Synthetic Methods

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Controllable Chemoselectivity in Visible-Light Photoredox Catalysis: Four Diverse Aerobic Radical Cascade Reactions**

Xinfei Liu, Xinyi Ye, Filip Bureš, Hongjun Liu, and Zhiyong Jiang**

Abstract: *Reported is the controllable selectivity syntheses of four distinct products from the same starting materials by visible-light photoredox catalysis. By employing a dicyanopyrazine-derived chromophore (DPZ) as photoredox catalyst, an aerobic radical mechanism has been developed, and allows the reactions of N-tetrahydroisoquinolines (THIQs) with N-itaconimides to through four different pathways, including addition-cyclization, addition-elimination, addition-coupling, and addition-protonation, with satisfactory chemoselectivity. The current strategy provide straightforward access to four different but valuable N-heterocyclic adducts in moderate to excellent yields.*

Controllable chemoselectivity for a reaction involves the same set of starting substrates for the generation of distinct products through different highly chemoselective processes.[1] This strategy can improve molecular diversity, and thus has been recognized as one of the most promising paradigms in drug discovery.[1] To date, however, only a few variants[2] in visible-light photoredox catalysis[3] have been disclosed. Rueping et al.[2a] introduced an example of chemoselective reactions involving *N*,*N*-dimethyl anilines with activated alkenes catalyzed by an iridium(III) complex, and oxygen was employed as a chemical switch to allow either an intermolecular addition and an intramolecular radical addition/cyclization. Cho and co-workers[2b] presented an iridium(III)-complex-catalyzed chemoselective difluoroalkylation of alkenes, thus affording difluoroalkylated alkanes and alkenes depending on the base employed. Therefore, the development of photoredox catalytic reactions in a diverse and controllable manner remains highly desirable, especially those producing more than two types of products, and represents a formidable task. Undoubtedly, the efficient control of the radicals in the process is a major challenge.

Catalytic oxidation of an a C(sp^3)–H bond adjacent to the nitrogen atom of amines is a straightforward pathway to affording N-containing organic compounds.[4] The first example in photoredox catalysis was presented by Stephenson and co-workers for aza-Henry reactions of N-aryl tetrahydroisoquinolines (THIQs).[5] Since then, a number of corresponding photoredox catalytic methodologies have been established, and most are focused on the reactions of THIQs.[6] A survey[5,6] reveals that THIQs always generates iminium ions by a two-electron oxidation of amines when in the presence of molecular oxygen as an oxidant, and Mannich-type reactions subsequently occur by the addition of nucleophiles (Scheme 1 a). Alternatively, in the absence of oxygen, the α-amino radicals of THIQs can be trapped by activated alkenes to produce addition adducts (Scheme 1 a).[7] Nevertheless, the photoredox reaction of THIQs with electrophiles in the presence of oxygen through a radical pathway would be fascinating because of the convenience of the process and the access to unusual products, but it had not yet been reported. One of the challenges is that α-amino radicals of THIQs are very easily oxidized into iminium ions to yield amides.[7b]

Previously, we developed a dicyanopyrazine-derived chromophore (DPZ) as a novel photoredox organocatalyst in a series of reactions (Scheme 1 b). In most cases low catalyst loadings (between 1.0 mol% and 0.01 mol%) were necessary.[8] The investigations on the electronic properties indicated that the HOMO–LUMO gap of DPZ ($Eg = 2.82$ eV) facilitates generation of the α-amino radical by single-electron transfer (SET). More importantly, the planar and polarizable π-system of DPZ would help to stabilize the radical anion, that is, DPZ $H^{\cdot-}$, through delocalization, and should be conducive to postponing its subsequent oxidation by oxygen and ultimately delay the formation of an iminium ion from the α-amino radical. Accordingly, we envisioned that DPZ as a photoredox catalyst would promote the radical addition of THIQs. Herein we report a DPZ-catalyzed photoredox radical reaction in the presence of oxygen, and THIQs react with *N*-itaconimides, as electrophiles, to undergo either addition-cyclization, addition-elimination, addition-coupling, or addition-protonation, by modulating the reaction media, temperature, and additive (Scheme 1 b). Four series of products, containing the main cores of many compounds which have important biological properties (e.g., **I**–**IV**,[9] **V**[10] and **VI**),[11] were obtained with satisfactory results (Scheme 1 c).

[*] X. Liu,[+] Prof. Dr. H. Liu, Prof. Dr. Z. Jiang
Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Jinming Campus
Kaifeng, Henan, 475004 (P.R. China)
E-mail: chmjzy@henu.edu.cn
X. Ye[+]
Division of Chemistry and Biological Chemistry, Nanyang Technological University, 21 Nanyang Link, 637371 (Singapore)
E-mail: orgyxy@hotmail.com
Prof. Dr. F. Bureš
Institute of Organic Chemistry and Technology, University of Pardubice, Faculty of Chemical Technology
Studentská 573, Pardubice, 53210 (Czech Republic)
[+] These authors contributed equally to this work.

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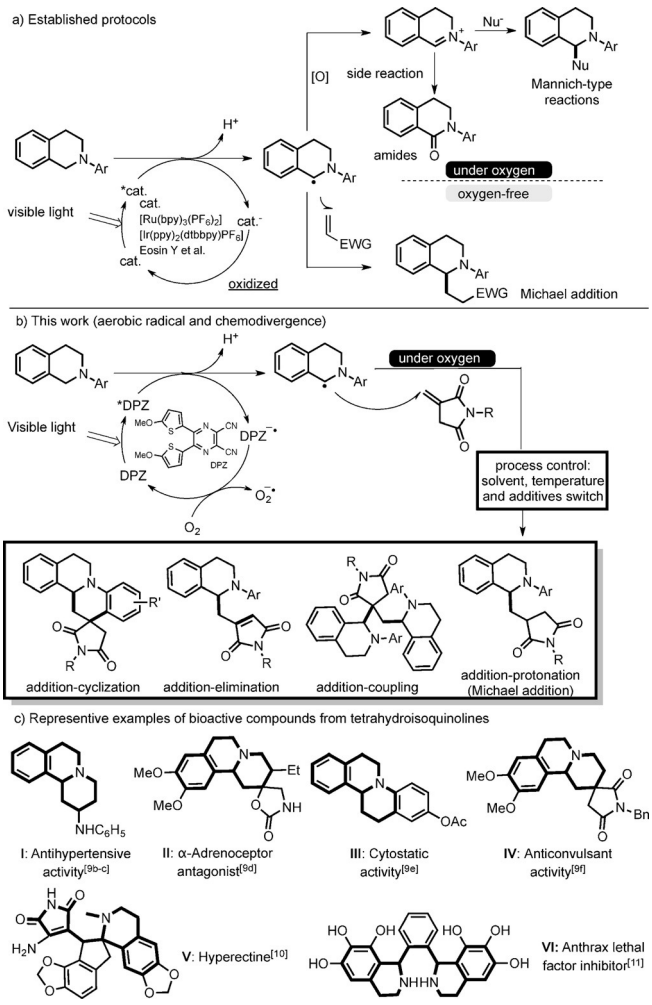
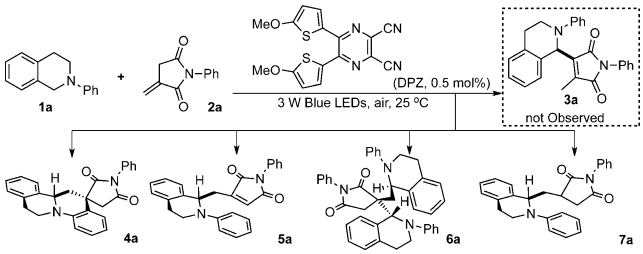


Scheme 1. Photoredox catalytic variants of N-aryl-tetrahydroisoquinolines and representative compounds with significant biological activities. EWG = electron-withdrawing group.

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



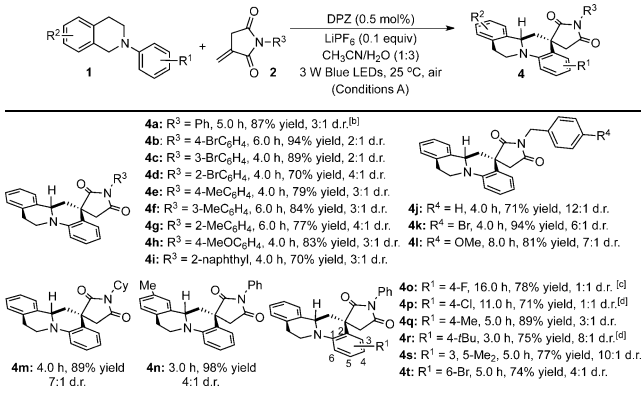
Nr.	Solvent	Additive (equiv)	*t* [h]	Product	Yield [%][b]
1	CH_3CN	–	7	**4a**/**5a**	37/24
2	CH_3CN/H_2O (1:1)	–	7	**4a**	43
3	CH_3CN/H_2O (1:1)	$LiPF_6$ (0.5)	7	**4a**	72
4	CH_3CN/H_2O (1:3)	$LiPF_6$ (0.1)	6	**4a**	89
5	CH_3CN/H_2O (1:1)	KF (0.5)	7	**5a**	50
6	CH_3CN/H_2O (1:1)	Li_3PO_4 (0.5)	7	**5a**	54
7[c]	CH_3CN/H_2O (1:1)	Li_3PO_4 (0.5)	7	**5a**	64
8	CH_2Cl_2	–	36	**6a**	31
9[d]	CH_2Cl_2	–	18	**6a**	81
10[e]	CH_2Cl_2	–	18	**6a**/**7a**	57/22
11[f]	CH_2Cl_2	K_3PO_4 (2.0)	70	**7a**	61

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.05 mmol), DPZ (2.5×10^{-4} mmol), 3 W blue LEDs (λ = 450–455 nm), 25 °C, ambient atmosphere, 0.5 mL solvent. [b] Yield of isolated product (average of two runs). [c] 1.0 mL solvent was used. [d] 2.0 mol% of DPZ, −10 °C, **1a**:**2a** = 5:1. [e] 2.0 mol% of DPZ, −40 °C, **1a**/**2a** = 5:1. [f] 2.0 mol% of DPZ, −40 °C, **1a**/**2a** = 3:1.

Our investigation was initiated with the model reaction between the THIQ **1a** and *N*-phenyl itaconimide (**2a**) in the presence of 0.5 mol% of DPZ at 25 °C under irradiation from a 3 W blue LEDs (λ = 450–455 nm) (Table 1).[12] *N*-itaconimides[13] feature an activated exocyclic alkene and enolizable amide moiety, thus enabling them to act as either electrophiles or nucleophiles to generate succinimide derivatives.[14] According to established reports,[13] **2a** would follow the Mannich pathway and act as a nucleophile to react with the iminium ion derived from **1a** to form the Mannich-type adduct **3a**. However, **3a** was not detected. Instead the spirotricyclic amine **4a**, a [4+2] cycloaddition product, was obtained in 37% yield along with the vinylogous Mannich-type adduct **5a** in 24% yield when using acetonitrile as the solvent (entry 1). The yield of **4a** was increased to 43% when using CH_3CN/H_2O (1:1) as the solvent (entry 2). To improve the reactivity, several Lewis acids (0.5 equiv) were used as additives to activate the LUMO of **2a**,[12] with $LiPF_6$ giving the optimal results and providing **4a** in 72% yield (entry 3). When the reaction was performed in the presence of 0.1 equivalents of $LiPF_6$ in CH_3CN/H_2O (1:3), **4a** was obtained in 89% yield (entry 4). Alternatively, we were delighted to discover that employing a weak base as an additive would promote the formation of **5a** (entries 5–7), and 0.5 equivalents of Li_3PO_4 in a more dilute solution gave **5a** in 64% yield (entry 7). When the solvent was replaced with CH_2Cl_2, to our surprise, the compound **6a**, derived from two molecules of **1a** and one molecule of **2a**, was obtained as the major product (entry 8). It was found that a lower temperature favors generation of **6a**, and it was obtained in 81% yield when the reaction was performed at −10 °C (entry 9, 2.0 mol% of DPZ and **1a**/**2a** = 5:1). Interestingly, when the temperature was −40 °C, the conjugate addition product **7a** was obtained in 22% yield (entry 10). Inorganic bases as additives were found to increase the yield of **7a**, and when 2.0 equivalents of K_3PO_4 were used, **7a** was obtained in 61% yield (entry 11).

With the optimal reaction conditions established, the substrate scope of the [4+2] cycloaddition was first examined (Conditions A), using *N*-aryl THIQs (**1**) having various substituents on the aromatic rings and a series of N-aryl-, benzyl-, and alkyl-substituted itaconimides (**2**; Table 2). The results show that all reactions worked smoothly and were complete within 3.0–16.0 hours, thus providing adducts (**4a**–**t**) in moderate to excellent yields (70–98%). When the reaction of **1a** and **2a** was performed without irradiation, no product was detected, thus confirming that photoactivation by light is critical for this reaction to succeed (see footnote [b] in Table 2). Under irradiation, trace amounts of **4a** were observed when no DPZ and $LiPF_6$ were utilized, and the reaction employing 0.1 equivalents of $LiPF_6$ but no DPZ

Table 2: The synthesis of **4**.[a]

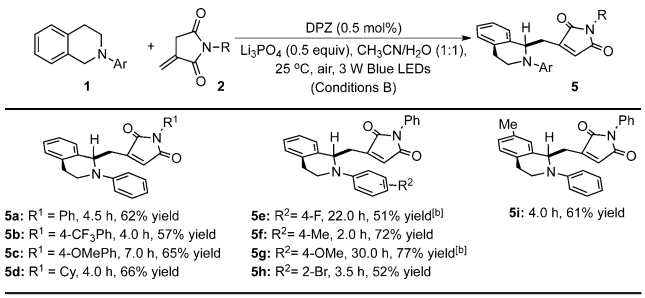


[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.2 mmol), DPZ (0.001 mmol), $LiPF_6$ (0.02 mmol), 3 W blue LEDs ($\lambda = 450$–455 nm), 25 °C, ambient atmosphere, 2.0 mL CH_3CN/H_2O (1:3, v/v). Yield of isolated product given (average of two runs). Trace amounts of **5** were detected as the by-product. [b] When the reaction was performed in the dark, no reaction occured. When no DPZ and $LiPF_6$ were used, $t = 48$ hours, trace amounts of **4a** were detected and the amide from **1a** was the main product. When no DPZ was used under the conditions, $t = 36$ h, the yield of **4a** was 73%. [c] 160 μL CH_2Cl_2 was used. [d] 200 μL CH_2Cl_2 was used.

provided **4a** in 73% yield after 36 hours (see footnote [b] in Table 2). Thus, it could be deduced that a photoresponsive EDA (electron donor–acceptor) mechanism[15] is operative and $LiPF_6$ is crucial as a Lewis acid cocatalyst for producing the cyclization adducts. The relative configurations of the cyclization products were assigned based on X-ray crystallographic analysis of a single crystal of **4a**.[16] Notably, these [4+2] cyclization adducts are analogues of **IV** which has anticonvulsant activity (Scheme 1).

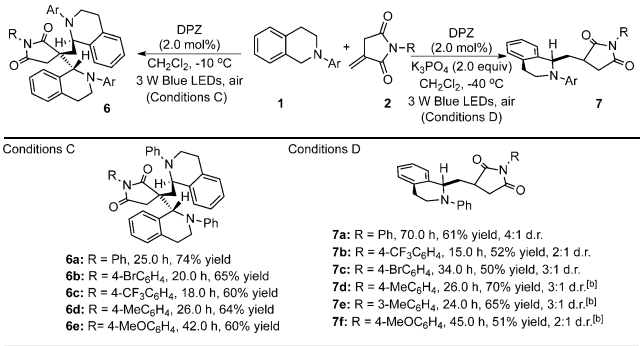
Next, we performed studies on the preparation of various vinylogous Mannich-type products (**5**) from the reactions of **1** and **2** (Table 3). It was found that most of reactions were finished within 2.0–7.0 hours, thus leading to the products **5a**–**d**, **5f**, and **5h**,**i** in 52–72% yields. Because of the poor solubility of the corresponding THIQs extra CH_2Cl_2 was used to afford **5e** and **5g** in 51 and 77% yield, respectively, after a prolonged reaction time.

Table 3: The synthesis of **5**.[a]



[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.2 mmol), DPZ (0.001 mmol), Li_3PO_4 (0.02 mmol), 3 W blue LEDs ($\lambda = 450$–455 nm), 25 °C, ambient atmosphere, 2.0 mL CH_3CN/H_2O (1:1, v/v). Yield of isolated product given (average of two runs). About 10–15% of **4** and 10–15% of an unknown compound were detected as by-products. [b] 0.4 mL of CH_2Cl_2 was used.

Table 4: The syntheses of **6** and **7**.[a]

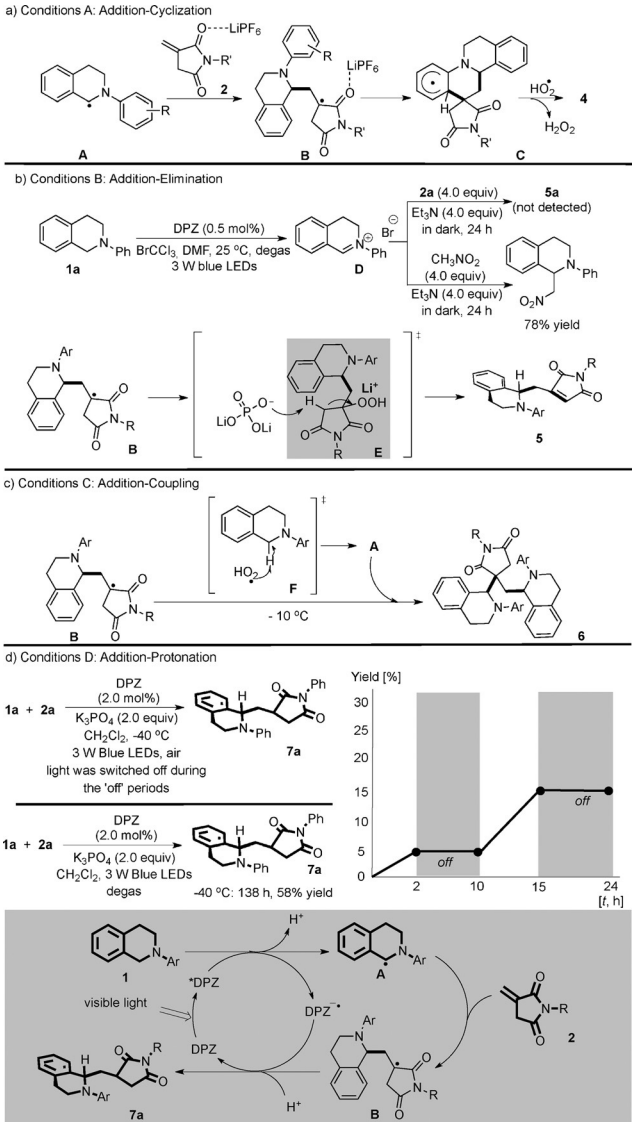


[a] Conditions C: **1a** (1.0 mmol), **2a** (0.2 mmol), DPZ (0.004 mmol), 3 W blue LEDs ($\lambda = 450$–455 nm), −10 °C, ambient atmosphere, 4.0 mL CH_2Cl_2. Conditions D: **1a** (0.6 mmol), **2a** (0.2 mmol), DPZ (0.004 mmol), K_3PO_4 (0.4 mmol), 3 W blue LEDs ($\lambda = 450$–455 nm), −40 °C, ambient atmosphere, 1.0 mL CH_2Cl_2. Yield of isolated product given (average of two runs). Under Conditions C, 5–10% of **4** and 15–20% of **7** were detected as by-products. Under reaction Conditions D, 5–10% of **4** and 20–25% of **6** were detected as by-products. [b] DPZ (0.008 mmol), −30 °C.

We then conducted the aerobic photoredox reactions of **1** and **2** (Table 4). The adducts **6a**–**e** were obtained in 60–74% yields within 20–61 hours. The relative configurations of **6** were determined by X-ray diffraction analysis of a single crystal of **6b**.[16] The photoredox reactions of **1** and **2** were also attempted under Conditions D (Table 4). As shown, the reactions were completed within 15–70 hours and afforded the conjugate adducts **7a**–**f** in 50–70% yield.

On the basis of the obtained results, four plausible radical pathways are individually proposed (Scheme 2). Under the reaction Conditions A, the reaction should go through a radical addition-cyclization pathway to afford the [4+2] cycloaddition products **4** (Scheme 2a).[2a,17] $LiPF_6$ as a Lewis acid cocatalyst plays a significant role, that is, accelerating the nucleophilic addition of the radical **A** to **2**, and stablizing the formed radical **B**. The radical **B** cannot oxidize the radical anion DPZ $H^{\bullet-}$ and the subsequent cyclization step becomes possible.[17]

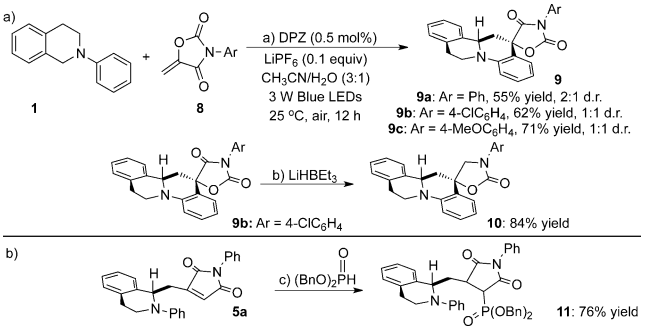
In principle, when the enolizable *N*-itaconimides react with electrophiles, doubly substituted succinimides (**3**) are favored, and no example of vinylogous addition is reported.[13d–e] However, the results in Table 3 (Conditions B) indicated that only vinylogous Mannich-type products (**5**) were obtained. To explore the mechanism, we firstly attempted to oxidize **1a** to the iminium **D** as the Mannich acceptor, by employing $BrCCl_3$[17] in DMF at 25 °C and under visible-light irradiation, but the desired **5a** was not detected after 4.0 equivalents of **2a** and Et_3N were added and the reaction run for 24 h (Scheme 2b).[19] Notably, an aza-Henry adduct was obtained in 78% yield when CH_3NO_2 was added, thus demonstrating the existence of **D**. Moreover, TEMPO (2.0 equiv), as a radical inhibitor, was found to suppress this reaction. Therefore, the adducts **5** should come from a radical addition-elimination pathway, in which Li_3PO_4 serves as a base to deprotonate the adduct **E** to address a H_2O_2 elimination (Scheme 2b).



Scheme 2. Mechanistic investigations and proposal of four reaction pathways.

A radical addition-coupling approach to access the adducts **6** is proposed (Scheme 2c). Under the reaction Conditions C, the low temperature (−10 °C) can effectively generate **B**. Another radical, **A**, is generated from $HO_2^{\bullet}$ dehydrogenating **1** (transition-state **F**). The subsequent coupling of **A** with **B** affords **6**. In contrast, a radical addition-protonation mechanism was deduced to yield the products **7** on the basis of the following experimental outcomes (Scheme 2d). First, an experiment in which the light source was switched on and off for the reaction of **1a** and **2a** was performed, and the results clearly excluded the possibility of a radical chain process in this reaction system. Second, the reaction was evaluated in deoxygenated CH_2Cl_2 under the reaction Conditions D and a similar yield with prolonged reaction time was obtained.

The versatility and synthetic value of this work were also evaluated. To access anologues of the α-adrenoceptor antagonist **II** (Scheme 3), we attempted the reactions of **1a** with



Scheme 3. Reaction conditions: a) **1** (0.6 mmol), **7** (0.2 mmol), DPZ (0.001 mmol), $LiPF_6$ (0.02 mmol), 3 W blue LEDs (λ = 450–455 nm), 25 °C, ambient atmosphere, 2.0 mL CH_3CN/H_2O (3:1, v/v); b) $LiHBEt_3$ (3.0 equiv), THF, −78 °C, 4 h, 84% yield. c) $(BnO)_2POH$ (1.0 equiv), TBD (1.0 equiv), toluene, 25 °C, 0.5 h, 76% yield. TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

2,4-oxazolidinediones (**8**) using the reaction Conditions A. The reactions worked smoothly in a 1:3 solvent mixture of CH_3CN and H_2O, thus affording the adducts **9a–c** in 55–71% yields after 12 hours. The reduction of **9b** by $LiHBEt_3$ provided **10**, an anologue of **II**, in 84% yield (Scheme 3a). In view of an activated alkene, the products **5** could be employed as Michael acceptors to introduce various functional groups. Thus, a phospha-Michael addition of dibenzylphosphite to **5a** was examined. It was found that the adduct **11** was obtained in 76% yield by using 1.0 equiv of TBD (Scheme 3b).

In summary, we have successfully developed an efficient and practical strategy for controlling the selective syntheses of four diverse products from the same starting materials by using visible-light photoredox catalysis. By employing DPZ as a photoredox catalyst, the aerobic reactions of THIQs with *N*-itaconimides proceed by four different radical cascade pathways, including addition-cyclization, addition-elimination, addition-coupling, and addition-protonation, with moderate to excellent chemoselectivity, through modulating the reaction media, temperature, and additive. These methods provide convenient ways for the synthesis of four kinds of valuable N-heterocycles. Moreover, the addition-cyclization strategy was suitable for 2,4-oxazolidinediones, as electrophiles, reacting with THIQs to form a series of α-adrenoceptor antagonist anologues. This study is the first example showing THIQs as electrophiles in the presence of oxygen in photoredox catalysis. Further investigations, which will involve the bioactivities of these products and the extension of DPZ as a catalyst in photoredox catalysis, are in progress in our laboratory.

Keywords: heterocycles · photochemisty · radicals · reaction mechanisms · synthetic methods

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[12] For detailed investigations on reaction conditions, see the Supporting Information. Several commonly used photoredox catalysts, such as $[Ru(bpy)_3(PF_6)_2]$, Eosin Y, and Rose Bengal, were also evaluated to produce the adducts **4**–**7** under the established reaction conditions, and the results are summarized in the Supporting Information.

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[19] The reaction was messy and the desired **5a** was not detected. We also examined the reaction using extra Li_3PO_4 (0.5 equiv), and **5a** was still not observed yet.

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