Porphyrin-Catalyzed Oxidation of N-Substituted Tetrahydroisoquinolines to Dihydroisoquinolones

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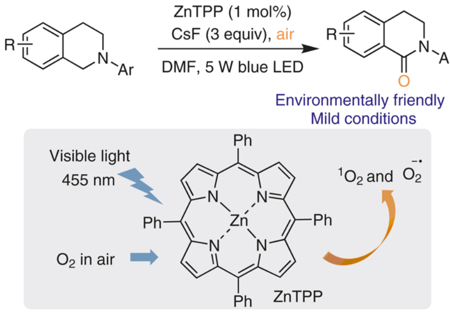

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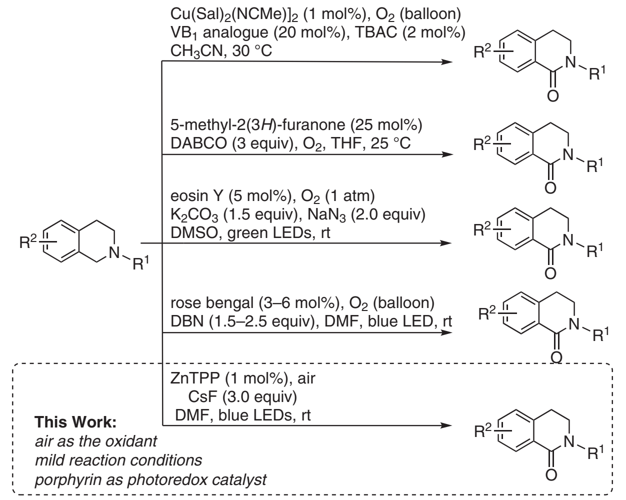
Abstract A visible-light-induced direct α-oxygenation of N-substituted 1,2,3,4-tetrahydroisoquinoline derivatives has been successfully developed. Tetraphenylporphyrinatozinc(II) has been identified as an effective and inexpensive photocatalyst for this transformation with a wide range of substrates. This protocol provides a convenient route to the desired products in moderate to good yields at room temperature under air.

Key words photocatalysis, oxidation, porphyrins, zinc catalysis, dihydroisoquinolones

Oxidation is one of the most important reactions in organic synthesis. Most reported oxidation reactions rely on stoichiometric amounts of such oxidants as metal oxidants, DDQ, PhI(OAc)$_2$, or peroxides.[1] Air, as a natural oxidant, plays an important role in various life processes to provide energy, and is also widely used in oxidation reactions.[2] One of the desired goals of green chemistry is to make rational use of air to realize conversions of specific substances to replace conventional oxidation.

Porphyrin derivatives exist widely in Nature, serving as photosensitizers in photosynthesis[3] as well as oxidative reaction centers of heme enzymes, such as peroxidases, catalases, and cytochromes P450, which show excellent characteristics in the utilization of light and oxygen.[4] As photosensitizers, porphyrins can be easily prepared and modified[5], and they have recently been used to catalyze the epoxidation of α,β-unsaturated ketones and the oxidation of primary amines and secondary amines.[6] More environmentally friendly oxidative reactions using porphyrin as photosensitizer and air as oxidant need to be explored.

Because amines and lactams form a large group of bioactive substances, α-oxidation of amines to form lactams is a useful oxidative transformation.[7] Dihydroisoquinolone moieties are present in many natural products and biologically active molecules.[8] Many efficient methods have been developed for the construction of dihydroisoquinolones.[2a,8b,9] Among the reported methods, the α-oxidation of tetrahydroisoquinolines is a particularly direct and attractive strategy.[10] Besides conventional metal oxidants, the use of metal-free oxidants to achieve this synthesis has attracted much attention; examples include oxidation by NaClO$_2$ and an aerobic oxidation catalyzed by cobalt(II) porphyrins.[11] In particular, recently reported oxygen oxidations using 5-methylfuran-2(3*H*)-one or a binuclear copper com-



Scheme 1 Methods for the synthesis of dihydroisoquinolones by α-oxidation with dioxygen

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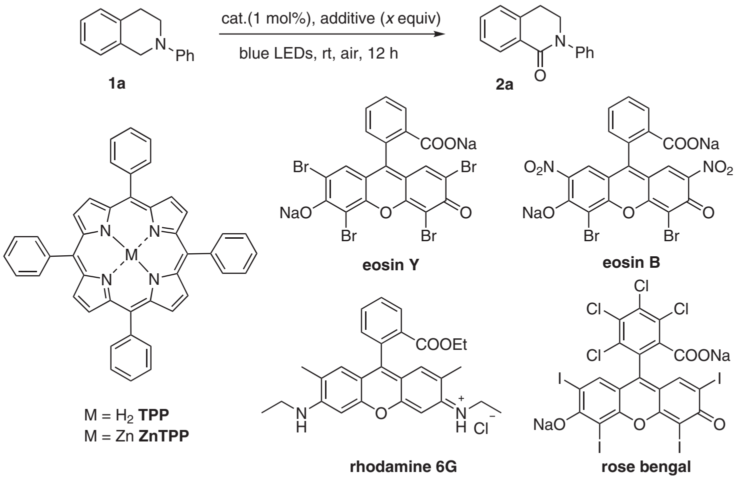
plex combined with a vitamin B_1 analogue as catalysts, as well visible-light-induced oxidations, have attracted much attention (Scheme 1).[7d,12] Among these, visible-light-induced α-oxidations have been shown to be effective and environmentally friendly metal-free strategies. Therefore, there is great interest in developing simple and environmentally friendly photocatalytic oxidation reactions. Here we report an efficient aerobic oxidation of N-substituted 1,2,3,4-tetrahydroisoquinolines to 3,4-dihydroisoquinolin-1(2*H*)-ones through organophotocatalysis using a porphyrin as a photosensitizer under mild conditions.

Initially, we selected *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) as a model substrate and oxygen (air) as a green oxidant to explore the feasibility of the target α-carbonylation (Table 1). When the reaction was performed in the presence of tetraphenylporphyrinatozinc(II) (ZnTPP) in DMF with irradiation by a 5 W blue LED for 12 hours at room temperature, *N*-phenyl-3,4-dihydroisoquinolin-

Table 1 Screening of Conditions for Visible-Light-Induced Direct α-Oxygenation of the N-Substituted Tetrahydroisoquinoline **1a**[a]



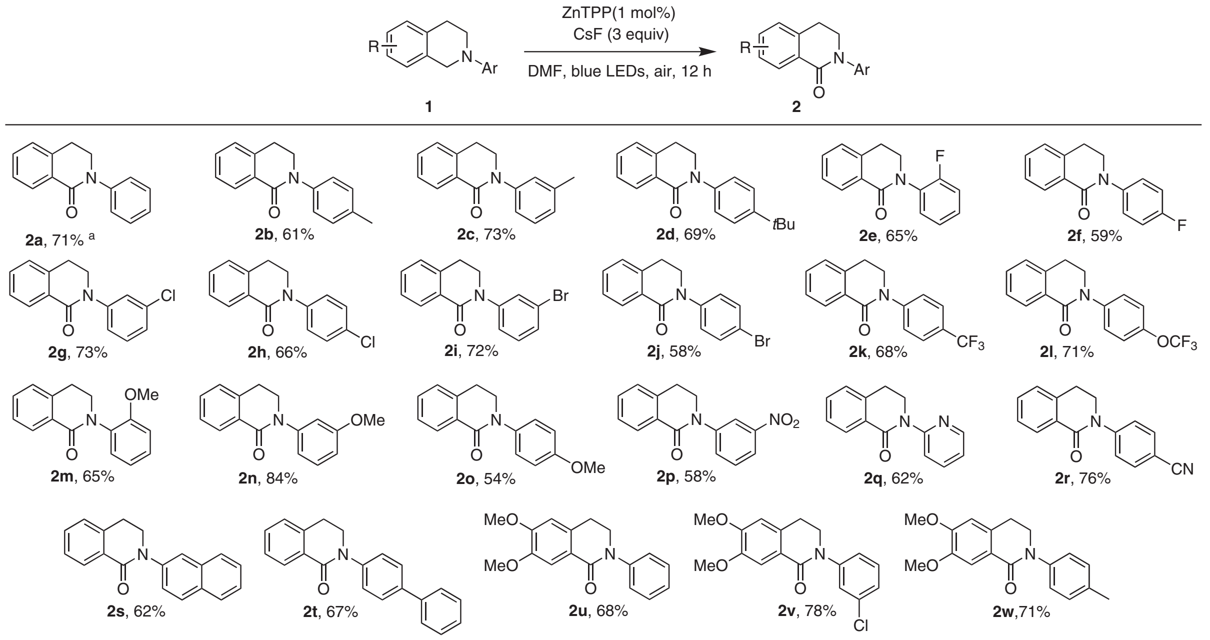
Entry	Catalyst	Additive (equiv)	Solvent	Yield[b] (%)
1	ZnTPP	–	DMF	23
2	ZnTPP	CsF (3.0)	DMF	71
3	ZnTPP	NaF (3.0)	DMF	15
4	ZnTPP	KF (3.0)	DMF	25
5	ZnTPP	Na_2CO_3 (3.0)	DMF	15
6	ZnTPP	K_2CO_3 (3.0)	DMF	45
7	ZnTPP	Cs_2CO_3 (3.0)	DMF	41
8	ZnTPP	CsF (1.0)	DMF	62
9	ZnTPP	CsF (5.0)	DMF	62
10	TPP	CsF (3.0)	DMF	60
11	eosin Y	CsF (3.0)	DMF	41
12	eosin B	CsF (3.0)	DMF	29
13	rose bengal	CsF (3.0)	DMF	54
14	rhodamine 6G	CsF (3.0)	DMF	–[c]
15	ZnTPP	CsF (3.0)	DMSO	41
16	ZnTPP	CsF (3.0)	MeCN	9
17	ZnTPP	CsF (3.0)	CH_2Cl_2	8
18	ZnTPP	CsF (3.0)	THF	6

[a] Reaction conditions: **1a** (0.10 mmol), photocatalyst (0.001 mmol), additive, solvent (1.0 mL), 5 W blue LEDs, rt, 12 h, air atmosphere.
[b] Determined by ^1H NMR with Ph_2CHCN as an internal standard.
[c] No reaction.

1(2*H*)-one (**2a**) was obtained in 23% yield (Table 1, entry 1). To our delight, on addition of 3.0 equivalents of CsF, an obvious enhancement in the yield of **2a** to 71% (entry 2) was detected. Subsequently, other additives, such as NaF, KF, and Cs_2CO_3 were also tested, but did not improve the reaction yield (entries 3–7). Other organophotocatalysts were then tested in this reaction at room temperature. Eosin B, eosin Y, and rose bengal provided the desired product **2a** in yields of 41, 29, and 54%, respectively (entries 11–13), whereas rhodamine 6G did not promote the formation of the target product. Compared with ZnTPP as a photocatalyst, the free base TPP gave a lower 60% yield (entry 10). Various solvents such as dimethyl sulfoxide (DMSO), acetonitrile, dichloromethane, and tetrahydrofuran (THF) were also surveyed (entries 15–18), but the results were unsatisfactory. Our results showed that the photocatalyst, oxygen (air), and visible light are all essential for the *ortho*-α-oxygenation reaction.

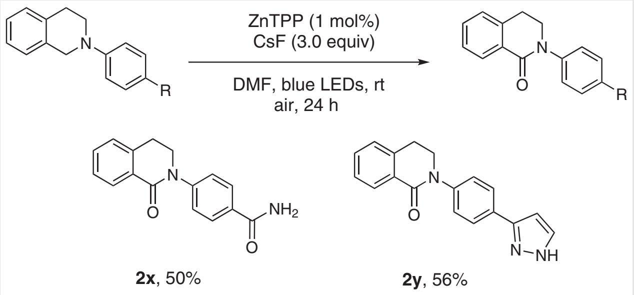
Subsequently, we investigated the visible-light-induced direct α-oxygenation of various N-substituted tetrahydroisoquinolines **1** in the presence of ZnTPP (1 mol%) and CsF (3 equiv) in DMF at room temperature for 12 hours (Scheme 2). Tetrahydroisoquinolines bearing various *N*-aryl groups with either electron-donating or electron-withdrawing substituents afforded the corresponding products **2a**–**t** in yields of 54–84%. Substrates containing various *para*-substituted *N*-phenyl groups gave similar yields; for example, yields of **2b**, **2f**, **2j**, and **2o** were moderate, ranging from 54 to 61%, although both electron-donating (methyl in **2b**, and methoxy in **2o**) and electron-withdrawing substituents (halogen in **2f** and **2j**) were involved. Interestingly, substrate **1r** with an electron-withdrawing *para*-cyano substituent gave **2r** in a higher yield of 76%. On the other hand, in the case of substrates with *meta*-substituted *N*-phenyl groups, those with electron-rich substituents gave higher yields than those with electron-withdrawing ones (e.g., **1c** and **1n** versus **1i** and **1p**). We also obtained good yield of products with *ortho*-substituted *N*-phenyl groups (**2e** and **2m**; 65% yield), an *N*-2-naphthyl group (**2s**; 62%), and an *N*-2-pyridyl group (**2q**; 62%). We then explored the effects of substituents on the tetrahydroisoquinoline moiety. Yields of **2v** and **2w**, (78 and 71%, respectively) were slightly higher than those of the corresponding substrates with no substituents on the tetrahydroquinoline moiety **2g** (73%) and **2b** (61%), probably indicating that substituents on the tetrahydroisoquinolines ring have an important effect on this reaction. Compared with the reaction using eosin Y as photosensitizer and NaN_3 as the additive,[12a] the reaction using ZnTPP as a photosensitizer gave the dihydroisoquinolones in lower yields, but under conditions that were more environmentally friendly, without using the toxic substance NaN_3.

Based on our experience with direct α-oxidation of tertiary amines to lactams, we became interested in applying this method to the synthesis of pharmaceuticals. In particular, dihydroisoquinolone derivatives can inhibit mitochondrial branched-chain aminotransferase (BCATm).[13] Targeted drug molecules were synthesized under our optimized re-



Scheme 2 Substrate scope of the visible-light-induced direct α-oxygenation. *Reagents and conditions*: **1a** (0.10 mmol), ZnTPP (0.001 mmol), CsF (3 equiv), DMF (1.0 mL), 5 W blue LEDs, rt, 12 h, air atmosphere. Isolated yields are reported. [a] A 51% yield was obtained and 17% of **1a** was recovered when the reaction was conducted on a 5 mmol scale.

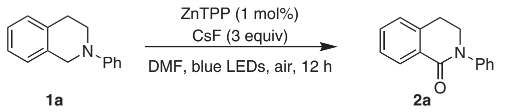
action conditions (Scheme 3). To our delight, both of the desired inhibitors **2x** and **2y** were obtained efficiently in yields of 50 and 56%, respectively from the corresponding *N*-aryl-substituted tetrahydroisoquinolines in one-step under our mild conditions. Compared with the previously reported methods involving two-step reactions,[13] the synthesis through direct α-oxidation is more efficient with a higher yield. These results showed that this method has the potential for broad application in the functionalization of drug molecules and natural products.



Scheme 3 Synthesis of bioactive chemicals

To gain some insight into the reaction mechanism, we conducted several control experiments (Table 2). The reaction did not proceed under an argon atmosphere, indicating that the added oxygen atoms in the desired product were mainly obtained from molecular oxygen (Table 2, entry 1). The reaction did not proceed in the absence of light or a photocatalyst (entries 2 and 3), suggested that both light and the photocatalyst are driving forces for this α-oxygenation reaction. When (2,2,6,6-tetramethyl-1-piperidinyl)oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the model reaction, the oxidation process was completely suppressed (entries 4 and 5), indicating that the reaction might involve a radical process. Furthermore, the reaction was significantly inhibited in the presence of the singlet-oxygen inhibitor 1,4-diazabicyclo[2,2,2] octane (DABCO) (entry 6). Therefore, singlet oxygen might be responsible for the oxygenation reaction. Additionally, we also found that adding large amounts of water to the reaction system had only a slight effect on the yield, suggesting the reaction conditions are not too rigorous.

Table 2 Control Experiments[a]



Entry	Controlled parameter	Yield (%)
1	Ar instead of air	trace
2	no light	–
3	no catalyst	–
4	TEMPO (10 equiv)	58
5	BHT (10 equiv)	22
6	DABCO (2.5 equiv)	26
7	H_2O (5 equiv)	68
8	H_2O (25 equiv)	61

[a] Reaction conditions: **1a** (0.10 mmol), ZnTPP (0.001 mmol), CsF (0.30 mmol), DMF (1.0 mL), 5 W blue LEDs, rt, 12 h, air atmosphere.

To obtain further information on the photocatalytic mechanism, we performed Stern–Volmer fluorescence-quenching experiments (Figure 1). As the substrate concentration was increased, a dramatic decrease in the fluorescence intensity was observed. In contrast, added CsF and dioxygen did not interact with the excited state of the photocatalyst. These results suggested that the luminescence of ZnTPP was quenched by *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**).

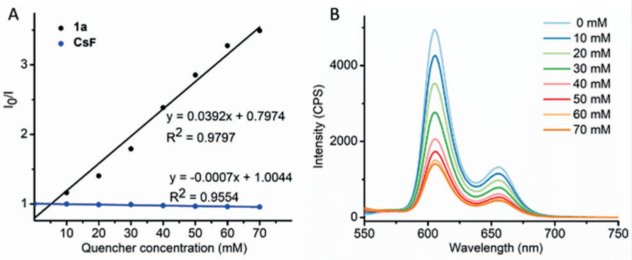
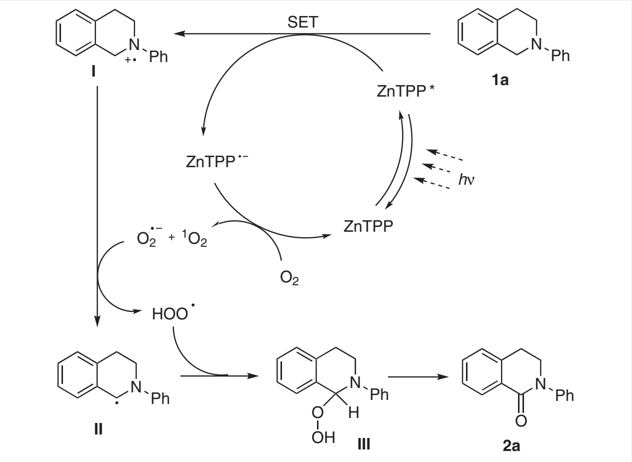


Figure 1 (A) Stern–Volmer luminescence quenching experiments using a 20 μM solution of ZnTPP and various concentrations of **1a** and CsF in DMF. (B) The fluorescence spectra for titration of **1a** with ZnTPP (20 μM) in DMF.

On the base of the above experimental results and previous reports in the literature,[12a] a possible mechanism for this oxidation reaction is proposed in Scheme 4. First, the photocatalyst is excited by visible-light irradiation to generate an excited-state species ZnTPP*. A single-electron transfer from ZnTPP* to **1a** provides two radicals, **I** and $\text{ZnTPP}^{\cdot-}$. Singlet oxygen ($^1O_2$) and superoxide radical anion($O_2^{\cdot-}$) are produced from O_2 through energy transfer from $\text{ZnTPP}^{\cdot-}$. $O_2^{\cdot-}$ reacts with the aminyl cation radical **I** to give intermediate **II** and a peroxide radical ($HOO^{\cdot}$). Subsequently, the reaction between the peroxide radical and radical **II** results in the formation of intermediate **III**. Finally, the desired product **2a** is obtained by elimination of a water molecule.

In conclusion, we have successfully developed a sustainable and cost-effective method for α-oxygenation of cyclic tertiary amines by a photocatalyzed reaction of *N*-aryltetrahydroisoquinolines in the presence of ZnTPP under visible-light irradiation.[13] Under the optimal reaction conditions, a broad range of substrates were tolerated well, providing highly practical access to various valuable dihydroisoquinolone compounds in moderate to good yields. More significantly, this is a potent method for the oxygenation of natural products and for the synthesis of bioactive chemicals. In



Scheme 4 Proposed reaction mechanism

addition, porphyrins are easily prepared and modified, and therefore have great potential in photocatalytic reactions. Further research on the application of porphyrins in other types of photocatalytic reactions is currently underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1345-3491.

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(14) **3,4-Dihydroisoquinolin-1(2*H*)-ones 2a–t; General Procedure**
The appropriate *N*-aryltetrahydroquinoline **1** (0.1 mM, 1 equiv), ZnTPP (0.001 mM, 1% equiv, 0.68 mg), and CsF (0.3 mM, 3 equiv, 46 mg) were added to DMF (0.1 M), and the mixture was stirred at rt and irradiated by blue LEDs under air overnight. The mixture was then extracted with CH_2Cl_2 and the extracts were washed with H_2O. The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure, and the crude product was purified by column chromatography (silica

gel, PE–EtOAc).

2-Phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (2a)

White solid; yield: 15.8 mg (71%); mp 100–101 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.4 Hz, 1 H), 7.40 (dq, *J* = 16.8, 8.0 Hz, 5 H), 7.25 (d, *J* = 10.5 Hz, 2 H), 4.00 (t, J = 6.4 Hz, 2 H), 4.00 (t, 3.15 (t, *J* = 6.4 Hz, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.2, 143.1, 138.3, 132.0, 129.7, 128.9, 128.7, 127.2, 126.9, 126.2, 125.3, 49.4, 28.6. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{13}NNaO$: 246.0895; found: 246.0889.