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Visible-light photoredox catalyzed oxidative Strecker reaction[†]

Magnus Rueping,* Shaoqun Zhu and René M. Koenigs

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An aerobic photocatalytic oxidative cyanation of tertiary amines providing valuable α -aminonitriles in good to excellent yields was developed. Mild reaction conditions and low catalyst loading are attractive features of the protocol.

 α -Aminonitriles are an important class of versatile intermediates for a wide range of natural products and pharmaceuticals since the nitrile function can be readily hydrolyzed to produce α -amino acids.¹ Nucleophilic additions to α -aminonitriles provide access to valuable α -amino aldehydes, ketones and β-amino alcohols. Alternatively, nitriles can be easily hydrogenated to yield useful 1,2-diamines. Therefore, it is not surprising that great efforts have been devoted to the development of new methods for the construction of α -aminonitriles. Among the different approaches available for the preparation of these structural motives, the catalytic oxidative cyanation of sp³ C–H bonds adjacent to nitrogen atoms represents one of the most straightforward and convenient methods for the synthesis of α -aminonitriles.²⁻⁵ Previous efforts showed that treatment of tertiary amines with different metal catalysts in the presence of stoichiometric amounts of oxidants allows the generation of highly reactive iminium ion intermediates that can be intercepted with HCN to yield the corresponding α-cvanation products.^{2,3} In a similar manner, non-catalytic metal-free methods using stoichiometric amounts of tropylium ions^{4a} or hypervalent iodine^{4b} or electrochemical methods⁵ can be applied for the oxidative cyanation reaction.

The use of visible light in synthetic organic chemistry has recently attracted significant interest as visible light is a ubiquitous, renewable and clean source of energy.^{6–9} Among the different photosensitizers that have been applied in the development of new synthetic methods under irradiation with visible light, inorganic ruthenium and iridium based polypyridyl complexes play a pivotal role, as they possess well-known photochemical properties and can readily be tuned by the choice of the right ligands.⁶ Based on the work on photochemical oxidation of tertiary amines,^{8,9} we decided to investigate an aerobic photochemical oxidative cyanation reaction that would allow an operationally simple access to

valuable $\alpha\text{-aminonitriles}$ using readily available KCN as cheap CN^- source.

We initiated our studies on the cyanation reaction by examining the photochemical oxidation of *N*-phenyl tetrahydroisoquinoline **1a** in the presence of KCN and acetic acid. To our delight, we could isolate the desired α -aminonitrile in very high yield (90%) using only 1 mol% of the [Ir(ppy)₂bpy]PF₆ (ppy = 2-phenyl-pyridine, bpy = 2,2'-bipyridine) photocatalyst (Table 1, entry 1). Acetic acid proved to be crucial in this transformation. This can be attributed to the liberation of HCN in the presence of AcOH, as otherwise only little CN⁻ is present in solution. Thus, AcOH acts as a co-catalyst in this process.¹⁰

To validate this hypothesis, the reaction was carried out without acid, yet only trace amounts of the desired reaction product were observed (Table 1, entry 2). TMSCN and $CH_2(CN)_2$ were also reported as efficient sources of CN^- in metal catalyzed oxidative cyanation reaction.¹² To our great delight, the corresponding cyanation product was also obtained with good yield using TMSCN or $CH_2(CN)_2$ (Table 1, entries 3 and 4, 83% and 65% respectively), which can be attributed to the liberation of HCN from TMSCN or $CH_2(CN)_2$ in the presence of water.

As solvent has a great influence on aerobic photochemical cross dehydrogenative coupling reactions, different solvents were investigated (Table 1, entries 1, 5–9). Whereas, apolar

Table 1 Influence of CN⁻ source and solvent

Ia		[Ir(ppy) ₂ bpy]PF ₆ (3a) CN [−] source, additive 5 W fluorescent bulb solvent		Za CN	
Entry ^a	CN ⁻ source	Additive	Solvent	Time ^b /h	Yield ^c (%)
1	KCN	AcOH	MeCN	20	94
2	KCN		MeCN	32	Trace
3	TMSCN		MeCN	18	83
4	$CH_2(CN)_2$		MeCN	36	65
5	KCN	AcOH	THF	16	90
6	KCN	AcOH	MeOH	28	86
7	KCN	AcOH	DMF	16	90
8	KCN	AcOH	Toluene	32	72
9	KCN	AcOH	AcOH	24	68

^{*a*} Reaction conditions: 0.1 mmol **1a**, 1 mol% **3a**, 1 mL solvent, CN^- source (1.2 equiv.) and additive (5.0 equiv. or none), 5 W fluorescent bulb. ^{*b*} Refers to the time until all starting material is consumed. ^{*c*} Yield of the isolated product.

RWTH Aachen University, Institute of Organic Chemistry, Landoltweg 1, D-52074 Aachen, Germany.

E-mail: magnus.rueping@rwth-aachen.de; Fax: + 49 241 8092665 † Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc15643h

 Table 2
 Scope of the photoredox catalyzed oxidative cyanation reaction

1a-1	N _R ¹ [Ir(tbp-py) KCN, A 5 W fluo	₂ (bpy)]PF ₆ cOH, MeC rescent bu	(3b) N Ib 2	b) → N _R ¹ 2a-I CN		
Entry ^a	\mathbf{R}^1	2	Time ^b /h	Yield ^c (%)		
1	Phenyl	2a	20	97		
2	4-Me-phenyl	2b	12	97		
3	4-Et-phenyl	2c	12	77		
4	4-MeO-phenyl	2d	12	84		
5	4-F-phenyl	2e	32	76		
6	4-Br-phenyl	2f	48	82		
7	4-Biphenyl	2g	48	79		
8	3-MeO-phenyl	2h	36	86		
9	2-Me-phenyl	2i	72	76		
10	2,4-Me ₂ -phenyl	2j	72	81		
11	2-Naphthyl	2k	48	88		
12	Allyl	21	12	51		

^{*a*} Reaction conditions: 0.1 mmol **1a–l**, 1 mol% photocatalyst **3b**, 1 mL MeCN, 1.2 equiv. of KCN, 5.0 equiv. of AcOH, 5 W fluorescent bulb. ^{*b*} Refers to the time until all starting material is consumed. ^{*c*} Yield of the isolated product.

and protic solvents gave poor results and required prolonged reaction time (Table 1, entries 6, 8 and 9), polar and aprotic solvents (THF, DMF and MeCN; Table 1, entries 1, 5 and 7) gave excellent yields, of which MeCN proved to be the best (94%).

To further improve this oxidative cyanation reaction, we tested a series of Ir(III) and Ru(II) photoredox catalysts. In general, all iridium and ruthenium based photocatalysts gave the desired α -aminonitrile in good to excellent yields.¹¹ In view of both best reaction yield and shortest reaction time, catalyst **3b** ([Ir(tbp-py)₂(bpy)]PF₆; tbp-py = 2-(4-*t*Bu-phenyl)-pyridine) was selected to further investigate the substrate scope of this oxidative cyanation reaction. Initially, a variety of different *N*-aryl tetrahydroisoquinolines were subjected to the optimal reaction conditions (Table 2).

In general, the corresponding cyanation products **2a–I** were obtained in good to excellent yields. Substrates bearing electronwithdrawing substituents and *meta-* and *ortho-*substituted *N-*aryl groups could be subjected to this oxidative cyanation reaction only under prolonged reaction times. To our delight, the *N-*allyl substituted tetrahydroisoquinoline could also be efficiently applied under the present reaction conditions.

To further investigate the substrate scope, we decided to subject different acyclic tertiary amines **4a–e** to the photoredoxcatalyzed oxidative cyanation reaction. The oxidation of aniline derivatives using metal based photoredox catalysts is scarce and only few examples have been realized to date. However, under the present reaction conditions different dialkyl anilines could be efficiently subjected to the photochemical oxidation reaction, yielding the valuable α -aminonitriles **5a–e** in high yields (Table 3).

We could show that the photochemical oxidation is not only applicable to cyclic benzylic amines, but also linear aliphatic tertiary amines can be readily oxidized to the reactive iminium ion. In the presence of both a benzyl- and an ethyl-group, we could observe the selective oxidation of the benzyl group and the corresponding amino nitrile **5e** was obtained in 84% yield.
 Table 3
 Evaluation of different N,N-dialkylaniline derivatives in the oxidative cyanation

$Ar \qquad R^1 \qquad R^1 \qquad R^2 \qquad 4a-e$		[Ir(tbp-py) ₂ (bpy)]PF ₆ (3b) KCN, AcOH, MeCN 5 W fluorescent bulb		Ar F	$Ar \qquad R^{1} \qquad CN \qquad R^{2} \qquad 5a-e$	
Entry ^a	5	Ar	\mathbf{R}^1	R ²	Yield (%)	
1	5a	Phenyl	Н	Н	82	
2	5b	3-Me-phenyl	Н	Н	70	
3^b	5c	Phenyl	Me	Me	74	
4^b	5d	Phenyl	Pr	Pr	78	
5^b	5e	Phenyl	Ph	Me	84	

^a Reaction conditions: 0.1 mmol 4a–e, 1 mol% 3b, 1 mL MeCN,
 1.2 equiv. of KCN, 5 equiv. of AcOH, 5 W fluorescent bulb, 12–96 h.
 ^b Reaction performed under an oxygen atmosphere; yield determined by ¹H NMR.

From a mechanistic point of view, the formation of the amine cation radical intermediate, the iminium ion intermediate and the reoxidation of the photoredox catalyst by molecular oxygen are well-known.⁹ Yet, in the recent literature on the photoredox catalyzed oxidative functionalization of tertiary amines, the mechanism of the formation of the iminium ion intermediate **C** (Scheme 1) was often assumed to take place by hydrogen atom (H[•]) abstraction from the amine cation radical **A** by the superoxide anion $(O_2^{\bullet-})$ that is formed upon reoxidation of the photoredox catalyst.

In contrast to the recent literature we now suggest that the iminium ion is generated on a different, ionic pathway. From a mechanistic perspective, two different pathways which differ in the order of deprotonation and single electron transfer are possible (Scheme 1). On the one hand, the amine radical **A** can undergo a [1,2]-hydrogen shift, furnishing the carbon centred radical **B**, which can now be easily deprotonated by a base (tertiary amine or superoxide anion radical $O_2^{\bullet-}$), yielding the desired iminium ion **C** after electron transfer to Ir(III), Ir(III)* or HOO[•]. On the other hand, the deprotonation may initially take place, providing carbon centred neutral radical **D**, which can then undergo electron transfer to give the iminium ion **C**.

Conclusively, both discussed pathways provide a mechanistic rationale for the generation of the desired iminium ion intermediate, while the hydrogen atom (H^{\bullet}) abstraction by the superoxide anion is probably not taking place.

In summary, we have developed the first efficient aerobic, photocatalytic oxidative cyanation of tertiary amines employing cheap and readily available KCN as CN^- source that yields valuable α -aminonitriles under mild reaction conditions and



Scheme 1 Mechanism of iminium ion formation.

with low catalyst loadings.¹² In addition, we could present that photoredox catalyzed oxidation reactions can be applied for the functionalization of acyclic aniline derivatives. Furthermore, an alternative pathway for the generation of the iminium ion intermediate was proposed. The generation of the carbon centred neutral radical intermediate suggested thereby can be further explored to design radical-type processes.

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