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### COMMUNICATION

## Photocatalytic hydrogen-evolution of 1-tetralones to $\alpha$ -naphthols by continuous-flow technology

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Taking advantage of the synergy between photocatalysis and cobaloxime catalysis, the keto-enol radical cation of 1-tetralones becomes compatible with the transformation of various 1-tetralones into  $\alpha$ -naphthols and H<sub>2</sub> by virtue of the continuous-flow approach without any sacrificial oxidants under unusually mild conditions.

 $\alpha$ -Naphthol compounds, a common core in organic chemistry, serve as an integral part of valuable pharmaceuticals, agrochemicals, polymers and natural products.<sup>1</sup> Industrial methods to make naphthol compounds rely on the alkali fusion of naphthalene sulfonic acid or  $\alpha$ -naphthylamine hydrolysis at elevated-temperature and high pressure (Scheme 1a).<sup>2</sup> However, these procedures suffer from harsh conditions, high toxicity and large amounts of wastes production. Selective dehydrogenative aromatization of cyclohexanones has been used as an attractive approach to construct substituted phenols.<sup>3,4</sup> The absence of strong acid or strong base made the third approach (Scheme 1b) more attractive than the other two methods, the naphthalene sulfonic acid and naphthylamine hydrolysis. Nonetheless. the dehydrogenation of 1-tetralones to  $\alpha$ -naphthols requires much high temperature, sacrificial oxidants and precious metal catalysts. Thus, the developing of an effective synthetic strategy to  $\alpha$ -naphthol compounds that is suitable for the economical and feasible production of  $\alpha$ -naphthol compounds with high reactivity under mild and oxidant-free condition is highly desirable.

Photoredox catalysis has recently emerged as a powerful platform.<sup>5,6</sup> Particularly, one step hydroxylation of benzene to phenol with water under oxidant-free conditions has been established.<sup>7</sup> As for naphthols, this strategy unfortunately failed to yield any desired products under irradiation (see the



Supporting Information for details). Although the direct hydroxylation of naphthalene has also been accomplished to  $\alpha$ -naphthols, the poor selectivity and excess amount of oxidizing reagents such as H<sub>2</sub>O<sub>2</sub> are unavoidable.<sup>8</sup> In this regard, we questioned whether we could directly synthesize  $\alpha$ naphthol compounds via the dehydrogenation of 1-tetralone with hydrogen evolution under oxidant-free conditions (Scheme 1c).9 In this transformation, the key step is the enolization of ketones. The keto-enol tautomerism in neutral molecules is sufficiently known in chemistry.<sup>10</sup> However, the simple enol form is often less stable than its keto tautomer and exists only at very low concentration under equilibrium condition. In contrast to neutral molecules, the radical cation of enol becomes more stable than its keto tautomer.11 Considering the high one-electron oxidative potential of 1tetralone (2.51 V vs. SCE, Fig. S4), the crucial step is the electron transfer oxidation of 1-tetralone to enol radical cation. Commercially available 1-methylquinolinium perchlorate (QuH<sup>+</sup>) or 3-cyano-1-methylquinolinium perchlorate (QuCN<sup>+</sup>) both show high reductive potential at excited state ( $E_{red} = 2.54$ V vs. SCE for QuH<sup>+</sup> and 2.72 V vs. SCE for QuCN<sup>+</sup>),<sup>12</sup> which is thermodynamically feasible for the oxidation of 1-tetralone 1a. On the other hand, the generated enol radical cation B needs

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to further eliminate proton and electron to afford **C** or **D** and thereby converting 1-tetralone **1a** into  $\alpha$ -naphthol **2a** with sequential electron and proton transfer strategy.<sup>13</sup> Cobaloxime complexes,<sup>14</sup> the most versatile proton reduction catalysts, have the ability to capture electrons in each catalyst turnover and to reduce the protons eliminated from substrates into molecular hydrogen gas (**Scheme 2**).

Accordingly, as outlined in Scheme 2, excitation of the photocatalyst (PC) may lead to electron transfer from 1a to the excited-state photocatalyst PC\* to produce 1-tetralone radical cation A and PC radical anion (PC\*). The later species can deliver an electron to the cobaloxime to yield Co<sup>I</sup> species and regenerate the ground state PC, thus completing the first photocatalytic cycle. On the other hand, A species may undergo keto-enol tautomerization to the enol radical cation B, which is much more stable than its corresponding keto tautomer (see above). Then, B eliminates a proton to produce a radical species C or D. The eliminated proton would be captured by the reduced CoI to release CoIII-H. The CoIII-H intermediate would be attacked by proton and further accept an electron from the radical **C** or **D** to return to Co<sup>II</sup> cocatalyst, thus completing the second cycle of cobalt catalysis. As a result,  $\alpha$ -naphthol **2a** is achieved without additional oxidants in one pot under ambient condition.

Our initial investigation was carried out in dry and degassed  $CH_3CN$  solution at room temperature and atmospheric pressure. Typically, 5 mL solution of **1a** (0.2 mmol), photocatalyst (5 mol%) and cobalt cocatalyst (3 mol%) in a Pyrex reactor was irradiated with a 500 W medium pressure mercury lamp. After 5 hour irradiation the

Table 1 Optimization of reaction conditions <sup>a</sup>					View Article Online
		PC (5 mol%) Co catalyst (3 mol%) λ > 300 nm, CH <sub>3</sub> CN (5 mL) Ar, rt, 5 h		DOI: 10.1 mL) 2a	1039/C9CY00753A PH + H <sub>2</sub>
Entry	PC	Со	additives <sup>b</sup>	conv. <b>1a</b> (%) <sup>c</sup>	Yield <b>2a</b> (%) <sup>d</sup>
1	QuH⁺	I	—	48	65
2	QuH⁺	П	_	40	52
3	QuH⁺	ш	—	45	62
4	QuH⁺	IV	_	25	60
5	QuCN⁺	I.	_	30	53
6	QuCN⁺	п	_	53	70
7	QuCN⁺	- 11	$BF_3 \cdot Et_2O$	78	77
8	QuCN⁺	_	$BF_3 \cdot Et_2O$	n.d.	—
9	_	П	$BF_3 \cdot Et_2O$	n.d.	—
10 <sup>e</sup>	QuCN⁺	Ш	$BF_3 \cdot Et_2O$	n.d.	

<sup>a</sup> Reaction conditions: 0.2 mmol of 1-tetraone **1a** was irradiated by medium mercury lamp ( $\lambda > 300$  nm) in CH<sub>3</sub>CN (5 mL) for 5 h under argon atmosphere at room temperature. <sup>b</sup> 20 mol% additive was added. <sup>c</sup> Determind by <sup>1</sup>H NMR with *n*-tetradecane as the internal standard. <sup>d</sup> Yields of **2a** based on the consumption of **1a** <sup>e</sup> No light.



conversion of the starting material could reach 50 %, and the yield of product 2a (based on the consumption of 1a) was near 70%. As shown in Table 1, six combinations between photocatalysts and cocatalysts were all capable of transforming 1a to 2a (Table 1, entries 1-6). In particular, the combination of QuCN<sup>+</sup> and Co<sup>II</sup>(dmgBF<sub>2</sub>)<sub>2</sub>(MeCN)<sub>2</sub> (II) gave the best result (Table 1, entry 6). Given the key step for 1tetralones to  $\alpha$ -naphthols is enolization of ketones, Lewis acid pair  $BF_3$ ·Et<sub>2</sub>O with the potential to promote the enolization and lower the oxidative potential of 1a was added to the reaction system (See Figure S5, S9-S10). To our delight the yield of naphthol was increased to 77% (Table 1, entry 7). Moreover, the cobalt cocatalyst, the photocatalyst and the irradiation conditions were all essential for this transformation (Table 1, entries 8-10) (see supporting information for details). The competitive experiment with a 1:1 mixture of 1a and D<sub>2</sub>-**1a** under standard conditions provided the KIE value  $(k_{\rm H} / k_{\rm D} =$ 1.2) (Scheme 3), suggesting that the deprotonation is not the rate-determining step and the crucial step for initiating such transformation should be the electron transfer oxidation of 1a (see supporting information for details).

To shed light on the initiated step of this transformation, the fluorescence quenching experiments were performed. Figure 1 shows that the excited state of QuCN<sup>+</sup> could be quenched by both of **1a** and Co<sup>II</sup>(dmgBF<sub>2</sub>)<sub>2</sub>(MeCN)<sub>2</sub> (II), respectively. However, the quenching extent of QuCN<sup>+</sup> by 1a was much larger than that of QuCN<sup>+</sup> with  $Co^{II}(dmgBF_2)_2(MeCN)_2$  (II), where their concentration ratios were identical to those using in the reaction system (Fig. 1a). It indicated that dehydrogenation of 1a was triggered by single

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Fig. 1 (a) Fluorescence spectra of QuCN<sup>+</sup> (2 $\times10^{\,5}$  M) in the presence of II (1.2  $\times10^{\,5}$  M) and 1a (4 $\times10^{\,4}$  M) in degassed CH<sub>3</sub>CN. (b) UV-Vis absorption spectra of system containing QuCN<sup>+</sup> (1 $\times10^{\,4}$  M), II (6 $\times10^{\,5}$  M) and 1a (2 $\times10^{\,3}$  M) in degassed CH<sub>3</sub>CN before and after irradiation.

electron transfer from QuCN<sup>+</sup> excited state to **1a**. Moreover, UV-Vis absorption spectrum changed after irradiation of the diluted reaction solution for 10 min. The absorption band at 440 nm assigned for Co<sup>II</sup>(dmgBF<sub>2</sub>)<sub>2</sub>(MeCN)<sub>2</sub> (II) was decreased and a new absorption in the range of 500-600 nm was increased (for Co<sup>I</sup>) (**Fig. 1b**). These observations demonstrated that the cobalt cocatalyst Co<sup>II</sup>(dmgBF<sub>2</sub>)<sub>2</sub>(MeCN)<sub>2</sub> (II) is able to accept the electron to generate Co<sup>I</sup> species<sup>15</sup> during the reaction process.

It was noteworthy that even using the best combination of the photocatalyst and the cobalt cocatalyst, the conversion of the starting material and the yield of the product were yet ideal (Table 1). The low conversion might originate from the competitive absorption of the product accumulated in the solution and thus resulted in the degradation of the product during irradiation. Indeed, 2a absorbs light in the wavelength range similar to that of QuCN<sup>+</sup> (Fig. S11), and the reaction rate decreased as the irradiation was prolonged. In order to avoid the competitive absorption problem, we carried out this transformation by using continuous-flow reactor (see Fig. S1). The high specific surface areas of channels in the typical continuous-flow reactor ensure the uniform irradiation of the entire reaction mixture, eliminating the accumulation of the product(s) in the irradiated area<sup>16</sup> and reducing the inner filter effect of the concentrated photocatalyst and/or product(s). This technology may thus lead to shorter reaction time and high product yields. As expected, the flow chemistry approach afforded the conversion of 1a increasing from 60% in the batch reaction in 5 hour irradiation to 66% in the flow reactor upon 30 min reaction time and the yield of 2a (based on the consumption of 1a) was dramatically increased from 77% to more than 99% (Scheme 4).

Having the optimal continuous-flow conditions, we sought to examine the scope of 1-tetralones. From the analysis of the product results in **Scheme 4**, we could get the following conclusions: First, the electron-withdrawing groups on aromatic rings (R<sub>1</sub>) including halogens and esters showed good compatibility. Moderate to good yield of products  $\alpha$ naphthalol and an equivalent H<sub>2</sub> were obtained (**2b-2k**). Specifically, fluoro-bearing 1-tetralones were more effective than chloro-bearing ones (**2b-2g**). Ester groups with different chain lengths or branched methyl group successfully generated the desired products in moderate yield (**2h-2k**). Second, the variations of chloride in 5-, 6-, and 7- positions gave similar results. Third, the electron-donating groups such as methoxy



Isolated yield (yields of **2** based on consumed **1**) were given in sequence. <sup>a</sup> In 1 mmol scale,  $t_R = 1 h$ .

Scheme 4 The scope of 1-tetralones in continuous-flow conditions.

unfortunately could not react to give any desired product, probably because the substrate with a lower oxidation potential was found to possess higher bond dissociation energy of the scissile C-H bond,<sup>17</sup> or the backward electron transfer between the electron-donating substituted 1tetralones and the photocatalyst is too fast to initiate the transformation, so the methoxy substituent tetralone almost remained unchanged during the reaction (21). Fourth, the compatibility of alicyclic fragments (R<sub>2</sub>) was established with a diverse array of tetralones bearing a functional group at 2- or 4-position. Despite Halogen, alkyl and aryl substituents were all viable to produce the target products in remarkable yields (2m-2p). Furthermore, different 4-aryl substituted substrates companied with 6-position halogenation were also competent in this transformation and the products were obtained in reasonable to good results (2q-2t). Fifth, the scaled-up experiment to synthesize 2n (1 mmol, 158.2 mg) was carried out. When reaction time was prolonged to 1 hour,  $\alpha$ -naphthol 2n was obtained in 58% isolated yield and 92% yield based on the conversion of 1n.

#### Conclusions

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In summary, we have developed a photocatalytic way to  $\alpha$ naphthols from 1-tetralons under ambient conditions. By virtue of the single electron transfer oxidation process, ketoenol radical cation becomes available for the dehydrogenation of 1-tetralones to  $\alpha$ -naphthols in one pot reaction without any sacrificial oxidants under mild conditions, and an equivalent amount of H<sub>2</sub> is generated as the sole byproduct. More importantly, the continuous-flow approach enables the transformation of a diverse array of 1-tetralones to  $\alpha$ naphthols in high yield and efficiency with shorter reaction time. Further investigation to broaden the synthetic application, explore the more suitable photocatalysts to accelerate single electron transfer process and the keto-enol tautomerization-driven radial cation formation are actively pursued in our laboratory, and the results will be reported in due course.

#### **Conflicts of interest**

There are no conflicts of interest to declare.

#### Acknowledgements

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A photoredox platform for the dehydrogenation of 1-tetralones to  $\alpha$ -naphthols is disclosed. Further improvement is achieved by the continuous-flow approach.