

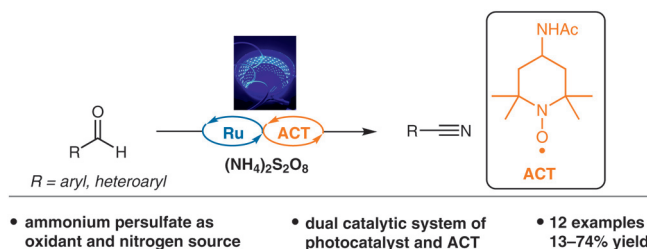
Combining Oxoammonium Cation Mediated Oxidation and Photoredox Catalysis for the Conversion of Aldehydes into Nitriles

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Abstract A method to oxidize aromatic aldehydes to nitriles has been developed. It involves a dual catalytic system of 4-acetamido-TEMPO and visible-light photoredox catalysis. The reaction is performed using ammonium persulfate as both the terminal oxidant and nitrogen source.

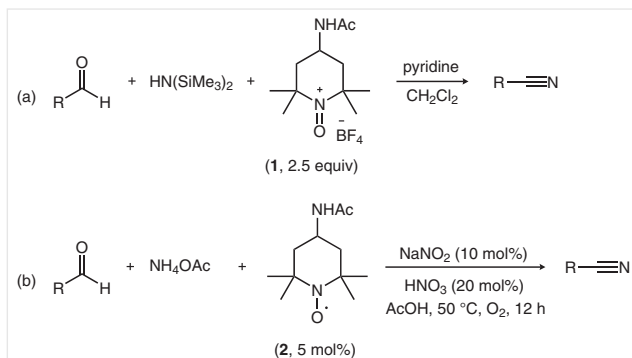
Key words photooxidation, nitriles, ammonium persulfate, oxoammonium cations, visible light

Nitriles are important compounds in their own right, the motif being found in many agrochemicals and pharmaceuticals.¹ The nitrile group is also a versatile intermediate in organic chemistry, readily being transformed into numerous other functional groups, such as amides, carboxylic acids, esters, or amines.² Conventional methods to synthesize nitriles include the Sandmeyer reaction involving diazonium salt, or transition-metal-catalyzed coupling reactions of aryl halides with a cyanide source.^{3,4} However, the toxicity of most metal-based cyanide salts such as potassium cyanide or copper cyanide poses operational challenges. These issues can be allayed by the use of nonmetallic cyanide sources⁵ or potassium hexacyanoferrate.⁶

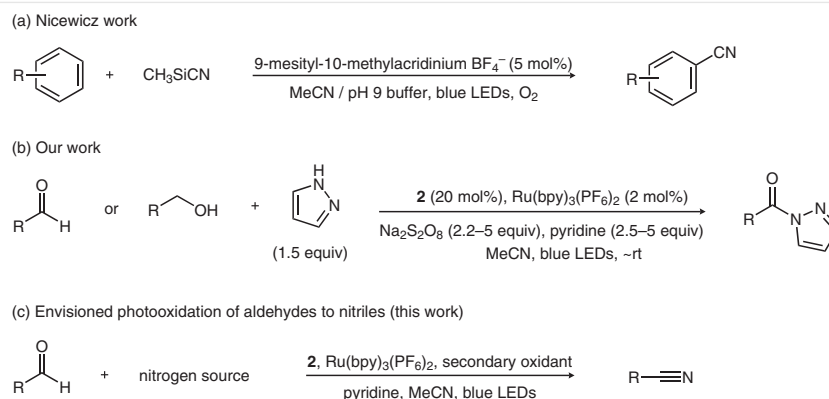
An alternative approach to the preparation of nitriles is based on oxidation chemistry. This can involve direct synthesis from nitrogen-containing compounds by means of either metal-catalyzed or metal-free oxidation reactions of primary amines⁷ or the oxidation of alcohols or aldehydes by a catalytic or stoichiometric amount of oxidant in the presence of an ammonia source.⁸

Oxoammonium cations such as **1** have proven to be valuable metal-free oxidants for performing various oxidative transformations.^{9,10} They are bench stable, recyclable,

and can be synthesized conveniently in large scale.^{10a} Our group has reported a facile, metal-free oxidation of aldehydes to nitriles by employing a super-stoichiometric amount of **1** with hexamethyldisilazane (HMDS) as the nitrogen source and pyridine as base (Scheme 1, a).¹¹ Of the known catalytic oxidants, 2,2,6,6-tetramethylpiperidine 1-oxyl (commonly known as TEMPO) is among the most widely employed, particularly on industrial scales.¹² TEMPO and its derivatives (notably 4-acetamido-TEMPO (**2**) also known as ACT) facilitate an array of oxidative transformations, but are best known for the oxidation of alcohols to carboxylic acids, aldehydes, or ketones. In such reactions, the nitroxyl species are not themselves oxidants but rather pro-oxidants. A secondary oxidant enables the active oxidizing species, an oxoammonium cation, to be generated in situ *via* a single-electron transfer (SET) oxidation. A catalytic approach to nitrile synthesis has been designed that comprises aerobic oxidation of aldehydes with a **2**/NO_x system and ammonium acetate (NH₄OAc) as the nitrogen source (Scheme 1, b).¹³



Scheme 1 Synthesis of nitriles from aldehydes by 4-acetamido-TEMPO (**2**) and its derivative **1**



Scheme 2 Photoredox catalysis

Photoredox catalysis has attracted much attention in the chemical community.¹⁴ It is possible to perform traditional as well as nontraditional bond-formation reactions by utilizing visible-light energy. Processes involve SET from a photoexcited catalyst to an organic or organometallic substrate. This can reduce/oxidize organic substrates or activate secondary catalysts that are usually nonfunctional in absence of light. This approach opens up a completely new avenue of catalysis. To this end, our group has devised a strategy to perform photooxidation¹⁵ and photoamidation¹⁶ reactions in a catalytic manner by using **2** in conjunction with photoredox catalysis and a terminal oxidant (Scheme 2, b). Upon absorption of light, the excited state of the photocatalyst, Ru(bpy)₃(PF₆)₂, converts **2** into the active oxidant **1** by SET. Oxidation of the organic substrate then takes place by hydride abstraction, and **2** is subsequently regenerated by means of an inexpensive, terminal oxidant, sodium persulfate.

Visible-light-mediated generation of nitriles has recently been explored by Nicewicz by means of the C–H activation of arenes using an acridinium photoredox catalyst, albeit with toxic trimethyl cyanide as the source of cyanide.¹⁷ The reaction is performed under basic conditions to avoid formation of HCN gas (Scheme 2, a). In parallel to this, electrochemical methods have also been employed to convert alcohols and aldehydes into nitriles using nitroxides as catalysts.¹⁸ Inspired by our previous work, we embarked on a program of research focused on merging catalytic oxidation and photoredox chemistry for the conversion of aldehydes into nitriles and present our results here (Scheme 2, c).

As a starting point for our methodology development, we turned to the optimized reaction conditions from the photoamidation reaction developed by our group.¹⁶ This involves the use of 2 mol% of Ru(bpy)₃(PF₆)₂ as the photocatalyst, 20 mol% of **2** as the primary oxidant, and 2.2 equiv of sodium persulfate as the terminal oxidant. Pyridine (3 equiv) is utilized as a base for the reaction. We chose *p*-methoxybenzaldehyde (**3a**) as our test substrate and HMDS (2.5 equiv) as the nitrogen source. Dry sodium persulfate

and 3 Å molecular sieves were used as a precaution to minimize the formation of undesired hydrolysis products such as the corresponding carboxylic acid or amide that are often produced as off-target compounds in such reactions.^{11,19} Since the oxidative reaction between an aldehyde and HMDS yields an *N*-trimethylsilyl nitrilium ion intermediate, we added tetrabutylammonium fluoride (TBAF) after the photooxidation process in order to cleave the N–Si bond and furnish the desired nitrile **4a**. Using our photoamidation conditions with the addition of HMDS resulted in a 56% conversion by ¹H NMR spectroscopy into **4a**. The mixture also contained 40% unreacted started material along with some 4-methoxybenzoic acid, 4-methoxybenzamide, and an unidentified side product/intermediate. In an attempt to improve the product conversion, we performed the reaction for 48 h and did observe a slight increase in nitrile formation (Table 1, entry 2). Some photoreactions are photon-limited and require more powerful light sources.²⁰ We therefore tried moving from blue LED strips to a more powerful 34 W blue LED lamp. However, only an incremental in-

Table 1 Optimization of Reaction Conditions for the Photooxidation of Aldehydes to Nitriles Using HMDS as the Nitrogen Source^a

Entry	Reaction conditions	Conversion (%) ^b
1	24 h	56
2	48 h	67
3	48 h, blue LED lamp in place of LED strip	71

^a Reactions performed using 1 mmol **3a**, ca. 0.2 g of 3 Å molecular sieves, ca. r.t. (with fan), 2 ml acetonitrile, 0.6 ml of TBAF solution (1 M in THF) added after the allotted reaction time and stirred for 1 h.

^b Conversion determined by integration of signals in the ¹H NMR spectrum of the crude product mixture.

crease in conversion into **4a** was observed (Table 1, entry 3). At this stage, with the product mixture containing a number of byproducts, we wanted to determine the ease of product isolation. Unfortunately, the separation of **4a** from the byproducts proved challenging using column chromatography.

We decided to change our nitrogen source to ammonium persulfate. We posited that this may solve our product isolation issue and in addition could serve as the terminal oxidant in place of sodium persulfate. We started by replacing the HMDS and sodium persulfate with ammonium persulfate (2.2 equiv) and performed the reaction both at approximately 50 °C (in the absence of fan cooling) and at room temperature (cooling the reaction mixture with a fan), while keeping all other reagents and parameters the same as before. We obtained isolated product yields of **4a** of 24% and 19%, respectively (Table 2, entries 1 and 2). Choosing to operate in the absence of fan cooling, increasing the loading of pyridine from 3 equiv to 6 equiv essentially doubled the isolated yield of **4a** (Table 2, entry 3) but further increase in pyridine loading did not improve product formation, and neither did increasing the ruthenium photocatalyst loading to 5 mol% or using either [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*1,*N*1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C] iridium(III) hexafluorophosphate ([Ir(dF(CF₃)ppy)₂(dtbpy)](PF₆)) or 9-mesityl-10-methyl acridinium tetrafluoroborate (MesAcr⁺BF₄⁻) as the photocatalyst (Table 2, entries 4–7). Increasing the loading of **2** or ammonium persulfate did not increase product formation (Table 2, entries 8 and 9), and performing the reaction in dichloromethane as the solvent instead of acetonitrile had a deleterious effect on product yield (Table 1, entry 10). As expected, **1** could also be used in place of **2** as the primary oxidant added at the start of the reaction (Table 1, entry 11). Next, we performed a series of control experiments to confirm that light, photocatalyst, pyridine, and molecular sieves are all essential to the successful outcome of the reaction (Table 1, entries 12–15). Surprisingly, a 33% conversion into **4a** was obtained in the absence of photocatalyst (Table 1, entry 13). This can be explained by thermal decomposition of (NH₄)₂S₂O₈ to generate sulfate radical ions that can undertake hydrogen atom transfer (HAT) and engage in a radical-chain process to facilitate the oxidation reaction. Such an observation has also been made by Stephenson et al. in the oxidation of dialkylamides.²¹ Pyridine was found to be an essential reagent for this transformation (Table 1, entry 14). This gave us some mechanistic insight into the reaction, suggesting *in situ* formation of an aldimine intermediate **6** followed by hydride transfer from **6** to **1** (Scheme 4). Previous computational studies support the latter event in the oxidation of primary amines to nitriles by **1** in presence of pyridine.^{7a} At this point, we deemed the optimization of our reaction complete and elected to move forward using **2** (20 mol%), Ru(bpy)₃(PF₆)₂ (2 mol%), pyridine (6 equiv), 3 Å molecular

sieves (0.2 g), and (NH₄)₂S₂O₈ (2.2 equiv), employing acetonitrile as the solvent, and irradiating the reaction mixture with blue LEDs for 24 h at ca. 50 °C (Table 2, entry 3).

Table 2 Optimization of Reaction Conditions for the Photooxidation of Aldehydes to Nitriles Using Ammonium Persulfate as the Nitrogen Source^a

Entry	Reaction conditions ^b	Yield (%) ^c
1	2 (20 mol%), Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (3 equiv), (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	24
2	2 (20 mol%), Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (3 equiv), (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN, r.t.	19
3	2 (20 mol%), Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	50
4	2 (20 mol%), Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (12 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	48
5	2 (20 mol%), Ru(bpy)₃(PF₆)₂ (5 mol%) , pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	46
6	2 (20 mol%), MesAcr⁺BF₄⁻ (2 mol%) , pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	35
7	2 (20 mol%), [Ir(dF(CF₃)ppy)₂(dtbpy)](PF₆) (2 mol%) , pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	– ^{d,e}
8	2 (30 mol%) , Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	45
9	2 (20 mol%), Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (6 equiv) , (NH₄)₂S₂O₈ (4 equiv) , molecular sieves, MeCN	49
10	2 (20 mol%), Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, CH₂Cl₂	17
11	1 (20 mol%) , Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	44
Control experiments		
12	no 2 , Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	– ^{e,f}
13	2 (20 mol%), no Ru(bpy)₃(PF₆)₂ , pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	33 ^e
14	2 (20 mol%), Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), no pyridine , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN	1 ^e
15	2 (20 mol%), Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), pyridine (6 equiv) , (NH ₄) ₂ S ₂ O ₈ (2.2 equiv), molecular sieves, MeCN, no LEDs	9 ^e

^a Reactions performed using 1 mmol **3a**, ca. 0.2 g of 3 Å molecular sieves, ca. 50 °C (no fan), 2 ml solvent, blue LED strips, 24 h.

^b Conditions changed from entry 1 are highlighted in **bold**.

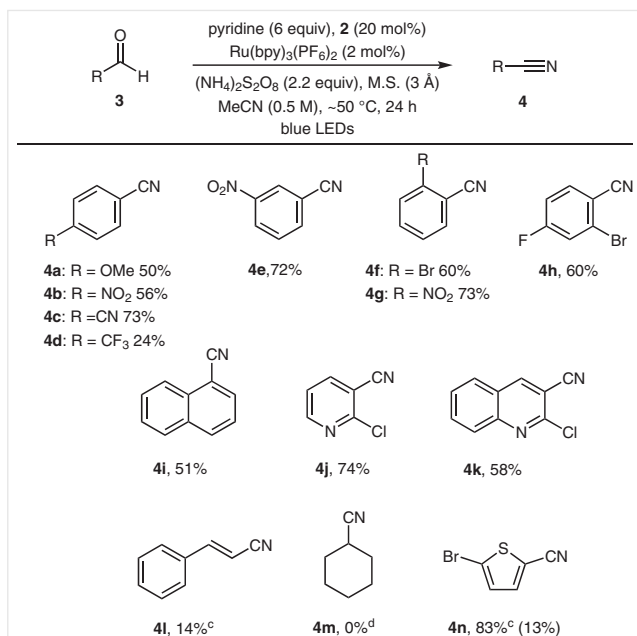
^c Isolated yield unless noted otherwise.

^d Performed using 4-methylbenzaldehyde as the starting material and obtaining 80% carboxylic acid and 20% oxidized products including amide, nitrile, among others.

^e Conversion determined by integration of signals in the ¹H NMR spectrum of the crude product mixture.

^f Mixture of oxidized products formed including carboxylic acid and amide along with several unidentified products.

We then moved to a substrate screen using our optimized reaction conditions (Scheme 3).^{22,23} A range of *para*-substituted benzaldehydes with electronically different substituents, such as methoxy, nitro, cyano, and trifluoromethyl, were examined. They were all found to be well-tolerated (**4a–d**). Likewise, *ortho*- and *meta*-substituted benzaldehydes gave the corresponding nitrile product in fair yields (**4e–g**). A polysubstituted benzaldehyde, 2-bromo-4-fluorobenzaldehyde, also afforded the expected nitrile in 60% yield (**4h**), and 1-naphthaldehyde was converted into the desired nitrile in good yield (**4i**). We also screened two heteroaromatic substrates, 2-chloro-3-pyridinecarboxaldehyde and 2-chloro-3-quinolinecarboxaldehyde. They underwent oxidation to their corresponding nitriles in moderate yield (**4j,k**). To expand the methodology beyond aromatic substrates, we screened *trans*-cinnamaldehyde but obtained only a 14% yield of the desired nitrile by NMR spectroscopy (**4l**). Under our reaction conditions, saturated aliphatic aldehydes such as cyclohexanecarboxaldehyde yielded a mixture of oxidation products including carboxylic acid, amide, and dimeric ester (**4m**). A thiophene example (5-bromo-2-thiophenecarboxaldehyde) gave an 83% conversion into the desired nitrile product **4n** by NMR spectroscopy, but isolation and purification of the product proved troublesome, resulting in an isolated yield of only 13%.



Scheme 3 Substrate scope for the photooxidation of aldehydes to nitriles^{a,b}

^a Conditions unless otherwise noted: **3** (1.0 mmol, 1 equiv), **2** (20 mol%), Ru(bpy)₃(PF₆)₂ (2 mol%), pyridine (6 equiv), dry (NH₄)₂S₂O₈ (2.2 equiv), ca. 0.2 g of 3 Å molecular sieves, ca. 50 °C (no fan), 2 ml acetonitrile, blue LEDs, 24 h. ^b Isolated yields unless otherwise noted. ^c Conversion determined by integration of signals in the ¹H NMR spectrum of the crude product mixture. ^d Product mixture analyzed by GC–MS.

Based on our previous reports on photoamidation of aldehydes and photooxidation of alcohols,^{15,16} we posit the following possible series of steps to explain the formation of nitriles: The first step of the process is the generation of a photoexcited Ru(II)* (**8**) complex upon irradiation with blue light. The excited photocatalyst then undergoes oxidative quenching by the persulfate anion to form a Ru(III) (**9**) complex. The persulfate anion itself undergoes a disproportionation reaction to yield a sulfate anion and a sulfate radical anion species. Subsequently, **9** ($E_{1/2}^{\text{red}}[\text{Ru}^{\text{III}}/\text{Ru}^{\text{II}}] = 1.29 \text{ V vs SCE}$)^{14a} oxidizes **2** to its oxoammonium cation **1** ($E_{1/2}^{\text{ox}} = [\text{ACT}/\text{ACT}^+] = 0.61 \text{ vs SCE}$) by SET.^{7c,24} The condensation of the aldehyde **3** with ammonia results in *in situ* formation of the aldimine **6**.²⁵ Next, **1** oxidizes aldimine **6** by means of a hydride transfer to afford the nitrile **4** and is itself converted into the corresponding hydroxylamine **5**. Importantly, pyridine facilitates this hydride transfer by coordinating with **6**.^{7a} Finally, **5** undergoes HAT to the sulfate radical anion to regenerate **2**, the catalytic cycle is then complete (Scheme 4).^{24,26}

In summary, a merger of photoredox catalysis and 4-acetamido-TEMPO (**2**) has been employed for the oxidation of aldehydes to nitriles using visible light. Ammonium persulfate was found to be an efficient and inexpensive terminal oxidant that also acts as a nitrogen source for this transformation. The methodology has been employed for the generation of a range of nitrile products in good yield.

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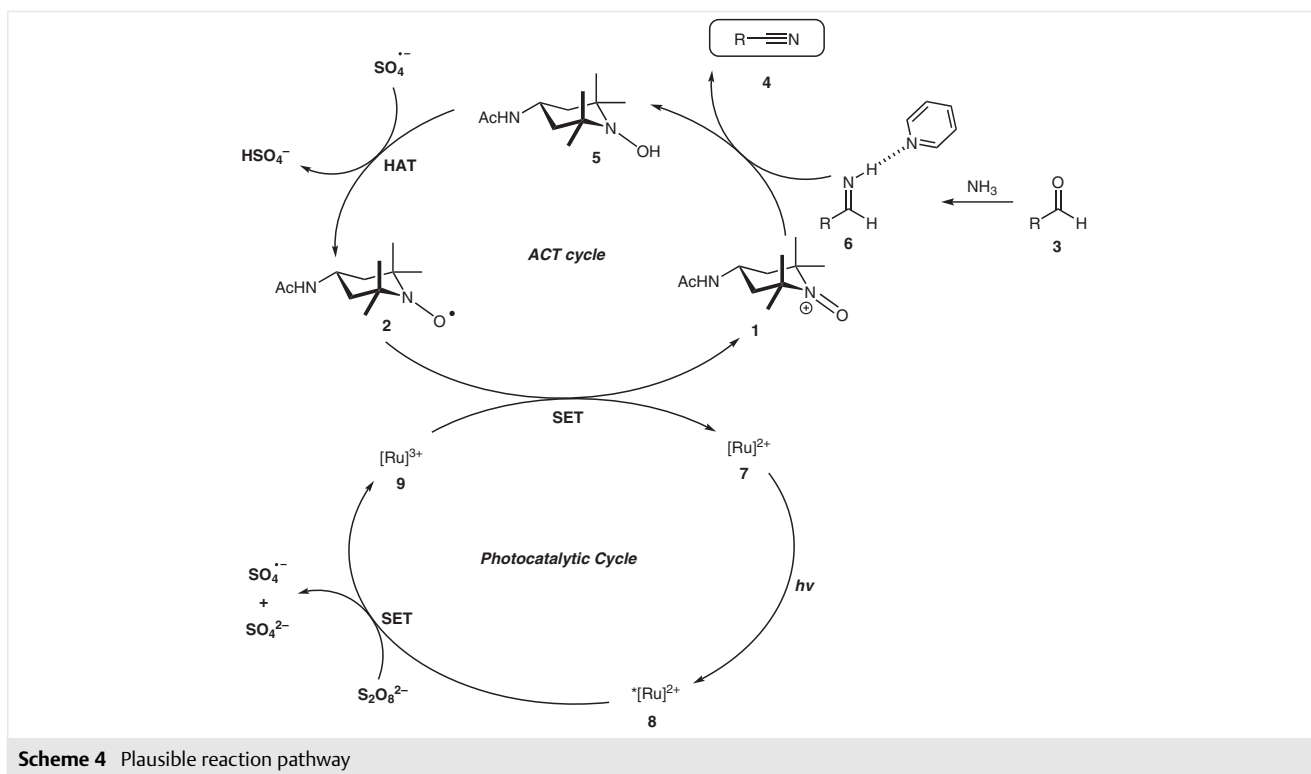
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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1610272>.

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- (22) **Representative Procedure – Preparation of 4-Methoxybenzonitrile (4a)**
 To an oven-dried 2 ml reaction vial equipped with a stir bar was added the aldehyde **3a** (0.136 g, 1 mmol, 1 equiv) and pyridine (0.474 g, 6.0 mmol, 6 equiv), followed by acetonitrile (2 ml, 0.5 M in **3a**). The vial was then charged with Ru(bpy)₃(PF₆)₂ (0.017 g, 0.02 mmol, 0.02 equiv), **2** (0.043 g, 0.20 mmol, 0.20 equiv), (NH₄)₂S₂O₈ (0.501 g, 2.2 mmol, 2.2 equiv), and activated 3 Å molecular sieves (ca. 0.2 g), sealed with a cap, and irradiated in blue LED reactor for 24 h. In the absence of fan cooling, the temperature of the reaction mixture plateaued at approximately 50 °C. After the irradiation was complete, the reaction mixture was quenched with EtOAc and transferred to a separatory funnel. Further EtOAc (30 ml) was added, followed by 0.5 M HCl_(aq) (30 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 ml). The organic layers were then combined and washed with 0.5 M 0.5 M HCl_(aq) (2 × 20 ml), saturated aqueous sodium bicarbonate (2 × 20 ml), and finally brine (20 ml). The organic layer was then dried over sodium sulfate and the solvent removed *in vacuo* to afford the crude product. The resulting crude mixture was adhered to silica gel using 1.5 weight equivalents of SiO₂ (relative to the theoretical yield). The dry-packed material was gently added on top of a silica gel plug. The plug was washed with an excess of hexanes (ca. 5 column volumes). The desired product was eluted off the plug via a 90:10 by volume mixture of hexanes/EtOAc (3–4 column volumes). The solvent was removed *in vacuo* by rotary evaporation affording the pure nitrile **3c** (0.066 g, 50%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ = 7.58 (d, *J* = 8.9 Hz, 2 H), 6.95 (d, *J* = 8.9 Hz, 2 H), 3.86 (s, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 162.98, 134.11, 119.34, 114.88, 104.13, 55.67 ppm. IR (neat, ATR): ν = 2941, 2215, 1603, 1506, 1457, 1303, 1254, 1173, 1020, 826, 681, 544, 497 cm⁻¹. MS (EI): *m/z* (%) = 133 (100) [M⁺], 118 (10), 104 (12), 103 (41), 90 (49), 76 (10), 64 (14), 63 (16).
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