,5-HAT to form the remote alkyl radical intermediate and radical–radical coupling with cyanoarenes, and is applicable to a broad scope of unactivated remote C(sp^3)–H bonds like β-C(sp^3)–H bonds of *o*-iodoaryl-substituted alkanones and α-C(sp^3)–H bonds of *o*-iodoarylamides. Experimental findings are supported by computational studies (DFT calculations), revealing that this method operates *via* a radical-relay stepwise mechanism involving multiple SET, XAT, 1,5-HAT and radical–radical coupling processes.

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Site selective functionalization of inert C(sp^3)–H bonds for targeted increase of molecular complexity and upgrading abundant hydrocarbon feedstocks into value-added compounds represents a prominent theme in chemistry.[1–3] In the field, direct C(sp^3)–H arylation of saturated carbonyl compounds, such as ketones, amides, aldehydes, esters and acids, has been recognized as one of the most powerful methodologies for the site selective incorporation of an aryl functionality into the alkyl chain to construct a wealth of biologically relevant aryl motif-containing molecules and synthetic intermediates.[2,3] In contrast to the well-explored arylation of C(sp^3)–H bonds at the α-position in carbonyl compounds,[1,2] direct arylation of C(sp^3)–H bonds at the β-position or at remote positions in the carbonyl compounds is largely underdeveloped and remains a great challenge in site selectivity control due to the competitive reactions, such as the more acidic α-C(sp^3)–H bond arylation.[3–6] Typically, transition-metal-catalyzed chelation-assisted β-C(sp^3)–H arylation reactions as reliable methods for producing β-aryl carbonyl systems have been intensively developed, where the vast majority of which concerned directing group (DG)-possessing amides,[3,4a–d] and ketones/aldehydes (using amino-acid based transient directing groups).[4e–m] Alternatively, the β-C(sp^3)–H arylation of ketones and esters *via* α,β-dehydrogenation using transition-metal redox catalysis obviating the need for the directing group installation and removal redundant phases has been developed.[5] However, these strategies suffer from the limited examples for heteroarylation, and the need for precious transition metal catalysts and stoichiometric additives (such as lithium amides and silver salts), thus hampering wide synthetic application.

Recent advances have indicated that manipulations of the radical strategy, especially photoredox catalysis, provide a broader scope of substrates, lower cost and milder conditions, and more precise site selectivity than what can be accessed

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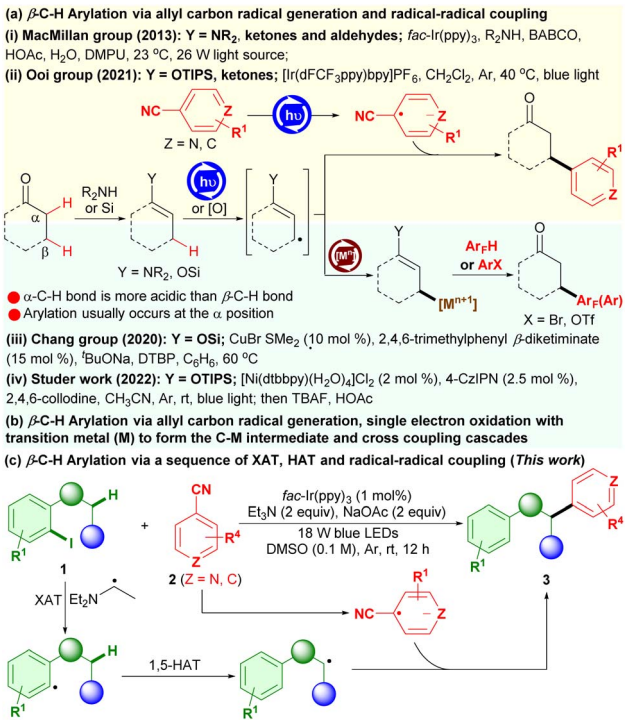
using the conventional transition-metal catalysis.[6] For example, a breakthrough has been achieved by the MacMillan group in radical-mediated β-C(sp^3)–H arylation of ketones and aldehydes with electron-deficient cyanoarenes as the aryl coupling partners *via* radical–radical coupling using a cooperative photoredox and enamine catalysis, enabling the construction of β-aryl ketones and aldehydes (Scheme 1a(i)).[6a] Along this radical strategy, Ooi and coworkers have developed a photoredox β-C(sp^3)–H arylation of preformed silyl enol ethers with 4-cyanopyridines through a sequence of single-electron transfer (SET)/deprotonation to generate allyl β-carbon-centered radicals and radical–radical coupling to achieve β-heteroarylation of ketones (Scheme 1a(ii)).[6b] Chang and co-workers have established a new copper-catalyzed β-C(sp^3)–H arylation of carbonyls, including ketones, aldehydes and esters, in which silyl enol ethers were initially prepared from carbonyls followed by copper-catalyzed oxidative dehydrogenative coupling with polyfluoroarenes *via* a pathway of allyl radical generation and C–Cu single-electron oxidative formation, affording highly valuable β-polyfluoroaryl carbonyl compounds (Scheme 1b(iii)).[6c] Studer and Liu have reported a formal β-C–H arylation of readily prepared silyl enol ethers with (hetero)aryl bromides (such as aryl bromides, vinyl bromides and alkynyl bromides) using a cooperative nickel and photoredox catalysis though photoredox generation of the silyl enol ether radical cations, deprotonation, single electron oxidation with the Ni^0 species to form the C–Ni^I intermediates and cross-coupling cascades, realizing β-C(sp^3)–H arylation of aldehydes and ketones (Scheme 1b(iv)).[6d] Despite being efficient and applicable for synthetic purposes, these methods necessitate preinstallation of specific feedstocks (such as enamines and silyl enol ethers) for ready oxidative generation of the radical cations and then deprotonation to form the crucial allylic β-sp^3-carbon-centered radicals, which may be actually considered as a mode of the activated allyl C(sp^3)–H functionalization. Until now, it is still difficult to render direct functionalization of C(sp^3)–H bonds at the β-position or at remote positions of saturated carbonyls in radical-mediated reactions. Thus, there is a high demand for innovation of new radical strategies that directly access the crucial carbon-centered radicals at the β-position or at remote positions, preferably with readily accessible carbonyl feedstocks, for their site-selective remote C(sp^3)–H arylation.



Scheme 1 β-C(sp^3)–H radical arylation of carbonyls.

Herein, we report the first iodoarene-directed photoredox β-C–H arylation of 1-(*o*-iodoaryl)alkan-1-ones, which can be conveniently prepared from readily available 2-iodoarylaldehydes, with cyanoarenes *via* halogen atom transfer (XAT) and 1,5-hydrogen atom transfer (HAT), enabling the preparation of a diverse array of β-aryl arylalkanones with high efficiency (Scheme 1c). Therein, photooxidation/deprotonation of a triethylamine generates the diethylamino-ethyl radical, which serves as the halogen-atom transfer agent for the activation of aryl iodides to undergo XAT[7] and generate the aryl radicals, followed by directed 1,5-HAT[8] to afford the remote β-sp^3-carbon-centered radicals and then radical–radical coupling. This iodoarene-directed photoredox strategy can also be applicable to α-C(sp^3)–H arylation of *N*-(*o*-iodoaryl)amides for functionalized (hetero)arenes.

We commenced our studies by exploring the photoredox remote C(sp^3)–H arylation of 1-(2-iodophenyl)-3-methyl-butan-1-one **1a** with isonicotinonitrile **2a** (Table 1). After extensive screening of the reaction parameters, a combination of 1 mol% *fac*-Ir(ppy)$_3$, 2 equiv. Et_3N, 2 equiv. NaOAc, DMSO solvent and 18 W blue LEDs light was found to be optimal for the photoredox remote C(sp^3)–H arylation of substrate **1a** with isonicotinonitrile **2a**, affording the desired product **3aa** in 71% yield (entry 1). Other photocatalysts, such as Ir(ppy)$_2$(dtbbpy)PF_6, Ru(bpy)$_3$$Cl_2$, 4-CZIPN, 3DPA2FBN and eosin Y, were evaluated (entries 2–6): they showed less efficiency than *fac*-Ir(ppy)$_3$. Control experiments show that both Ir(ppy)$_3$ (entry 7) and Et_3N (entry 8) are crucial for success as omitting either led to no detectable product **3aa**. A series of amines, including ^{i}Pr$_2$NEt, 1,4-diazabicyclo[2.2.2]octane (DABCO), 2,2,6,6-tetramethyl-piperidine (HTMP), 1,2,2,6,6-pentamethylpiperidine (PMP) and ^{i}Pr$_2$NH, were reactive, but all were inferior to Et_3N (entries 9–12). Notably, the reaction could occur in the absence of NaOAc, albeit with diminished yield (45% yield; entry 13). In contrast, other inorganic bases like K_2CO_3 and NaO^{t}Bu were found to inhibit the reaction (entries 14 and 15). These results indicate that the organic bases like Et_3N mainly serve as the electron transfer reagents for photoreductive cleavage of the C(sp^2)–I bonds, and the inorganic bases as the iodine removal reagents. Further screening of the solvent effect demonstrated DMSO as the optimal option (entry 1 *versus* entries 16 and 17). The reaction cannot occur without blue LEDs light (in the dark) (entry 18). Gratifyingly, the optimal conditions are amenable to a scale up to 1 mmol **1a**, giving **3aa** in satisfactory yield (entry 19).

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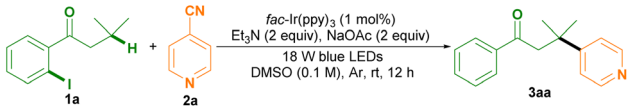
Table 1 Optimization of reaction conditions[a]

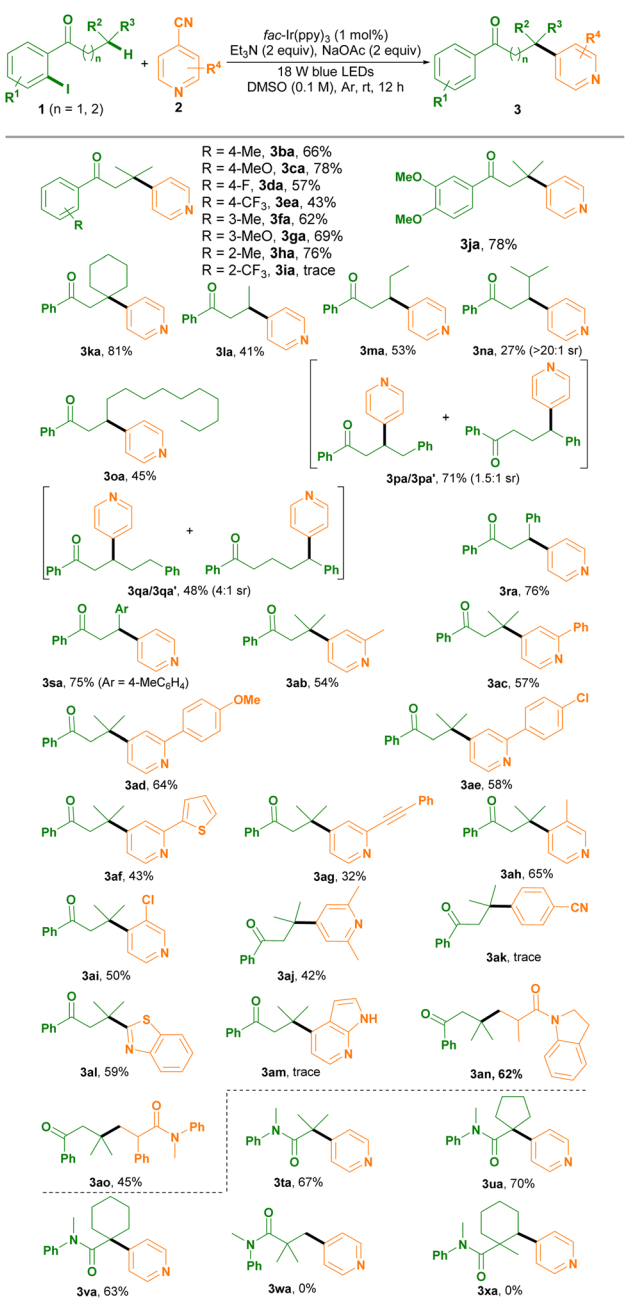


Entry	Variation from the standard conditions	Yield[b] (%)
1	None	71
2	$Ir(ppy)_2(dtbbpy)PF_6$ instead of *fac*-$Ir(ppy)_3$	65
3	$Ru(bpy)_3Cl_2$ instead of *fac*-$Ir(ppy)_3$	Trace
4	4-CZIPN instead of *fac*-$Ir(ppy)_3$	33
5	3DPA2FBN instead of *fac*-$Ir(ppy)_3$	42
6	Eosin Y instead of *fac*-$Ir(ppy)_3$	Trace
7	Without *fac*-$Ir(ppy)_3$	0
8	Without Et_3N	0
9	$^iPr_2NEt$ instead of Et_3N	68
10	DABCO instead of Et_3N	11
11	HTMP or PMP instead of Et_3N	<5
12	$^iPr_2NH$ instead of Et_3N	34
13	Without NaOAc	45
14	K_2CO_3 instead of NaOAc	43
15	NaO^tBu instead of NaOAc	10
16	DMF instead of DMSO	53
17	CH_3CN instead of DMSO	31
18	Without light (in the dark)	0
19[c]	None	62

[a] Standard reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), *fac*-$Ir(ppy)_3$ (1 mol%), Et_3N (2 equiv.), NaOAc (2 equiv.), DMSO (2 mL), 18 W blue LEDs, argon, room temperature, and 12 h. Some by-products, including 3-methyl-1-phenylbutan-1-one **4a**, 3,3-dimethyl-2,3-dihydro-1*H*-inden-1-one **5a** and *N*,*N*-diethyl-1-iodoethan-1-amine **6**, were detected by GC-MS analysis and HRMS analysis. [b] Isolated yield. [c] **1a** (1 mmol) and 24 h.

After establishing the optimized conditions, we set out to investigate the scope of this photoredox remote C(sp^3)–H arylation protocol (Table 2). As shown in Table 2, a variety of 1-(2-iodoaryl)-1-ketones **1b–h** bearing a functionality, such as Me, MeO, F and CF_3, on the aryl ring at the *para*- or *meta*-position were compatible with the optimized conditions, affording **3ba–ha** in moderate to good yields. Moreover, the electron nature and the steric hindrance effect affected the reactivity. While in the presence of isonicotinonitrile **2a**, *fac*-$Ir(ppy)_3$, Et_3N and NaOAc the electron-donating 4-MeO-substituted 1-(2-iodoaryl)-1-ketone **1c**, for example, was converted to **3ca** in 78% yield; using the electron-withdrawing 4-CF_3-substituted substrate **1e** or the more sterically hindered 3-MeO-substituted one **1g** resulted in slightly diminished yields (**3ea**, **3ga**). 1-(2-Iodoaryl)-1-ketone **1h** with a Me group at the *ortho*-position of the aryl ring also exhibited high reactivity, giving **3ha** in 76% yield. However, the 1-(2-iodoaryl)-1-ketone possessing the electron-withdrawing CF_3 group substituted at the *ortho*-position of the aryl ring **1i** showed no reactivity for the reaction. 3,4-DiMeO-substituted (2-iodoaryl)-1-ketone **1j** was suitable for efficiently constructing **3ja**. Using 2-cyclohexyl-1-(2-iodophenyl)ethan-1-one **1k** delivered **3ka** in 81% yield. For chain extended 1-(2-iodophenyl)-1-ketones **1l–m**, site selective 3-arylation efficiently occurred *via* XAT and 1,5-HAT cascades (**3la–oa**). Interestingly,

Table 2 Variation of the 1-(2-iodoaryl)-1-ketone (**1**) and isonicotinonitrile (**2**)[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), *fac*-$Ir(ppy)_3$ (1 mol%), Et_3N (2 equiv.), NaOAc (2 equiv.), DMSO (0.1 M; 2 mL), 18 W blue LEDs, argon, room temperature, and 12 h. The site-selectivity ratio (sr) is given in parentheses.

1-(2-iodophenyl)-4-methyl-pentan-1-one **1n** containing a tertiary carbon at position 4 site selectively underwent 3-arylation, not 4-arylation, albeit with a low yield (**3na**). Whereas 1-(2-iodoaryl)-1-ketone **1p** possessing a phenyl ring at position 4 underwent 3-arylation and 4-arylation in 71% yield and 1.5 : 1 site selectivity (sr) (**3pa**/**3pa**′). In the case of 1-(2-iodoaryl)-1-ketone **1q** containing a phenyl ring at position 5, both 3-arylation and 5-

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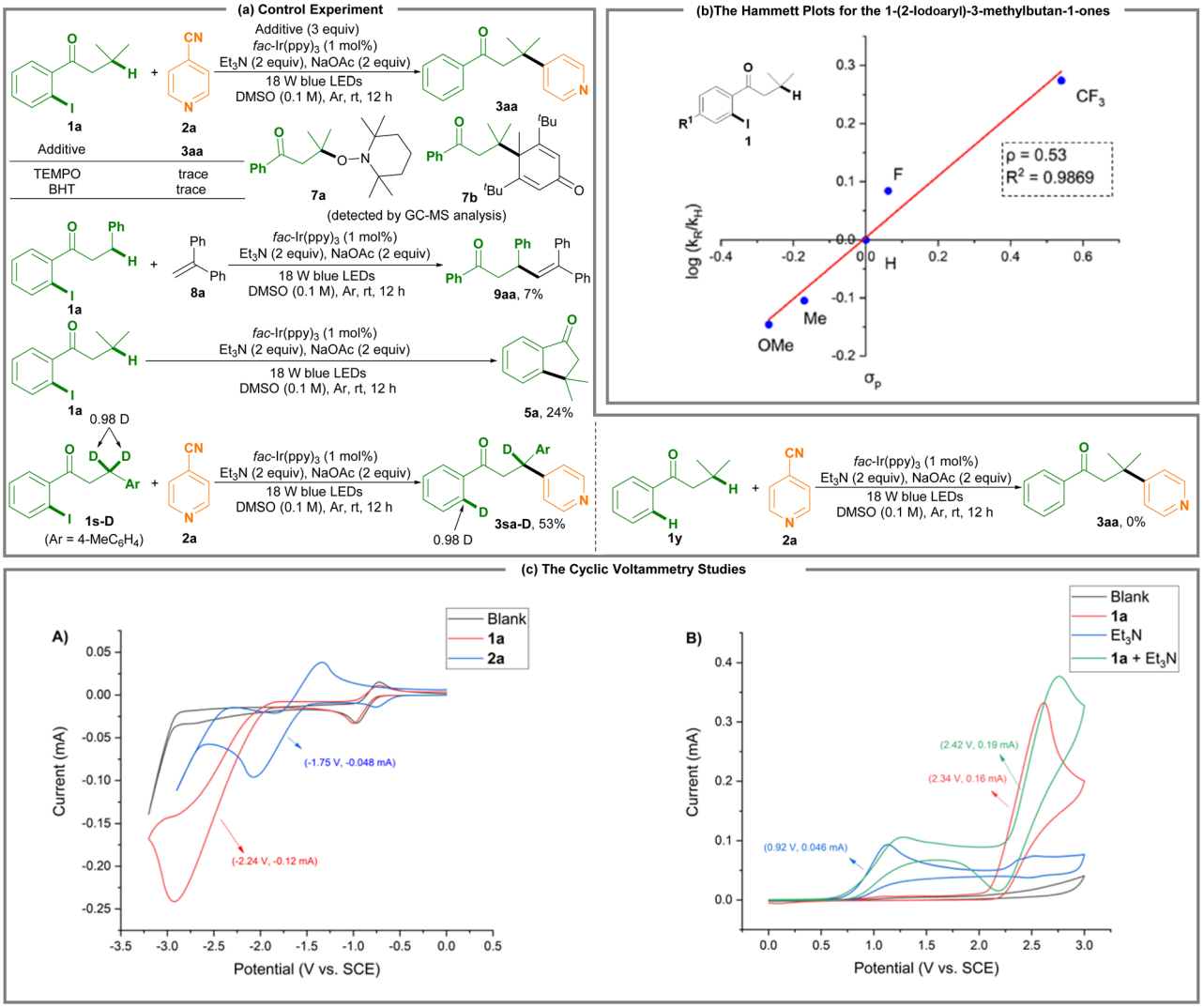
arylation happened, giving **3qa** and **3qa′** in 48% yield and 4 : 1 sr. 1-(2-Iodoaryl)-1-ketones **1r–s** having an aryl ring (such as phenyl or 4-methylphenyl) exhibited high reactivity for furnishing **3ra–sa** in good yields.

A variety of isonicotinonitriles **2b–j** were found to be compatible with the optimized conditions, site selectively delivering **3ab–aj** in moderate yields. We found that a wide range of functionalities, namely Me, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, thiophen-3-yl and phenylethynyl, on the pyridine ring at position 2 were compatible for site selectively assembling the 3-arylation products **3ab–ag** in 32–64% yields. Isonicotinonitriles **2h–i** bearing a Me or a Cl group at position 3 executed the photoredox remote C(sp^3)–H arylation protocol smoothly (**3ah–ai**). For 2,6-diMe-substituted isonicotinonitrile **2j** the reaction successfully occurred and delivered **3aj** in moderate yield. However, terephthalonitrile **1k** had no reactivity (**3ak**). Additionally, heterocyclic cyanoarenes **2l** and **2m** were investigated. Benzo[*d*]thiazole-2-carbonitrile (**2l**) was converted efficiently into **3al** in 59% yield, whereas 1*H*-pyrrolo[2,3-*b*]pyridine-4-carbonitrile (**2m**) had no reactivity. Notably, we investigated electron-deficient alkenes **2n** and **2o** under the standard conditions, affording the alkylated products in 45–62% yields.

This photoredox remote C(sp^3)–H arylation protocol was applicable to *N*-(2-iodoaryl)amides (**3ta–va**), thus offering a new α-C(sp^3)–H arylation strategy. For example, *N*-(2-iodophenyl)-isobutyramide **1t** executed α-C(sp^3)–H arylation *via* a sequence of XAT and 1,5-HAT, affording **3ta** in 67% yield. However, *N*-(2-iodophenyl)-*N*-methylpivalamide (**1w**) and *N*-(2-iodophenyl)-*N*-1-dimethylcyclohexane-1-carboxamide (**1x**) showed no reactivity for the construction of β-C(sp^3)–H arylation products.

Using a radical scavenger like TEMPO or BHT led to complete suppression of the remote C(sp^3)–H photoredox arylation reaction, along with the detectable **7a** and **7b** by GC-MS analysis (Scheme 2a). Using 1,1-diphenylalkene **8a** as a radical scavenger delivered alkyl alkene **9aa** in 7% yield. The results indicate that the alkyl radical may be formed, which is supported by the results of the intramolecular cyclization of 1-(2-iodophenyl)-3-methylbutan-1-one **1a** where 3,3-dimethyl-2,3-



Scheme 2 Mechanistic investigations.

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dihydro-1*H*-inden-1-one **5a** is produced in 24% yield. The deuterium-labeled experiments suggest a 1,5-hydride shift process. However, 3-methyl-1-phenylbutan-1-one **1y**, a non-*o*-iodo-substituted substrate, could not undergo the target reaction (**3aa**).

Hammett studies were performed to determine the electronic effect of the substituents of the 1-(2-iodoaryl)-3-methylbutan-1-ones **1** on the reaction rates (Scheme 2b and Fig. S5; ESI†). The Hammett curve indicated an increase in the k value with the strong electron-withdrawing substrates ($k_{\text{1-(2-iodo-4-(trifluoromethyl)phenyl)-3-methylbutan-1-one}} \gg k_{\text{1-(2-iodo-4-methoxyphenyl)-3-methylbutan-1-one}}$). The relative rates of such substituted 1-(2-iodoaryl)-3-methylbutan-1-ones **1** appear to have a good linear correlation ($R^2 = 0.9869$) between the $\log(k_X/k_H)$ and the σ_p values of the respective substituents. The Hammett plot gives a slope of $\rho = 0.53$. The linear relationship in the Hammett plot with a positive slope suggests the generation of a negative charge on the aryl ring in the reaction.

Scheme 2c shows the cyclic voltammetry (CV) studies, revealing a reduction potential peak at $E_{p_{1/2red}} = -2.24$ V *vs.* standard calomel electrode (SCE) for 1-(2-iodophenyl)-3-methylbutan-1-one **1a** and a reduction potential peak at $E_{p_{1/2red}} = -1.75$ V *vs.* SCE for isonicotinonitrile **2a** (Fig. S6 and S7; ESI†). Upon the catalytic activity of the *fac*-Ir(ppy)$_3$ catalyst ($E_{p_{1/2red}} = -1.73$ V *vs.* SCE), the reductive conversion of **1a** is very difficult because of its lower negative reduction potential, and thus photoreduction of isonicotinonitrile **2a** takes precedence over that of **1a**. On the other hand, 1-(2-iodophenyl)-3-methylbutan-1-one **1a** exhibited an oxidation potential peak at $E_{p_{1/2ox}} = 2.34$ V *vs.* SCE (red line; Scheme 2c(B)) and Et$_3$N has an oxidation potential peak at $E_{p_{1/2ox}} = 0.92$ V *vs.* SCE (blue line; Scheme 2c(B)). Moreover, a mixture of **1a** and Et$_3$N reveals an increasing oxidation potential and current (from $E_{p_{1/2red}} = 2.34$ V, 0.16 mA to $E_{p_{1/2red}} = 2.42$ V, 0.19 mA) (green line; Scheme 2c(B)). These results suggest that Et$_3$N is more reactive than **1a** for anodic oxidation, and this protocol involves a Et$_3$N reacting with **1a** process.

The Stern–Volmer fluorescence quenching experiments revealed that the Ir(ppy)$_3$ luminescence was obviously decreased by Et$_3$N (Fig. S1; ESI†), and slightly decreased by 1-(2-iodophenyl)-3-methylbutan-1-one **1a** (Fig. S2†) or cyanopyridine **2a** (Fig. S3†), suggesting that the reaction operates *via* a canonical photoredox radical cycle consisting of a photoreductive quenching by Et$_3$N. The light on–off experiments show that visible light is crucial as no desired reaction was detected in the absence of the additional blue light (Fig. S4†).

According to the present results and previous reports, state-of-the-art density functional theory (DFT) calculations were

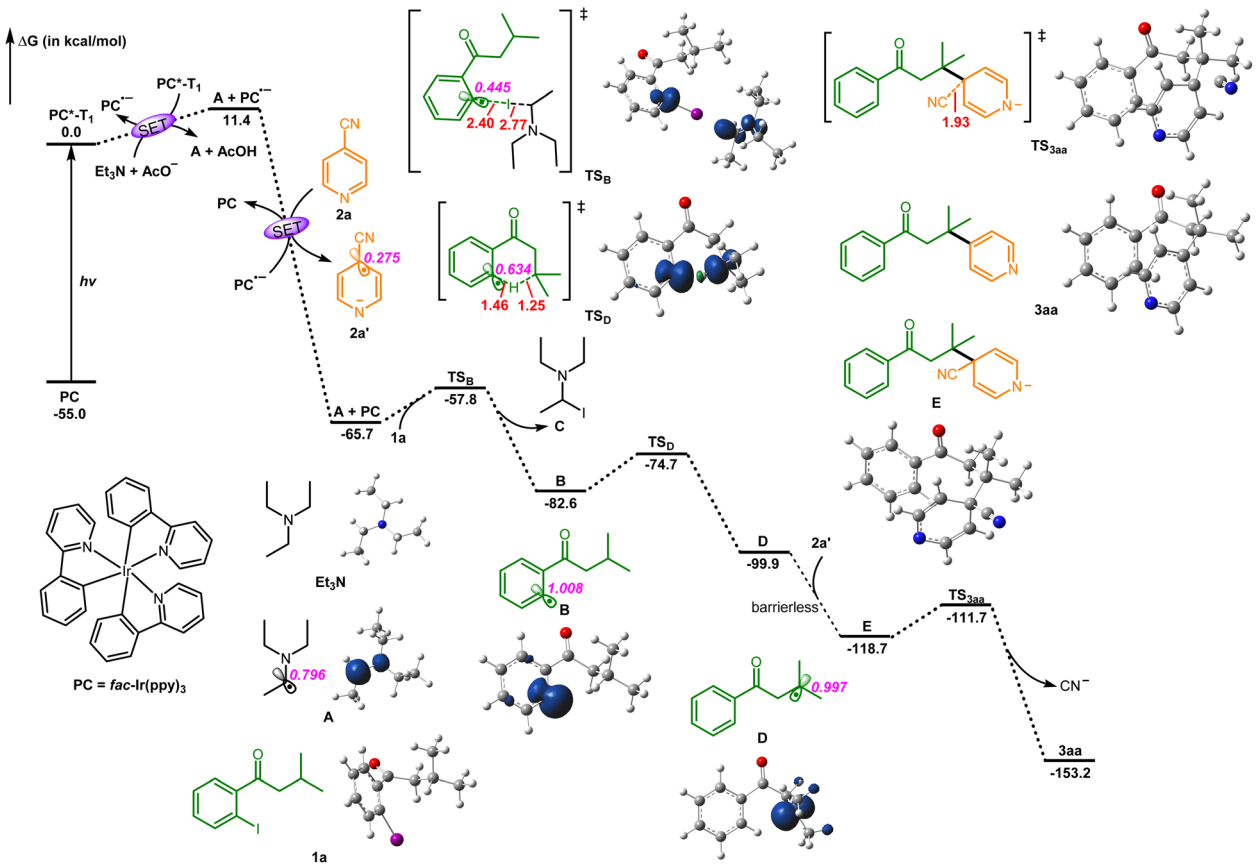

Fig. 1 DFT-calculated energy profiles of the mechanistic pathway. Optimized intermediate and transition-state structures (key bond distances in Å) as well as the spin density plots (isovalue: 0.008 au) of key radical species are given. The Gibbs free energies (ΔG) are given in kcal mol^{-1}. The italic numbers in purple are the corresponding Mulliken atomic spin populations of the radical centered atom.

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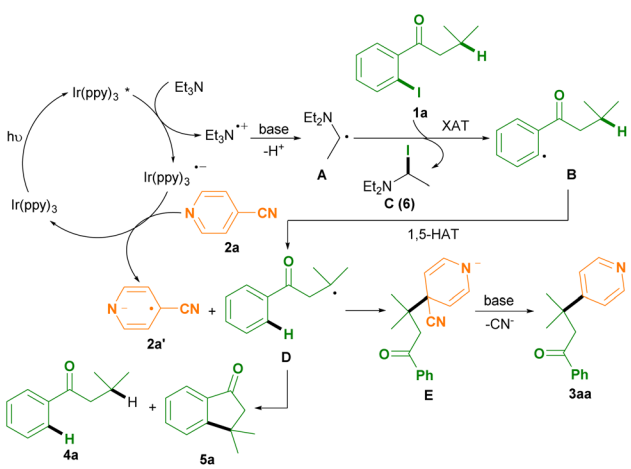
performed at the SMD-M06-2X/6-311+G(d,p)/SDD//SMD-M06-2X/6-31G(d,p)/Lanl2DZ theoretical level to further elucidate the reaction mechanism (Fig. 1). Initially, the photocatalyst **PC** (*fac*-Ir(ppy)$_3$) is excited to the excited state **PC*-T$_1$** under blue LED illumination. Following this, **PC** undergoes two consecutive single-electron transfer (SET) processes. In the first SET, the excited state **PC*-T$_1$** reacts with Et$_3$N to generate the radical anion **PC**$^{\bullet-}$. Simultaneously, Et$_3$N loses a hydrogen proton, which is abstracted by AcO$^-$, leading to the creation of the radical intermediate **A**.[9] In the second SET, **2a** reacts with **PC**$^{\bullet-}$, resulting in the formation of the radical **2a**′ and the return of **PC** to its ground state **PC**. Next, the radical intermediate **A** engages in iodine atom transfer (XAT) with the substrate **1a**, overcoming an energy barrier of 7.9 kcal mol^{-1}, generating intermediates **B** and **C**. Radical intermediate **B** then undergoes 1,5-hydrogen atom transfer (1,5-HAT) *via* transition state **TS$_D$**, surpassing a moderate activation energy of 7.9 kcal mol^{-1}, thereby yielding the radical intermediate **D**. Subsequently, a barrierless radical–radical coupling between intermediate **D** and **2a**′ leads to the formation of intermediate **E** (Fig. S8†). Finally, intermediate **E** overcomes a 7.0 kcal mol^{-1} energy barrier, facilitating the cleavage of the C–C bond and releasing 34.5 kcal mol^{-1} of free energy. Ultimately, this process yields the final product **3aa** after the departure of the cyanide group. The entire process is highly exergonic, with a free energy release of 153.2 kcal mol^{-1}. Therefore, our computational study provides additional support for the experimental findings, demonstrating that the reaction proceeds through a stepwise mechanism involving multiple SET, XAT, 1,5-HAT, and radical–radical coupling processes.

Consequently, a plausible mechanism for this photoredox remote C(sp^3)–H arylation protocol as outlined in Scheme 3 was proposed.[6–8] Photooxidation of Et$_3$N by the excited state Ir(ppy)$_3$* affords the Ir(ppy)$_3$ radical anion and the Et$_3$N radical cation, followed by deprotonation to generates the diethylaminoethyl radical intermediate **A** with the aid of bases (such as NaOAc and cyanoarenes).[6–8] The XAT between the diethylaminoethyl radical intermediate **B** and 1-(2-iodophenyl)-3-methylbutan-1-one **1a** produces the phenyl radical intermediate **B** and *N*,*N*-diethyl-1-iodoethan-1-amine **C** (**6**) (determined by HRMS analysis).[7] The intermediate **B** subsequently undergoes an intramolecular 1,5-HAT to deliver the alkyl radical intermediate **D**.[8] Meanwhile, single electron reduction of isonicotinonitrile **2a** by the Ir(ppy)$_3$ radical anion gives rise to the formation of the isonicotinonitrile radical anion **2a**′ and regeneration of the Ir(ppy)$_3$ photocatalyst.[6] Radical–radical coupling between the alkyl radical intermediate **D** and the isonicotinonitrile radical anion **2a**′ affords the anion intermediate **E**, followed by decyanation with the aid of bases to access the desired product **3aa**.



Scheme 3 Possible reaction mechanism.

Conclusions

In summary, we have developed a new, site selective iodoarene-directed photoredox β-C(sp^3)–H arylation of 1-(*o*-iodoaryl)alkan-1-ones with cyanoarenes *via* XAT and 1,5-HAT for producing β-aryl arylalkanones. Using an aryl radical, which is generated from XAT between an iodoarene and the diethylaminoethyl radical, renders site selective 1,5-HAT to form the remote sp^3-carbon radical and then radical–radical coupling, thus achieve iodoarene-directed remote C(sp^3)–H arylation and prohibiting undesired radical pathways. This mild and selective iodoarene-directed photoredox XAT and HAT method for remote C(sp^3)–H arylation delivers a diverse array of functionalized (hetero)arenes with high site-selectivity, a good tolerance of functionalization and a broad scope of remote C(sp^3)–H bonds.

Data availability

The datasets supporting this article have been uploaded as part of the ESI† material.

Author contributions

Q. S., M. H., D.-L. H. and J.-H. L. conceptualized the project. L. Z., C.-H. X., M. H. and X.-H. O. performed the experimental studies. X.-Y. Z. and Q. S. performed the DFT calculations. Q. S., M. H., D.-L. H. and J.-H. L. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

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