

RESEARCH ARTICLE

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View Journal | View IssueCite this: *Org. Chem. Front.*, 2022, 9, 2534Visible-light-driven photoredox-catalyzed C(sp³)-C(sp³) cross-coupling of *N*-arylamines with cycloketone oxime esters†Sheng-Yun Zhou,^{‡a} Ding Zhang,^{‡a} Xiao-Jie Liu,^a Jing-Hao Qin,^a Zheng-Li Fu,^a Shuang-Long Li,^a Fang-Jun Cai,^a Yang Li^{✉*a} and Jin-Heng Li^{✉**a,b}Received 24th January 2022,
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A novel photoredox-catalyzed C(sp³)-C(sp³) cross-coupling between *N*-arylamines and cycloketone oxime esters under mild conditions has been accomplished. The redox-neutral reaction proceeds with good functional group tolerance and excellent regioselectivity without any extra base or ligand control. In addition, this approach was successfully applied for the late-stage modification of short peptides and analogues.

Introduction

Functional amines are regarded as an important class of structural motifs that exist in a large number of pharmaceutically important molecules and natural products. Due to their rich chemical and biological activities, the discovery of a general methodology for the preparation or modification of these compounds has attracted more and more attention.^{1,2} Among them, the alkylation of *N*-arylamines is one of the most efficient pathways to produce N-containing organic compounds, which introduce a C(sp³) moiety to change the spatial conformation, and increase both the lipophilicity and hydrophilicity as drug candidates. A typical method for the alkylation of *N*-arylamines mainly relies on CDC (cross-dehydrogenative coupling) reactions;³ although significant advances have been made along this line, there are still some considerable limitations: (1) most approaches rely heavily on activated alkyl substrates, whose C(sp³)-H bonds are adjacent to the heteroatom (such as O, S and N) or the electron-withdrawing group (such as a nitrile, an ester, a ketone and an amide) and (2) super-stoichiometric oxidants and high temperatures are usually required, leading to poor chemoselectivity and atom economy. Therefore, the development of mild and sustainable synthetic strategies to accomplish challenging C(sp³)-C(sp³)

cross-coupling through α -amino C-H functionalization is still highly desirable.

Visible light photocatalysis has been developed as a powerful tool for organic transformation due to its environmental friendliness and sustainability,^{4,5} and recently applied in alkylation of *N*-arylamines.⁶ In 2017, Yu and co-workers reported a novel visible-light-driven palladium-catalyzed radical alkylation of *N*-arylamines with alkyl bromides; various tertiary, secondary, and primary unactivated alkyl bromides undergo this simple reaction for the construction of quaternary centers (Scheme 1a).^{6a} Soon after, Cong and co-workers developed the visible light photoredox decarboxylative alkylation of *N*-arylamines with *N*-(acyloxy)phthalimides, using erythrosine B sensitized TiO₂ as the photocatalyst.^{6b} Zhang and co-workers described a similar decarboxylative alkylation through the photoactivation of an electron donor-acceptor (EDA) complex (Scheme 1b).^{6c} In addition to alkyl bromides and *N*-(acyloxy)phthalimides, Katritzky salts also proved to be efficient, with regard to alkyl radical precursors in the visible-light-mediated deaminative alkylation of *N*-arylamines (Scheme 1c).^{6d,e} Although these methods provide an efficient way to access alkylation of *N*-arylamines, they mainly focus on such three active alkyl radical sources, the distal unactive alkyl radical for the alkylation of *N*-arylamines was still rare.

Recently, redox-active cycloketone oxime esters have been intensively explored as radical precursors under transition-metal or photoredox catalysis *via* C-C bond activation.^{7,8} In 2021, Gong, Lu and co-workers developed a direct C-H cyanoalkylation of glycine derivatives with cyclobutanone oxime esters; the key of this transformation is the combination of Fe(NTf₂)₂ and pyridine-oxazoline ligands as an efficient catalytic system. Moreover, the 2-amino carbonyl moiety was essential to achieve chelation between the catalyst system and glycine

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Scheme 1 Photocatalytic radical alkylation of *N*-arylamines.

derivatives.⁹ Inspired by the above work, we wondered whether it would be possible to exploit the radical coupling of *N*-arylamines and cycloketone oxime esters under photoredox conditions.

Herein, we report a novel metal-free $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ cross-coupling between *N*-arylamines and cycloketone oxime esters involving direct $\text{C}(\text{sp}^3)\text{-H}$ functionalization; various *N*-arylamines and cycloketone oxime esters can be transformed into the corresponding products in good to excellent yields under mild conditions (Scheme 1d). This reaction proceeds *via* a sequence of the iminyl radical generation, C–C bond cleavage to produce a cyanoalkyl radical, single electron transfer to form a nitrogen radical cation, deprotonation and radical–radical coupling.

Results and discussion

We started our investigations using 2-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** and cyclobutylidene methyl 4-(trifluoromethyl)benzoate **2a** as the model reaction partners to clarify the standard reaction conditions (Table 1). We found that *N*-aryamine **1a** underwent successfully the α -amino C–H functionalization with cycloketone oxime ester **2a**, with 3CzClIPN as a photocatalyst and acetonitrile as a solvent at room temperature under irradiation with blue LEDs for 12 h, affording the desired 4-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butanenitrile **3aa** in 86% isolated yield (entry 1). The reaction did not occur in the absence of irradiation or a photocatalyst (entries 2 and 3). The photocatalyst as a crucial factor was investigated; metal photocatalysts such as *fac*-Ir(ppy)₃ and

Table 1 Screening of the optimal reaction conditions^a

Entry	Variation from the standard conditions	Yield (%)
1	None	86
2	Without blue LEDs	0
3	Without 3CzClIPN	0
4	<i>fac</i> -Ir(ppy) ₃ instead of 3CzClIPN	41
5	Ru(bpy) ₃ Cl ₂ instead of 3CzClIPN	58
6	Eosin Y instead of 3CzClIPN	38
7	[Acr-Mes] ⁺ (ClO ₄) ⁻ instead of 3CzClIPN	40
8	Rhodamine B instead of 3CzClIPN	19
9	Methylene blue instead of 3CzClIPN	58
10	3CzClIPN (1 mol%)	48
11	3CzClIPN (5 mol%)	87
12	DCE instead of MeCN	61
13	MeOH instead of MeCN	65
14	Toluene instead of MeCN	13
15	DMSO instead of MeCN	43
16 ^b	None	80

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), 3CzClIPN (3 mol%), MeCN (2 mL), RT, 5 W blue LEDs, argon, and 12 h. ^b **1a** (1 g) for 36 h.

Ru(bpy)₃Cl₂ resulted in good catalytic activity but were less efficient than 3CzClIPN (entries 4 and 5). Other organophotocatalysts including Eosin Y, [Acr-Mes]⁺(ClO₄)⁻, rhodamine B and methylene blue all turned out to be inferior to 3CzClIPN (entries 6–9). Screening of photocatalyst loading revealed that a lower catalytic amount of 3CzClIPN (1 mol%) reduced the yield sharply and a higher catalytic amount (5 mol%) affected the yield slightly (entries 10 and 11). When other solvents such as dichloroethane, methanol, toluene and DMSO were employed to replace acetonitrile, a notable decrease of the yield was observed (entries 12–15). To our delight, the reaction scaled up to **1g** of 2-phenyl-1,2,3,4-tetrahydroisoquinoline **1a** also smoothly delivered **3aa** in 80% yield (entry 16).

With the optimized reaction conditions in hand, we evaluated the generality of this reaction with *N*-aryl tetrahydroisoquinolines **1** and cycloketone oxime esters **2**. As shown in Table 2, the substrates bearing different kinds of groups including methyl **1b**, methoxy **1c**, fluoro **1d**, bromo **1e** and tri-

Table 2 Variation of the *N*-aryl tetrahydroisoquinolines and cycloketone oxime esters (**2**)^a

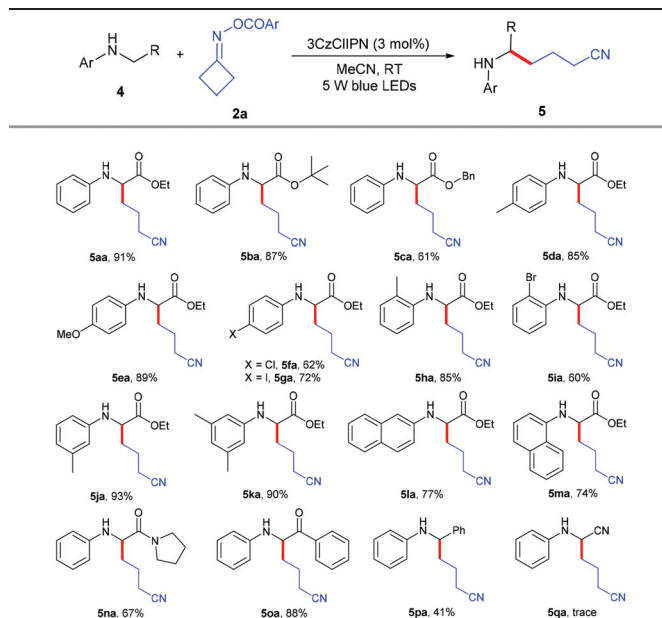
^a Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), 3CzClIPN (3 mol%), MeCN (2 mL), RT, 5 W blue LEDs, argon, and 12 h.

fluoromethyl **1f** groups at the *para* position of the *N*-phenyl ring were well tolerated, affording the C(sp³)-C(sp³) coupling products **3ba–3fa** in 48%–84% yields; the *ortho* and *meta* position substituents **1g** and **1h** did not affect the reaction and produced the corresponding products in good yields. Furthermore, substrate **1i** with the naphthalene group at the nitrogen atom was also highly active. 2-Methyl-1,2,3,4-tetrahydroisoquinoline **1j** was not suitable under the standard conditions; the *N*-aryl group might be essential for the electron transfer. Several kinds of electron-donating and electron-withdrawing groups **1k–1o** at different positions of the benzene ring smoothly transformed into selective alkylation products in 72%–93% yields. A series of cycloketone oxime esters **2b–2i** could serve as suitable substrates to afford the desired products **3ab–3ai** under mild conditions. Symmetric monosubstituted cyclobutanone oximes bearing various functional groups such as alkyl **2b**, ester **2c**, and phenyl **2d** substituents at the 3-position all underwent ring-opening processes to give the corresponding products **3ab–3ad** in 68%–81% yields. The disubstituted cycloketone oxime ester **2e** was compatible with the reaction. The heterocyclobutanone oxime esters oxetan-3-one **2f** and 1-Boc-3-azetidinone **2g** also showed comparable reactivity, delivering the corresponding products **3af** and **3ag** in 82% and 70% yields. To our surprise, this protocol was not only suitable for four-membered ring oxime esters, but other less-strained substrates such as cyclopentanone **2h** and cyclo-

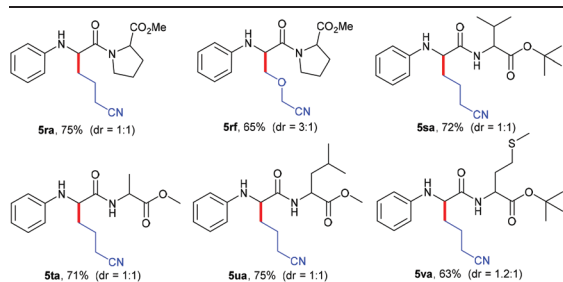
hexanone oxime ester **2i** were also converted to the desired products in 65% and 53% yields.

We further explored the scope of α -amino carbonyl compounds **4** with cycloketone oxime ester **2a** (Table 3). The ethyl **4a**, tertiary butyl **4b** and benzyl **4c** esters of *N*-aryl glycine were amenable for this catalytic system, giving the corresponding products in 61%–91% yields. Various functional groups **4d–4j** on the benzene ring of glycine derivatives were examined; the results showed that electron-donating groups performed better than electron-withdrawing groups, and the position nature had no detrimental effect on the reaction. The dimethyl-substituted and naphthalenyl groups of glycine esters **4k–4m** were also tolerated to give the corresponding products **5ka–5ma** in 74%–90% yields. Not only glycine esters, other α -amino carbonyl compounds such as amide **4n** and ketone **4o** could also smoothly transform into the desired products in excellent yields, which indicated that this protocol could be used to modify peptides. Even *N*-benzylaniline **4p** could successfully give the alkylation product **5pa** in 41% yield. Unfortunately, *N*-phenylglycinonitrile **4q** was not suitable for this transformation.

Next, the practicability of these mild conditions for the site-selective modification of peptides was tested (Table 4). *N*-Phenyl protected dipeptide **4r** was successfully coupled with cycloketone oxime ester **2a** and heterocyclobutanone oxime ester **2f** in good yields. Other dipeptides **4s–4u** bearing different units also selectively underwent alkylation at the α -position of glycine carbonyl in 71%–75% yields. Even substrate **4v** containing the sensitive thiomethyl group could smoothly transform into the corresponding product **5va** in a moderate yield.

Table 3 Variation of the α -amino carbonyl compounds (**4**)^a

^a Reaction conditions: **4** (0.2 mmol), **2a** (0.24 mmol), 3CzClIPN (3 mol%), MeCN (2 mL), RT, 5 W blue LEDs, argon, and 12 h.

Table 4 Site-selective modification of short peptides^a

^a Reaction conditions: **4** (0.2 mmol), **2** (0.24 mmol), 3CzClIPN (3 mol%), MeCN (2 mL), RT, 5 W blue LEDs, argon, and 12 h.

To gain insight into this photoredox-catalyzed cross coupling reaction, mechanistic studies were conducted with radical trapping experiments. When TEMPO, hydroquinone and BHT were added into the standard conditions, the reaction was completely suppressed (Scheme 2a), and the radical generated from cycloketone oxime ester **2a** was trapped by TEMPO to give product **6** in 19% yield; the radicals from substrates **1a** and **2a** could be identified through HRMS (see the ESI[†]). In addition, Stern–Volmer quenching studies indicated that *N*-aryl tetrahydroisoquinoline **1a** quenched the excited state of 3CzClIPN (Scheme 2b). These results implied that the reaction involves a radical process.

Based on the obtained results and previous reports,⁶ a plausible mechanism for this visible-light-driven photoredox-catalyzed C(sp³)-C(sp³) cross-coupling reaction was proposed, as shown in Scheme 3. Firstly, the photocatalyst 3CzClIPN is excited under visible light irradiation to produce its excited state species 3CzClIPN* ($E_{1/2} [PC^*/PC^{*-}] = +1.56$ V vs. SCE in MeCN),^{4j} which oxidizes *N*-arylamine **1a** ($E_p^{0/+1}(\mathbf{1a}) = +1.04$ V versus SCE in MeCN)^{6p} to give radical cation **A** and 3CzClIPN⁻. 3CzClIPN⁻ ($E_{1/2} [PC/PC^{*-}] = -1.16$ V vs. SCE in MeCN) undergoes another SET process with cycloketone oxime ester **2a** ($E_p^{0/-1}(\mathbf{2a}) = -0.99$ V versus SCE in MeCN)^{8j} to form iminyl radical **B** and the 4-(trifluoromethyl)benzoate anion, along with the regeneration of 3CzClIPN. Subsequently, iminyl radical **B** undergoes a ring-opening to give the highly reactive



Scheme 3 Possible mechanism.

cyanoalkyl radical **C**; radical cation **A** undergoes deprotonation with the 4-(trifluoromethyl)benzoate anion to produce the benzylic radical **D**. Finally, radical–radical coupling between intermediate **C** and intermediate **D** provides the desired product **3aa**.

Conclusions

In summary, we have developed a new site selective photoredox-catalyzed C(sp³)-C(sp³) cross-coupling between *N*-arylamines and cycloketone oxime esters without employing any extra base or ligand control. A variety of *N*-aryl tetrahydroisoquinolines, glycine derivatives and cycloketone oxime esters can be transformed into the corresponding products in good to excellent yields. In addition, this protocol is also successfully applied in the alkylated modification of short peptides, which is highly attractive for medicinal chemistry and organic synthesis.

Conflicts of interest

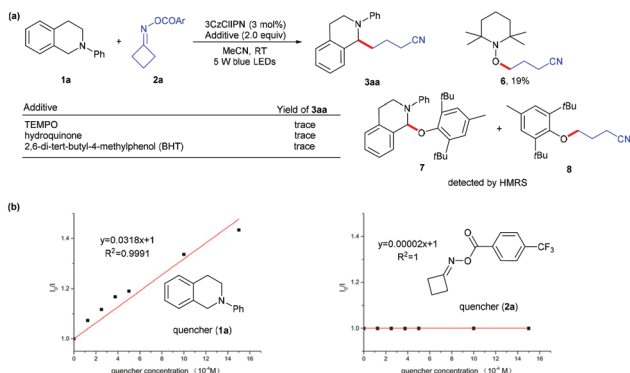
There are no conflicts to declare.

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