



Visible-light-induced cyanation of aza-Baylis–Hillman adducts: a Michael type addition



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ABSTRACT

Visible-light-induced aerobic oxidative cyanation of aza-Baylis–Hillman (aza-BH) adducts providing valuable allylic cyanides in good to excellent yields has been developed. The protocol involves in situ formation of 4π conjugated iminium ion intermediates, which undergo cyanation at the γ -position to afford Michael type adducts. This is the first example of visible-light-induced catalytic functionalization of aza-BH adducts using air (O_2) as an economical and ecosustainable oxidant and TMSCN as a convenient and readily available cyanide source.

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Recently, visible-light-induced catalytic oxidation of sp^3 C–H bonds adjacent to nitrogen providing reactive iminium ions has become a powerful toolkit for amine functionalization.¹ Amines often act as single electron donors in visible-light-induced photoredox processes and are oxidized to nitrogen radical cations to execute iminium ion formation under aerobic conditions. This has led to the development of several useful synthetic transformations of relevance to material and pharmaceutical sciences.²

However, the benzylic amine substrates acting as an electron donor are very limited and mostly realized on *N*-aryltetrahydroisoquinoline derivatives.¹ Thus, investigations on novel benzylic amine precursors for their exploitation in photosensitized SET (single electron transfer) processes are highly desirable. Baylis–Hillman adducts are useful substrates for diverse and highly functionalized molecules which are required for the synthesis of various interesting natural and unnatural products of medicinal importance.³ Our continued efforts for implementation of new substrates in visible-light-photoredox reactions⁴ and functionalization of BH adducts,⁵ prompted us to choose aza-BH adducts for the present study as depicted in Scheme 1.

The development of new methods in synthetic organic chemistry using photoredox catalysis has attracted significant interest, as visible light is a ubiquitous, sustainable and clean source of energy.^{1,2,6} The pioneering work from the groups of MacMillan,^{7d}

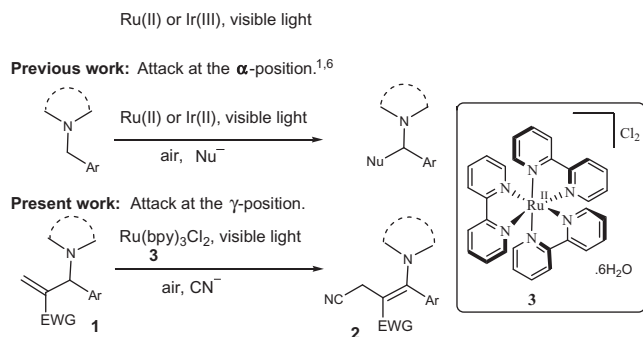
Yoon,^{7e} and Stephenson^{1h,7a–c} has demonstrated that ruthenium and iridium based polypyridyl complexes play a pivotal role in SET processes, as they possess well known photocatalytic properties and can readily be tuned by the choice of right ligands.⁷ The photocatalytic aerobic oxidation of amino benzylic C–H bonds to generate reactive iminium ion intermediates has been frequently reported in the recent years.^{1,6} Among different diverging approaches from this structural motif, the cyanation of sp^3 C–H bonds adjacent to a nitrogen atom represents one of the most straightforward and convenient methods for the synthesis of α -amino nitriles.^{1d,g} Besides this, such highly reactive iminium ions have been subsequently trapped with diverse nucleophiles such as enol silane,^{6a} TMSCF₃,^{6b} phosphonates,^{6c} indole,^{6d} terminal alkynes,^{6c,d} etc.⁶

The use of atmospheric oxygen as an oxidant in organic synthesis remains very limited although it is readily available, economical and ecosustainable oxidant.⁸ The field of visible-light-photoredox catalysis has opened up a new route to utilize atmospheric oxygen, where it is mostly employed as an oxidant to regenerate Ru^{+2} from Ru^{+1} to complete the catalytic cycle and the superoxide radical ($O_2^{\cdot-}$) thus formed plays a key role in the synthetic process.^{1,6}

In view of the above valid facts and widening the substrate scope for the visible-light-photoredox reactions, amino benzylic carbon in conjugation with a double bond was considered as a novel system for the present study. In the current photoredox catalytic process a 4π conjugated iminium ion is generated and

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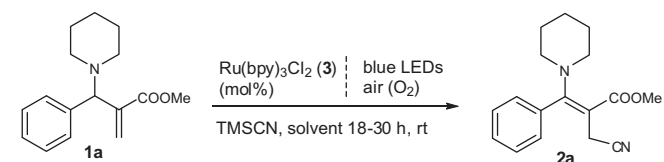


Scheme 1. Visible-light-induced functionalization of benzylic amines.

subsequently attacked by the cyanide ion at the γ -position to afford an allylic cyanide, whereas in the previous cases the attack takes place at the α -position (Scheme 1).^{1,6} The known methods available for the cyanation of amines involve the use of hypervalent-iodine⁹/I₂,¹⁰ tropylium ion¹¹ and copper¹² catalysis and electrolysis,¹³ which are of limited scope and selectivity.

In order to verify the practicability of the envisaged protocol for the target molecule, a model reaction was carried out with aza-Baylis–Hillman adduct **1a**, in CH₃CN containing 1 mol % of Ru(bpy)₃Cl₂ (**3**) as a photocatalyst and TMSCN (1.5 equiv) as a cyanide source. The reaction mixture was open to an air atmosphere (but no air bubbling) and irradiated with visible light (blue light emitting diodes (blue LEDs),¹⁴ $\lambda_{\text{max}} = 447.5$ nm) at rt. It was highly satisfying that the reaction delivered the desired allylic cyanide **2a** in 85% isolated yield after 18 h (Table 1, entry 1). Following this experiment, a series of control experiments were performed, which demonstrated that either there was no product formation or it was formed in traces in the absence of any one of the reagents/catalyst (Table 1, entries 2–4). Only a trace of product was detected under an N₂ atmosphere (Table 1, entry 5). Moreover, the use of another catalyst Ir(bpy)₃PF₆ (1 mol %) or eosin Y

Table 2
Optimization of reaction conditions^a



Entry	3 (mol %)	Solvent	Time (h)	Yield ^b (%)
1	1	CH ₃ CN	18	85
2	1	DMF	18	80
3	1	DMSO	18	65
4	1	THF	18	43
5	1	EtOH	18	47
6	1	DCE	18	55
7	2	CH ₃ CN	18	85
8	0.5	CH ₃ CN	30	67

^a Reaction conditions: **1** (1 mmol), **3** (0.5–2 mol %), solvent (3 mL), TMSCN (1.5 equiv), open to air (without bubbling air, irradiation through the flask's bottom side using Luxeon Rebel high power blue LEDs).

^b Isolated yield of pure product **2a**.

(2 mol %) was not as effective as Ru(bpy)₃Cl₂ (1 mol %) (Table 1, entry 1 vs 6 and 7). Irradiation with a household light (18 W CFL) produced considerably lower yield in a longer time as compared to blue LEDs irradiation (Table 1, entry 1 vs 8). The presence of O₂ (air) was found to be essential, because only a trace of product formation was detected under the degassed condition or in an N₂ atmosphere (Table 1, entry 1 vs 4 and 5). Moreover, the reaction was quenched with TEMPO (1 mol %) (Table 1, entry 9) showing that it follows a radical reaction pathway.

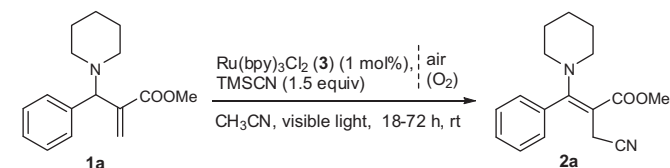
Then, the reaction was optimized for an effective solvent system and catalyst loading (Table 2). CH₃CN was found to be the best among the tested solvents DMF, DMSO, DCE, EtOH, and THF, hence it was used throughout the present study (Table 2, entry 1 vs 2–6). The optimum catalyst loading delivering the highest yield in minimum reaction time was 1 mol %, because lowering the amount of the catalyst to 0.5 mol % decreases the yield significantly and takes a longer reaction time (Table 2, entry 1 vs 8), while there was no effect on the yield and reaction time on increasing the catalytic loading from 1 to 2 mol % (Table 2, entry 7).

To investigate the scope of the substrate, we tried various types of aza-BH adducts **1**, which successfully underwent the reaction to produce the corresponding allylic nitriles in good to excellent yields (Table 3). Many functionalities like MeO, NO₂, Cl, Br, CN, and COOMe are well tolerated in the present reaction conditions. The aza-BH adducts **1** bearing an electron-withdrawing group on the aromatic ring undergo slower reaction and give slightly lower yields as compared to those containing an electron-donating group (Table 3, entries 2 and 3 vs 4–6). The requisite aza-BH adducts **1** were prepared by the method reported in the literature.^{12b,16}

Based on the above observations and the literature precedents,^{1,7,10,12} a plausible mechanistic pathway is depicted in Scheme 2. The benzylic tertiary amine **1** undergoes SET to generate the radical cation **A** and Ru(I) with activated Ru(II)* in the presence of blue LEDs. Ru(I) is oxidized to Ru(II) with atmospheric oxygen, which is reduced to superoxide radical anion (O₂^{•−}) to complete the photoredox cycle. The radical cation **A** is converted into iminium ion **B** by H-abstraction from the benzylic position by the superoxide radical anion (O₂^{•−}). The conjugated iminium ion thus generated in situ undergoes nucleophilic addition with the cyanide ion to afford the desired allylic cyanides **2**.

In conclusion, we have disclosed aza-BH adducts as a novel substrate for visible-light-mediated functionalization at the γ -position with respect to the amino group. The protocol involves an aerobic oxidative photocatalytic γ -cyanation of aza-BH adducts to provide

Table 1
Screening and control experiments^a



Entry	Visible light	Photocatalyst	Air	Time (h)	Yield ^b (%)
1	+	+	+	18	85
2	—	+	+	24	n.r. ^c
3	+	—	+	24	n.r.
4	+	+	—	24	Trace ^d
5	+	+	N ₂	24	Trace
6	+	+	+	18	72 ^e
7	+	+	+	18	57 ^f
8	+	+	+	24	55 ^g
9	+	+	+	72	Trace ^h

^a Reaction conditions: **1** (1 mmol), **3** (1 mol %), CH₃CN (3 mL), TMSCN (1.5 equiv), open to air (without bubbling air), irradiation through the flask's bottom side using Luxeon Rebel high power blue LEDs.

^b Isolated yield of pure product **2a**.

^c Reaction was carried out in dark; n.r. = no reaction.

^d Reaction was performed under degassed condition.

^e Ir(bpy)₃PF₆ · 6H₂O (1 mol %) was used as the catalyst.

^f Eosin Y (2 mol %) was used as the catalyst.

^g Reaction was performed using 18 W CFL (compact fluorescent lamp, Philips).

^h Reaction was quenched with TEMPO (1 mol %).

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