Visible Light-Induced γ-Alkoxynitrile Synthesis *via* Three-Component Alkoxycyanomethylation of Alkenes

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Abstract: A three-component alkoxycyanomethylation of alkenes is achieved using the iridium photoredox catalyst [fac-Ir(ppy)₃]. This catalytic radical difunctionalization accomplishes both alkylation and alkoxylation of alkenes in one pot. Various alcohols can serve as the alkoxy sources in this transformation. In addition, the introduced cyano group can undergo further transformations into various useful functional groups.

Keywords: alkyl halides; photocatalysis; radical difunctionalization; radical reaction; visible light

Free radical generation from alkyl halides (mostly alkyl bromides and iodides) is a useful method to access reactive intermediates, which have widespread usage in various domains of organic synthesis.^[1] These carbon-centered radicals are typically prepared via halide abstraction with organotin hydrides (X₃SnH, usually present in stoichiometric quantities), which have dominated free radical chemistry and are extensively used in radical ring closures, ring expansions and cascade reactions.^[2] However, stannane reagents are notorious for their toxicity, hazardous handling and disposal of toxic garbage. Thus, many non-stannane based protocols have been developed,^[3] among which transition metal-mediated free radical generation through reductive scission of the carbon-halogen bond represents an attractive approach.^[4] Despite the fact that some processes have been successfully achieved using transition metals, this single-electron transfer (SET) process always requires high temperature or other harsh condition which limits further application of this methodology. Thus, the development of mild conditions to generate free radicals from alkyl halides is highly desirable.

Recently, visible light photoredox catalysis has received widespread attention due to its low cost, easy availability and environmental benignness.^[5] Over the vears, various useful chemical transformations via visible light photoredox catalysis have been demonstrated.^[6] The ruthenium(II) polypyridine complexes and cyclometalated iridium(III) derivatives have been successfully utilized to generate alkyl radicals from activated alkyl halides irradiated with visible light.^[7] Under visible light, the ATRA reactions or Hecktype alkenylations which are usually proceeding with transition metals, can be achieved with photoredox catalysis under mild conditions.^[8] According to the proposed mechanism, a carbocation is one possible intermediate. If a nucleophile is introduced, the key intermediate carbocation could be trapped by a suitable nucleophile and yield the three-component product of alkene difunctionalization.^[9] Using this photo-induced C-Br activation strategy, we successfully achieved a visible light-induced γ -alkoxynitrile synthesis via the three-component alkoxycyanomethylation of alkenes (Scheme 1).

We started our evaluation of the reaction parameters with 4-*tert*-butylstyrene (1a) and bromoacetonitrile (2a) as the model substrates. The anticipated difunctionlization product 4a could be achieved in 90% yield in the presence of 0.5 mol% [*fac*-Ir(ppy)₃], 2.0 equivalents NaHCO₃ using methanol (3a) as both the nuclephile and solvent under a 25 W household fluorescent lamp. In the control experiments, no desired product was observed without either photoredox catalyst or light indicating that the photoredox catalysis is essential to this process (Table 1, entries 2 and 3). Considering that other nucleophiles, such as isopropyl alcohol, may not be a good solvent for this



Scheme 1. C–Br bond activation by photoredox catalysis under visible light and successive three-component reactions.

Table 1. Optimization of the reaction conditions for the visible light-induced synthesis of γ -alkoxynitriles.





- [a] Reaction conditions: 0.50 mmol olefin, 1.0 mmol bromoacetonitrile, 2.0 mL solvent (solvent was used as nucleophile), 0.0025 mmol [fac-Ir(III)ppy)₃], 1.0 mmol base.
- ^[b] Without catalyst.
- ^[c] Without light.
- ^[d] Solvent:nucleophile = 1.8 mL:0.2 mL.
- ^[e] CH₂Cl₂:*i*-PrOH (1.0 mL:1.0 mL).
- ^[f] GC yield with biphenyl as the inner reference.
- ^[g] Isolated yield.

photoredox reaction, further optimization of various co-solvents was carried out (Table 1, entries 4–9). To our delight, the same result was obtained when using DCM as the co-solvent (Table 1, entries 1 and 6). However, replacing MeOH with isopropyl alcohol led to a relative lower yield (Table 1, entry 10). Fortunately, changing the base to K_3PO_4 and modifying the ratio of nucleophile and co-solvent solved the prob-

Table 2. The scope of the olefin in the synthesis of $\gamma\text{-alkoxy-nitriles.}^{[a]}$



^[a] Standard reaction conditions: 0.50 mmol olefin, 1.0 mmol bromoacetonitrile, 0.0025 mmol [*fac*-Ir(III)ppy)₃], 1.0 mmol NaHCO₃, 2.0 mL MeOH, *hv* (incandescent), 24 h. Isolated yield.

^[b] 1.5 mol% [*fac*-Ir(III)(ppy)₃], 48 h.

^[c] The reaction time was 48 h.

 $^{[d]}\,$ 1.0 mol % catalyst, blue LED, 12 h.

lem, giving the desired difunctionalization product in moderate yield (Table 1, entry 12).

Then, we investigated different olefins under the established conditions and the results are summarized in Table 2. This reaction was successfully amenable to a wide range of substituted styrenes, and moderate to excellent yields were achieved with substrates bearing functional groups such as t-Bu (4a), Me (4b), F (4c), Cl (4d), Br (4e), OMe (4f). In addition, styrene (1g) and 2-methylstrene (1h) also worked well to give the products in 87% (4g) and 80% (4h) yield, respectively. However, styrenes substituted with electron-withdrawing groups (CF₃ or CN) did not furnish any desired product. The 1,1-disubstituted olefins (4i, 4j) were also suitable for this reaction and the corresponding products were achieved. Surprisingly, 3,4-dihydro-2H-pyran underwent the transformation to achieve a 52% yield (4k, about 1:1 dr). However, trans-stilbene and allylbenzene did not afford the desired product under the standard conditions.



Table 3. The scope of the alcohols in the synthesis of γ -alk-

Entry	Product 4	R	Alcohol	Yield ^[d] [%]
1 ^[b]	4 a	Me	3a	90
2 ^[b]	41	Et	3b	89
3	4m	<i>n</i> -Pr	3c	63
4	4n	<i>n</i> -Bu	3d	71
5	40	yyyy	33	69
6	4p	<i>i</i> -Pr	3f	69
7 ^[c]	4 q	-24	3g	40
8 ^[c]	4 r	22	3h	54



Scheme 2. The visible light-induced γ -nitrile synthesis using aniline as the nucleophile.



 ^[a] Standard reaction conditions: 0.50 mmol olefin, 1.0 mmol bromoacetonitrile, 0.0025 mmol Ir(ppy)₃, 1.0 mL CH₂Cl₂, 1.0 mL ROH, 1.0 mmol K₃PO₄, 24 h.

^[b] Without co-solvent and the base was NaHCO₃.

^[c] 1.0 mol% catalyst, 48 h.

^[d] Isolated yield.

We next applied the optimized reaction conditions to examine different alcohols (Table 3). Reactions of 1a with primary alcohols such as MeOH, EtOH, n-PrOH and *n*-BuOH gave the expected products in good to excellent yields (4a, 4l-4o). The secondary alcohol was also suitable for this reaction (4p). In addition, the sterically hindered tertiary alcohols resulted in slightly lower yields (4q, 4r). Although tertiary alcohols led to relatively lower yields, the present photocatalytic alkoxycyanomethylation is highly efficient and regioselective, regardless of the oxygen nucleophiles. The reactions can smoothly introduce a cyanomethyl group into an alkene and construct ether functionalities. To further expand the application of this methodology, different nucleophilic partners were also tried. For the thiols (para-toluenethiol, n-butyl mercaptan, tert-butyl mercaptan), they all underwent hydrothiolation of alkenes, which had been previously reported by Yoon and co-workers.^[10] When the nucleophile was an alkylamine such as benzylamine or butylamine, the alkene did not react at all because of the nucleophilic substitution reactions between amine and bromoacetonitrile. Fortunately, aniline could afford the three-component reaction product in 22% yield (Scheme 2). When using a carboxylate (like ammonium formate, sodium acetate) as nucleophile, the Heck-type products were mainly obtained.

Scheme 3. The visible light-induced γ -alkoxynitrile synthesis using 2-bromopropanenitrile.

In addition, 2-bromopropanenitrile (containing β hydrogens) also reacted very well (Scheme 3) giving the desired product in 88% yield (**4t**, *dr*=1:1.3) under the standard conditions. However, 2-bromo-2-methylpropanenitrile and 2-bromo-2-phenylacetonitrile gave only traces of product mainly because of the debromination of the bromo nitriles. To obtain some insights into the mechanism, luminescent quenching experiments were carried out. As shown in Figure 1, the fluorescence quenching process between Ir(ppy)₃* and BrCH₂CN was obviously observed. Therefore, the above luminescent quenching experiments confirmed that the single electron transfer (SET) process between Ir(ppy)₃* and BrCH₂CN could go through an



Figure 1. Luminescent quenching experiments.

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Figure 2. Time profile of the photocatalytic reaction with and without visible light.

oxidative quenching process. The time profile of photocatalytic reaction shown in Figure 2 indicated that continuous irradiation of visible light is essential to achieve this photocatalytic transformation.

Based on the previous reports^[8c,9b] and experimental results, a plausible reaction mechanism was proposed in Scheme 4. Firstly, the photocatalyst $[fac-Ir(III)(ppy)_3]$ is excited by visible light irradiation (425 nm)generate the excited species to $[fac-Ir(III)(ppy)_3]^*$, which then undergoes single electron transfer (SET) process to bromoacetonitrile generating cyanomethyl radical 5, a bromide anion and $[fac-Ir(IV)(ppy)_3]$. The generated cyanomethyl radical 5 reacts with alkene 1 to afford the C-C coupling adduct 6, which is oxidized by the $[fac-Ir(IV)(ppy)_3]$ (path a) or bromoacetonitrile (path b) to form the carbocation intermediate 7 through the single electron transfer (SET) process. Subsequent nucleophilic attack of alcohol on the carbocation intermediate and final deprotonation in the presence of base generated



Scheme 4. A plausible mechanism for the synthesis of γ -alk-oxynitriles

the three-component coupling product **4**. The atom transfer radical addition (ATRA) followed by nucleophilic attack by the alcohol with the assistance of base could be another possible reaction pathway. Although we cannot completely exclude this possibility, ATRAtype product is not observed during this process. Additionally, there was no ATRA-type product as well and mainly Heck-type product was formed under the standard conditions without the alcohol. As a result, the ATRA reaction pathway is not favored.

In conclusion, we have developed a three-component alkoxycyanomethylation of alkenes using the photoredox catalyst [fac-Ir(ppy)₃]. This highly regioselective reaction can proceed smoothly under mild conditions (room temperature under sunlight or a household lamp). Both cyanomethylation and alkoxylation of alkenes are achieved in one pot with this catalytic radical difunctionalization. Various alcohols can serve as the alkoxy sources. In addition, the introduced cyano group can undergo further transformations into various useful functional groups.

Experimental Section

General Procedure

A dried Schlenk tube equipped with a stir bar was loaded with sodium bicarbonate (84 mg, 1.0 mmol, 2.0 equivalents) and *fac*-Ir(ppy)₃ (1.6 mg, 0.0025 mmol, 0.5 mol%). The tube was evacuated and refilled with nitrogen before alkene (0.5 mmol), bromoacetonitrile (120 mg, 1.0 mmol, 2.0 equivalents) were added through a syringe. Then 2.0 mL solvent were added into the reaction tube *via* a syringe. The reaction mixture was degassed by the freeze-pump-thaw method and then irradiated with a 24 W fluorescent household light bulb (distance app. 10 cm) for 24 h. After the completion of the reaction, the pure product was obtained by flash column chromatography on silica gel.

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