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Aerobic α-Oxidation of *N*-Substituted Tetrahydroisoquinolines to Dihydroisoquinolones *via* Organo-photocatalysis

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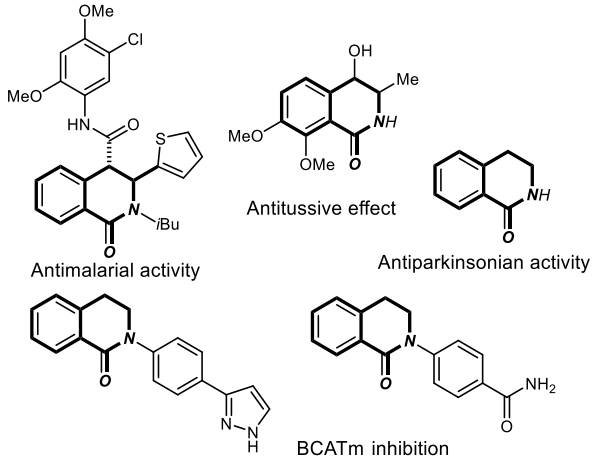
Abstract. An efficient visible-light-induced α-oxidation of *N*-substituted tetrahydroisoquinolines to dihydroisoquinolones has been developed using eosin Y as an organo-photocatalyst and oxygen as a green oxidant. The reactions were carried out under mild reaction conditions; the desired dihydroisoquinolones were obtained in up to 96% yield at room temperature under oxygen atmosphere. This transformation provides a convenient route to dihydroisoquinolones with a wide range of substrates.

Keywords: aerobic oxidation, dihydroisoquinolones; lactams; photoredox catalysis

Oxidation is one of the most common and important transformations in organic chemistry. Therefore, numerous oxidation methods have been developed. The most commonly employed conditions for this process include the use of stoichiometric amounts of oxidants or metal-mediated reactions.[1] Furthermore, green activation modes have been explored in response to the continuous interest in the development of environmentally benign oxidation processes. These include organo-oxidation methods using DMSO[2] or hypervalent iodine compounds. [3] A more appealing method, aerobic oxidation, which employs molecular oxygen (O_2 or air), has also been examined due to the abundant, inexpensive, and environmentally friendly nature of oxygen.[4] In addition, visible-light-induced processes have recently emerged as efficient tools for various oxidation reactions.[5] Given the importance of the oxidation reaction in general, it is crucial to develop new methods to this process.

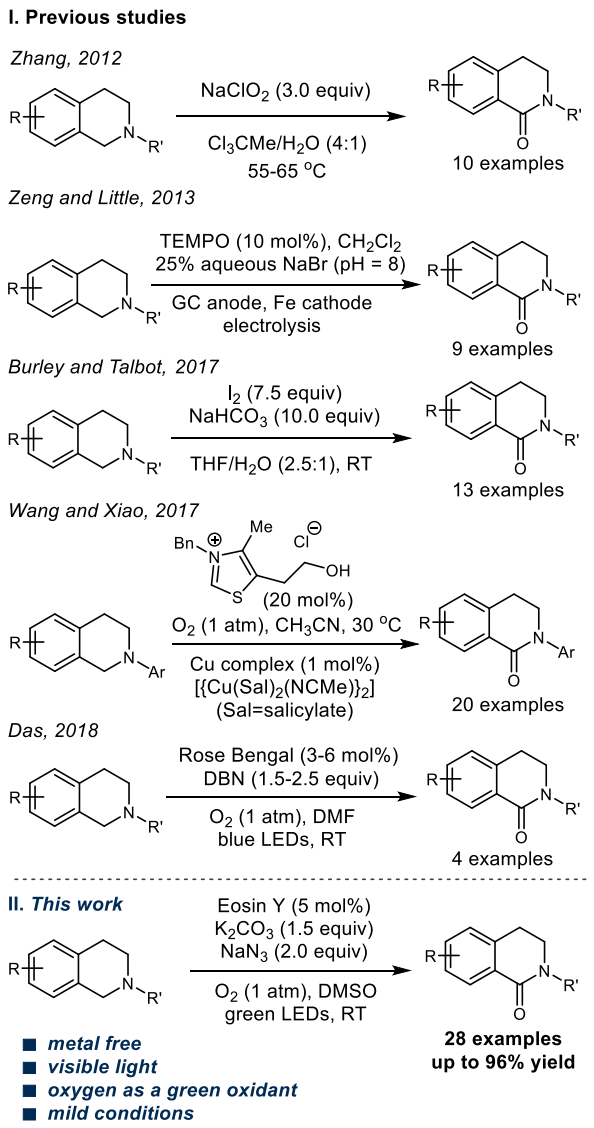
The direct α-oxidation of amines to lactams have proved to be a useful oxidative transformation.[6] This approach allows the formation of dihydroisoquinolones from tetrahydroisoquinolines through an α-oxidation. In particular, dihydroisoquinolones represent useful synthetic precursors of various organic molecules and bioactive compounds.[7] In addition, these compounds exhibit numerous important biological activities such as antimalarial,[8] antitussive,[9] and antiparkinsonian properties,[10] and display a mitochondrial branched chain aminotransferase (BCATm) inhibition effect (Scheme 1).[11]



Scheme 1. Bioactive compounds containing the dihydroisoquinolone moiety.

Common methods for the synthesis of dihydroisoquinolones rely on transition metal-mediated reactions and/or multi-step processes.[7b, 12] However, the α-oxidation of tetrahydroisoquinolines is considered as the most efficient and direct approach for their preparation.[6g] While the significance of this transformation has increased, only a limited number of reports of this method are known.[13] For example, Zeng and Little examined the electrochemical oxidative functionalization of benzylic C-H bonds for the synthesis of *N*-substituted tetrahydroisoquinolones.[13e] More recently, Wang and Xiao reported on a direct oxidation procedure for the synthesis of *N*-aryl dihydroisoquinolones from *N*-

aryl tetrahydroisoquinolines using a binuclear copper complex. (Scheme 2, I).[6g]



Scheme 2. Synthetic approaches to dihydroisoquinolones *via* an α-oxidation of amines

However, these studies require specific reaction techniques such as cyclic voltammetry and electrolysis or the use of metal-based catalysts. Metal-free procedures have also been reported by the groups of Zhang,[13d] and Burley and Talbot[13g] with the use of stoichiometric amounts of oxidants and/or heating. Very recently, the Das group reported an efficient α-oxygenation of tertiary amines to amides *via* organo-photocatalysis (Scheme 2, I).[14] Furthermore, additional studies report the formation of dihydroisoquinolones from *N*-substituted tetrahydroisoquinolines as by-products in cross dehydrogenative coupling (CDC) reactions.[15] However, there are several limitations connected to the aforementioned methods. More specifically, the use of stoichiometric amounts of oxidants and metal-containing catalysts or reagents is cause for both environmental and economic concerns. In addition, the limited substrate scope and operational difficulties of these methods imply the ongoing demand for a novel and efficient approach. Herein, we report an efficient aerobic oxidation of *N*-substituted tetrahydroisoquinolines to dihydroisoquinolones *via* organo-photocatalysis under mild reaction conditions (Scheme 2, II).

We envisioned that the α-oxidation of *N*-substituted tetrahydroisoquinolines might be accomplished *via* a visible-light-induced process using oxygen as a green oxidant. In an effort to test this hypothesis, we employed 2-phenyl-1,2,3,4-tetrahydroisoquinoline **1aa** as a starting material and tested various reaction conditions (selected examples are summarized in Table 1). To achieve a green reaction mode, organic dyes such as eosin Y, rose bengal, and rhodamine B were examined. While low yields were detected in the cases of rose bengal (33%, not shown) and rhodamine B (40%, not shown), eosin Y was found to be more effective for this transformation, giving the desired product **2aa** in 53% yield (entry 1). Furthermore, a noticeable improvement in the yield was observed with the addition of K_2CO_3 to the reaction (entries 2–5). In fact, varying the amount of K_2CO_3 affected the outcome of the reaction, with a high yield being obtained in the presence of 1.5 equivalents of K_2CO_3 (73%, entry 4). Although other bases such as Na_2CO_3, Cs_2CO_3 and pyridine were also tested (entries 6–8), K_2CO_3 gave a higher reaction yield (entry 4). Solvent screening experiments revealed that diminished yields were obtained in DMF (44%, entry 9) and acetonitrile (27%, entry 10). Notably, varying the amount of eosin Y did not improve the yield (entries 11–13), even though the reaction still progressed in the presence of 0.5 mol% of eosin Y (61% yield, entry 13). However, eosin Y was deemed necessary for the reaction to proceed, since almost no transformation took place in its absence. (entry 14). Moreover, changing the light source diminished the reaction yield, giving the desired product **2aa** in 43% and 67% yields when blue or white LED light, respectively, was employed (entries 15 and 16). Importantly, no desired product was observed when the reaction was performed in the dark (entry 17). Furthermore, the reaction yield decreased when the transformation was performed under air (entry 18), and expectedly, no reaction was observed under argon atmosphere (entry 19). Interestingly, a significant improvement in the yield was obtained with the addition of NaN_3, which is known to be a strong singlet oxygen ($^1O_2$) quencher (entry 20). We assumed that NaN_3 would quench the singlet oxygen, thereby preventing the formation of additional side products during the reaction. Based on the results from the optimization studies, we concluded that a photocatalyst, visible light, and oxygen are necessary for this transformation to take place efficiently.

Table 1. Optimization of the reaction conditions.[a]

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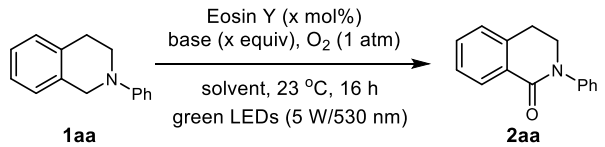


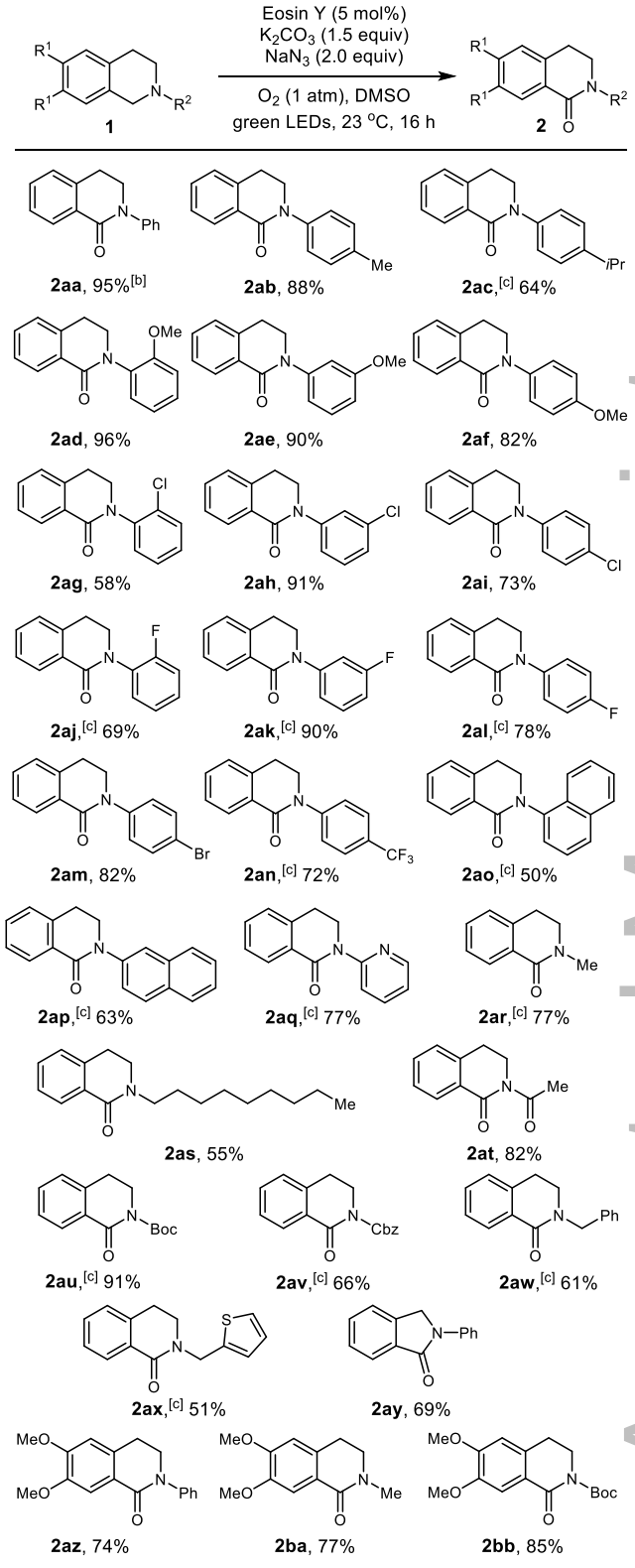
1aa **2aa**

Entry	mol% of eosin Y	Base (equiv)	Solvent	Yield (%)[b]
1	5	none	DMSO	53
2	5	K_2CO_3 (0.5)	DMSO	64
3	5	K_2CO_3 (1.0)	DMSO	68
4	5	K_2CO_3 (1.5)	DMSO	73
5	5	K_2CO_3 (3.0)	DMSO	69
6	5	Na_2CO_3 (1.5)	DMSO	70
7	5	Cs_2CO_3 (1.5)	DMSO	52
8	5	Pyridine (1.5)	DMSO	no rxn
9	5	K_2CO_3 (1.5)	DMF	44
10	5	K_2CO_3 (1.5)	CH_3CN	27
11	2.5	K_2CO_3 (1.5)	DMSO	61
12	1.0	K_2CO_3 (1.5)	DMSO	62
13	0.5	K_2CO_3 (1.5)	DMSO	61
14	none	K_2CO_3 (1.5)	DMSO	trace
15[c]	5	K_2CO_3 (1.5)	DMSO	43
16[d]	5	K_2CO_3 (1.5)	DMSO	67
17[e]	5	K_2CO_3 (1.5)	DMSO	no rxn
18[f]	5	K_2CO_3 (1.5)	DMSO	31
19[g]	5	K_2CO_3 (1.5)	DMSO	no rxn
20[h]	**5**	**K_2CO_3 (1.5)**	**DMSO**	**95**
21[i]	5	K_2CO_3 (1.5)	DMSO	74

[a]Reactions were conducted on a 0.5 mmol scale.
[b]Yields are of the isolated products after column chromatography.
[c]Under blue LED light irradiation
[d]Under white LED light irradiation
[e]In the dark
[f]Under air atmosphere
[g]Under Ar atmosphere
[h]NaN_3 (2.0 equiv) was added.
[i]NaN_3 (1.0 equiv) was added.

With the optimized reaction conditions in hand, we next explored the scope of the synthesis of dihydroisoquinolones (Table 2). Notably, the reaction was tolerant to various *N*-substituted tetrahydroisoquinolines. The desired α-oxidation products were obtained in moderate to high yields (50–96%). Various *N*-aryl substituted tetrahydroisoquinolines provided the desired dihydroisoquinolones in the presence of both electron-donating (**2ab**–**2af**) and electron-withdrawing (**2ag**–**2an**) substituents (58–96%). Moreover, the products derived from the *ortho*-, *meta*-, and *para*-substituted *N*-aryl tetrahydroisoquinolines were also obtained successfully (**2ad**–**2al**, 58–96%). However, diminished reaction yields were observed with electron-withdrawing substituents at the *ortho*-, and *para*-positions (**2ad** *vs* **2ag**, **2aj**, and **2af** *vs* **2ai**, **2al**, **2an**). In contrast, a noticeable electronic effect of *meta*-substituents was not observed in terms of the reaction yield (**2ae** *vs* **2ah**, **2ak**). Nevertheless, longer reaction times were required for fluoro- and trifluoromethyl-substituents (36 h: **2aj**–**2al**, **2an**).

Table 2. Substrate scope.[a]



[a]Reactions were conducted on a 0.5 mmol scale. Yields are of the isolated products after column chromatography.[b]Reaction was conducted on a 5 mmol scale [c]Performed for 36 h. For details, see the Supporting Information.

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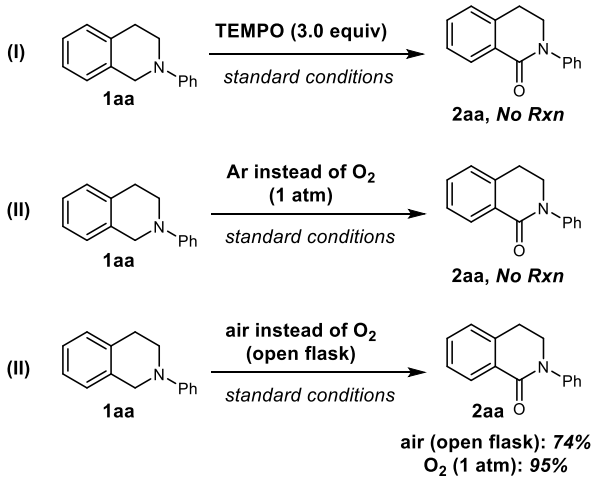
In addition, decreased reaction yields were observed with sterically demanding substituents containing methyl (**2ab**) and isopropyl (**2ac**) groups at the *para*-position of the benzene ring. Similarly, sterically hindered naphthyl substituted tetrahydroisoquinolines provided the desired products in moderate yields under the reaction conditions (**2ao**: 50%, **2ap**: 63%). Predominantly, these bulky substrates also required longer reaction times (36 h: **2ac**, **2ao**, **2ap**). We also examined other amine protecting groups such as methyl, acetyl, Boc, Cbz and benzyl groups (**2ar**, **2at**–**2aw**, **2ba**, **2bb**). The results showed that these protecting groups were all suitable under the reaction conditions, giving the desired products in moderate to high yields (61–91%). Furthermore, this method could be applied to the five-membered ring system, the desired isoindolinone **2ay** was obtained in good yield (69%).

In order to gain a mechanistic insight into this transformation, we performed various control experiments (Scheme 3). First, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was employed as a radical inhibitor, which did not afford the desired product, thereby indicating that the reaction mechanism includes a radical pathway. Additionally, the fact that no desired product was observed under argon atmosphere and the yield slightly decreased in air (open flask) prove that oxygen is the key oxidation source in this reaction.



Scheme 3. Control experiments.

To further probe the reaction mechanism, a Stern-Volmer quenching study was performed. The results showed that the luminescence of eosin Y could be readily quenched by 2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1aa**) (Figure 1). In contrast, no effect was observed with the addition of NaN_3 or K_2CO_3 (see the Supporting Information for details). Next, to determine the active species of oxygen in this transformation, an electron paramagnetic resonance (EPR) study was carried out. When we employed DMPO (5,5-dimethyl-1-pyrroline *N*-oxide) as the radical trapping agent, a characteristic signal of superoxide radical anion ($O_2^{\cdot-}$) was observed by EPR spectra (see the Supporting Information).[16] In addition, no desired product was observed when the reaction was performed in the presence of 2.0 equivalents of $FeSO_4$ which could react with the hydroperoxyl radical ($HOO^{\cdot}$).[15g]

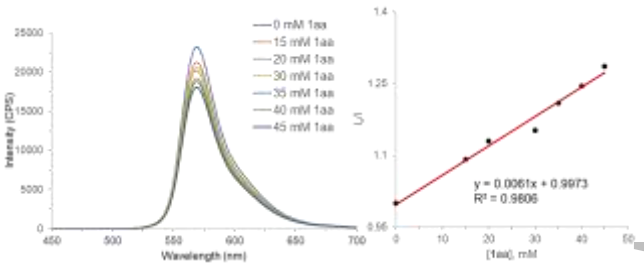
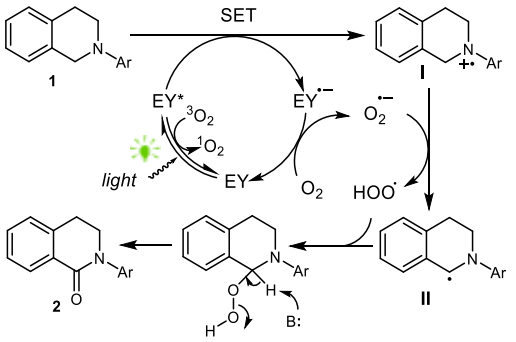


Figure 1. Catalyst quenching experiment. Fluorescence titration of 20 μM eosin Y (DMSO) while increasing the concentration of **1aa**. I_0 and I are the fluorescence intensities before and after the addition of **1aa**.

Based on the results from the present study and previous reports,[15g, 17] a proposed reaction pathway is shown in Scheme 4. First, eosin Y (EY) is excited under visible light irradiation to generate an excited state species (EY*). A single electron transfer from **1** to the excited state of eosin Y (EY^*) then generates aminyl cation radical **I** and $EY^{\cdot-}$. Subsequently, the reaction between oxygen and $EY^{\cdot-}$ results in the formation of a superoxide radical anion ($O_2^{\cdot-}$), which could then react with aminyl cation radical **I** to afford intermediate **II**. Followed by a reaction with the hydroperoxyl radical ($HOO^{\cdot}$), a proton abstraction by a base (B:) would provide the desired product **2**. In addition, EY* could also interact with O_2 to generate a singlet oxygen ($^1O_2$) *via* an energy transfer.[18] However, we assume that NaN_3 would quench the $^1O_2$ to suppress the formation of additional side products during the reaction.



Scheme 4. Proposed reaction pathway.

In summary, we have developed an efficient α-oxidation reaction of *N*-substituted tetrahydroisoquinolines to dihydroisoquinolones. The transformation features a visible-light-induced organo-photo catalyzed reaction with oxygen acting

as a green oxidant. Notably, this transformation did not require any metal catalysts or reagents. This method would provide a straightforward access to dihydroisoquinolones, which are important scaffolds of various bioactive compounds and other key synthetic intermediates.

Experimental Section

Typical Procedure for the α-oxidation reaction of tetrahydroisoquinolines

N-Substituted tetrahydroisoquinoline **1** (0.5 mmol, 1.0 equiv), eosin Y (0.025 mmol, 5 mol %), K_2CO_3 (0.75 mmol, 1.5 equiv), and NaN_3 (1.5 mmol, 2.0 equiv) were dissolved in dry DMSO (0.25 M). The reaction mixture was stirred and irradiated by 5 W green LEDs (530 nm) at room temperature under O_2 atmosphere for 16-36 h. After the reaction was completed, water (10 mL) and EtOAc (10 mL) were added, and the mixture was extracted by EtOAc (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography afforded the corresponding product.

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UPDATE

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