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lodoarene-directed photoredox β -C(sp³)–H arylation of 1-(o-iodoaryl)alkan-1-ones with cyanoarenes via halogen atom transfer and hydrogen atom transfer†

Liang Zeng,‡^{ab} Chong-Hui Xu,‡^a Xiu-Yuan Zou, ^b Qing Sun, ^b Ming Hu,*^{ab} Xuan-Hui Ouyang, ^b De-Liang He ^b *a and Jin-Heng Li *b** Aind Sunday Su

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.

synthetic application.

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Site selective functionalization of inert C(sp³)–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(sp³)–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

α-position in carbonyl compounds, 1,2 direct arylation of C(sp³)-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(sp³)-H bond arylation.³⁻⁶ Typically, transition-metal-catalyzed chelation-assisted β-C(sp³)-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 aminoacid 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

contrast to the well-explored arylation of C(sp³)-H bonds at the

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

[&]quot;State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China. E-mail: huming0731@163.com; delianghe@hnu.edu.cn; jhli@hnu.edu.cn

^bKey Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China. E-mail: sunqing@nchu.edu.cn

State Key Laboratory Base of Eco-Chemical Engineering, College of Chemical Engineering, Qingdao University of Science and Technology, Qingdao 266042, China

dState Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

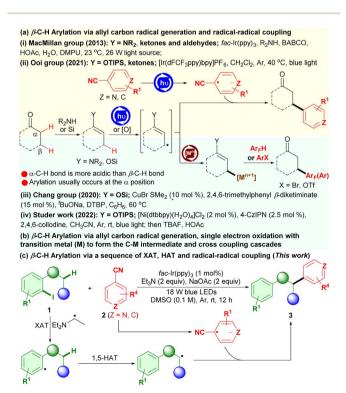
^eSchool of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 475004, China

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 $[\]ddagger$ These authors contributed equally to this work.

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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(sp³)-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)).64 Along this radical strategy, Ooi and coworkers have developed a photoredox β-C(sp³)-H arylation of preformed silyl enol ethers with 4-cyanopyridines through a sequence of single-electron transfer (SET)/ deprotonation to generate allyl \beta-carbon-centered radicals and radical-radical coupling to achieve β-heteroarylation of ketones (Scheme 1a(ii)).66 Chang and co-workers have established a new copper-catalyzed β-C(sp³)-H arylation of carbonyls, including ketones, aldehydes and esters, in which silvl 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 Ni⁰ species to form the C-Ni^I intermediates and cross-coupling cascades, realizing β-C(sp³)-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



Scheme 1 β -C(sp³)-H radical arylation of carbonyls.

and silyl enol ethers) for ready oxidative generation of the radical cations and then deprotonation to form the crucial allylic β-sp3-carbon-centered radicals, which may be actually considered as a mode of the activated allyl C(sp3)-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(sp³)-H arylation.

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 XAT7 and generate the aryl radicals, followed by directed 1,5-HAT8 to afford the remote β-sp3-carboncentered radicals and then radical-radical coupling. This iodoarene-directed photoredox strategy can also be applicable to α -C(sp³)-H arylation of N-(o-iodoaryl)amides for functionalized (hetero)arenes.

We commenced our studies by exploring the photoredox remote C(sp³)-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. Et₃N, 2 equiv. NaOAc, DMSO solvent and 18 W blue LEDs light was found to be optimal for the photoredox remote C(sp3)-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) PF₆, Ru(bpy)₃Cl₂, 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 Et₃N (entry 8) are crucial for success as omitting either led to no detectable product 3aa. A series of amines, including ¹Pr₂NEt, 1,4-diazabicyclo[2.2.2]octane (DABCO), tetramethyl-piperidine (HTMP), 1,2,2,6,6-pentamethylpiperidine (PMP) and iPr2NH, were reactive, but all were inferior to Et₃N (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 K2CO3 and NaO t Bu were found to inhibit the reaction (entries 14 and 15). These results indicate that the organic bases like Et₃N 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).

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 ₃ N	0
9	ⁱ Pr ₂ NEt instead of Et ₃ N	68
10	DABCO instead of Et ₃ N	11
11	HTMP or PMP instead of Et ₃ N	<5
12	ⁱ Pr ₂ NH instead of Et ₃ N	34
13	Without NaOAc	45
14	K ₂ CO ₃ instead of NaOAc	43
15	NaO ^t Bu instead of NaOAc	10
16	DMF instead of DMSO	53
17	CH ₃ CN 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%), Et₃N (2 equiv.), NaOAc (2 equiv.), DMSO (2 mL), 18 W blue LEDs, argon, room temperature, and 12 h. Some byproducts, 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(sp³)-H arylation protocol (Table 2). As shown in Table 2, a variety of 1-(2iodoaryl)-1-ketones 1b-h bearing a functionality, such as Me, MeO, F and CF₃, on the aryl ring at the para- or meta-position were compatible with the optimized conditions, affording 3baha 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, Et₃N 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-CF₃-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 electronwithdrawing CF₃ group substituted at the ortho-position of the aryl ring 1i showed no reactivity for the reaction. 3,4-DiMeOsubstituted (2-iodoaryl)-1-ketone 1j was suitable for efficiently constructing 3ja. Using 2-cyclohexyl-1-(2-iodophenyl)ethan-1one 1k delivered 3ka in 81% yield. For chain extended 1-(2iodophenyl)-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 $_3$ N (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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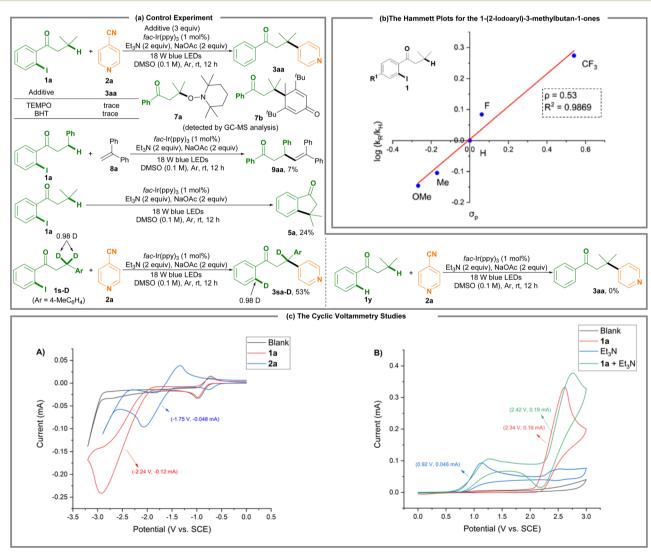
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arylation happened, giving 3qa and 3qa' in 48% yield and 4:1 sr. 1-(2-Iodoaryl)-1-ketones 1r-s having an aryl ring (such as phenyl or 4-methylphenyl) exhibited high reactivity for furnishing 3ra-sa in good yields.

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-MeOC₆H₄, 4-ClC₆H₄, thiophen-3-yl and phenylethynyl, on the pyridine ring at position 2 were compatible for site selectively assembling the 3arylation 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(sp³)-H arylation protocol smoothly (3ahai). For 2,6-diMe-substituted isonicotinonitrile 2j the reaction successfully occurred and delivered 3ai in moderate yield. However, terephthalonitrile 1k had no reactivity (3ak). Additionally, heterocyclic cyanoarenes 2l and 2m were investigated. Benzo[d]thiazole-2-carbonitrile (21) was converted efficiently into 3al in 59% yield, whereas 1H-pyrrolo[2,3-b]pyridine-4carbonitrile (2m) had no reactivity. Notably, we investigated electron-deficient alkenes 2n and 20 under the standard conditions, affording the alkylated products in 45-62% yields.

This photoredox remote C(sp3)-H arylation protocol was applicable to N-(2-iodoaryl)amides (3ta-va), thus offering a new α -C(sp³)-H arylation strategy. For example, N-(2-iodophenyl)isobutyramide 1t executed α -C(sp³)-H arylation via a sequence of XAT and 1,5-HAT, affording 3ta in 67% yield. However, N-(2iodophenyl)-N-methylpivalamide (1w) and N-(2-iodophenyl)-N-1-dimethylcyclohexane-1-carboxamide (1x) showed no reactivity for the construction of β -C(sp³)–H arylation products.

Using a radical scavenger like TEMPO or BHT led to complete suppression of the remote C(sp3)-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-(2iodophenyl)-3-methylbutan-1-one 1a where 3,3-dimethyl-2,3-



Scheme 2 Mechanistic investigations

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 $(k_{1-(2-iodo-4-(trifluoromethyl)phenyl)-3-methylbutan-1-one})$. 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 $\log(k_{\rm X}/k_{\rm H})$ and the $\sigma_{\rm p}$ 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 $E_{\rm p_{1/2red}}=-2.24~{\rm V}~vs.$ standard calomel electrode (SCE) for 1-(2-iodophenyl)-3-methylbutan-1-one 1a and a reduction potential peak at $E_{\rm p_{1/2red}}=-1.75~{\rm V}~vs.$ SCE for isonicotinonitrile 2a (Fig. S6 and S7; ESI†). Upon the catalytic activity of the *fac*-Ir(ppy)₃ catalyst

 $(E_{\rm p_{1/2red}}=-1.73~{\rm V}~vs.~{\rm SCE})$, the reductive conversion of ${\bf 1a}$ is very difficult because of its lower negative reduction potential, and thus photoreduction of isonicotinonitrile ${\bf 2a}$ takes precedence over that of ${\bf 1a}$. On the other hand, 1-(2-iodophenyl)-3-methylbutan-1-one ${\bf 1a}$ exhibited an oxidation potential peak at $E_{\rm p_{1/2ox}}=2.34~{\rm V}~vs.~{\rm SCE}$ (red line; Scheme $2c({\rm B})$) and ${\rm Et_3N}$ has an oxidation potential peak at $E_{\rm p_{1/2ox}}=0.92~{\rm V}~vs.~{\rm SCE}$ (blue line; Scheme $2c({\rm B})$). Moreover, a mixture of ${\bf 1a}$ and ${\rm Et_3N}$ reveals an increasing oxidation potential and current (from $E_{\rm p_{1/2red}}=2.34~{\rm V},$ 0.16 mA to $E_{\rm p_{1/2red}}=2.42~{\rm V},$ 0.19 mA) (green line; Scheme $2c({\rm B})$). These results suggest that ${\rm Et_3N}$ is more reactive than ${\bf 1a}$ for anodic oxidation, and this protocol involves a ${\rm Et_3N}$ reacting with ${\bf 1a}$ process.

The Stern–Volmer fluorescence quenching experiments revealed that the $Ir(ppy)_3$ luminescence was obviously decreased by Et_3N (Fig. S1; $ESI\dagger$), and slightly decreased by 1-(2-iodophenyl)-3-methylbutan-1-one $\mathbf{1a}$ (Fig. S2 \dagger) or cyanopyridine $\mathbf{2a}$ (Fig. S3 \dagger), suggesting that the reaction operates via a canonical photoredox radical cycle consisting of a photoreductive quenching by Et_3N . 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 \dagger).

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

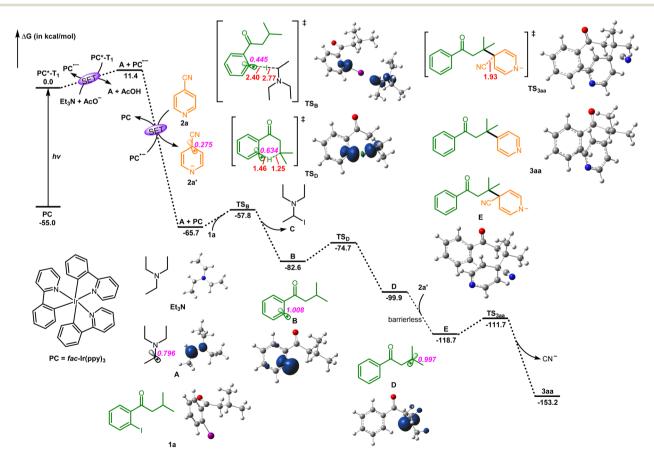


Fig. 1 DFT-calculated energy profiles of the mechanistic pathway. Optimized intermediate and transition-state structures (key bond distances in Å) as well as the spin density plots (isovalue: 0.008 au) of key radical species are given. The Gibbs free energies (ΔG) are given in kcal mol⁻¹. The italic 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*-T₁ under blue LED illumination. Following this, PC undergoes two consecutive single-electron transfer (SET) processes. In the first SET, the excited state PC*-T₁ reacts with Et₃N to generate the radical anion PC'-. Simultaneously, Et₃N 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*-, 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 TSD, surpassing a moderate activation energy of 7.9 kcal mol⁻¹, thereby yielding the radical intermediate D. Subsequently, a barrierless radicalradical 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(sp³)–H arylation protocol as outlined in Scheme 3 was proposed.⁶⁻⁸ Photooxidation of Et₃N by the excited state Ir(ppy)₃* affords the Ir(ppy)₃ radical anion and the Et₃N 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

Scheme 3 Possible reaction mechanism.

by HRMS analysis).⁷ The intermediate **B** subsequently undergoes an intramolecular 1,5-HAT to deliver the alkyl radical intermediate \mathbf{D} .⁸ Meanwhile, single electron reduction of isonicotinonitrile $\mathbf{2a}$ by the $\text{Ir}(\text{ppy})_3$ radical anion gives rise to the formation of the isonicotinonitrile radical anion $\mathbf{2a}'$ and regeneration of the $\text{Ir}(\text{ppy})_3$ photocatalyst.⁶ Radical-radical coupling between the alkyl radical intermediate \mathbf{D} and the isonicotinonitrile radical anion $\mathbf{2a}'$ affords the anion intermediate \mathbf{E} , followed by decyanation with the aid of bases to access the desired product $\mathbf{3aa}$.

Conclusions

In summary, we have developed a new, site selective iodoarene-directed photoredox β -C(sp³)–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 sp³-carbon radical and then radical–radical coupling, thus achieve iodoarene-directed remote C(sp³)–H arylation and prohibiting undesired radical pathways. This mild and selective iodoarene-directed photoredox XAT and HAT method for remote C(sp³)–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(sp³)–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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