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Eosin Y as a Redox Catalyst and Photosensitizer for Sequential Benzylic C-H Amination and Oxidation

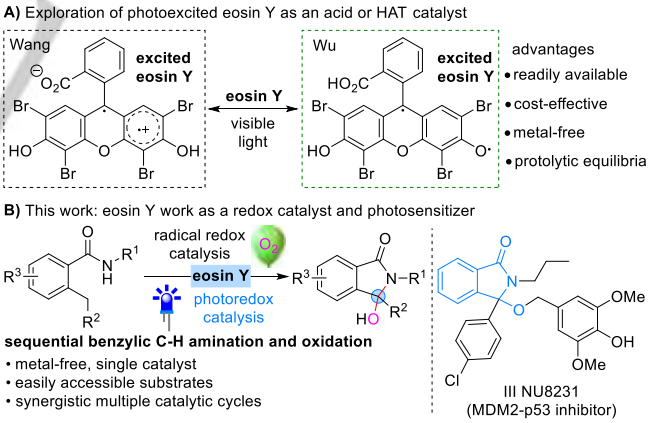
Dong-Mei Yan, Quan-Qing Zhao, Li Rao, Jia-Rong Chen,* and Wen-Jing Xiao*

Abstract: *A new synergistic multicatalytic activation mode of eosin Y has been discovered for the first time by exploiting the redox potential of its ground state and excited state. This catalytic strategy proves to be an enabling new tool for visible light-driven sequential benzylic C-H amination and oxidation of o-benzyl-N-methoxyl-benzamides when using Selectfluor as HAT reagent and O_2 as oxidants. Efficient synthesis of a range of diversely functionalized 3-hydroxyisoindolinones can thus be achieved with good yields and selectivity at mild reaction conditions. Preliminary mechanistic studies and DFT calculations suggest that eosin Y works as a redox catalyst and photosensitizer.*

Visible light-driven photoredox catalysis has recently been established as a mild and powerful platform for organic molecule activation and invention of many unique and valuable chemical reactions.[1] However, in many cases, visible light-driven synthetic transformations typically capitalize on the excited state of photocatalysts since they are more reducing and more oxidizing than their ground states. The merger of photocatalysts with suitable transition metals or organocatalysts has brought about a variety of versatile dual-catalyst methods that provide access to the development of distinct and highly enabling activation modes.[2] Moreover, rational design of light-responsive chiral complexing agents, ligands or catalysts has provided a potentially fruitful tool for engineering the stereocontrol in photochemical reactions.[3,4] Despite their impressive catalytic performances, key to the success of each of the aforementioned methods mainly relies on the single electron transfer (SET)-based activation of the substrates triggered by the excited state photocatalysts through a single photocatalytic cycle, thus limiting the synthetic scope of photocatalysis to somewhat extent.

Instead of modifying the molecular structure of the photocatalysts, stimuli-driven adjustment of their redox potential has emerged as another attractive strategy for activation of much stronger chemical bonds. With fluorescent dye perylene diimide as a photocatalyst, the Konig group pioneered the application of consecutive photoinduced electron transfer to the reduction of stable aryl halides into aryl radicals by utilizing the energies of two photons in a single catalytic cycle.[5a] The same group has also discovered that using different light color enabled finely regulating the redox potential of rhodamine 6G, thus controlling selective and sequential C-H photoarylations of arenes and heteroarenes.[5b] On the other hand, MacMillan,[6] Nicewicz,[7] Knowles,[8] and others[9] disclosed that incorporation of hydrogen atom transfer (HAT) into visible light photocatalysis by adding external organic radical precursors allowed the activation of the inert C-H bonds to proceed with minimal dependence on the electronic or steric properties of substrates. Surprisingly, to the best of our knowledge, the potential of using both of the ground state and excited state of photocatalysts in synergistic multiple catalytic cycles has remained largely unexplored.

Eosin Y has been widely used as economically and ecologically superior alternative to transition metal complexes in organic photochemistry due to its low cost, easy handling, and eco-friendly.[1d,10] It has mostly been employed as a SET oxidant or reductant upon conversion to its excited state by visible light irradiation. Interestingly, the Wang group recently reported that photoexcited eosin Y could function as phenolic acid to catalyze direct addition of alcohols to glycols, allowing stereoselective synthesis of 2-deoxyglycosides (Scheme 1a).[11a] In contrast, Wu and coworkers identified photoexcited eosin Y as a direct hydrogen atom transfer (HAT) catalyst to enable general alkylation of C-H bonds with electron-deficient alkenes.[11b] These two inspiring discoveries opened a new way to explore the new photocatalytic activity mode of eosin Y.



Scheme 1. Exploration of new catalytic modes of eosin Y catalyst and reaction design of sequential C-H amination/oxidation. HAT = hydrogen atom transfer.

As a matter of fact, the ground state of eosin Y itself also has a redox potential, though relatively lower compared to its excited state; until now, such a property has never been explored in the context of catalysis. Drawing inspiration from the recent utility of N-oxyl radicals[12a] and thiyl radicals[12b] in catalytic radical reactions, we proposed that the ground state eosin Y might be oxidized by external oxidant to form the related radical species in situ, which would then serve to activate C-H bonds by a HAT process. Further combination of this activity with visible light-driven photoredox catalysis would probably enable the

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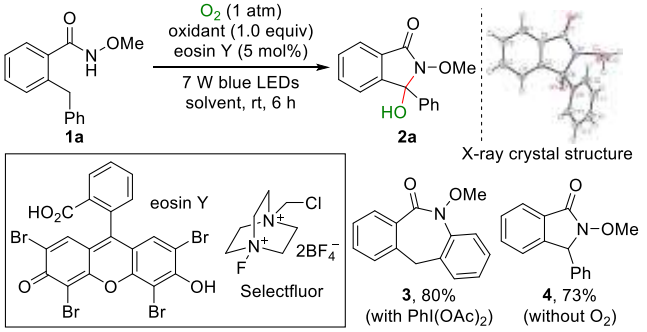
development of synergistic multiple catalytic cycles. Here, we describe the first example of this concept, displaying that the ground state and excited state of eosin Y serve as a redox catalyst and photosensitizer, respectively. With this hypothesis in mind and based on our continuing interest in photocatalytic amination and oxidation,[13] we chose to develop a sequential C-H amination and oxidation of *o*-benzyl-N-methoxyl-benzamides for the first time (Scheme 1B).[14,15] Such reaction would provide a facile access to various biologically and synthetically useful 3-hydroxyisoindolinone derivatives, such as inhibitor of the in MDM2-p53 interaction, III NU8231.[16]

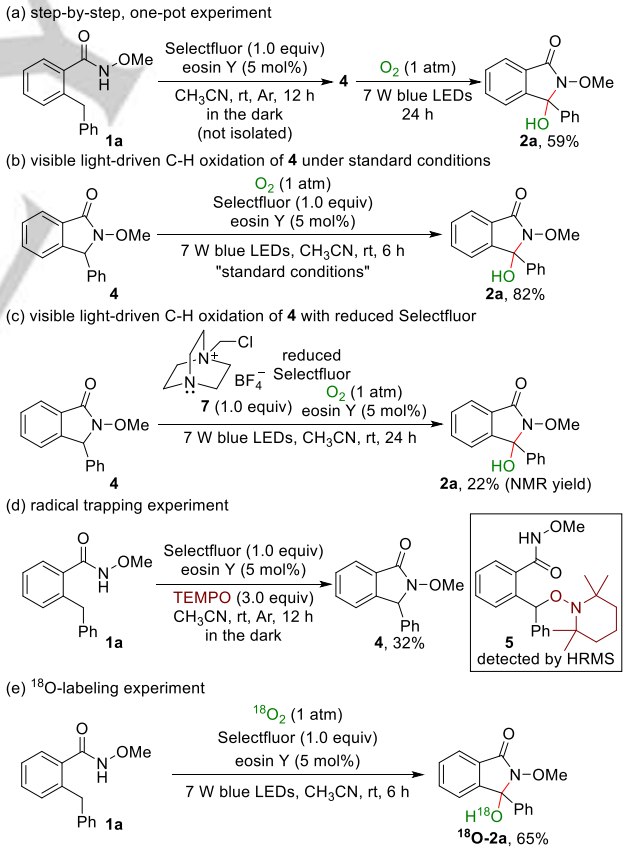
Table 1: Optimization of the reaction conditions.[a]



Entry	Oxidant	O_2	Solvent	Yield [%][b]
1	**Selectfluor**	**+**	**CH_3CN**	**87(85)[c]**
2[d]	Selectfluor	+	CH_3CN	68[c]
3	Selectfluor	+	THF	15
4	Selectfluor	+	CH_2Cl_2	13
5	Selectfluor	+	MeOH	9
6	Selectfluor	+	toluene	4
7	Selectfluor	+	DMSO	0
8	$PhI(OAc)_2$	+	CH_3CN	0[e]
9	Selectfluor	-	CH_3CN	0[f]
10	-	+	CH_3CN	0
11[g]	Selectfluor	+	CH_3CN	31
12[h]	Selectfluor	+	CH_3CN	39

[a] Reaction conditions: **1a** (0.1 mmol), oxidant (0.1 mmol), eosin Y (5 mol%), solvent (2.0 mL), 7 W blue LEDs, 1 atmosphere of O_2, at room temperature for 6 h. [b] Determined by ^{1}H NMR analysis with triphenylmethane as an internal standard. [c] Isolated yield. [d] Using green LEDs as a light source. [e] No desired product **2a** was detected, and aryl sp^2 C-H amination product **3** was formed exclusively in 80% yield. [f] No desired product **2a** was detected, and isoindolinone **4** was isolated in 73% yield. [g] Without photocatalyst eosin Y. [h] Without visible light irradiation.

Our study began with the sequential C-H amination and oxidation of readily accessible *o*-benzyl-N-methoxyl-benzamide **1a** under visible light irradiation and an oxygen atmosphere using Selectfluor as an external oxidant because of its unique oxidizing ability (Table 1).[17] Moreover, the Selectfluor-derived N-radical dication might also initiate a HAT process.[18] Pleasingly, a brief screen of commonly used photocatalysts revealed that the eosin Y catalyst proved to be superior to others, leading to a clean reaction and giving the desired 3-hydroxyisoindolinone **2a** exclusively in 85% isolated yield (entry 1),[19] which was also unambiguously confirmed by single crystal X-ray crystallographic analysis.[20] However, switching the blue LEDs to green LEDs as the light source resulted in a significant decrease of the yield (entry 2). A simple evaluation of the reaction media showed that the reaction is very sensitive to the solvent; and no product or only moderate NMR yields were observed when using THF, CH_2Cl_2, MeOH, toluene or DMSO as the solvents (entries 3-7). In sharp contrast, the use of $PhI(OAc)_2$ as an oxidant resulted in exclusive formation of aryl sp^2 C-H amination product **3** instead with 80% yield (entry 8). To confirm the necessity of all of the reaction parameters such as Selectfluor, oxygen, eosin Y and visible light for the present sequential C-H amination and oxidation, a set of control experiments were then carried out. Interestingly, we successfully isolated isoindolinone **4** as the sole product when the reaction was performed under Ar atmosphere (entry 9), indicating that **4** might be the reaction intermediate. In the absence of Selectfluor, the reaction did not give any desired product **2a** (entries 10). Interestingly, in the absence of photocatalyst, or without visible light irradiation, the desired product **2a** was formed in moderate NMR yields (entries 11 and 12). These results show that background reaction proceeding through Selectfluor-mediated oxidation of benzylic C-H to carbonyl group and ring-closing tautomerization might also work to somewhat extent.[17b,19] Notably, replacement of Selectfluor with other commonly used oxidants, such as ^{t}BuOOH, $K_2S_2O_8$, $AgNO_3$, and MnO_2 resulted in no formation of **2a**. However, combination of these oxidants with quinuclidine under otherwise identical conditions resulted in moderate yields of **2a**.[19] These results implied that Selectfluor may not only serve as an oxidant, but also play another important role, such as a HAT reagent.



Scheme 2. Mechanistic studies.

To gain insights into the reaction mechanism, a set of control and comparison experiments were then conducted with model substrate **1a** (Scheme 2). First, inspired by the formation of isoindolinone **4** observed during the course of optimization study

(Table 1, entry 9), we hypothesized that the reaction might proceed through the intermediacy of such compound. Interestingly, a series of control reactions confirmed that only in the presence of Selectfluor and eosin Y can the substrate **1a** be transformed to isoindolinone **4** in 73% yield even in the dark under Ar atmosphere. Specifically, the C-H bond amination step (**1a→4**) is not a visible light-driven photocatalytic process, but eosin Y is critical to this step.[19] Notably, Shi, Houk, and their coworkers recently disclosed an elegant iodoarene-catalyzed intramolecular C-H amination of *o*-alkyl-N-methoxyl-benzamides for the synthesis of analogues of isoindolinone **4** using m-CPBA as oxidant under thermal conditions.[21] Then, we carried out a step-by-step, one-pot reaction of **1a** (Scheme 2a). Upon almost full conversion of **1a** to **4**, we subjected the reaction mixture to an atmosphere of oxygen under irradiation of 7 W blue LEDs for another 24 h. Though the reaction proceeded with lower efficiency compared to that carried out under standard conditions (Table 1, entry 1), we successfully isolated desired product **2a** in 59% yield. Interestingly, the reaction of the isolated compound **4** under the standard conditions of entry 1 of Table 1 completed within 6 h, affording **2a** in 82% yield (Scheme 2b). This result suggests that the C-H oxidation of compound **4** might proceed through an oxidative quenching cycle, since Selectfluor could easily oxidize the photoexcited eosin Y* (supporting information, Fig. S5).[10] Moreover, replacement of Selectfluor with its reduced form **7** under otherwise same conditions could also facilitate the conversion of **4** into product **2a** though with relatively lower efficiency (Scheme 2c). Taken together, these results verify that **4** is the reaction intermediate, and both of Selectfluor and reduced form **7** might be involved in the catalytic cycles. In the presence of 3.0 equiv of radical scavenger TEMPO, the yield of **4** was reduced to 32%; and TEMPO-adduct **5** was also detected by HRMS analysis of the reaction mixture (Scheme 2d).[19] These findings suggest the involvement of a benzyl radical species in this transformation. As expected, the isotope labeling experiment of **1a** showed that the oxygen of hydroxyl group in product **2a** originated from molecular dioxygen (Scheme 2e).

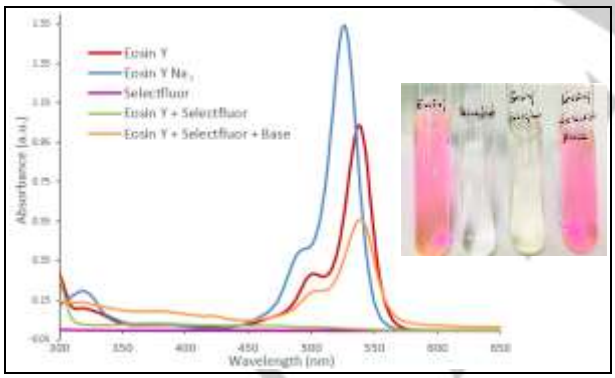
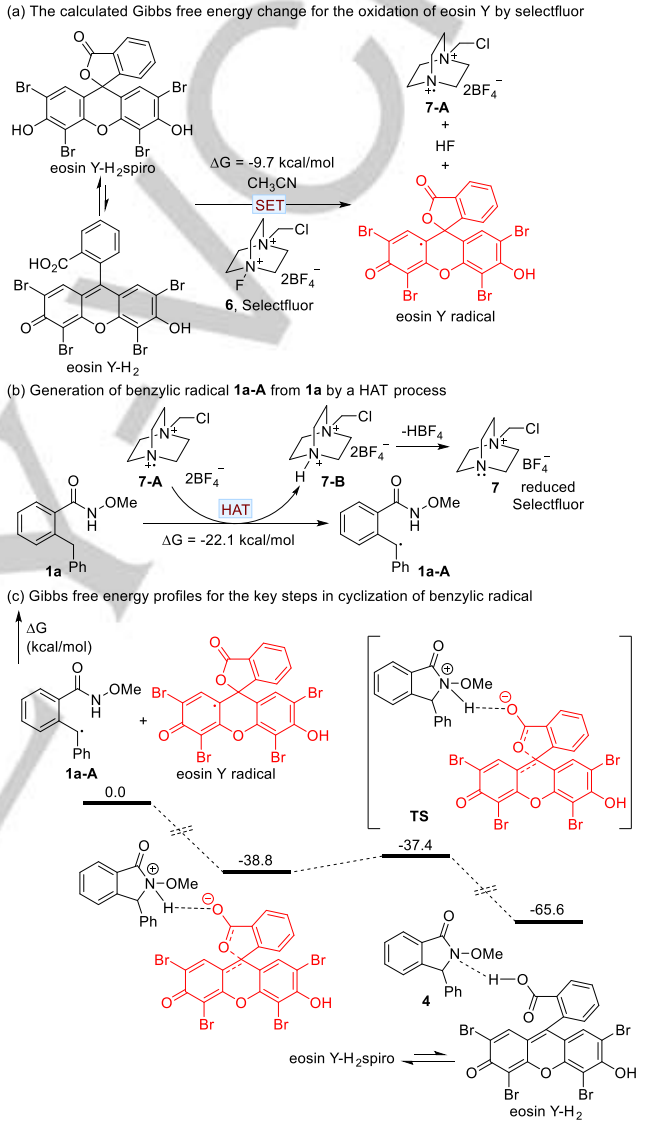


Figure 1. UV-Vis absorption spectra of the related mixtures recorded in CH_3CN. Base = Na_2CO_3. The dianionic eosin Y Na_2 shows absorption peak at 528 nm.

Eosin Y has pronounced acid-base properties due to its unique structural scaffold, and can exist as an equilibrating mixture of four components depending on the reaction conditions (solvents), including the neutral spirocyclic eosin Y-H_2spiro and ring-opened eosin Y-H_2, monoanionic form and dianionic form.[10] These four structures typically exhibit different visible absorption and photocatalytic activity. To assist the understanding of the interaction involved between Selectfluor and eosin Y, we examined the effect of Selectfluor on the absorption of eosin Y. To our surprise, the solution of eosin Y and Selectfluor in acetonitrile was light yellow instead of usual red color.[19] Though the neutral eosin Y has a characteristic absorption peak at ~539 nm caused by its monoanionic form (Figure 1, red line),[10] the addition of Selectfluor resulted in complete disappearance of its characteristic absorption peak (green line). Thus, we believe this to be a consequence of facile acid-base equilibration of the eosin Y, since the max absorption peak at ~539 nm appeared again upon addition of base Na_2CO_3 (orange line).



Scheme 3. DFT calculation studies on the benzylic C-H amination.

To better understand the mechanism, we first performed DFT calculations to investigate the possibility of SET process between the ground state eosin Y and Selectfluor.[19] The calculations indicate that the SET oxidation of neutral eosin Y by Selectfluor is exothermic by 9.7 kcal/mol, producing delocalized spirocyclic eosin Y radical and Selectfluor radical cation **7-A** (Scheme 3a). Then, Selectfluor radical cation **7-A** serves as a HAT reagent to abstract a hydrogen atom from **1a** to give ammonium ion **7-B** and benzyl radical **1a-A**,[22] which is also a exothermic process (ΔG = -22.1 kcal/mol) (Scheme 3b). Fortunately, we successfully isolated reduced Selectfluor **7** by simple workup procedure, which was fully characterized by NMR and HRMS methods.[19]

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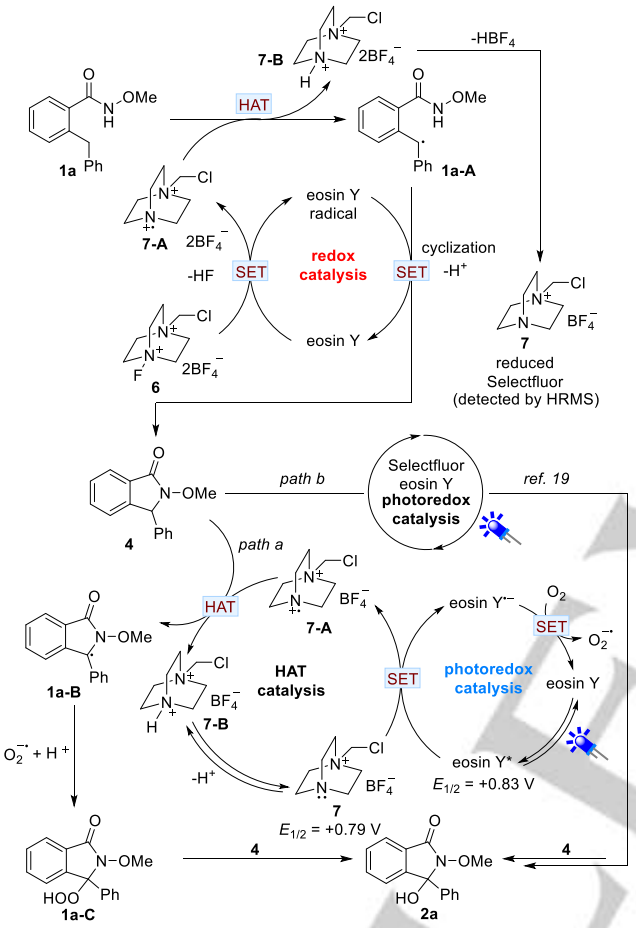
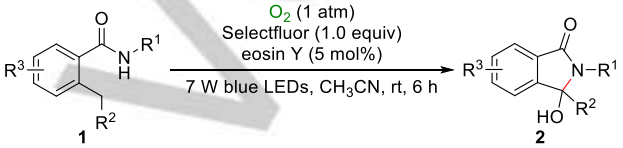
Moreover, the cyclization of benzyl radical **1a-A** is exergonic by means of eosin Y radical-promoted concerted SET/cyclization (ΔG = -38.8 kcal/mol) (Scheme 3c). The subsequent deprotonation has an activation energy barrier of just 1.4 kcal/mol, resulting in facile formation of C-H amination product **4** and regeneration of neutral eosin Y. Overall, the cyclization of benzyl radical **1a-A** is exergonic by 65.6 kcal/mol. Taken together, the benzylic C-H amination step (**1→4**) should proceed through a redox catalytic cycle (Scheme 4). In this catalytic cycle, the ground state eosin Y serves as a redox catalyst, and Selectfluor acts as an external oxidant and HAT reagent.

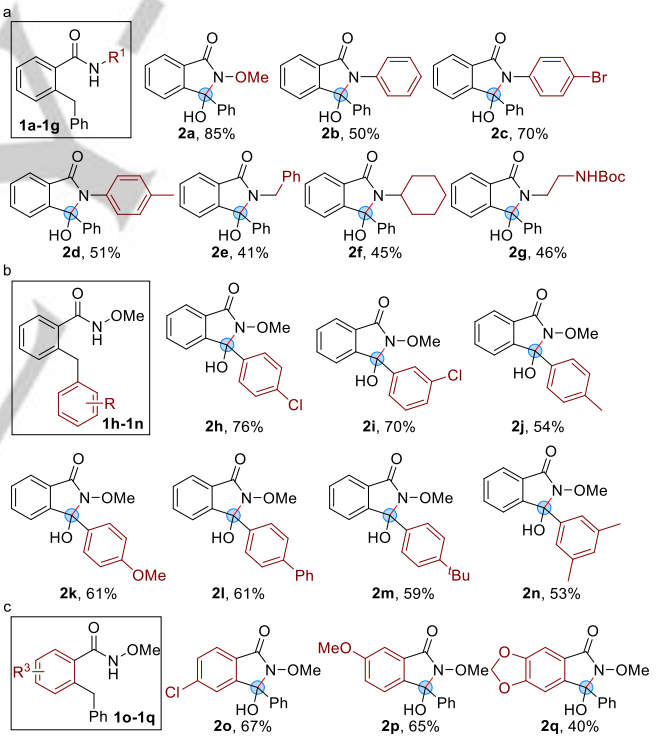


Scheme 4. Possible mechanism.

Moreover, drawing from the mechanistic insights obtained in the control experiments and recent HAT catalysis of tertiary amine,[9,22] we thus presume that amine **7** could also participate in the proposed synergistic HAT and photoredox catalysis to promote benzylic C-H oxidation (**4→2a**) (Scheme 4, path a). At this stage, visible light irradiation of the ground state eosin Y produces the long-lived excited state eosin Y* ($E_{1/2}^{red}$ = +0.83 V), which is sufficiently oxidizing to undergo reduction quenching by the HAT reagent **7** ($E_{1/2}^{ox}$ = +0.79 V vs SCE in CH_3CN)[19] via an SET process, generating amine radical cation **7-A** and the reduced form of eosin Y.[22] Then, the reduced photocatalyst can be oxidized by O_2 to regenerate the ground state eosin Y with release of O_2 radical anion, closing the photoredox catalytic cycle. We believe that the transiently formed electron-defficient amine radical cation **7-A** would then engender a kinetically favorable HAT event at the benzylic position of **4**, thereby delivering benzyl radical **1a-B** and ammonium ion **7-B** and completing the HAT catalytic cycle after deprotonation. Then, the radical species **1a-B** could be intercepted by O_2 radical anion, followed by protonation to furnish hydroperoxide **1a-C**. Reduction of **1a-C** by another molecule of isoindolinone **4** leads to formation of the final product **2a**. It should be noted that based on the control experimental results of Scheme 2b, Selectfluor ($E_{1/2}$ = +0.33 V vs SCE in CH_3CN)[17] might also be involved in this C-H oxidation step through oxidative quenching cycle given their oxidation potential of the excited state eosin Y* ($E_{1/2}^{ox}$ = -1.11 V vs SCE in CH_3CN) (path b).[19,15k] Although the system is complex, and a precise understanding of the roles of eosin Y awaits further studies, these control experiments actually also confirm that eosin Y should be critical to both C-H amination and oxidation steps.[11b,23] Future studies along this line will be carried out in the near future.

Table 2: Substrate scope.[a,b]

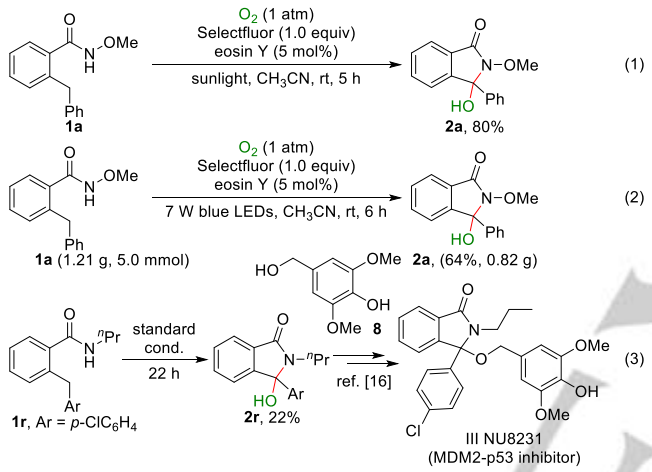




[a] Reaction conditions: **1a** (0.2 mmol), Selectfluor (0.2 mmol), eosin Y (5 mol%), CH_3CN (4.0 mL), 7 W blue LEDs, 1 atmosphere of O_2, at room temperature for 6 h. [b] Isolated yields.

With this synergistic multicatalytic activation mode of eosin Y established, we then evaluated its synthetic potential across a representative set of substrates on a 0.2 mmol scale. As shown in Table 2, the catalytic system shows wide substrate scope and good functional group tolerance. First investigation into the effect of the R^1 group on the nitrogen atom displays that, in addition to the methoxyl group, neutral phenyl ring as well as those with electron-withdrawing (e.g., Br) or weakly electron-donating (e.g., Me) groups are well tolerated, giving the corresponding products

2b-**2d** in 50-70% yields (Table 2a). When R^1 are alkyl groups, such as labile benzyl, cyclohexyl, and protected amino ethyl, the reactions all proceeded smoothly to deliver products **2e**-**2g** with good yields. Next, we examined the effect of variation of the R^2 substituent on the reaction (Table 2b). With R^2 as an aryl group, we found that the reactions of substrates **1h**-**1m** bearing a chloro, methyl, methoxyl, phenyl or *tert*-butyl group at the *para*-position or *ortho*-position of the phenyl ring worked well to furnish products **2h**-**2m** in a range of 54-76% yields. As shown in the synthesis of multi-substituted **2n**, the substitution pattern and steric hindrance of the aromatic ring has no influence on the reaction either. As a limitation of the method, however, substrates with R^2 substituent being alkyl groups proved to be not suitable for the reaction at the current stage (results not shown). Notably, the reactions of substrates **1o**-**1q** with R^3 group being chloro, methoxyl or other alkoxyl groups also underwent the expected benzylic C-H amination and oxidation efficiently to give the corresponding products **2o**-**2q** in 40-67% yields.



To further demonstrate the synthetic potential of this protocol, we also carried out the model reaction of **1a** under sunlight irradiation; and comparable yield was still obtained after 5 h (80% yield) [Eq. (1)]. Moreover, the scalability of this procedure was demonstrated by a 5.0 mmol (1.21 g) reaction of **1a** under the standard conditions, which proceeded smoothly to give **2a** in 64% yield (0.82 g) [Eq. (2)]. The standard conditions also proved to be suitable for substrate **1r** to give hydroxyisoindolinone **2r**, which allows easy further synthesis of MDM2-p53 inhibitor III NU8231 by conversion to chloride and treatment with syringic alcohol **8** in a two-step, one-pot manner [Eq. (3)].[16]

In summary, we have developed a synergistic multicatalytic activation mode of eosin Y for the first time by exploiting both of the redox properties of its ground state and excited state. This catalytic strategy provides an enabling new tool for visible light-driven sequential benzylic C-H amination and oxidation of o-benzyl-N-methoxyl-benzamides. Efficient synthesis of a range of diversely functionalized 3-hydroxyisoindolinones can thus be achieved with good yields at mild conditions.[24] Preliminarily evidence suggests that Eosin Y works as a redox catalyst and photosensitizer. More detailed mechanistic studies and efforts to extend eosin Y to other C-H bond functionalization are currently ongoing.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: photoredox catalysis • redox catalysis • oxidation • amination • isoindolinones

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[19] See the Supporting Information for detailed optimization study, control experiments, cyclic voltammetry study, DFT calculations, and mechanisms.

[20] CCDC 1820863 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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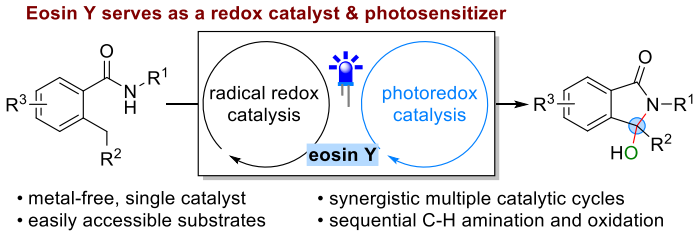

Dong-Mei Yan, Quan-Qing Zhao, Li Rao, Jia-Rong Chen, and Wen-Jing Xiao**

Page No. – Page No.

Eosin Y as a Redox Catalyst and Photosensitizer for Sequential Benzylic C-H Amination and Oxidation

A new synergistic multicatalytic activation mode of eosin Y has been discovered for the first time by exploiting the redox potential of its ground state and excited state. This catalytic strategy proves to be an enabling new tool for visible light-driven sequential benzylic C-H amination and oxidation of o-benzyl-N-methoxyl-benzamides when using Selectfluor as HAT reagent and O_2 as oxidants. Efficient synthesis of a range of diversely functionalized 3-hydroxyisoindolinones can thus be achieved with good yields and selectivity at mild reaction conditions. Preliminary mechanistic studies and DFT calculations suggest that Eosin Y works as a redox catalyst and photosensitizer.