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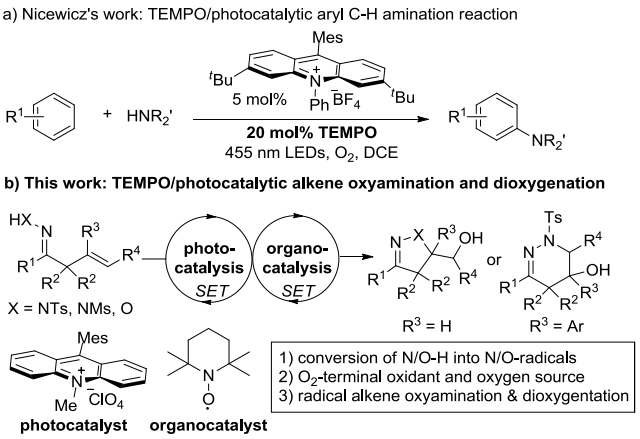
Organophotocatalytic Generation of N- and O-Centred Radicals Enable Aerobic Oxyamination and Dioxygenation of Alkenes

Xiao-Qiang Hu, Jun Chen, Jia-Rong Chen,* Dong-Mei Yan, and Wen-Jing Xiao

Abstract: *A cooperative TEMPO and photoredox catalytic strategy was applied for the first time to the direct conversion of N-H and O-H bonds into N- and O-centred radicals, enabling a general and selective oxidative radical oxyamination and dioxygenation of various β,γ-unsaturated hydrazones and oximes. In the reaction, O_2 was employed not only as a terminal oxidant but also as the oxygen source. This protocol provides efficient access to the synthesis of various synthetically and biologically important pyrazoline, pyridazine and isoxazoline derivatives under metal-free and mild reaction conditions. Mechanistic studies revealed that the cooperative organophotocatalytic system functions via two single-electron transfer (SET) processes.*

Cooperative catalysis that involves two distinct catalytic entities in a transformation is currently a major focus of research in the field of catalytic science.[1] Application of this strategy can often enable otherwise inaccessible catalytic reactivity modes. In the last decade, visible-light photoredox catalysis and organocatalysis have developed into two new essential branches of catalysis because of their unique and mild activation modes.[2,3] Given their high functional group compatibility, the combination of these two catalytic strategies has recently been demonstrated to be a powerful platform for new reaction development and selectivity control.[4] Employing this cooperative catalytic mode, significant advances have thus been achieved. Elegant examples include highly efficient and stereoselective radical functionalization of various carbonyl compounds,[5] tertiary amines,[6] and alkenes[7]. Despite these important advances, development of general, efficient and conceptually new cooperative organophotocatalytic systems to activate relatively inactive chemical bonds and engineer new chemical transformations remains an important but challenging task.

In recent years, visible-light photocatalytic alkene difunctionalization reactions have been established as an efficient and mild approach for the construction of various C-C or C−X (X = heteroatom or halogen) bonds.[8] In this context, the photocatalytic *N*- or *O*-centred radical-mediated oxidative oxyamination and dioxygenation of alkenes remain largely unexplored because of the limited methods for their efficient generation.[9] The seminal studies by the groups of MacMillan,[10a] Sanford[10b] and others[10c-f] have demonstrated that the incorporation of a photolabile moiety into the amine substrates enable photocatalytic formation of N-centred radicals and the subsequent C-N bond formation. We[11a, b] and Knowles[11c] have independently reported that visible-light photocatalysis enabled the recalcitrant N-H bonds to be directly converted into N-centred radicals via oxidative deprotonation electron transfer (ODET) or concerted proton-coupled electron transfer (PCET) activation, respectively. Quite recently, Chen and co-workers reported the first example of the generation of important alkoxyl radicals by photocatalytic cleavage of the pre-formed N-O bond or the in-situ-derived I-O bond.[12] Most of these reactions rely on the use of a single photocatalyst or N- and O-functionalized precursors, limiting the substrate scope owing either to the inherent oxidation state of the photocatalyst or to the tedious preparative procedure of the substrates. To our knowledge, no general and efficient catalytic systems have been developed for the direct conversion of N-H and O-H bonds into N- or O-centred radicals and the application of these reactive species to radical oxyamination and dioxygenation of alkenes.[13]



Scheme 1. Reaction design: oxidative radical oxyamination and dioxygenation of unactivated alkenes by cooperative TEMPO and photoredox catalysis.

TEMPO, 2,2,6,6-tetramethyl-1-piperidinyl-*N*-oxyl, is a well-known and stable nitroxyl radical with wide applications in radical trapping and hydrogen atom transfer (HAT) processes; and its oxoammonium salt has also been widely exploited as a catalytic or stoichiometric cooxidant in transition-metal-mediated transformations.[14] However, very few examples of the use of TEMPO as a single-electron transfer (SET) cocatalyst in visible-light-induced photocatalysis have been reported. In 2015, Nicewicz and co-workers developed an elegant TEMPO and acridinium photooxidant-based dual catalytic system for site-selective aryl C-H amination reactions, where TEMPO served as an HAT catalyst (Scheme 1a).[15] Very recently, Chen's group exploited TEMPO as a redox mediator and achieved a visible-light-induced ARS-sensitized TiO_2-catalysed heterogeneous oxidation of organic sulphides.[16] Inspired by these works and

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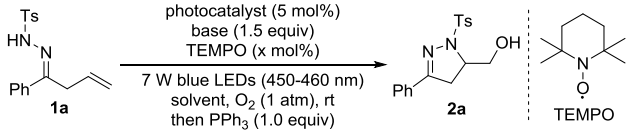
based on our ongoing programme of research on visible-light-induced dual catalysis,[17] we envisaged that a suitable cooperative TEMPO/photocatalytic system would likely provide a new method for N- and O-centred radical-mediated difunctionalization of alkenes, where molecular oxygen (O_2) is used as a green terminal oxidant and oxygen source.[18] Herein, we present the implementation of this blueprint and its application to the radical oxyamination and dioxygenation of β,γ-unsaturated hydrazones and oximes (Scheme 1b).

In our initial screening for reactivity, we selected the readily accessible β,γ-unsaturated hydrazone **1a** as the model substrate and examined the combination of a photocatalyst, 9-mesityl-10-methylacridinium perchlorate (**PC-I**) (5 mol%),[19] and TEMPO (5 mol%) under a balloon of O_2 by irradiation with 7 W blue LEDs. To our delight, the reaction proceeded smoothly to give the hydroxyamination product **2a** upon subsequent treatment with PPh_3; an increase of TEMPO loading (20 mol%) substantially improved the yield from 30% to 83% (entries 1-3). A further brief investigation of reaction parameters such as the reaction medium, base and photocatalyst gave the optimal conditions: the combination of 5 mol% of **PC-1** and 20 mol% of TEMPO as the cooperative organophotocatalytic system, 1.5 equivalents of K_2CO_3 as the base, in CH_3CN at room temperature, giving an 85% yield of **2a** (entry 4).[20] To verify the necessity for each component involved in this reaction, we performed a series of control experiments on **1a** (Table 1, entries 6-9). The results clearly revealed that the photocatalyst, TEMPO, visible light, and O_2 were all critical to the reaction. Interestingly, although K_2CO_3 was not required for the model reaction (entry 10), subsequent studies of the substrate scope showed that the addition of stoichiometric K_2CO_3 obviously improved the yield, especially in the case of substrates with electron-withdrawing substituents.[20]

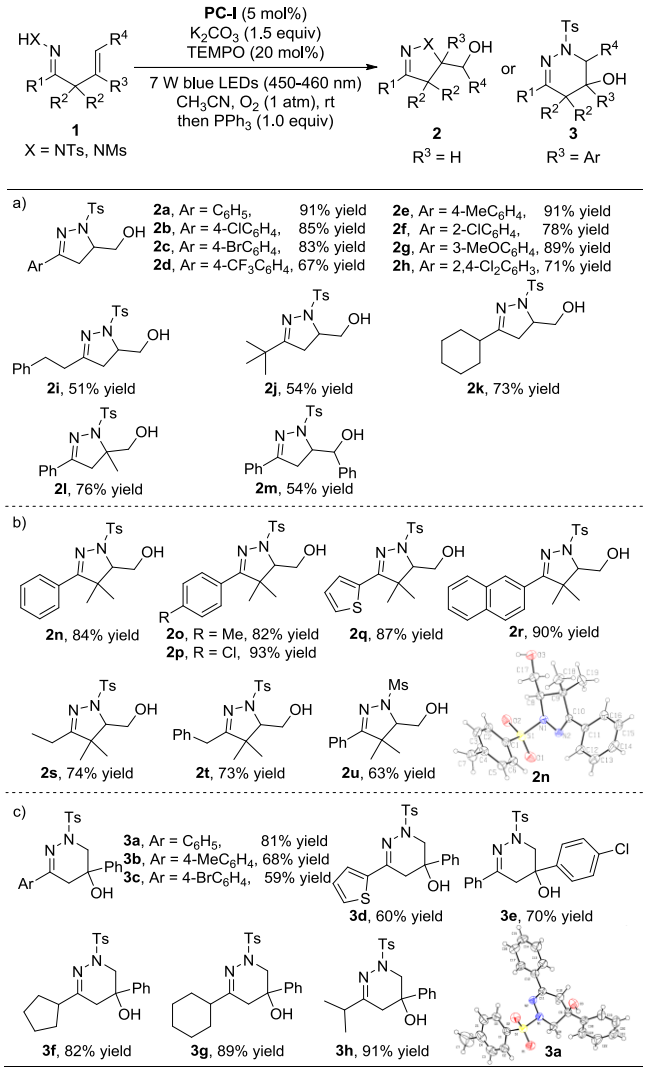
Table 1: Optimization of the cooperative TEMPO/photocatalytic oxidative radical oxyamination of β,γ-unsaturated hydrazones.[a]



Entry	Cat.	Solvent	Base	x	Yield [%][b]
1	**PC-I**	CH_3CN	$NaHCO_3$	5	30
2	**PC-I**	CH_3CN	$NaHCO_3$	10	56
3	**PC-I**	CH_3CN	$NaHCO_3$	20	83
4	**PC-I**	CH_3CN	K_2CO_3	20	85
5	**PC-II**	CH_3CN	K_2CO_3	20	83
6[c]	_	CH_3CN	K_2CO_3	20	0
7[d]	**PC-I**	CH_3CN	K_2CO_3	_	32
8[e]	**PC-I**	CH_3CN	K_2CO_3	20	0
9[f]	**PC-I**	CH_3CN	K_2CO_3	20	0
10[g]	**PC-I**	CH_3CN	_	20	86

[a] Reaction conditions: **1a** (0.20 mmol), photocatalyst (5.0 mol%), TEMPO (20 mol%), O_2 balloon, solvent (4.0 mL) at room temperature for 5 h under irradiation by 7 W blue LEDs (450-460 nm); PPh_3 (0.2 mmol, 1.0 equiv) was then added, and the mixture was stirred for another 10 min. [b] Yield of the isolated product. [c] Without photocatalyst. [d] Without TEMPO. [e] Without light. [f] Without O_2 balloon. [g] Without K_2CO_3. **PC-I**: 9-Mesityl-10-methylacridinium perchlorate. **PC-II**: $Ru(bpy)_3Cl_2{\cdot}6H_2O$. TEMPO: 2,2,6,6-tetramethylpiperidine-*N*-oxyl.

Table 2: Substrate scope of the cooperative TEMPO/photocatalytic oxidative radical oxyamination of β,γ-unsaturated hydrazones.[a, b]



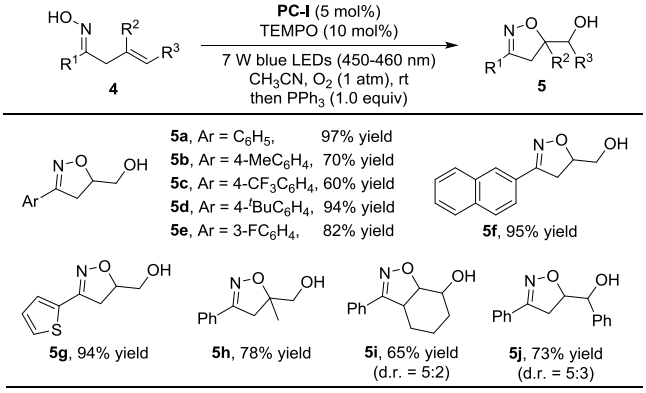
[a] For **2a-u**, reactions were performed with **1** (0.3 mmol), K_2CO_3 (0.45 mmol), **PC-I** (5 mol%), TEMPO (20 mol%), and O_2 balloon in CH_3CN (6.0 mL) at room temperature for 5-12 h under the irradiation by 7 W blue LEDs (450-460 nm); PPh_3 (0.3 mmol, 1.0 equiv) was then added and the mixture was stirred for another 10 min; for **3a-h**, TEMPO (10 mol%). [b] Yield of the isolated product.

We then investigated the substrate scope of this photocatalytic oxidative radical oxyamination by using a range of diversely substituted β,γ-unsaturated hydrazones. As shown in Table 2, the electronic properties and substitution patterns of the aromatic ring of β,γ-unsaturated hydrazones did not obviously influence the reaction efficiency. The hydrazones **1a-h** bearing electron-withdrawing (Cl, Br, CF_3) or electron-donating substituents (Me, MeO) at the *para*- or *meta*-position of the

phenyl ring underwent the desired reaction smoothly, giving the expected products **2a**-**h** in 67-91% yield. Moreover, a range of hydrazones **1i**-**k** with linear or branched aliphatic moieties also proved to be suitable for this reaction, with the products **2i**-**k** formed in 51-73% yield. Encouraged by these results, we continued to investigate the variation of the alkene moiety. As expected, the hydrazone **1l** bearing a methyl substituent at the 2-position of alkene could also undergo the oxyamination reaction efficiently to deliver the product **2l** in 76% yield. The reaction of hydrazone **1m** with an internal alkene also proceeded smoothly to furnish a 54% yield of **2m**. Notably, this protocol could to be successfully extended to diversely substituted β,γ-unsaturated hydrazones with geminal methyl groups at the α-position. For example, a wide range of hydrazones **1n-t** bearing aromatic, heteroaromatic, and aliphatic functional groups were all well tolerated, and the corresponding products **2n**-**t** were obtained with 73-93% yield. Moreover, replacement of the Ts protecting group of nitrogen by Ms group also furnished the corresponding product **2u** in 63% yield.

Employing this cooperative organophotocatalytic strategy, we further attempted a 6-*endo* oxidative radical oxyamination of β,γ-unsaturated hydrazones by introducing an aryl group into the 2-position of the alkene. According to our previous DFT calculation studies on the cyclization of hydrazonyl radicals across the alkene,[11b] the regioselectivity of the hydrazonyl radicals was highly dependent on the substitution patterns of the alkene moiety. The incorporation of an aryl group into the 2-position of alkene could stabilize the newly generated benzyl radical intermediate, thus leading to a 6-endo radical cyclization process. Indeed, the reactions of a wide variety of aryl and aliphatic hydrazones with diverse electronic or steric characteristics proceeded efficiently to produce the biologically important pyridazine derivatives **3a**-**h** in generally high yields (59-91%), highlighting the synthetic potential of this protocol. The structures of **2n** and **3a** were also unambiguously determined by X-ray crystallographic analysis.[21]

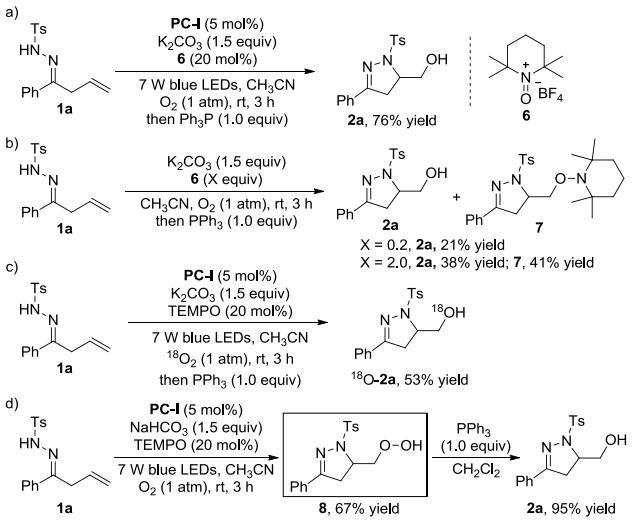
Table 3: Substrate scope of TEMPO/photocatalytic oxidative radical dioxygenation of β,γ-unsaturated oximes.[a, b]



[a] Reactions were performed with **4** (0.3 mmol), **PC-I** (5 mol%), TEMPO (10 mol%), and O_2 balloon in CH_3CN (6.0 mL) at room temperature for 12-24 h under irradiation by 7 W blue LEDs (450-460 nm); PPh_3 (0.3 mmol, 1.0 equiv) was then added and the mixture was stirred for another 10 min. [b] Yield of the isolated product.

Oxygen radicals are another important class of reactive intermediates with broad applications in both biological processes and organic transformations. The direct cleavage of the O-H bond for their generation is an attractive but thermodynamically challenging pathway.[22] Gratifyingly, our mild catalytic system allowed for a series of diversely substituted β,γ-unsaturated oximes to undergo efficient O-radical-mediated 5-*exo* oxidative radical dioxygenation reactions (Table 3). An array of electronically diverse phenyl rings with electron-donating or electron-withdrawing groups at the *para*- or *meta*-position and a heteroaryl group were all well tolerated, delivering products **5a**-**g** in 60-97% yield. Once again, similar to the alkene moiety, substrates with 2-methyl-substituted alkene (**4h**) or internal alkenes (**4i** and **4j**) also proved to be suitable for this transformation, conferring the corresponding products **5h**-**j** in satisfactory yields (65-78%).

Notably, this protocol represents the first example of visible light photocatalytic radical dioxygenation of oximes without any transition-metal catalyst,[23a] stoichiometric radical initiator or oxidant.[13a,23b] Thus, this reaction provides an economical and mild alternative access pathway to diverse synthetically useful isoxazoline derivatives.

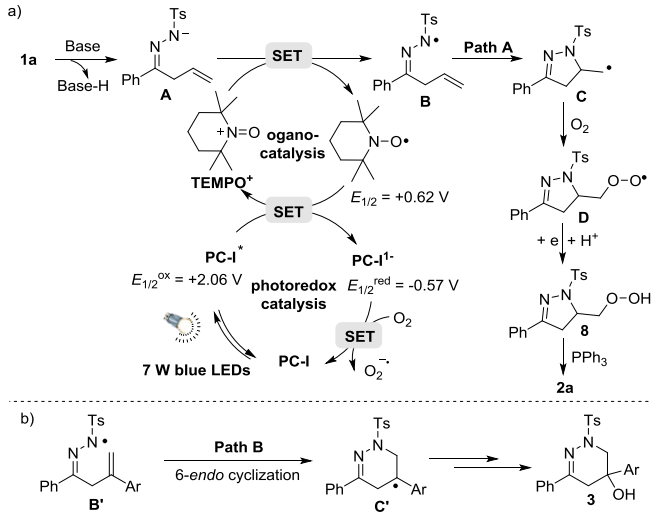


Scheme 2. Mechanistic studies.

To gain some insight into the possible reaction mechanism, a series of control experiments were then carried out using **1a** (Scheme 2). First, we observed that the use of 20 mol% of TEMPOnium-BF_4 **6** under the otherwise identical conditions produced results comparable to those obtained using TEMPO, with **2a** being isolated in 76% yield (Scheme 2a). In the absence of the photocatalyst and visible light, the addition of 20 mol% of **6** only gave a 21% yield of **2a**, whereas a stoichiometric amount of **6** resulted in complete conversion of substrate **1a**, furnishing a mixture of **2a** and TEMPO-adduct **7** in 38% and 41% yield, respectively (Scheme 2b). These results suggest that TEMPO may be initially oxidized by the photoexcited **PC-1*** into $TEMPO^+$ species that then serve as the reactive SET oxidant. The half-

wave redox potential of TEMPO ($E_{1/2}$ = +0.62 V vs. Ag/AgCl) also points to this possibility.[15,24] To verify the origin of the oxygen atom in the final product, we performed $^{18}O_2$-labelling experiments with **1a** under an $^{18}O_2$ atmosphere (Scheme 2c). As expected, the ^{18}O-labeled product ^{18}O-**2a** was obtained in 56% yield under the standard conditions, suggesting that O_2 indeed participated in the reaction and was incorporated into the final products. Notably, we observed that alkylhydroperoxide **8** was successfully isolated in 67% yield when $NaHCO_3$ was used as the base and that it was further easily transformed into **2a** with 95% yield upon treatment with PPh_3, indicating that alkylhydroperoxide **8** was the key intermediate in the oxyamination reaction (Scheme 2d).

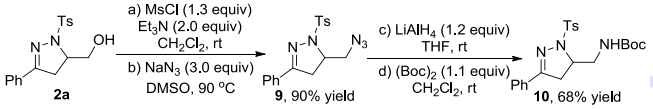
To gain greater insight into the photoredox catalytic cycle, we performed a series of emission quenching experiments. The results indicated that the photoexcited **PC-1*** was more efficiently quenched by TEMPO than substrates **1a** and **4a**. Additionally, the photoexcited **PC-1*** was quenched more rapidly by **1a** under basic conditions than in the absence of a base. These observations are consistent with the fact that the addition of a catalytic amount of TEMPO and stoichiometric K_2CO_3 can substantially accelerate the reaction and improve the yield. Moreover, the results of on-off light experiments implied that the radical chain process is not the predominant pathway in this transformation, although it cannot be completely ruled out at the current stage.[20]



Scheme 3. Proposed mechanism.

On the basis of the aforementioned experimental results, it seems that current reactions proceed through a pathway that appears to be distinct from our previously developed single photocatalyst-mediated hydroamination.[11a,b] Thus, a cooperative organophotocatalytic mode that functions via two single-electron transfer (SET) processes is proposed as shown in Scheme 3a. First, photoexcitation of the photocatalyst **PC-I** generates the excited-state **PC-I*** species via irradiation by 7 W blue LEDs. The excited-state photocatalyst **PC-I*** ($E^{ox}_{1/2}$ = +2.06 V)[13] then serves as an 1e-oxidant to oxidize TEMPO ($E_{1/2}$ = +0.62 V) into its highly oxidizing state, $TEMPO^+$, via an SET process,[24] with the release of the reduced photocatalyst **PC-I**$^{1-}$. Subsequently, another SET oxidation of the nitrogen anion **A**, generated from substrate **1a** via deprotonation, by the highly oxidizing $TEMPO^+$ gives rise to the key *N*-centred radical intermediate **B**, together with the regeneration of TEMPO to close the organocatalytic cycle. A 5-*exo* radical cyclization of *N*-radical **B** gives rise to *C*-centred radical **C** (Scheme 3a, Path A) that could be easily trapped by O_2 to afford alkylhydroperoxy radical **D**.[25] Then, the intermediate **D** undergoes a sequential SET reduction and protonation to give alkylhydroperoxide **8**. Finally, reduction of alkylhydroperoxide **8** by PPh_3 furnishes the target product **2a**. The reduced photocatalyst **PC-I**$^{1-}$ species can be oxidized by O_2 or hydroperoxy radical **D** to regenerate the ground state photocatalyst **PC-I** and finish the photocatalytic cycle. It should be noted that a 6-*endo* cyclization of N-centred radical **B'** would be a predominant pathway when R^3 is aryl group due to the stability of the newly generated benzyl radical intermediate **C'** (Scheme 3b, Path b). Then, the intermediate **C'** undergoes a same sequential SET reduction and protonation process to give the desired six-membered ring product **3**. In addition, the mechanistic studies indicated that the the oxidative dioxygenation of oximes proceeded by a same pathway. [20]

To demonstrate the synthetic potential of our newly developed method, we also carried out a gram-scale reaction of **1a**. The reaction still proceeded efficiently, and product **2a** was isolated in 76% yield.[20] Moreover, the hydroxyl group of **2a** was easily transformed into a synthetically valuable azido group via two routine elaborations, giving the product **9** in 90% yield (Scheme 4). The azide **9** underwent a further reduction/protection sequence to furnish the important compound **10** with 68% yield.[26]



Scheme 4. Synthetic transformations.

In conclusion, we developed a cooperative TEMPO/photocatalytic system for direct conversion of N-H and O-H bonds into N- and O-centred radicals, enabling a general and selective oxidative radical oxyamination and dioxygenation of β,γ-unsaturated hydrazones and oximes. In this protocol, O_2 was employed not only as the sole terminal oxidant but also as the oxygen source. As such, the O_2 was incorporated into a wide range of synthetically and biologically important pyrazoline, pyridazine and isoxazoline derivatives with generally high yields under mild and metal-free conditions. Furthermore, detailed control experiments were conducted to elucidate the cooperative catalytic mode. Further intensive study and application of this cooperative organophotocatalytic system is currently underway.

Experimental Section

1a (94.2 mg, 0.3 mmol), **PC-I** (5 mol%), K_2CO_3 (62.2 mg, 0.45 mmol) and TEMPO (20 mol%) were dissolved in CH_3CN (6.0 mL) with a O_2 balloon. After that, the solution was stirred at a distance of ~5 cm from a 7 W blue LEDs (450-460 nm) at room temperature until the reaction was completed. Then, Ph_3P (1.0 eq.) was added to the mixture and the mixture was stirred at

room temperature for another 10 min. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 10:1~2:1).

Acknowledgements

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Keywords: organophotocatalysis • N-centred radical • O-centred radical • hydrazones • oximes

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[20] See the Supporting Information for more details.

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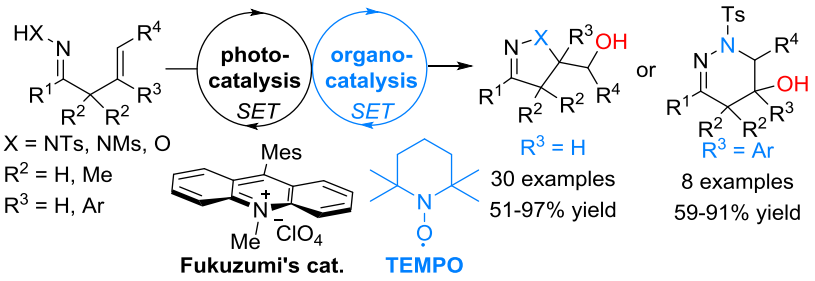
Organophotocatalysis



cooperative catalysis: A cooperative TEMPO and photoredox catalytic strategy was applied for the first time to the direct conversion of N-H and O-H bonds into N- and O-centred radicals, enabling a general and selective oxidative radical oxyamination and dioxygenation of various β,γ-unsaturated hydrazones and oximes. In the reaction, O_2 was employed not only as a terminal oxidant but also as the oxygen source. This protocol provides efficient access to the synthesis of various synthetically and biologically important pyrazoline, pyridazine and isoxazoline derivatives under metal-free and mild reaction conditions. Mechanistic studies revealed that the cooperative organophotocatalytic system functions via two single-electron transfer (SET) processes.

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