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Visible Light Photocatalytic Aerobic Oxygenation of Indoles and pH as Chemoselective Switch

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ABSTRACT: An efficient chemodivergent strategy for visible light photocatalysis is developed. In the presence of dicyanopyrazine-derived chromophore (DPZ) photocatalyst, aerobic photooxygenation of indoles could present either isatins or formylformanilides in satisfactory yields by judiciously selecting inorganic salts or modulating reaction pH. The current chemodivergent method is also effective to 2-substituted indoles, opening straightforward synthetic routes to valuable 2,2-disubstituted 3-oxindoles, formylformanilide derivatives and benzoxazinones. Mechanistic investigations involving cyclic voltammetry studies further confirm that reaction pH influences the electrochemical properties of DPZ, thus affecting the oxidative pathway which indoles are being transformed.

KEYWORDS: *photocatalysis, visible light, electron transfer, energy transfer, chemodivergence*

Introduction

Tunable reactions that allow chemoselectivity under controlled experimental conditions greatly expands molecular diversity.[1] Therefore such reaction strategy is greatly important in organic and medicinal chemistry.[1] In recent years, visible light photocatalysis has attracted significant attention,[2] and as a result several elegant solutions to address chemoselective switch have been developed.[3] For example, molecular oxygen O_2 was found to influence and switch chemical routes by triggering the radical addition/cyclization pathway, while in its absence a more straightforward intermolecular addition pathway between tertiary amines and electron-deficient alkenes is operative.[3a] Inorganic salts were also found to effectively regulate radical processes, producing selectively more than two kinds of products.[3b,c] In these examples, the chemical manipulation of reactants to undergo different reaction pathways and be transformed to different products is challenging but rewarding.

Photocatalysts are known to activate organic substrates via photosensitization,[2a] which could be attributed by two main mechanistic considerations, namely the photoredox single electron transfer (SET) or energy transfer (ET). While there are a number of reports on photocatalysts which primarily behave as a photoredox agent,[2] there are also reports where photocatalysis is dominated by the energy transfer pathway.[4] In the same vein, if a single photocatalyst could be tuned by reaction conditions or additives and conferring it an amenable chemoselective character, this would allow versatility in the manipulation of substrates to the desired product efficiently and conveniently.

In recent years, we have developed visible light photocatalysis using dicyanopyrazine-derived chromophore (DPZ) based photocatalyst.[3c,5] Herein we report an expedient and efficient chemodivergent strategy catalyzed by DPZ towards photooxygenation of indoles and 2-substituted indoles (Figure 1). By adjusting reaction pH, electrochemical properties of DPZ could be tweaked thus allowing selective oxygenation pathways via two distinct pathways (see mechanistic proposal). Several pairs of diverse nitrogen-containing molecules, including isatins, trytanthrin, formylformanilides and derivatives, benzoxazinones, and 2-indole/methoxy-substituted 3-oxindoles could be synthesized with satisfactory results.

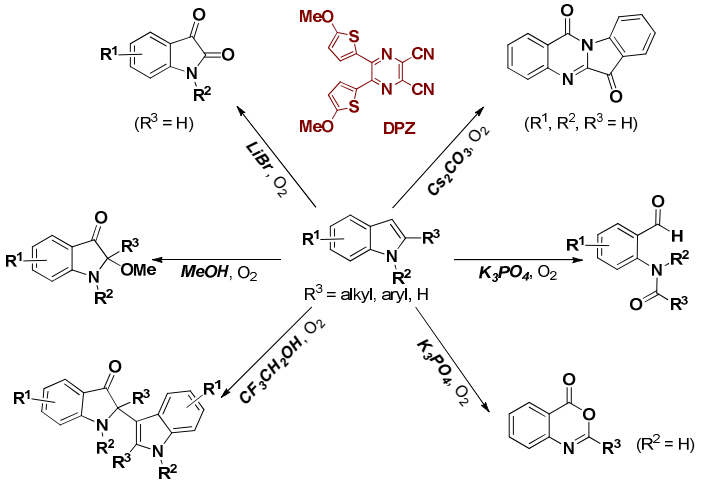


Figure 1. Chemodivergence in DPZ-catalyzed visible light aerobic photooxygenation of indoles and 2-substituted indoles.

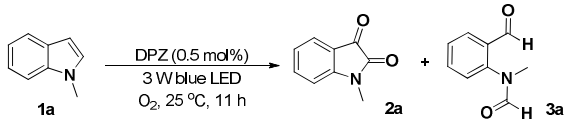
Catalytic oxidation[6] of readily available indoles has been acknowledged as a powerful tool to access valuable isatins[7]. However, no successful example with visible light photocatalysis has been reported to date. Hollmann and co-workers[8] demonstrated that visible light-driven oxygenation of indoles using chloroperoxidase as the catalyst afforded 2-indolinones but not isatins. The oxidative cleavage of C1-C2 double bonds of indoles to generate formylformanilides, that are the ubiquitous synthetic features of pharmaceuticals,[9-11] also representing a highly desirable task in visible light photocatalysis. The extensive employment of indoles in photocatalytic cross-dehydrogenative coupling (CDC) reactions[12] under ambient conditions and atmosphere precisely demonstrates their relative stability. Indoles featuring substituents on positions 2-, 3- or both are shown to more easily undergo oxygenation through SET[3a,13] or ET[14] process under visible light activation. However, only a few examples in photooxygenation of 2-substituted indoles to afford biologically important formylformanilide derivatives,[8–10] 2-indole/methoxy-subsituted 3-oxindoles[15] and benzoxazinones,[16] have been disclosed.[13a,14c-e]

Results and Discussion

Optimization of reaction conditions. We initiated our study with *N*-methyl indole **1a** as the model starting material using 0.5 mol% of DPZ as the photocatalyst under oxygen atmosphere at 25 ^{o}C and irradiation with a 3 W blue LED (450−455 nm) (Table 1). The reaction was first carried out in CH_2Cl_2 and toluene but the desired products were formed

only in negligible amounts (entries 1 and 2). However, by changing the solvent to acetonitrile, the reaction was completed within 11 hours affording two products, *N*-methyl isatin **2a** and 2'-formylformanilide **3a**, in the ratio of 5:1 (entry 3).

Table 1. Optimization of the Reaction Conditions[a]



entry	conditions	conv. (%)[b]	**2a**/**3a**[b]
1	CH_2Cl_2, 0.1 M	7	N.D.
2	Toluene, 0.1 M	6	N.D.
3	CH_3CN, 0.1 M	>99	5:1
4	NaH_2PO_4 (0.1 eq.), CH_3CN, 0.1 M	>99	9:1
5	LiBr (0.1 eq.), CH_3CN, 0.1 M	>99[c]	18:1
6	LiBr (0.2 eq.), H_2O (30 eq.), CH_3CN, 0.05 M	>99[d]	25:1
7	K_3PO_4 (1.0 eq.), CH_3CN, 0.1 M	13	1:3
8	K_3PO_4 (3.0 eq.), CH_3CN/H_2O = 10:1, 0.05 M	80[e]	1:20
9	LiBr (0.2 eq.), H_2O (30 eq.), CH_3CN, 0.05 M, ***no light***	N.R.	N.A.
10	K_3PO_4 (3.0 eq.), CH_3CN/H_2O = 10:1, 0.05 M, ***no light***	N.R.	N.A.
11	***no DPZ***, LiBr (0.2 eq.), H_2O (30 eq.), CH_3CN, 0.05 M, 48 h	N.R.	N.A.
12	***no DPZ***, K_3PO_4 (3.0 eq.), CH_3CN/H_2O = 10:1, 0.05 M, 48 h	N.R.	N.A.

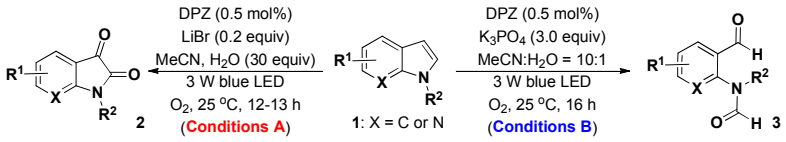
[a]The reaction was performed on a 0.05 mmol scale, 3 W blue LED (450−455 nm), 25 °C, ambient atmosphere. [b]Determined by ^{1}H NMR spectra of the crude reaction mixture. [c]Isolated yield of **2a** = 41 %. [d]Isolated yield of **2a** = 68 %. [e]Isolated yield of **3a** = 74 %. N.R. = no reaction. N.A. = not available.

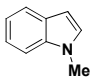
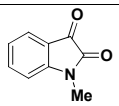
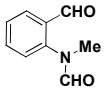
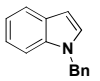
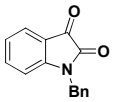
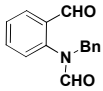
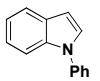
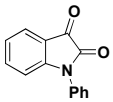
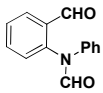
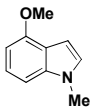
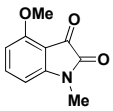
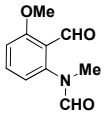
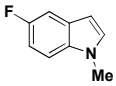
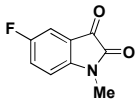
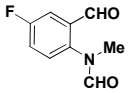
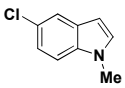
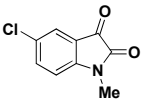
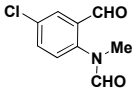
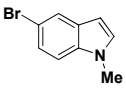
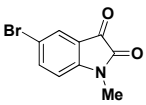
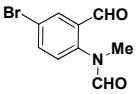
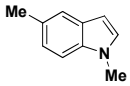
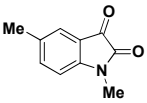
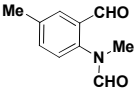
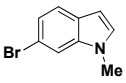
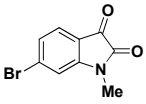
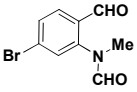
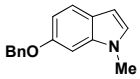
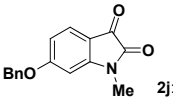
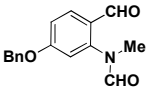
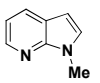
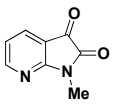
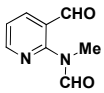
Subsequently, we attempted to screen various additives in order to improve the chemoselectivity (entries 4−5). It was found that the ratio increased to 18:1 when using 0.1 eq. of LiBr (entry 5). The isolated yield is 41 %, and an unknown precipitate was observed suspected due to radical polymerization.[17] The yield of **2a** increased to 68 % when the amount of LiBr was

increased to 0.2 eq. and an extra 30 eq. of H_2O was added to dilute the reaction mixture (entry 6). Alternatively, K_3PO_4 used as an additive was found to tune the chemoselectivity towards **3a** (entry 7). When 3.0 eq. of K_3PO_4 was used in CH_3CN/H_2O (10:1), **3a** was obtained as the major product in 74% yield (entry 8). No reaction was observed with just DPZ in absence of light (entries 9−10). Similarly, when no DPZ was added but under irradiation, no **2a** or **3a** products were observed (entries 11−12). Photoactivation thus requires the presence of both light and the photocatalyst DPZ as essential ingredients for the photooxygenation reaction to occur.

Substrate scope towards indoles. With the optimized conditions determined, we then extended the scope of oxygenation of indoles to isatins (0.5 mol% of DPZ, 0.2 eq. of LiBr, 30 eq. of H_2O, CH_3CN, 25 ^oC, 3 W blue LED, oxygen atmosphere: Conditions A) (Table 2). Indoles **1a-j** with various substituents at the *N*-, 4-, 5-, 6- and 7-positions underwent this reaction readily and delivered the expected isatins **2a-j** in moderate yields. Starting material **1k** with the fused pyridine ring was also compatible with the reaction conditions. Under Conditions A formylformanilides were not observed in all reactions. The same substrates **1a-k** were also examined in photooxygenation to formylformanilides under the reaction Conditions B (0.5 mol% of DPZ, 3.0 eq. of K_3PO_4, CH_3CN:H_2O = 10:1, 25 ^oC, 3 W blue LED, ambient atmosphere). A series of formylformanilides **3a-k** were obtained in 53−86% yields within 16 hours.

Table 2. Chemoselective Synthesis of 2 and 3[a]

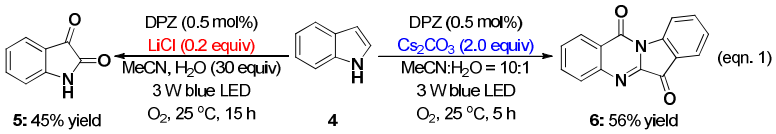


substrate		**2**, yield (%)[b] (Conditions A)		**3**, yield (%)[b] (Conditions B)	
	**1a**		**2a**: 63%		**3a**: 78% (86%)
	**1b**		**2b**: 65%		**3b**: 76% (96%)
	**1c**		**2c**: 67%		**3c**: 71% (85%)
	**1d**		**2d**: 60%		**3d**: 58%[c] (89%)
	**1e**		**2e**: 65%		**3e**: 75% (87%)
	**1f**		**2f**: 71%		**3f**: 86% (92%)
	**1g**		**2g**: 60%		**3g**: 72% (86%)
	**1h**		**2h**: 64%		**3h**: 66%[d] (84%)
	**1i**		**2i**: 66%		**3i**: 78% (88%)
	**1j**		**2j**: 56%		**3j**: 53%[e] (85%)
	**1k**		**2k**: 66%		**3k**: 62% (86%)

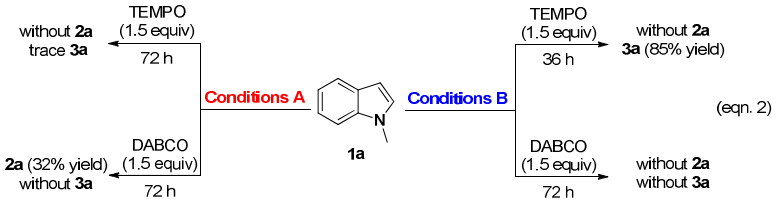
[a]The reaction was performed on a 0.1 mmol scale. See Supporting Information for detailed Conditions A and Conditions B. *In parentheses, the isolated yield was obtained by utilizing 10%*

TEMPO as additives after 17-18 h. [b]Yields of isolated products. [c]**2d** was obtained in 10% yield. [d]**2h** was obtained in 10% yield. [e]**2j** was obtained in 18% yield.

The unsubstituted *N*-H Indole **4** was attempted next (eqn. 1). Under the reaction Conditions A and using LiCl as the additive, the reaction completed in 15 hours, affording isatin **5** in 45% yield. Chemoselectivity switch was accomplished under the reaction Conditions B (Cs_2CO_3 instead of K_3PO_4 was used), giving tryptanthrin **6** in 56% yield. The tryptanthrin alkaloid **6** is an important bioactive compound, possessing antifungal, antibacterial and cytotoxic activity against B-16 melanoma cells.[18]



Mechanistic Observations. To gain mechanistic insights into this chemoselective reaction, investigations using *N*-methyl indole **1a** as the model substrate were further carried out (eqn. 2). Addition of TEMPO as radical scavenger under the reaction Conditions A suppressed the formation of **2a** and only traces of **3a** was detected. On the other hand, using 1.5 equivalents of a singlet-oxygen quencher DABCO, the reaction was sluggish but **2a** was obtained in 32% yield after 72 hours. Under the reaction Conditions B, DABCO effectively inhibited the reaction but surprisingly for TEMPO as additive, the yield of **3a** spiked to 85%. This led us to hypothesize that by inhibiting formation of reactive radical species through SET, the photosensitization pathway via ET will be preferred. When 10 mol % of TEMPO was used (versus none) **1** was transformed to formylformanilides **3** in significantly improved yields (84−96%, Table 2, see the data in parentheses). Taken together, the formation of isatins **2** would be believed to originate from SET process and alternatively, an ET process derives formylformanilides **3** from indoles **1**.



We looked next at how this photocatalytic process is affected by attenuating the redox properties of DPZ, and thus probed the catalyst with a series of cyclic voltammetry (CV) measurements.[19] First, LiBr was found to slightly enhance DPZ's redox ability but with K_3PO_4,

the oxidative cycle of DPZ was suppressed significantly. The pH under the reaction Conditions A and B were determined as 5.3 and 12.7 respectively, and under basic conditions a higher ratio of **3a**/**2a** was observed (Figure 2A). The same tendency could be duplicated when using diverse pH buffers instead of water under the reaction Conditions B but without K_3PO_4 (Figure 2B). Thus, reaction pH is crucial in affecting the redox properties of DPZ. When we measured the phosphorescence of DPZ, the emission maxima at 566 nm indicates a triplet state DPZ, ^{3}DPZ*. A robust decreasing tendency was observed when increasing the concentration of **2a** in phosphorescence quenching experiments.[19] So K_3PO_4 either suppresses the indole reduction of ^{3}DPZ* to DPZ$^{-\bullet}$ or the O_2 oxidation of DPZ$^{-\bullet}$ to DPZ in the SET cycle. Naturally by shutting down the SET pathway, ET would be operative instead. Our theoretical calculations indicate that the triplet energy (E_T) of DPZ is 46.4 kcal/mol,[19] which implies that triplet photosensitization of $^3O_2$ to $^1O_2$ ($E(^1\Delta\text{-}^3\Sigma)$ = 22.5 kcal/mol)[20] by the ^{3}DPZ* is feasible (see proposed mechanism Scheme 1). On the contrary, ET between ^{3}DPZ* and indole is impossible (e.g. *N*-methyl indole has E_T = 69.3 kcal/mol[21]). Based on the cyclic voltammogram, ^{3}DPZ* is a strong oxidant [E^t (S*/S$^{-\bullet}$) = 0.91 V vs SCE in CH_2Cl_2] and is able to oxidize indoles ($E^{red}_{1/2}$ ~ −0.04 V vs SCE)[13b] through a SET process. The generated DPZ$^{-\bullet}$ ($E^{red}_{1/2}$ = −1.45 V vs SCE in CH_2Cl_2) has the ability to reduce molecular oxygen ($E^{red}_{1/2}$ = −1.23 V vs SCE) to afford $O_2^{-\bullet}$ species. On the basis of these observations, it is reasonable that by modulating the reaction pH, electrochemical properties of DPZ could be tuned by different additives and generating either the reduced $O_2^{\bullet-}$ or excited singlet $^1O_2$ species. The outcome of ROS affects the oxidative pathway of indoles to either products **2** or **3**.

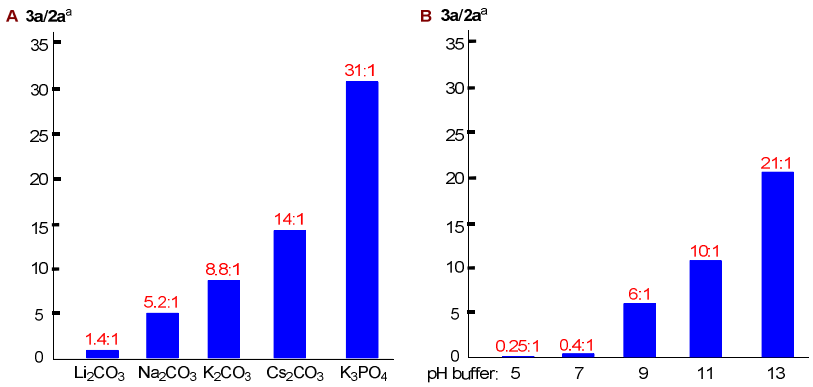
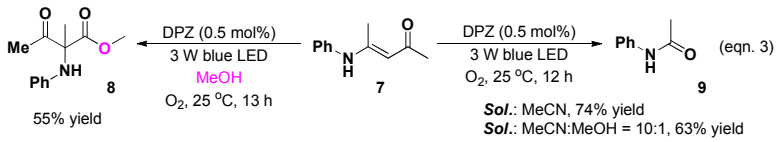


Figure 2. Chemoselectivity influenced by the strength of bases and pH buffers. [a]Determined by crude ^{1}H NMR.

To further demonstrate the utility of DPZ in generating $^1O_2$ species, aerobic oxidation of 4-(phenylamino)pent-3-en-2-one **7** employing DPZ as the catalyst under irradiation was carried out (eqn. 3). A secondary enamino ketone **8** was isolated in 55% yield, which is formed through singlet $^1O_2$ initiated 1,2-acyl migration as previously reported by Li[4c] and Wu[4d] groups. When the solvent was changed to MeCN, the chemoselectivity switched and the reaction proceeded by SET process affording amide **9** as the product in 74% yield. The SET process was also possible in a 10:1 mixture of CH_3CN and MeOH. To our knowledge, this is the first example of photocatalytic oxidative cleavage of secondary enamino ketones to generate amides.



Isotope-labeling studies were subsequently performed, and the results are summarized in Figure 3. When photo-oxygenation reaction of *N*-methyl indole **1a** was conducted under the reaction Conditions A and the ^{18}O-labeled $H_2{}^{18}O$ introduced, **2a** was found to have about 30% with single ^{18}O atom incorporation, while the rest were non-labeled **2a**. Subsequently, the reaction was attempted using $H_2{}^{16}O$ with $^{18}O_2$, and only single or double labeled-^{18}O **2a** was detected. Double ^{18}O-labeled **2a** was obtained in a ratio of 1.2:1 to single ^{18}O-labeled **2a**. When both $H_2{}^{18}O$ and $^{18}O_2$ were used, a high level of two ^{18}O-labeled **2a** was achieved. These results suggest that the complex reaction mechanism involves molecular oxygen and water to a lesser extent. Isotope-labeling studies for the transformation of **1a** to **3a** under the reaction Conditions B was also carried out. First, with ^{18}O-labeled water, **3a** was generated with single labeled ^{18}O atom in 1:1 ratio to non-labeled, suggesting that H_2O is involved in the reaction. The ^{18}O incorporation could originate from exchange between the aldehyde and water,[22] and since double ^{18}O-labeled **3a** (FW = 167) was not detected, the ^{16}O-^{18}O exchange could be slow. Reaction with heavy isotope $^{18}O_2$ and non-labeled water gave **3a** labeled by at least an ^{18}O atom, but the incorporation level of **3a** with FW = 165 was slightly higher, revealing that one oxygen atom stems from O_2 and another derived from H_2O. Meanwhile, the reaction in the presence of $H_2{}^{18}O$ and $^{18}O_2$ gave **3a** with FW = 167 in high incorporation degree.

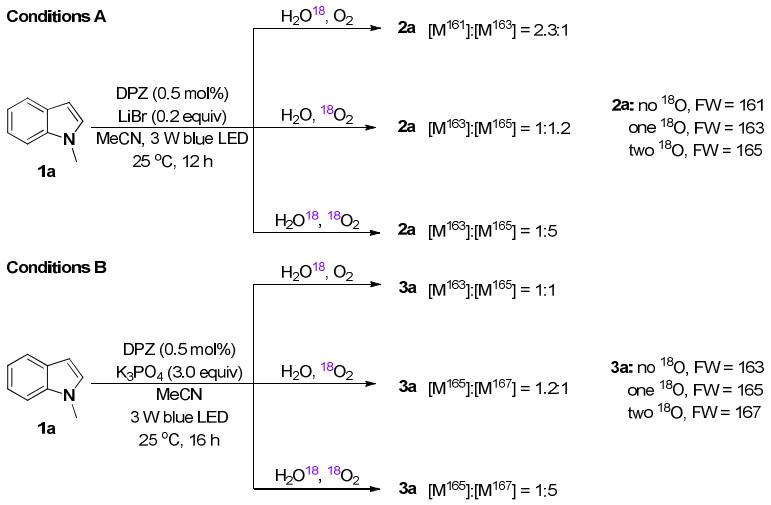
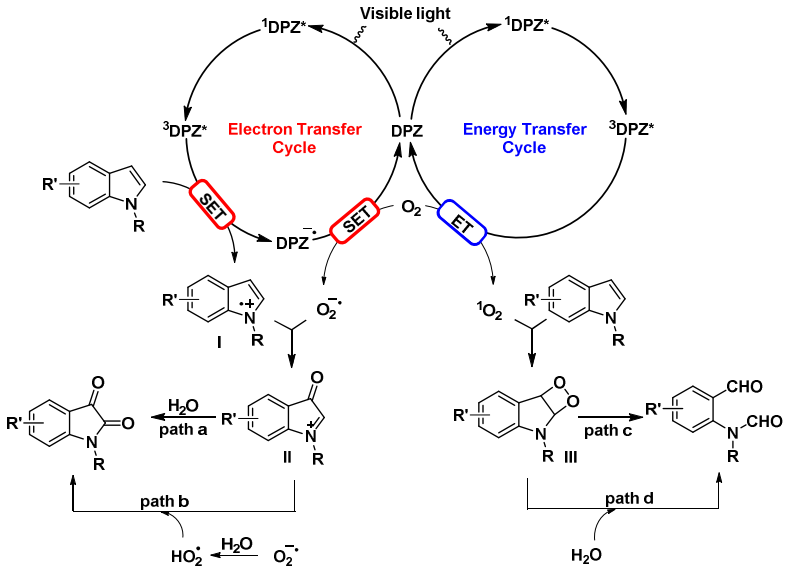


Figure 3. ^{18}O-Labeling Experiments. The ratio was determined by GC-MS analysis.

Two plausible mechanisms for visible light-driven aerobic photooxygenation of indoles are proposed in Scheme 1. Employing the reaction Conditions A, indole substrates could be oxidized by the triplet ^{3}DPZ* to indole radical cation **I** through a reductive quenching process. To further regenerate the catalyst, molecular oxygen is reduced to superoxide ion $O_2^{-\bullet}$ by $DPZ^{-\bullet}$ to regenerate DPZ. The highly reactive ROS, $O_2^{-\bullet}$ then oxidizes **I** to form iminium **II**. The iminium **II** is further reaction with water and two possible pathways involving addition (path a) or $HO_2^{\bullet}$ generated from $O_2^{-\bullet}$ (path b)[23] to form isatins could be operative. Conversely under the reaction Conditions B, the oxidative cycle of DPZ is postulated to be suppressed by K_3PO_4 and indoles will react with the $^1O_2$ generated by energy transfer and sensitization with ^{3}DPZ*. The dioxetane intermediate **III** then finally affords formylformanilides **3** possibly through paths c and d[24]. Our isotope-labeling studies do suggest that paths b and d are possible together with paths a and c.

Scheme 1. Proposed Mechanism.

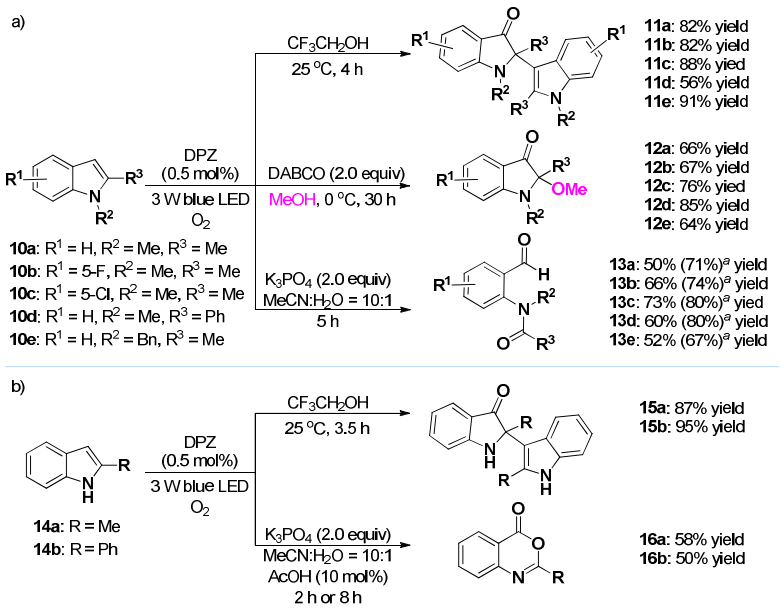


Substrate Scope of 2-Substituted Indoles. Encouraged by the potential of the discovery of a chemodivergent photo-oxidative synthesis of indoles, we extended our protocol in the aerobic oxygenation of 1,2-disubstituted indoles **10**, which are considered relatively stable (Scheme 2a).[25] First, we attempted the photoredox oxygenation under the slightly modified reaction Conditions A (CF_3CH_2OH as a solvent and in the absence of LiBr). It was observed that the reactions were accomplished within 12−13 hours, and a series of cross dimerized products, i.e. 2-indole-substituted 3-oxindoles **11a-e**, were achieved with good chemoselectivity. Most of the products (**11a-c**, **11e**) were obtained in excellent yields (82−91 %). Having a phenyl substituent in **10d** led only to moderate yield of **11d** possibly due to steric and electronic effects These results suggest that the an *insitu* iminium intermediate is generated and further attacked by nucleophiles. By using methanol as a nucleophile to afford 2-methoxy-3-oxoindoles, structurally important and bioactive molecules such as matemone,[15a] mitomycin C,[15b] and cephalinone B might be possible.[15c] The reaction with methanol was not highly chemoselective, but the desired methoxy derivatives **12a-e** were obtained in moderate to good yields when additional 2.0 eq. of DABCO was utilized.

We then conducted oxygenation of **10** under the reaction Conditions B. Products **13a-e**, the analogues of **3**, were attained in satisfactory yields. The employment of 10 mol% of DABCO was also effective to enhance the yields of **13** (Scheme 2a). Moreover, it was discovered that

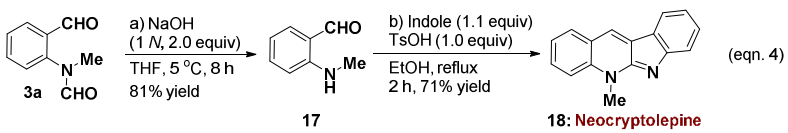
oxygenation of 2-substituted indoles **14** showed the same chemoselectivity (Scheme 2b). Products **15** and **16** were obtained under two reaction conditions in moderate to excellent yields. It is worth mentioning that products **16** are 2-substituted benzo[*d*]oxazinones representing key structural motifs in biologically relevant molecules.[16] The chemoselectivity was also realized in the oxidation of 1,3-disubstituted and 1,2,3-trisubstituted indoles.[19]

Scheme 2. Oxygenation of 2-Substituted Indoles 10 and 14.



[a]10 mol% of TEMPO was used, t = 17 hour

The Investigation on Utilities of Formylformanilides. This DPZ-catalyzed chemodivergent photooxygenation allowed access to a variety of *N*-heterocyclic compounds such as isatins, tryptanthrin, 2-methoxy-3-oxoindoles, and benzooxazinones that are of biological importance. The utility of this newly developed tool can further be demonstrated on transformations of formylformanilide **3a**. As shown in eqn. 4, hydrolysis of **3a** with NaOH afforded *N*-methylanthranilaldehyde **17** in 81% yield. And the subsequent condensation with indole provided smoothly neocryptolepine[9] **18** which exhibits antiplasmodia activity.



Conclusions

We have developed a novel and efficient chemodivergent photocatalytic method, using low-energy and operationally convenient visible light. By modulating reaction additives that affect pH the electrochemical properties of the DPZ photocatalyst is tuned, allowing selective catalytic aerobic photooxygenation of indoles: by either undergoing SET ($O_2^{\bullet-}$) or ET ($^1O_2$) oxidative process. As a result, two series of important *N*-heterocyclic compounds, i.e. isatins and formylformanilides (or tryptanthrin), were obtained in satisfactory yields. This methodology was also effective to furnish photooxygenation of 2-subsituted indoles, leading to expedient syntheses of four series of valuable *N*-containing molecules, especially including 2-methoxy-3-oxoindoles and 2-substituted benzoxazinones.

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. [§]These authors contributed equally.

Notes

The authors declare no competing financial interest.

Supporting Information.

Supporting Information Available: [Representative experimental procedures, cyclic voltammetry measurements, NMR spectral data for all the compounds, computational methods and data] This material is available free of charge via the Internet at http://pubs.acs.org.

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Graphical Abstract