

# Pyrenedione-Catalyzed $\alpha$ -Olefination of Nitriles under Visible-Light Photoredox Conditions

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achieve facile alcohol dehydrogenation under visible-light excitation, where aerobic oxygen is utilized as the terminal oxidant. The resulting carbonyl compound can be easily converted to vinyl nitriles in a single-pot reaction, at 60 °C in 6–8 h. This environmentally benign, organocatalytic approach has distinct advantages over transition-metal-catalyzed  $\alpha$ -olefination of nitriles, which often operate at a significantly higher temperature for an extended reaction time.



he construction of C–C and C–N bonds is a fundamentally important process in organic synthesis. Conventional methods toward their formation from an alcohol usually involve conversion of the alcohol into an alkyl halide or similar alkylating agent, followed by nucleophilic substitution with an appropriate C- or N- nucleophile. From the perspective of step economy and sustainability, in situ generation of electrophilic species from alcohols under mild reaction conditions is highly desirable.<sup>2</sup> In the context of C-C bond containing molecules, vinyl nitriles are important motifs<sup>3</sup> which are recurrent in a wide range of natural products and pharmaceuticals.<sup>4,5</sup> Additionally, they are crucial building blocks for optoelectronic materials as well as light-emitting diodes.<sup>6,7</sup> The traditional mode of preparation for vinyl nitriles involves Knoevenagel condensation, requiring a stoichiometric or substoichiometric amount of base.<sup>8</sup> However, multiple competing reactions, including aldol, Cannizzaro, and selfcondensation of nitriles, can generate a copious amount of byproducts under high base loading. Henceforth, their effective synthesis under milder reaction conditions is often sought after. Toward this direction, acceptorless dehydrogenation of alcohols,<sup>9-14</sup> followed by a condensation, has emerged as a very promising atom-economical tool to forge  $\alpha$ -olefinated nitriles.

Milstein has pioneered this transformation with a Mncatalyst which can operate under base-free conditions, but this reaction only includes primary alcohols as a test set.<sup>15</sup> Furthermore, the method required heating the reaction mixture at 135 °C for 43–60 h. Contemporaneously, Wang has reported a bimetallic rhodium-catalyzed preparation of acrylonitriles from only primary alcohols, at 110 °C.<sup>16</sup> Subsequent development from Gunanathan includes secondary alcohols in the substrate scope, but uses a Ru-MACHO (MACHO = Bis[2-(diphenylphosphino)ethyl] amine) catalyst.<sup>17</sup> Very recently another Mn-MACHO catalyst has been reported by Balaraman that also forms vinyl nitriles utilizing secondary alcohols (Scheme 1a).<sup>18</sup> All these transformations

Scheme 1. (a) Typical Metal-Catalyzed Preparation of Vinyl Nitrile; (b) Milder Synthesis with Organocatalyst PD



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are limited to transition metal catalysis, requiring a higher temperature (110-135 °C), an argon atmosphere, and often long reaction times. Therefore, there is a strong interest in designing an inexpensive, transition-metal-free system which may operate under milder reaction conditions, possibly under an aerobic atmosphere without generating hazardous waste.

Herein, we communicate a completely transition-metal-free synthesis of vinyl nitriles which can tolerate both primary and secondary alcohols as starting substrates and operates under very mild reaction conditions. The reaction utilizes an *ortho*-quinone, pyrenedione (**PD**), which functions under visible-light-induced conditions and an aerobic atmosphere. The dehydrogenating ability of **PD** relies on its ability to behave as a two-electron shuttle from alcohol to  $O_2$ . The overall dehydrogenative coupling reaction operates in a single-pot manner, at a mild reaction temperature of 60 °C. Use of such an inexpensive catalyst under very mild recation conditions demonstrates that the simple organic molecule such as **PD** overcomes the current limitation of the transition metal, high temperature, and elongated reaction time toward  $\alpha$ -olefination of nitriles.

Facile and reversible 2e<sup>-</sup>/2H<sup>+</sup> redox processes between obenzoquinone and catechol are well-known.<sup>19</sup> We have also shown recently that predominantly ligand-based 2e<sup>-</sup>/2H<sup>+</sup> redox involving the azo/hydrazo couple is very efficient in conducting N-alkylation of amines, C3-alkylation of indoles, and a few dehydrogenative coupling reactions.  $^{20-24}$  We surmise that an extended and delocalized  $\pi$ -cloud may further facilitate easy reduction of a dione to its monoreduced semiquinonato form. This fact prompts us to choose PD as the experimented molecule, where the pyrene core will likely allow the added electron to delocalize, conferring extra stability to the monoreduced form. Notably, a few quinone molecules showed promise in dehydrogenation reactions mostly operated under thermal conditions.<sup>25–28</sup> Gratifyingly, a combination of PD and a catalytic amount of base KO<sup>t</sup>Bu, under photoinduced conditions can provide convenient access to the target vinyl nitriles at a fairly mild reaction temperature of 60 °C. The use of benzyl alcohol and benzyl cyanide as the model substrates resulted in an 80% yield of the desired 2,3diphenylacrylonitrile.

A series of optimization studies revealed that the best yield can be obtained at only 3 mol % loading of **PD**, while a lower loading of the catalyst decreases the yield considerably (Table 1, entry 2). The reaction offers optimum yields of products at 3 mol % loading of **PD**, 30 mol % loading of the base KO<sup>t</sup>Bu, and stirring the reaction mixture at 60 °C for 6 h under blue LED (Table 1, entry 5).

While scanning the effect of bases (Table 1, entries 5-10), it was observed that NaOH, KOH, NEt<sub>3</sub>, and Na<sub>2</sub>CO<sub>3</sub> were inefficient in performing the reaction. Although KO<sup>t</sup>Bu proved to be the most efficient base, affording product in 80% yield, NaO<sup>t</sup>Bu can also provide a moderate amount of product (entry 8). Optimization of the reaction medium proved toluene to be very effective, whereas polar acetonitrile offered a poor yield (Table 1, entry 12). In other polar solvents such as DMF and DMSO (Table 1, entries 11, 13), the reaction does not proceed. Appropriate control reactions disclose that the reaction fails in the absence of **PD**, KO<sup>t</sup>Bu, and visible light, justifying the essential role of each component (Table 1, entries 1, 14, 15). Although to fix the light source and to quantify photochemical efficiency a blue LED strip (456 nm) was used, the reaction can be easily carried out by exposing it

#### Table 1. Screening of Optimal Reaction Conditions<sup>a</sup>

| (               | R1 ОН + R2 О     | CN<br>PD (x mol%)<br>KO <sup>t</sup> Bu (y mol%)<br><i>hv</i> , 60 °C | R1                 | CN        |
|-----------------|------------------|---|--------------------|-----------|
| entry           | catalyst loading | base  | solvent            | yield (%) |
| 1               | _                | KO <sup>t</sup> Bu (30 mol %)   | Toluene            | n.r.      |
| 2               | 1 mol %          | KO <sup>t</sup> Bu (15 mol %)   | Toluene            | 10        |
| 3               | 3 mol %          | KO <sup>t</sup> Bu (15 mol %)   | Toluene            | 33        |
| 4               | 3 mol %          | KO <sup>t</sup> Bu (20 mol %)   | Toluene            | 64        |
| 5               | 3 mol %          | KO <sup>t</sup> Bu (30 mol %)   | Toluene            | 80        |
| 6               | 3 mol %          | KOH (30 mol %)  | Toluene            | 5         |
| 7               | 3 mol %          | NaOH (30 mol %)   | Toluene            | 10        |
| 8               | 3 mol %          | NaO <sup>t</sup> Bu (30 mol %)  | Toluene            | 53        |
| 9               | 3 mol %          | NEt <sub>3</sub> (30 mol %)   | Toluene            | n.r.      |
| 10              | 3 mol %          | Na <sub>2</sub> CO <sub>3</sub> (30 mol %)                            | Toluene            | n.r.      |
| 11              | 3 mol %          | KO <sup>t</sup> Bu (30 mol %)   | DMSO               | n.r.      |
| 12              | 3 mol %          | KO <sup>t</sup> Bu (30 mol %)   | CH <sub>3</sub> CN | 28        |
| 13              | 3 mol %          | KO <sup>t</sup> Bu (30 mol %)   | DMF                | n.r.      |
| 14              | 3 mol %          | -   | Toluene            | n.r.      |
| 15 <sup>b</sup> | 3 mol %          | KO <sup>t</sup> Bu (30 mol %)   | Toluene            | 7         |

"Reaction conditions: **PD** ( $x \mod \%$ ), benzyl alcohol (1.2 mmol), benzyl cyanide (1 mmol), base ( $y \mod \%$ ), toluene (2 mL), 60 °C (oil bath), 6 h under blue light (GC-MS yield). <sup>b</sup>Reaction performed in dark.

to any visible light source, such as a CFL lamp in the laboratory or even sunlight.

With the optimized reaction conditions in hand, we surveyed the generality of the reaction by investigating its substrate scope (Table 2). When a variety of substituted benzyl alcohols were chosen along with benzyl nitrile, the corresponding vinyl nitriles (4a-4i) were obtained in very good to excellent yields. Interestingly, *p*-substituted benzyl alcohols with electron-donating -Et,  $-^{i}\text{Pr}$  (4f-4g) and electron-withdrawing fluoro (4j) assembled the respective vinyl nitriles in good yields (61-78%). Similarly, *o*- and *p*-halide substitutions in benzyl alcohols were well tolerated under the reaction conditions to furnish the product (4j-4n) in moderate to very good yields (64-74%). Furthermore, heterocyclic alcohols, such as furfuryl methanol and 2-pyridine methanol, reacted with benzyl cyanide resulting in the product 4o-4p in 63-72% yield.

Encouragingly, the aliphatic alcohols also offered moderate yields of the respective vinylated products. For example, neopentyl alcohol was converted to the nitrile product (4q) in 59% yield. It is noteworthy that the oxidation of aliphatic alcohols is often challenging, since these are considered as unactivated alcohols due to the higher C–H bond strength. Similarly, hexanol was converted to the respective vinylated product (4r) in synthetically useful 38% yield. Notably, dehydrogenative coupling of benzyl alcohol with 4-chlorophenyl acetonitrile and heteroaromatic 2-thiophene acetonitrile also afforded the corresponding vinyl nitriles in moderate to good yields (4s-4t).

Finally, the dehydrogenative couplings of the more challenging aliphatic nitriles were also performed which resulted in 40-43% yields of products (4u-4v), albeit under a slightly higher loading of base.

Next, we attempted to further expand the scope of the reaction by considering secondary alcohols (Table 3) as olefinating substrates. To our delight, a large array of secondary alcohols responded very well and furnished the desired

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PD (3 mol%) KO<sup>t</sup>Bu (30 mol%) R<sub>2</sub> + H<sub>2</sub>O + H<sub>2</sub>O `он R<sub>2</sub> R hv. 60 °C L CN 4a (80%) 4b (75%) 4c (79%) 4d (70%) Me<sub>2</sub>N Ĭ 1 4e (65%) 4f (78%) 4g (68%) 4h (61%) Ĭ 4i (72%) 4j (61%) 4k (65%) 41 (74%) 4n (70%) 4m (64%) 40 (72%) 4p (63%) 1 4q (59%) 4r (38%) 4s (53%) 4t (78%) 4v (40%)b 411 (43%)

Table 2. Scope of  $\alpha$ -Olefination of Nitriles with Primary Alcohols<sup>*a*</sup>

<sup>47</sup>Reaction conditions: **PD** (3 mol %, with respect to benzyl cyanide), **1** (1.2 mmol), **2** (1 mmol), KO'Bu (30 mol %), toluene (2 mL), 60 <sup>o</sup>C (oil bath), 6 h (isolated yield). <sup>b</sup>KO'Bu (60 mol %).

products in generally good to very good yields. The reaction proceeded smoothly with a slightly higher loading (5 mol %) of **PD**. Several substituted benzyl nitriles were coupled to cyclohexanol in a dehydrogenative fashion to result in the vinyl nitrile products (5a-51). Similarly, -Me, -Et, and  $-^{t}Bu$  substituted cyclohexanols also offered the products (5m-5p) in good (58-76%) yields.

Furthermore, nitrile components containing heterocyclic rings such as thiophene were well tolerated and the desired product (51) was isolated in good yield. More challenging substrates including adamantanol, 1-hydroxy-7-methoxy-1,2,3,4-tetrahydronaphthalene, and 3-pentanol also survived the reaction conditions and assembled the respective cross dehydrogenative products (5q-5s) in good (49-64%) yields. This broad substrate scope comprising both primary and secondary alcohols attests to the modularity of the methodology. To our delight, scaling up does not have a deleterious effect on efficiency, since a gram-scale synthesis of 2,3diphenylacrylonitrile gave us a 67% isolated yield (Figure 1b and Section 4d, Supporting Information (SI)). Overall, this simple system outperforms the metal-catalyzed synthetic methods for  $\alpha$ -olefination of nitriles. While expensive metal precursors, designer ligands with sensitive functionalities (like phosphines), high reaction temperatures (110-135 °C), and an extended reaction time were the earlier requirement, the current method is very mild and can be performed employing an extremely inexpensive organic molecule, under an aerobic atmosphere for a much shorter time span.

We have gathered some preliminary mechanistic information for this reaction. An appropriate control reaction suggests that Table 3. Scope of  $\alpha$ -Olefination of Nitriles with Secondary Alcohols<sup>*a*</sup>



<sup>a</sup>Reaction conditions: **PD** (3 mol %, with respect to benzyl cyanide), **3** (1.2 mmol), **2** (1 mmol), KO<sup>t</sup>Bu (30 mol %), toluene (2 mL), 60 <sup>o</sup>C (oil bath), 6 h (isolated yield).



Figure 1. (a) Radical quenching experiment. (b) Gram-scale synthesis. (c) X-band (9.32 GHz) EPR signal obtained from the semiquinone radical of PD at rt, after shining visible light to the reaction mixture. (d) Spin density (excess positive spin) in semiquinonate PD at isosurface 0.004 (e bohr<sup>-3</sup>)<sup>1/2</sup>.

the reaction is visible-light-mediated and almost stops under complete darkness. To prove that the reaction is truly transition-metal-free and no adventitious metal contamination is catalyzing the reaction, we analyzed the KO<sup>t</sup>Bu through an ICP-MS analysis (Section 4e, SI) that confirmed the absence of any transition metal contamination. Additionally, the reaction was performed using different batches of KO<sup>t</sup>Bu from disparate commercial sources, providing reproducible yields. The probability of catalysis by a trace amount of adventitious metal was also nullified by performing the reaction in new glassware, including a new magnetic stir bead,<sup>29</sup> where the yield of the reaction remained identical (Section 4e, SI).

The reaction is radical-mediated as evidenced by its complete stoppage when a radical inhibitor TEMPO was added in a 1 equiv amount (Figure 1a, Section 4c, SI). It is likely that, under photoinduced conditions, a very mild reductant like KO<sup>t</sup>Bu reduces PD to its semiguinonate form. Our hypothesis is consistent with Murphy's seminal work where electron transfer from KO<sup>t</sup>Bu has been facilitated at the excited state of benzophenone.<sup>30,31</sup> The electron transfer ability of KO<sup>t</sup>Bu has also been reported at the ground state, only when the appropriate potential window permits such redox processes, as evident by radical anion generation from 1,10-phenanthroline.<sup>32</sup> To validate that the excited PD is reductively quenched by the reductant, we examined the emission quenching of the luminophore with increasing concentration of the KO<sup>t</sup>Bu. Interestingly, the fluorescence intensity decreases gradually with increasing KO<sup>t</sup>Bu concentration and follows a clear Stern-Volmer pattern (Figure 2).



**Figure 2.** (a) Fluorescence emission intensity quenching of **PD** with increasing concentration of KO<sup>t</sup>Bu. (b) Stern–Volmer plot for the fluorescence quenching.

Intuitively, upon such reductive quenching, a semiquinonate anion radical forms. We note that such quenching is only feasible after visible-light irradiation to the **PD** and KO<sup>t</sup>Bu mixture. The orange-colored toluene solution of **PD** and KO<sup>t</sup>Bu changes to a deep green solution only after shining light into it.

Gratifyingly, the formation of a semiquinonate radical from the green-colored reaction mixture was evident when probed by X-band EPR spectroscopy. A strong EPR resonance was observed for the mixture at g = 2.004 without resolved hyperfine features (Figure 1c).<sup>33,34</sup> As interrogated by density functional theory calculations, the spin density in the semiquinonate form of **PD** hovers in the O-C-C-O framework with some delocalization in the pyrene backbone (Figure 1d). Additionally, mixing of PD with KO<sup>t</sup>Bu under visible-light-induced condition gives rise to a new absorption band at 690 nm, when probed by UV–vis spectroscopy. This intense new band can also be attributed to the semiquinonate generation.<sup>33</sup> As the dehydrogenation reaction relies on the  $2e^{-}/2H^{+}$  redox process, the catechol form of the PD, PDH<sub>2</sub> forms in the reaction medium, which we are able to trace from a stoichiometric inert reaction (Section 4b, SI).

In summary, we present an organocatalytic system comprising a quinone molecule that enables efficient preparation of a large number of vinyl nitriles under very mild reaction conditions. The catalyst system is very inexpensive and operates in an aerobic atmosphere, a significant improvement over multiple transition metal catalysts employed earlier for the targeted synthesis. Preliminary mechanistic investigation reveals that the reaction is radical promoted, which is also distinctly different from previous transition metal catalysts that rely on metal–ligand bifunctionality.<sup>35</sup>

### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00162.

Experimental details, spectroscopic data, characterization data, NMR spectra (PDF)

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#### Notes

The authors declare no competing financial interest.

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