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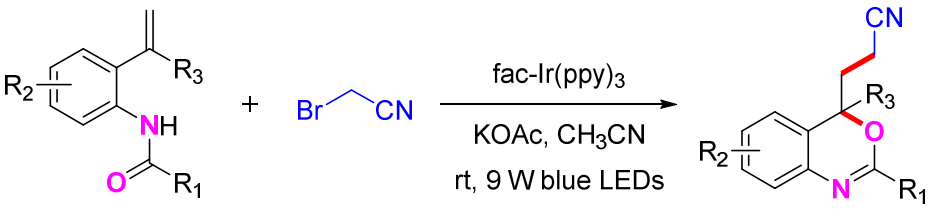
Graphical Abstract



redox neutral new C-C & C-O formation mild conditions

Redox-neutral photocatalytic cyanomethylation/cyclization cascade of olefinic amides: access to cyanomethylated benzoxazines

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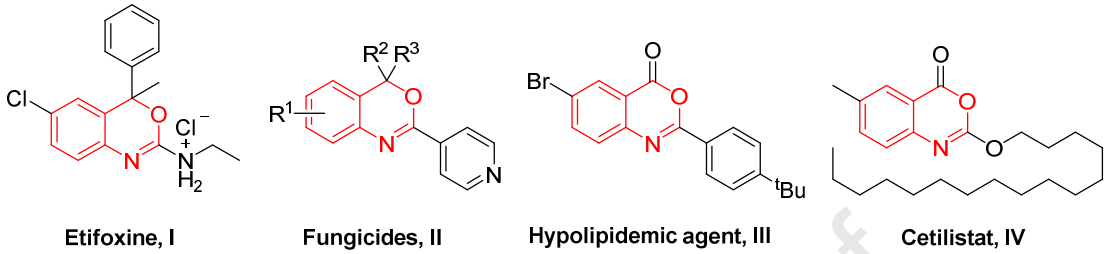
Abstract: A visible-light-induced photocatalytic cyanomethyl radical addition/intramolecular cyclization cascade reaction of olefinic amides has been developed under mild conditions. This reaction provides a novel method for the synthesis of various cyanomethyl-containing benzoxazines , which are useful pharmaceutical framework. The method exhibits good functional group tolerance and a wide range of substrate scope.

Keywords: visible-light; radical addition; cyclization cascade; cyanomethyl-containing benzoxazines

1. Introduction

Benzoxazines are a class of important compounds containing a nitrogen and oxygen heterocyclic skeleton, which are widely found in pharmaceutical and biologically related products.[1] For example, anticonvulsant (I),[2] fungicides (II),[3] hypolipidemic active agent (III),[4] and cetilistat (IV)[5] all contain this versatile framework (**Fig. 1**). Moreover, benzoxazines are also useful synthetic intermediates in organic synthesis. Thus, the study of benzoxazines has attracted great interest. In addition, cyano group is also found in natural products, dyes and pharmaceuticals.[6] Nitriles can be converted to different types of compounds such as carboxylic acids, amides, esters, amidines, aldehydes, ketones and tetrazoles.[7] Based on the importance of benzoxazines and nitriles, we deem that it would be intriguing to introduce the

versatile synthetic unit cyano group into benzoxazine to construct highly functional drug-like molecules. Studies on the synthesis of such compounds would enrich the current benzoxazine chemistry.



Etifoxine, I | Fungicides, II | Hypolipidemic agent, III | Cetilistat, IV

Fig. 1 Representative examples of benzoxazines.

Benzoxazines are typically synthesized by condensation of 2-aminobenzyl alcohols with aldehydes,[8] or the cyclization of acetylenic amides,[9] however, these methods generally have some disadvantages such as harsh reaction conditions and narrow substrate scope.[10] A number of strategies have been developed for the construction of various functionalized benzoxazine derivatives based on electrophilic cyclization of olefinic amides with halonium ions and even free radicals.[11-12] Recently, visible light catalyzed free radical addition to olefinic amides followed by intramolecular cyclization has led to the efficient synthesis of benzoxazines under mild conditions. For example, Xiao's group reported the oxytrifluoromethylation of olefinic amides by photocatalysis to synthesize CF_3-containing benzoxazines.[12a] Fu's group demonstrated visible-light-mediated oxydifluoromethylation of olefinic amides with difluoromethyl sulfones for the synthesis CF_2H-containing benzoxazines and oxazolines.[13]

There are very few studies on the synthesis of cyanomethylated benzoxazines. To the best of our knowledge, only Ji's group has so far reported two examples of the synthesis of benzoxazines. One is a copper-catalyzed reaction of olefinic amides with acetonitrile to access cyanomethylated benzoxazines using stoichiometric peroxide at 140 °C.[14] The other is a palladium-catalyzed reaction of olefinic amides with bromoacetonitrile to form cyanomethylated benzoxazines at a high temperature of 110 °C in the presence of a ligand and Ag_2CO_3.[15] Therefore, it is still highly desirable to find mild methods for the synthesis of this type of compounds.

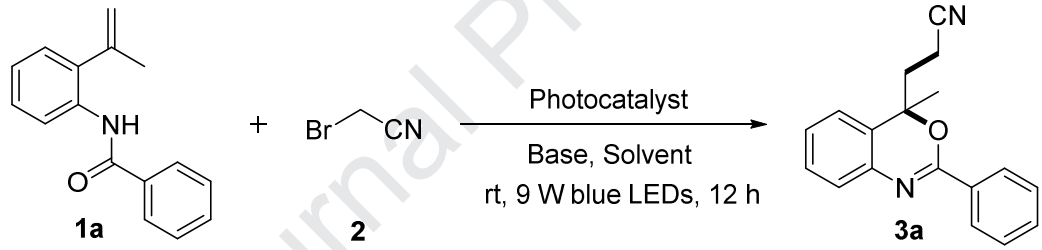
In light of the previous research, we designed a mild cascade reaction to synthesize cyanomethylated benzoxazines, which includes photocatalytic formation of cyanomethyl radical from bromoacetonitrile, addition of cyanomethyl radical to olefin amide, and intramolecular cyclization. This strategy avoids stoichiometric peroxides and high temperatures.

2. Results and discussion

The study was initiated with N-(2-(prop-1-en-2-yl)phenyl) benzamide (**1a**) and bromoacetonitrile (**2**) as model substrates (**1a/2** = 1:3, molar ratio). In the presence of *fac*-Ir(ppy)$_3$ (3% mol) as a photocatalyst and Na_2CO_3 (2.0 equiv) as a base in degassed dry CH_3CN under 23 W compact fluorescent lamp (CFL) irradiation for 12 h at room temperature, the desired product **3a** was isolated in 59% yield (**Table 1**, entry 1). When 9 W blue LEDs were used instead of 23 W CFL, the reaction yield increased to 68% (**Table 1**, entry 2), so we chose 9 W blue LEDs for subsequent experiments. In order to further improve the reaction efficiency, the reaction conditions were optimized by studying various parameters such as photocatalyst, solvent, base and molar ratio of substrates. Firstly, when other commonly used photocatalysts such as [Ir(dtbbpy)(ppy)$_2$][PF_6] (E^*_{red} Ir^{III}/Ir^{IV} = -0.89 V vs. SCE in CH_3CN),[16] $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (E^*_{red} Ru^{II}/Ru^{III} = -0.81 V vs. SCE in CH_3CN),[16] Rose Bengal (E^*_{red} = -0.99 V vs. SCE in CH_3CN)[17] and Eosin Y (E^*_{red} = -1.06 V vs. SCE in CH_3CN)[18] were used, no catalytic activity was observed for the reaction (**Table 1**, entries 3-6). A possible explanation is that the reduction potentials of the excited state of these photocatalysts are higher than the reduction potential of bromoacetonitrile **2** (E_{red} = -1.46 V vs. SCE in CH_3CN) (**Fig. S4**), so they cannot reduce **2**. In contrast, excited *fac*-Ir(ppy)$_3$ (E^*_{red} = -1.73 V vs. SCE in CH_3CN),[16] has a lower reduction potential than bromoacetonitrile **2**, so it can reduce **2** to allow the reaction to proceed. Next, several bases such as K_2CO_3, K_2HPO_4, KOAc, Et_3N, DABCO and 2,6-Lutidine were examined (**Table 1**, entries 7−12). To our delight, the yield of **3a** was increased to 73% by using KOAc as a base (**Table 1**, entry 9). Then, we investigated other solvents such as THF, DMF, DMSO, EtOH, and acetone, but none of them is better than acetonitrile (**Table 1**, entries 13–17).

Control experiments showed that photocatalyst and visible light irradiation are indispensable for the reaction (**Table 1**, entries 18–19). Moreover, when the reaction was performed in air instead of argon, the yield of **3a** dropped to 32% (**Table 1**, entry 20), indicating that the presence of oxygen is detrimental to the reaction. When the reaction was carried out in the absence of a base, only 32% yield of **3a** was isolated, and most of **1a** was recovered (**Table 1**, entry 21), suggesting that the addition of the base indeed promotes the reaction. Finally, we explored the effect of the amounts of **2a**, photosensitizer and base on the reaction, and found that when their amounts were reduced to 2.0 equiv, 2 mol%, 1.5 equiv, respectively, the reaction gave a satisfactory yield of 75% (**Table 1**, entry 22). Therefore, the optimized reaction conditions include: **1a** (1.0 equiv), **2** (2.0 equiv), KOAc (1.5 equiv), 2 mol% *fac*-Ir(ppy)$_3$, 9 W blue LED irradiation, and CH_3CN as a solvent.

Table 1. Optimization of reaction conditions.[a]



Entry	Photocatalyst	Base	Solvent	Yield[b] (%)
1[c]	*fac*-Ir(ppy)$_3$	Na_2CO_3	CH_3CN	59
2	*fac*-Ir(ppy)$_3$	Na_2CO_3	CH_3CN	68
3	[Ir(dtbbpy)(ppy)$_2$][PF_6]	Na_2CO_3	CH_3CN	0
4	Ru(bpy)$_3$Cl$_2$·6H$_2$O	Na_2CO_3	CH_3CN	0
5	Rose Bengal	Na_2CO_3	CH_3CN	0
6	Eosin Y	Na_2CO_3	CH_3CN	0
7	*fac*-Ir(ppy)$_3$	K_2CO_3	CH_3CN	58
8	*fac*-Ir(ppy)$_3$	K_2HPO_4	CH_3CN	66
9	*fac*-Ir(ppy)$_3$	KOAc	CH_3CN	73
10	*fac*-Ir(ppy)$_3$	Et_3N	CH_3CN	Trace
11	*fac*-Ir(ppy)$_3$	DABCO	CH_3CN	46
12	*fac*-Ir(ppy)$_3$	2,6-Lutidine	CH_3CN	17
13	*fac*-Ir(ppy)$_3$	KOAc	THF	50
14	*fac*-Ir(ppy)$_3$	KOAc	DMF	23
15	*fac*-Ir(ppy)$_3$	KOAc	DMSO	33
16	*fac*-Ir(ppy)$_3$	KOAc	EtOH	Trace

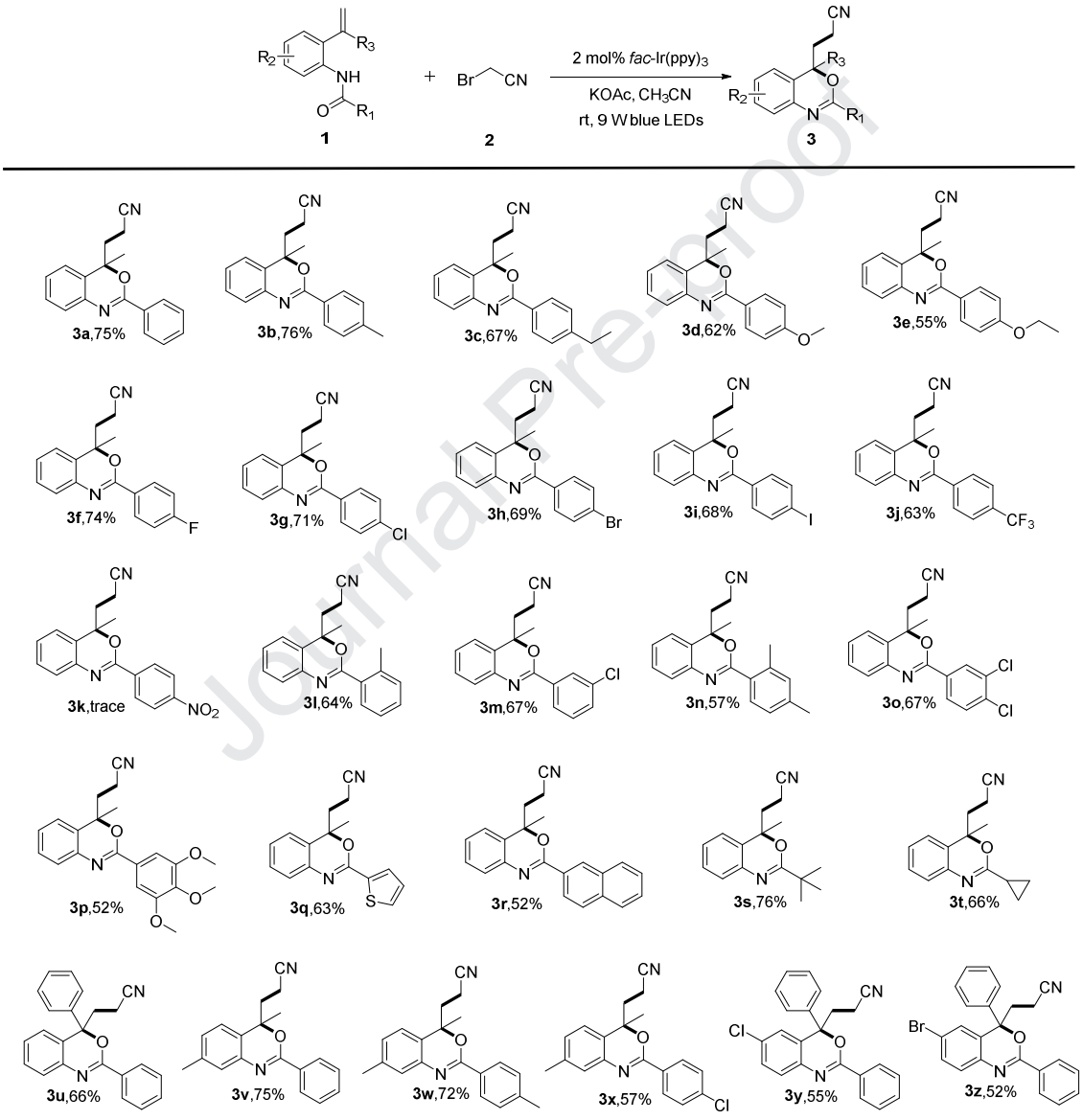
17	*fac*-Ir(ppy)$_3$	KOAc	Acetone	70
18	None	KOAc	CH_3CN	0
19[d]	*fac*-Ir(ppy)$_3$	KOAc	CH_3CN	0
20[e]	*fac*-Ir(ppy)$_3$	KOAc	CH_3CN	32
21	*fac*-Ir(ppy)$_3$	-	CH_3CN	32
22[f]	*fac*-Ir(ppy)$_3$	KOAc	CH_3CN	75

[a]Unless otherwise noted, reaction conditions: the mixture of **1a** (1.0 equiv, 0.2 mmol), **2** (3.0 equiv, 0.6 mmol), photocatalyst (3 mol%) and base (2.0 equiv, 0.4 mmol) in degassed dry solvent (1 mL) was irradiated by 9 W blue LEDs under Ar atmosphere at RT for 12 h. [b]Isolated yield after flash chromatography. [c]Under 23 W CFL irradiation. [d]In the dark. [e]Under air atmosphere. [f]**2** (2.0 equiv), *fac*-Ir(ppy)$_3$ (2 mol%), KOAc (1.5 equiv).

With the optimized reaction conditions in hand, we investigated the scope of olefinic amides for this visible-light-induced photocatalytic cyanomethylation/cyclization cascade reaction (**Table 2**). First, various electron-donating or electron-withdrawing groups such as Me, Et, MeO, EtO, F, Cl, Br, I, CF_3 at the *para*-position of the benzamide unit were tolerated, and led to desired products in good yields (**3b−3j**). However, when the *para*- position was substituted by strong electron-withdrawing substituent NO_2, the corresponding product cannot be obtained and the substrate was completely recovered (**3k**). The yield of the corresponding product lowered due to the steric hindrance effect when the *ortho*- position of the benzamide moiety was substituted (**3l** vs **3b**). In addition, the substrate bearing a meta-substituent showed good reactivity (**3m**). Both 2,4-disubstituted and 3,4-disubstituted, as well as 3,4,5-trisubstituted benzamide moiety were suitable to the reaction well, giving moderate yields (**3n-3p**). Furthermore, heteroarylamides and naphthylamides such as **1q** and **1r** also reacted smoothly, leading to the desired products **3q** and **3r** in yields of 63% and 52%, respectively. To our delight, the aliphatic amides **1s** and **1t** were also transformed into the corresponding products in 76% and 66% yields, respectively (**3s** and **3t**). Moreover, the olefinic amide bearing an aryl group at α position of the styrene unit also worked well, giving the corresponding product in 66% yield (**3u**). Olefinic amides with alkyl substituent on the styrene unit also participated in the reaction smoothly under the optimal conditions, and the target products were obtained with satisfactory yields (**3v-3x**). Considering the bioactive

structures shown in Fig. 1, similar substrates bearing Cl or Br on the phenyl ring of the styrene unit were examined, and the corresponding products (**3y** and **3z**) were obtained in moderate yields. Moreover, besides bromoacetonitrile, we have explored bromopropionitrile, chloroacetonitrile and trifluoromethanesulfonyl chloride as free radical precursors, but none of them reacted with **1a** to form the corresponding products.

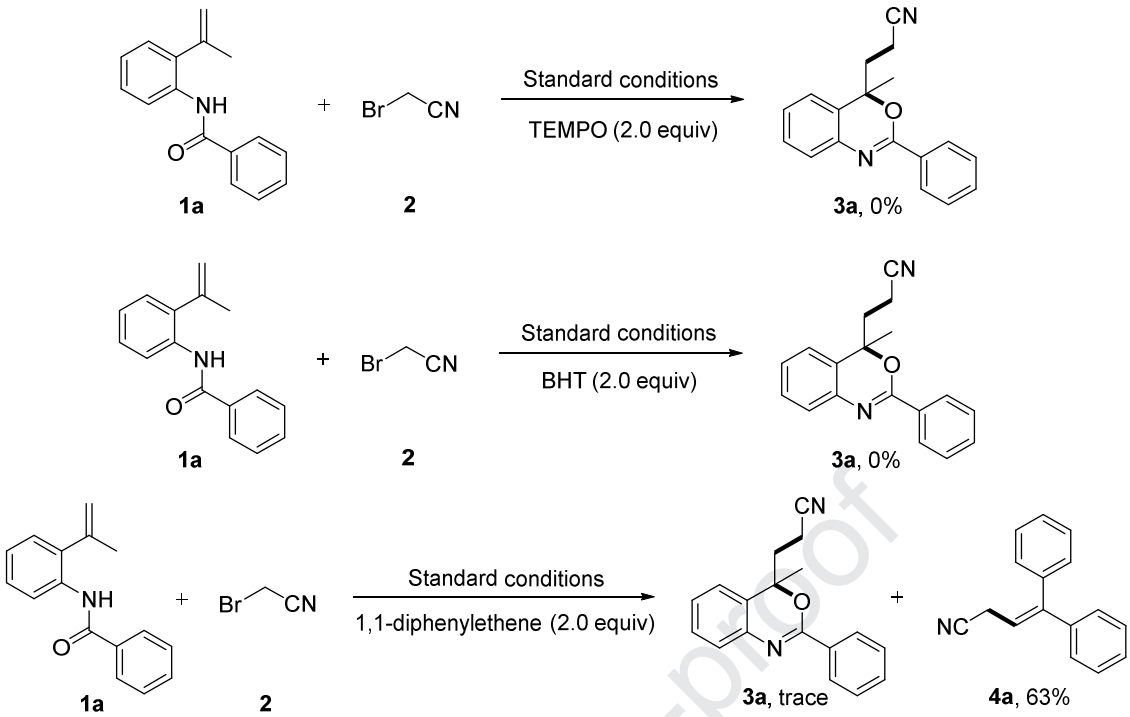
Table 2. Scope of substrates.[a,b]



[a]Reaction conditions: a mixture of **1** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), KOAc (0.3 mmol, 1.5 equiv), and *fac*-Ir(ppy)$_3$ (0.004 mmol, 2.0 mol%) in degassed dry CH_3CN (1.0 mL) was irradiated with 9 W blue LEDs under Ar atmosphere at RT for 10-24 h. [b]Isolated yield.

In order to explore the mechanism of the reaction, some control experiments were performed (**Scheme 1**). To verify whether the reaction involves a free radical process, the effects of some commonly used free radical scavengers on the reaction were investigated. When the radical scavengers TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and BHT (2,6-di-tert-butyl-4-methylphenol) were separately added to the reaction system, the reaction was remarkably suppressed without obtaining the desired product. When the radical scavenger 1,1-diphenylethene was used, the formation of **3a** was completely inhibited, but **4a** was isolated in 63% yield. The above experimental results indicated that the reaction may undergo a free radical process and involve the cyanomethyl radical. Subsequently, the light on/off experiments were performed to investigate the effect of photo-irradiation. The results showed that continuous irradiation of visible light is indispensable, indicating that there may be no free radical chain propagation process (**Fig. 2a**). In addition, the fluorescence quenching experiment was carried out and it was found that **2** could significantly quench the excited state of *fac*-Ir(ppy)$_3$, while the quenching effect of **1a** was not obvious, indicating that **2** may be involved in the oxidation process of the excited state *fac*-Ir(ppy)$_3$ (**Fig. 2b-d**). Finally, as described above, the results of cyclic voltammetry measurements suggested that **2** (E_{red} = -1.46 V vs. SCE in CH_3CN) (**Fig. S4**) can be reduced by excited *fac*-Ir(ppy)$_3$ (E^*_{red} = -1.73 V vs. SCE in CH_3CN). This further illustrated the possibility that the reaction is initiated by cyanomethyl radical, which is generated from **2** via its single-electron-transfer (SET) reduction by excited photocatalyst.

Scheme 1. Control experiments.



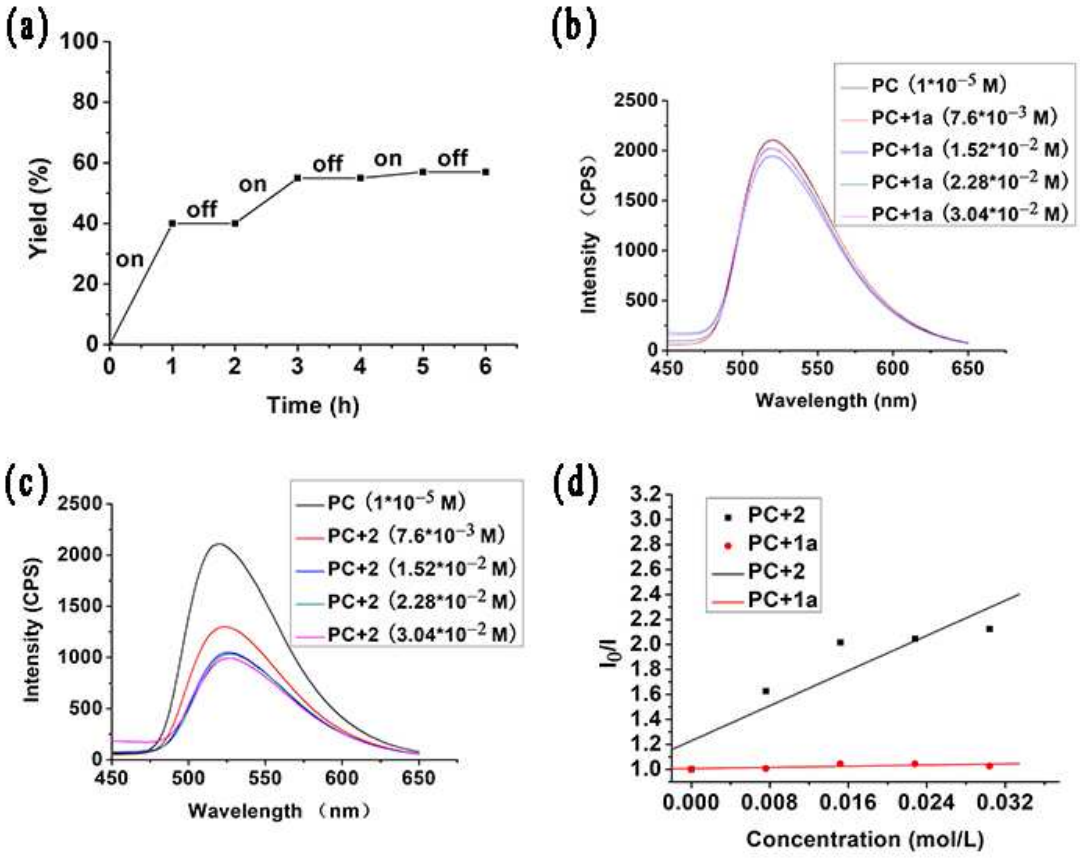
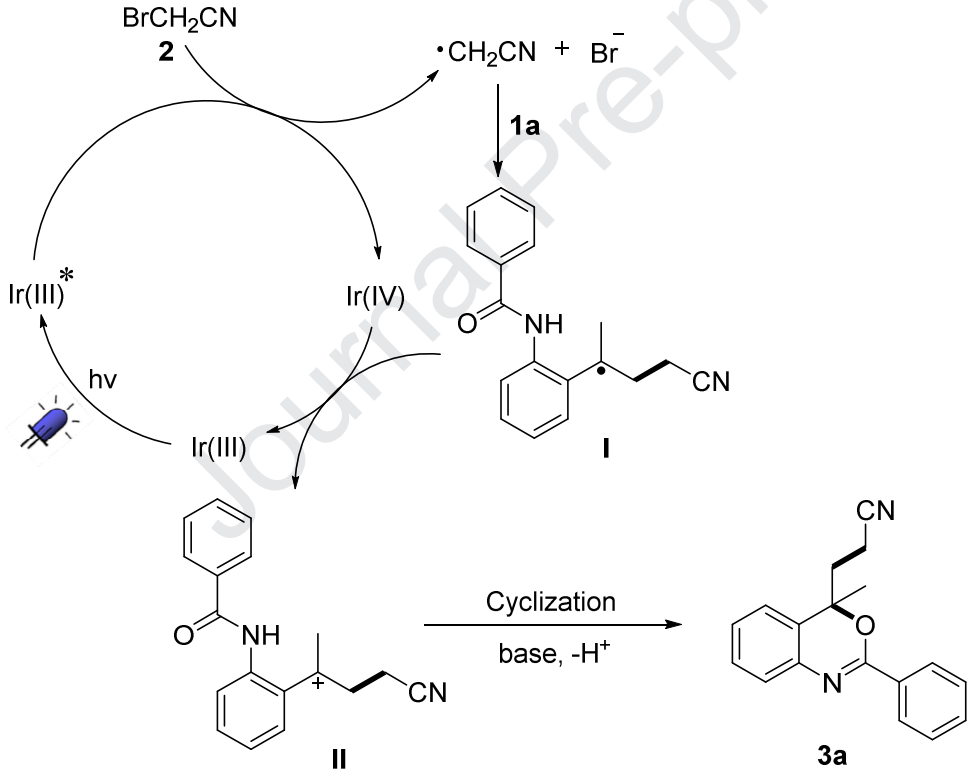


Fig. 2 (a) Light on/off experiment. (b) Quenching of *fac*-Ir(ppy)$_3$ fluorescence emission in the presence of **1a**. (c) Quenching of *fac*-Ir(ppy)$_3$ fluorescence emission in the presence of **2.** (d) Stern-Volmer plots of *fac*-Ir(ppy)$_3$ with quenchers **1a** and **2**.

Based on the above control experimental results and related literature reports,[10-12] a plausible reaction mechanism was proposed (**Scheme 2**). First, the [*fac*-Ir($_{III}$)(ppy)$_3$] is excited into [*fac*-Ir($_{III}$)(ppy)$_3$*] under irradiation of visible light, which is quenched with bromoacetonitrile **2** to [*fac*-Ir($_{IV}$)(ppy)$_3^+$] complex by a SET process, while producing the cyanomethyl radical. Subsequently, the cyanomethyl radical attacks the C-C double bond of olefinic amide **1a** to generate the radical intermediate **I.** Then, **I** is oxidized by [*fac*-Ir($_{IV}$)(ppy)$_3^+$] to give the carbocation **II** and [*fac*-Ir($_{III}$)(ppy)$_3$]. Finally, the intermediate **II** undergoes a cyclization reaction followed by deprotonation with the aid of a base to give the target product **3a.**

Scheme 2. Proposed reaction mechanism.



3. Conclusion

In summary, we have successfully developed a visible-light-induced cyanomethylation/cyclization tandem reaction of olefinic amides with readily available bromoacetonitrile for the synthesis of various cyanomethyl-containing benzoxazines. This redox-neutral photocatalytic reaction completes the synthesis of C-C and C-O bonds in one

pot without using any oxidizing agent. The reaction has the notable features of mild reaction conditions, simple operation, good functional group compatibility and wide range of substrate scope.

4. Experimental Section

4.1. General experimental details

Unless otherwise noted, materials obtained from commercial suppliers were used directly without further purification. Flash column chromatography was performed using 200-300 mesh silica gel at increased pressure. All ^{1}H NMR spectra and ^{13}C NMR spectra were respectively recorded on 600 or 400 MHz and 150 MHz or 100 NMR spectrometers using deuterochloroform ($CDCl_3$) as solvent at room temperature , all chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows (s = singlet; d = doublet; t = triplet; m = multiplet; q = quartet). The coupling constants, J, are reported in Hertz (Hz). High-resolution mass spectra were obtained by using ESI ionization sources (Varian 7.0 T FTICR-MS). Fluorescence emission was determined by fluorescence spectrophotometer (F-320 Gangdong, Tianjin). Melting points were taken on a WPX-4 apparatus and were uncorrected (Yice instrument equipment Co Ltd, Shanghai). The starting materials 1 were prepared according to the method reported in the literature.[19]

4.2. General procedure for the preparation of products **3**

A round bottomed flask equipped with a magnetic stirrer bar was charged with *fac*-$Ir(ppy)_3$ (2 mol %), olefinic amide **1** (0.2 mmol), KOAc (0.3 mmol) and bromoacetonitrile **2** (0.4 mmol). The flask was evacuated and backfilled with Ar (three times). Then degassed dry CH_3CN (1 mL) was injected under Ar. The resultant mixture was stirred at room temperature under irradiation of 9 W blue LEDs. The reaction was monitored by thin-layer chromatography (TLC), and the reaction was quenched with water (5 mL) after completion of the reaction. The resulting mixture was extracted with ethyl acetate (5 mL × 3). The organic layer was combined, and dried with anhydrous Na_2SO_4. The solvent was removed in vacuo,

and the residue was purified by flash column chromatography (petroleum ether/EtOAc = 5:1 to 10:1, v/v) to give the desired product **3**.

5. Spectral Data

*5.1. 3-(4-methyl-2-phenyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3a**):*[20]

Yellow oil; Yield = 75%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.8 Hz, 2H), 7.53-7.50 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.36-7.32 (m, 2H), 7.25-7.22 (m, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 2.53-2.44 (m, 2H), 2.41-2.32 (m, 2H), 1.70 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 138.8, 132.2, 131.7, 129.3, 128.4, 127.8, 127.2, 127.1, 125.8, 122.4, 119.2, 79.6, 77.3, 77.1, 76.8, 36.7, 28.1, 12.4 ppm.

*5.2. 3-(4-methyl-2-(p-tolyl)-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3b**)*:

Yellow oil; Yield = 76%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.1 Hz, 2H), 7.36-7.31 (m, 2H), 7.28-7.25 (m, 2H), 7.23-7.20 (m, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 2.51-2.44 (m, 2H), 2.42 (s, 3H), 2.40-2.33 (m, 2H), 1.69 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.1, 142.3, 138.9, 129.4, 129.3, 129.1, 127.9, 127.2, 126.9, 125.7, 122.3, 119.2, 79.5, 77.2, 77.0, 76.8, 36.7, 28.0, 21.6, 12.4 ppm. HRMS (ESI) m/z 313.1307 (M + Na^+), Cal. $C_{19}H_{18}N_2NaO^+$, 313.1311.

*5.3. 3-(2-(4-ethylphenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3c**):*[20]

Yellow oil; Yield = 67%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2 Hz, 2H), 7.34-7.28 (m, 4H), 7.24-7.19 (m, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.52-2.42 (m, 2H), 2.42-2.31 (m, 2H), 1.69 (s, 3H), 1.27 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.1, 148.5, 139.0, 129.8, 129.2, 128.1, 128.0, 127.3, 126.9, 125.8, 122.3, 119.3, 79.4, 77.3, 77.0, 76.8, 36.8, 28.9, 28.0, 15.3, 12.4 ppm.

*5.4. 3-(2-(4-methoxyphenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3d**):*[20]

Yellow oil;BYield = 62%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.8 Hz, 2H), 7.36-7.29 (m, 2H), 7.23-7.17 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.95 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 2.53-2.42 (m, 2H), 2.42-2.31 (m, 2H), 1.68 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6, 155.8, 139.1, 129.7, 129.2, 127.2, 126.7, 125.6, 124.7, 122.3, 119.3, 113.8, 79.4, 77.2, 77.0, 76.8, 55.4, 36.7, 28.0, 12.4 ppm.

*5.5. 3-(2-(4-ethoxyphenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3e**):*

Yellow oil; Yield = 55%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 2H), 7.33-7.31 (m, 2H), 7.21-7.18 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 2.52-2.41 (m, 2H), 2.41-2.31 (m, 2H), 1.68 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 155.9, 139.2, 129.7, 129.2, 127.1, 126.6, 125.5, 124.5, 122.3, 119.3, 114.2, 79.3, 77.2, 77.0, 76.8, 63.7, 36.7, 28.0, 14.7, 12.4 ppm. HRMS (ESI) m/z 343.1420 ($M + Na^+$), Cal. $C_{20}H_{20}N_2NaO_2^+$, 343.1417.

*5.6. 3-(2-(4-fluorophenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3f**):*[20]

Yellow oil; Yield = 74%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.15-8.13 (m, 2H), 7.37-7.31 (m, 2H), 7.25-7.22 (m, 1H), 7.13 (t, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 7.7 Hz, 1H), 2.51-2.43 (m, 2H), 2.42-2.32 (m, 2H), 1.70 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1 (d, *J* = 252.5 Hz), 155.0, 138.7, 130.1 (d, *J* = 8.9 Hz), 129.4, 128.5 (d, *J* = 2.7 Hz), 127.2, 127.1, 125.8, 122.4, 119.1, 115.5 (d, *J* = 21.9 Hz), 79.8, 77.2, 77.0, 76.8, 36.7, 28.2, 12.4 ppm.

*5.7. 3-(2-(4-chlorophenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3g**):*[20]

Yellow oil; Yield = 71%.; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.35-7.32 (m, 2H), 7.26-7.23 (m, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 2.49-2.41 (m, 2H), 2.41-2.32 (m, 2H), 1.69 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 138.5, 138.0, 130.7, 129.4, 129.2, 128.7, 127.4, 127.1, 125.9, 122.4, 119.1, 80.0, 77.2, 77.0, 76.8, 36.7, 28.2, 12.4 ppm.

*5.8. 3-(2-(4-bromophenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3h**):*[20]

Yellow oil; Yield = 69%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.35-7.32 (m, 2H), 7.26-7.23 (m, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 2.50-2.42 (m, 2H), 2.42-2.31 (m, 2H), 1.69 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.0, 138.6, 131.6, 131.2, 129.4, 129.3, 127.4, 127.1, 126.4, 125.9, 122.4, 119.1, 79.9, 77.2, 77.0, 76.8, 36.7, 28.2, 12.4 ppm.

*5.9. 3-(2-(4-iodophenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3i**):*

Yellow oil; Yield = 68%; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.85-7.79 (m, 4H), 7.35-7.31 (m, 2H), 7.26-7.23 (m, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 2.50-2.42 (m, 2H), 2.41-2.31 (m, 2H), 1.69 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.2, 138.6, 137.6, 131.8, 129.4, 129.3, 127.4, 127.2, 125.9, 122.4, 119.1, 98.8, 79.9, 77.2, 77.0, 76.8, 36.7, 28.2, 12.4 ppm. HRMS (ESI)

m/z 425.0118 (M + Na^+), Cal. $C_{18}H_{15}IN_2NaO^+$, 425.0121.

*5.10. 3-(4-methyl-2-(4-(trifluoromethyl)phenyl)-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3j**):*

Yellow oil; Yield = 63%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 4.0 Hz, 2H), 7.28-7.26 (m, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 2.51-2.45 (m, 2H), 2.43-2.35 (m, 2H), 1.72 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.5, 138.4, 135.7, 133.2 (q, *J* = 32.5 Hz), 129.5, 128.1, 127.8, 127.2, 126.2, 125.3 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 272.6 Hz) 122.5, 119.0, 80.2, 77.3, 77.0, 76.8, 36.8, 28.3, 12.5 ppm. HRMS (ESI) m/z 367.1030 (M + Na^+), Cal. $C_{19}H_{15}F_3N_2NaO^+$, 367.1029.

*5.11. 3-(4-methyl-2-(o-tolyl)-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3l**):*

Yellow oil; Yield = 64%; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.37-7.31 (m, 3H), 7.28-7.24 (m, 3H), 7.07 (d, *J* = 7.4 Hz, 1H), 2.63 (s, 3H), 2.53-2.44 (m, 2H), 2.44-2.33 (m, 2H), 1.73 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.8, 138.7, 138.2, 132.1, 131.5, 130.6, 129.5, 129.3, 127.3, 126.6, 125.9, 125.8, 122.3, 119.1, 80.0, 77.3, 77.0, 76.8, 36.7, 28.5, 21.7, 12.5 ppm. HRMS (ESI) m/z 313.1312 (M + Na^+), Cal. $C_{19}H_{18}N_2NaO^+$, 313.1311.

*5.12. 3-(2-(3-chlorophenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3m**):*

Yellow oil; Yield = 67%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.36-7.30 (m, 2H), 7.27-7.24 (m, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 2.63 (s, 3H), 2.50-2.44 (m, 2H), 2.42-2.32 (m, 2H), 1.70 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.6, 138.5, 134.5, 134.1, 131.6, 129.6, 129.4, 127.8, 127.5, 127.1, 126.0, 125.9, 122.4, 119.1, 80.1, 77.2, 77.0, 76.8, 36.7, 28.2, 12.4 ppm. HRMS (ESI) m/z 333.0759 (M + Na^+), Cal. $C_{18}H_{15}ClN_2NaO^+$, 333.0765.

*5.13. 3-(2-(2,4-dimethylphenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3n**):*

Yellow oil; Yield = 57%; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3Hz, 1H), 7.33 (d, *J* = 4.1Hz, 2H), 7.25-7.22 (m, 1H), 7.09-7.06 (m, 3H), 2.61 (s, 3H), 2.52-2.46 (m, 2H), 2.44-2.32 (m, 6H), 1.71 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.9, 141.1, 138.8, 138.3, 132.4, 129.7, 129.3, 129.0, 127.1, 126.6, 126.6, 125.7, 122.3, 119.2, 79.9, 77.2, 77.0, 76.8, 36.6, 28.4, 21.8, 21.3, 12.5 ppm. HRMS (ESI) m/z 327.1470 (M + Na^+), Cal. $C_{20}H_{20}N_2NaO^+$, 327.1468.

*5.14. 3-(2-(3,4-dichlorophenyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3o**):*

Yellow oil; Yield = 67%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.20 (d, *J* = 2.0 Hz, 1H), 7.97 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.37-7.32 (m, 2H), 7.27-7.25 (m, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 2.49-2.43 (m, 2H), 2.42-2.33 (m, 2H), 1.70 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.8, 138.3, 135.9, 132.8, 132.3, 130.4, 129.6, 129.5, 127.7, 127.0, 126.9, 126.1, 122.4, 119.0, 80.3, 77.2, 77.0, 76.8, 36.7, 28.3, 12.4 ppm. HRMS (ESI) m/z 367.0376 ($M + Na^+$), Cal. $C_{18}H_{14}Cl_2N_2NaO^+$, 367.0375.

*5.15. 3-(4-methyl-2-(3,4,5-trimethoxyphenyl)-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3p**):*

Yellow oil; Yield = 52%; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.42 (s, 2H), 7.39-7.34 (m, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 3.97 (s, 6H), 3.92 (s, 3H), 2.53-2.45 (m, 2H), 2.43-2.34 (m, 2H), 1.71 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 153.1, 141.6, 138.9, 129.3, 127.5, 127.1, 127.0, 125.7, 122.3, 119.2, 105.4, 79.8, 77.2, 77.0, 76.8, 60.9, 56.4, 36.6, 28.1, 12.4 ppm. HRMS (ESI) m/z 389.1472 ($M + Na^+$), Cal. $C_{21}H_{22}N_2NaO_4^+$, 389.1472.

*5. 16. 3-(4-methyl-2-(thiophen-2-yl)-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3q**):*[20]

Yellow oil; Yield = 63%; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.51 (d, *J* = 4.9Hz, 1H), 7.34-7.32 (m, 2H), 7.23-7.21 (m, 1H), 7.12 (t, *J* = 4.0 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 2.53-2.42 (m, 2H), 2.42-2.34 (m, 2H), 1.70 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.7, 138.6, 136.5, 130.7, 130.1, 129.3, 127.9, 127.2, 127.0, 125.5, 122.4, 119.2, 80.1, 77.2, 77.0, 76.8, 36.6, 27.8, 12.3 ppm.

*5.17. 3-(4-methyl-2-(naphthalen-2-yl)-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3r**):*[20]

Yellow oil; Yield = 52%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.98-7.97 (m, 1H), 7.91-7.87 (m, 2H), 7.58-7.53 (m, 2H), 7.41-7.35 (m, 2H), 7.27-7.24 (m, 1H), 7.11-7.10 (m, 1H), 2.57-2.49 (m, 2H), 2.48-2.36 (m, 2H), 1.76 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0, 138.9, 135.0, 132.8, 129.5, 129.4, 129.1, 128.4, 128.1, 127.8, 127.7, 127.3, 127.2, 126.6, 125.9, 124.4, 122.4, 119.2, 79.8, 77.2, 77.0, 76.8, 36.8, 28.2, 12.5 ppm.

*5. 18. 3-(2-(tert-butyl)-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3s**):*[20]

Yellow solid ; Yield = 76%; M.p. 71.3-72.7 ^{o}C. ^{1}H NMR (600MHz, $CDCl_3$) δ 7.29-7.26 (m, 1H), 7.22-7.17 (m, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 2.45-2.36 (m, 2H), 2.35-2.25

(m, 1H), 1.55 (s, 3H), 1.27 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 138.7, 129.1, 127.1, 126.8, 125.6, 122.1, 119.3, 78.6, 77.2, 77.0, 76.8, 37.3, 36.3, 28.1, 27.4, 12.4 ppm.

*5.19. 3-(2-cyclopropyl-4-methyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3t**):*

Yellow oil; Yield = 66%; ^{1}H NMR (600MHz, $CDCl_3$) δ 7.29-7.26 (m, 1H), 7.17-7.14 (m, 2H), 6.98-6.96 (m, 1H), 2.41-2.33 (m, 2H), 2.30-2.22 (m, 2H) 1.76-1.72 (m, 1H), 1.55 (s, 3H), 1.11-1.08 (m, 1H), 1.03-0.99 (m, 1H), 0.93-0.87 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8, 138.5, 129.3, 126.5, 126.4, 124.5, 122.3, 119.2, 79.4, 77.2, 77.0, 76.8, 36.5, 28.1, 14.6, 12.3, 7.3, 6.7 ppm. HRMS (ESI) m/z 241.1337 (M + H^+), Cal. $C_{15}H_{17}N_2O^+$, 241.1335.

*5. 20. 3-(2,4-diphenyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3u**):*[20]

Yellow solid; Yield = 66%; M.p. 108.5-109.9 °C. ^{1}H NMR (600MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.5 Hz, 2H), 7.55-7.53 (m, 1H), 7.50-7.47 (m, 2H), 7.44-7.37 (m, 2H), 7.34-7.24 (m, 7H), 2.86-2.78 (m, 2H), 2.62-2.52 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.1, 141.8, 139.4, 132.0, 131.9, 129.7, 128.7, 128.5, 128.5, 127.9, 127.0, 126.0, 125.7, 125.4, 123.9, 119.2, 82.8, 77.2, 77.0, 76.8, 36.3, 12.9 ppm.

*5.21. 3-(4,7-dimethyl-2-phenyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3v**):*

Yellow oil; Yield = 75%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.13 (d, *J* =7.4 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.18 (s, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 2.51-2.41 (m, 2H), 2.41-2.33 (m, 5H), 1.68 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0, 139.3, 138.6, 132.3, 131.6, 128.3, 127.8, 127.8, 126.3, 124.2, 122.2, 119.3, 79.7, 77.2, 77.0, 76.8, 36.8, 28.2, 21.1, 12.4 ppm. HRMS (ESI) m/z 313.1310 (M + Na^+), Cal. $C_{19}H_{18}N_2NaO^+$, 313.1311.

*5.22. 3-(4,7-dimethyl-2-(p-tolyl)-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3w**):*

Yellow oil; Yield = 72%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.17 (s, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 2.48-2.39 (m, 5H), 2.39-2.32 (m, 5H), 1.67 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.2, 139.2, 138.7, 129.5, 129.1, 127.8, 127.6, 126.2, 124.2, 122.2, 119.3, 79.6, 77.2, 77.0, 76.8, 36.8, 28.2, 21.6, 21.1, 12.4 ppm. HRMS (ESI) m/z 327.1470 (M + Na^+), Cal. $C_{20}H_{20}N_2NaO^+$, 327.1468.

*5.23. 3-(2-(4-chlorophenyl)-4,7-dimethyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3x**):*

Yellow oil; Yield = 57%; ^{1}H NMR (600MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.18 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 2.48-2.41 (m,

2H), 2.40-2.31 (m, 5H), 1.68 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.2, 139.4, 138.2, 137.9, 130.7, 129.2, 128.6, 128.1, 126.3, 124.0, 122.3, 119.2, 80.1, 77.2, 77.0, 76.8, 36.7, 28.3, 21.1, 12.4 ppm. HRMS (ESI) m/z 347.0924 ($M + Na^+$), Cal. $C_{19}H_{17}ClN_2NaO^+$, 347.0922.

*5.24. 3-(6-chloro-2,4-diphenyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3y**):*

Yellow oli; Yield = 55%; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.1 Hz, 2H), 7.57-7.47 (m, 3H), 7.37-7.27 (m, 7H), 7.20 (d, *J* = 2.1 Hz, 1H), 2.85-2.71 (m, 2H), 2.62-2.51 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 140.9, 138.0, 132.1, 131.5, 129.8, 128.9, 128.7, 128.6, 127.9, 127.5, 127.3, 125.3, 123.9, 118.9, 82.4, 77.3, 77.0, 76.7, 36.1, 12.8 ppm. HRMS (ESI) m/z 373.1104 ($M + H^+$), Cal. $C_{23}H_{18}ClN_2O^+$, 373.1102.

*5.25. 3-(6-bromo-2,4-diphenyl-4H-benzo[d][1,3]oxazin-4-yl)propanenitrile (**3z**):*

Yellow oli; Yield = 52%; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.3 Hz, 2H), 7.57-7.46 (m, 4H), 7.34-7.28 (m, 6H), 7.25-7.21 (m, 1H), 2.84-2.72 (m, 2H), 2.61-2.49 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 141.0, 138.6, 132.8, 132.1, 131.6, 128.9, 128.8, 128.6, 127.9, 127.7, 126.8, 125.3, 119.8, 119.0, 82.3, 77.4, 77.1, 76.7, 36.1, 12.9 ppm. HRMS (ESI) m/z 417.0597 ($M + H^+$), Cal. $C_{23}H_{18}BrN_2O^+$, 417.0597.

*5.26. 4,4-diphenylbut-3-enenitrile (**4a**):*[21]

White solid; Yield = 67%; M.p. 97.7-98.9 °C. ^{1}H NMR (600MHz, $CDCl_3$) δ 7.44-7.37 (m, 3H), 7.30-7.29 (m, 3H), 7.23-7.22 (m, 2H), 7.18 (d, *J* = 7.0 Hz, 2H), 6.04 (t, *J* = 7.4 Hz, 1H), 3.15 (d, *J* = 7.4 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.6, 140.7, 138.0, 129.4, 128.8, 128.4, 128.2, 128.1, 127.4, 118.1, 115.5, 77.2, 77.0, 76.8, 18.4 ppm.

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Highlights

- We first reported a novel method for the synthesis of cyanomethylated benzoxazines via visible-light catalyzed radical cascade cyclization.
- This redox-neutral photocatalytic reaction completes the synthesis of C-C and C-O bonds in one pot without using any oxidizing agent.
- The reaction has the notable features of mild reaction conditions, simple operation, good functional group compatibility and wide range of substrate scope.

Conflicts of interest

There are no conflicts to declare.