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Metal-Free Direct C-H Cyanoalkylation of Quinoxalin-2(1H)-ones by Organic Photoredox Catalysis

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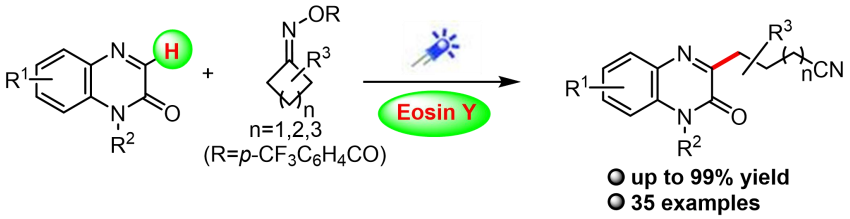


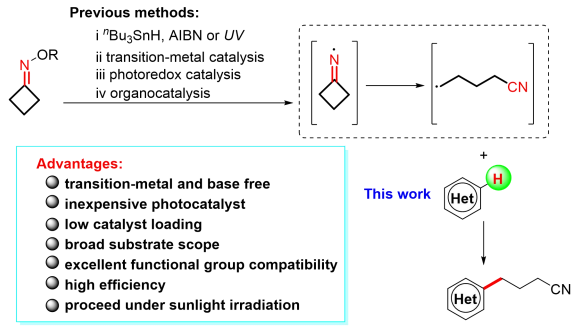
Abstract: A green and efficient C-C bond cleavage/cyanoalkylation of heteroarenes under visible-light or sunlight irradiation are described. The reaction proceeds under mild conditions at room temperature without transition-metal catalysts and extra bases. Notably, the products enable facile transformations to various significant organic compounds.

Introduction

Alkylnitriles represent a privileged class of structural motifs found in several nitrile-containing natural products and pharmaceuticals.[1 and 2] Owing to their biological and pharmaceutical properties, efficient incorporation of a cyanoalkyl group into structurally diverse molecules has attracted much attention. Cyanoalkylation is the most useful reaction, because the cyano group can be readily converted into other functional groups.[3] The traditional approach of the cyanoalkylation, is to generate carbanions from simple alkylnitriles to react with electrophiles.[4] This method is requiring the utilization of strong bases, which is usually incompatible with base-sensitive substrates. On the other hand, the generation of metalated nitriles is an attractive alternative route to activate alkylnitriles.[5] However, these reactions are

usually conducted at high temperature and the scope is usually limited. In addition, radical cyanoalkylation also represent an efficient approach to alkylnitriles.[6-8] Recently, much efforts in this area have been emphasized on cyanomethylation using α-cyanomethyl radicals.[6] In comparison, cyanoalkylation based on distal cyano-substituted alkyl radicals has been rarely studied, presumably due to the lack of suitable approaches for radical initiation. The cyclobutanone oxime used as an equivalent of γ-cyanoalkyl radical (Scheme 1), which using AIBN as a radical initiator, was firstly reported by Zard and co-workers.[8] Very recently, ring-opening of cyclobutanone oxime derivatives have been explored with transition metal catalysis, photoredox catalysis and organocatalysis.[7] Although much endeavours have been paid in this area as mentioned above, as we know, direct catalytic distal radical cyanoalkylation methodologies under metal-free conditions are still rare.

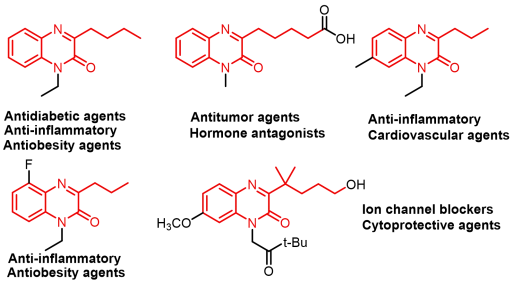
Scheme 1. The method for ring-opening of cyclobutanone oxime derivatives



Quinoxalin-2(1*H*)-ones are distributed in many compounds of enormous practical importance, ranging from bioactive natural products to pharmaceutical agents and material science.[9] Chemists have devoted extensive efforts to the synthesis of these aza-heterocycles. Direct modification of easily available quinoxalin-2(1*H*)-ones leads a rapid way to obtain diverse derivatives.[10-15] To date, several important advances have been established, such as radical arylation, phosphonation, amination, acylation, and trifluoromethylation of quinoxalin-2(1*H*)-ones. In comparison, C-H alkylation of quinoxalin-2(1*H*)-ones is still rare. In particular, the 3-alkylquinoxalin-2(1*H*)-one moiety as an important pharmacophore has appeared in numerous biological molecules (Figure 1).[16] Therefore, the development of environmentally benign and

synthetically efficient protocols to introduce alkyl substituents at the 3-position of quinoxalin-2(1*H*)-ones is still highly desirable, which might advance their use in new drug discovery and development.

Figure 1. Selected biological structures bearing a 3-alkylquinoxalin-2(1*H*)-one unit.



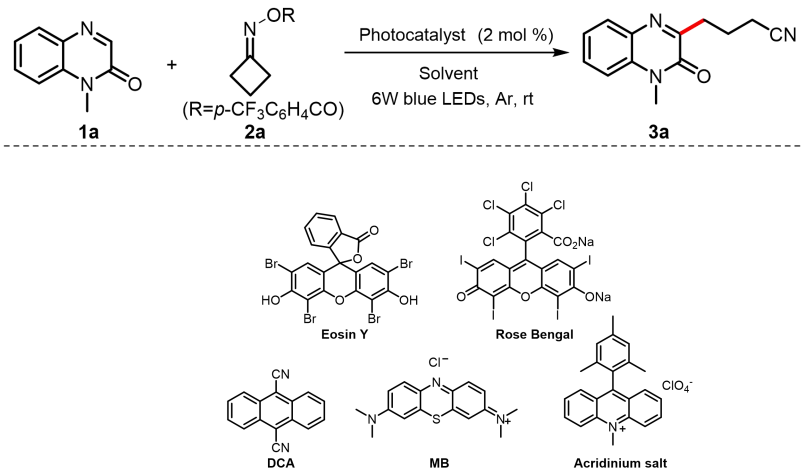
Visible-light photocatalysis has received wide attention from synthetic chemists in the past decade.[17] The outstanding feature is its ability to generate various high active species under mild conditions, which promoted the development of synthetic chemistry. Currently, cheap organic dyes have been proven to be a reliable option to the replacement of those metal photoredox catalysts in many valuable transformations.[17d,e] To the best of our knowledge, direct C − H cyanoalkylation of heteroarenes at room temperature without transition-metal catalyst has not been realized. Herein we developed extremely mild conditions to access the direct cyanoalkylation of quinoxalin-2(1*H*)-ones or other heteroarenes with cyclobutanone oxime esters under metal-free conditions. It is valuable noted that the reaction system is simple, no extra bases is needed and excess starting materials can easily be recycled.

Results and Discussion

Initially, we chose the 1-methylquinoxalin-2(1*H*)-one **1a** and cyclobutanone *O*-acyl oxime **2a** as model substrates to optimize the reaction conditions. The results are illustrated in Table 1. When the model reaction was carried out using 2 mol% Eosin Y

as photocatalyst in CH_2Cl_2 at room temperature under an argon atmosphere, the desired product **3a** was obtained in quantitative yield (Table 1, entry 1). Next, other organic photocatalysts, such as DCA, MB, Rose Bengal, Acridinium salt were investigated. Unfortunately, none of them showed good efficiency (Table 1, entries 2-5). Several solvents were then screened. As a result, all the other examined solvents gave the poor results than CH_2Cl_2 (Table 1, entries 6-10). The yield of the product remained approximately the same when the loading of the photocatalyst was further decreased to 1 mol% (Table 1, entry 11), accompanied by an extension of the reaction time. Control experiments indicated that photocatalysts, inert-atmosphere and blue-light sources were essential for the reaction efficiency (Table 1, entries 12-14).

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



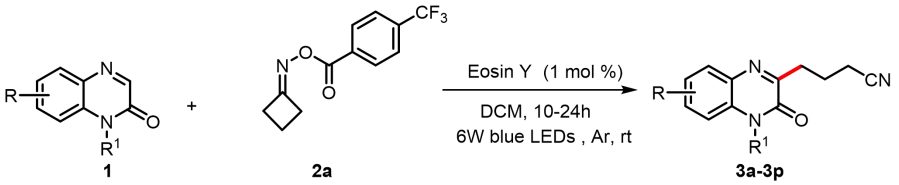
Entry	Photocatalyst	Time(h)	Solvent	Yield(%)[b]
1	EosinY	7	CH_2Cl_2	>99%
2	Rose Bengal	7	CH_2Cl_2	NR
3	DCA	7	CH_2Cl_2	NR
4	MB	7	CH_2Cl_2	NR
5	Acridinium salt	12	CH_2Cl_2	80
6	EosinY	7	EtOAc	NR
7	EosinY	7	DMF	NR

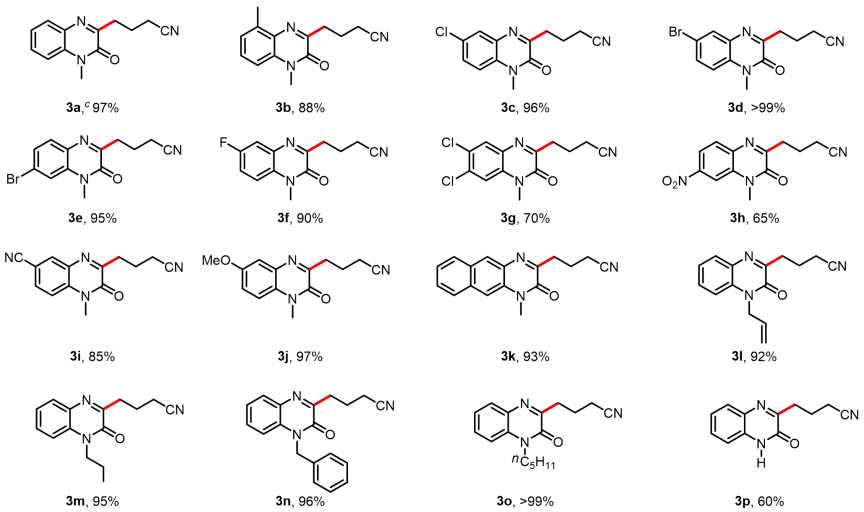
8	EosinY	10	MeOH	65
9	EosinY	36	$PhCH_3$	80
10	EosinY	7	H_2O	NR
11[c]	EosinY	12	CH_2Cl_2	97
12	-	12	CH_2Cl_2	NR
13[d]	EosinY	12	CH_2Cl_2	NR
14[e]	EosinY	12	CH_2Cl_2	NR

[a] Unless noted otherwise, Reaction conditions: **1a** (0.15 mmol, 1.5 equiv), **2a** (0.1 mmol, 1 equiv) and photocatalysts (0.002 mmol, 2.0 mol %) in indicated solvent (1.0 ml) at room temperature under an atmosphere of argon and the irradiation of 6w blue LEDs. [b] Isolated yield. [c] The catalyst loading was 1.0 mol %. [d] Under air. [e] In the dark. NR: no reaction.

With the optimal conditions in hand, we first examined the scope of various quinoxalin-2(1*H*)-ones **1** with cyclobutanone *O*-acyl oxime **2a** (Scheme 2). Various quinoxalin-2(1*H*)-ones bearing electron-donating and electron-withdrawing substituents on the arene rings exhibited good reaction efficiency, affording the corresponding 3-cyanopropylated products **3b-3k** in good to excellent yields. An array of functional groups including fluoro, chloro, bromo, nitro, cyano, methoxyl and naphthyl were well tolerated under the optimal conditions. After that, we screened different protecting groups of nitrogen. As a result, all of the protecting groups tested were tolerated, furnishing the corresponding products **3l-3o** in excellent yields. *N*-unsubstituted quinoxalin-2(1*H*)-one was also proceeded smoothly, giving the desired product **3p** in 60% yield.

Scheme 2. Substrate scope of quinoxalin-2(1*H*)-ones [ab]

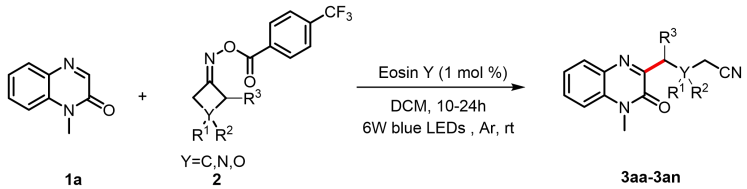


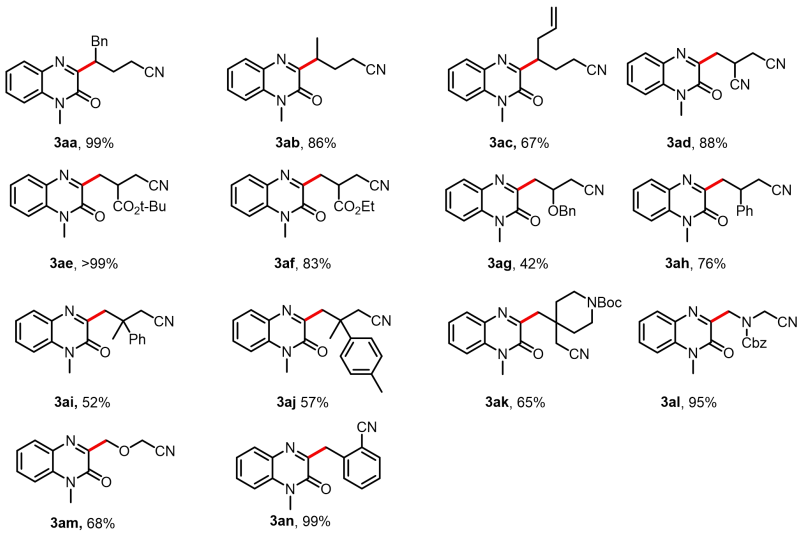


[a] Reaction conditions: **1** (0.15 mmol, 1.5 equiv), **2a** (0.1 mmol, 1 equiv), and Eosin Y (0.001 mmol, 1.0 mol %) in DCM (1.0 ml) at room temperature under an atmosphere of argon and the irradiation of 6W blue LEDs. [b] Isolated yield. [c] The structure of **3a** was determined by X-ray analysis.[19]

Encouraged by these results, we continued to investigate the substrate generality with a range of representative cyclobutanone *O*-acyl oximes **2** with **1a** under standard conditions (Scheme 3). To our delight, nonsymmetrical cyclobutanone derived acyl oximes **2b-2d** with benzyl, methyl and allyl groups at the 2-position were all well tolerated to furnish the expected products **3q-3s** (67-99% yields). Symmetric monosubstituted *O*-acyl oximes **2e-2i** with various functional groups, such as cyano, ester, ether and phenyl substituents at the 3-position, also proceeded smoothly to deliver the products **3t-3x** (42-99% yields). Furthermore, disubstituted substrates **2j-2l** were also compatible with our photocatalytic system, generating desired products **3y-3aa** in 52-65% yields. In addition, both 1-Cbz-3-azetidinone and oxetan-3-one derived *O*-acyl oximes **2m** and **2n** participated in the reaction very well to give the products **3ab-3ac** in good yields. Once again, the reaction of benzocyclobutenone-derived substrate **2o** proved to be suitable for the reaction, in which **3ad** was formed as the sole product in 99% yield.

Scheme 3. Substrate scope of cyclobutanone oxime esters [ab]

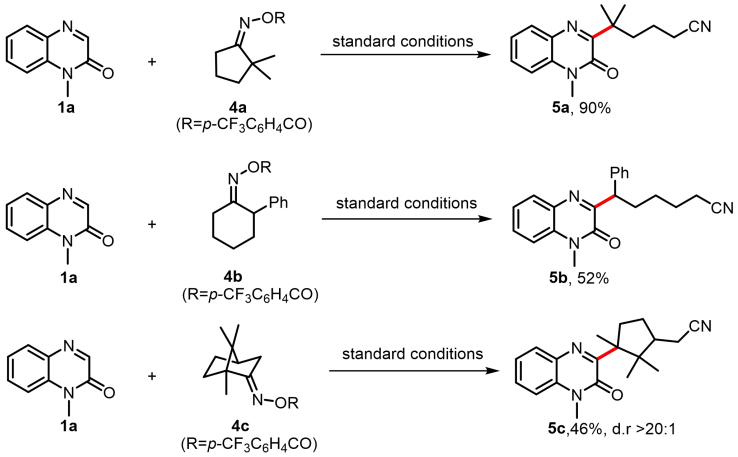




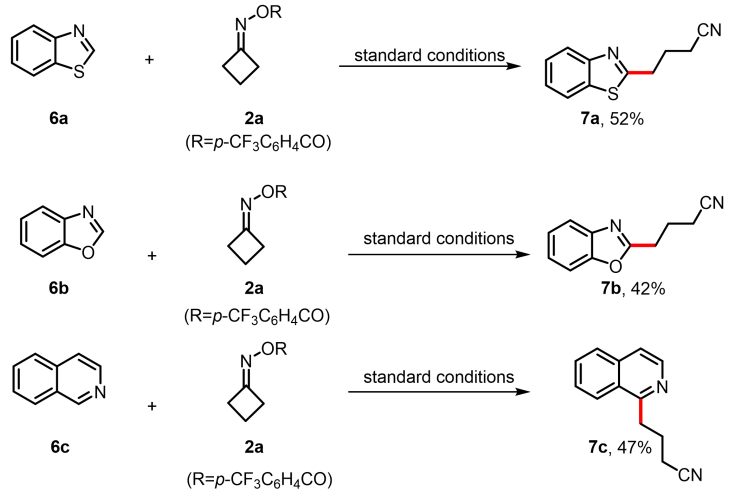
[a] Reaction conditions: **1a** (0.15 mmol, 1.5 equiv), **2** (0.1 mmol, 1 equiv), and Eosin Y (0.001 mmol, 1.0 mol %) in DCM (1.0 ml) at room temperature under an atmosphere of argon and the irradiation of 6W blue LEDs. [b] Isolated yield.

In contrast to transition-metal catalyzed ring-opening of cyclobutanone oximes,[18] a range of the more challenging unstrained oxime esters **4a-4c** from cyclopentanone, cyclohexanone and camphor (Scheme 4) could also participate in this cyanoalkylation strategy very well to give the desired products **5a-5c** in 46-90% yields. These results demonstrated the advantages of this procedure. To further explore the potential of our photocatalytic system, we attempted to apply this strategy to a series of significant natural bioactive skeletons, such as benzothiazole, benzoxazole and isoquinoline, that are readily accessible from commercial feedstocks (Scheme 5). As a result, treatment of **6a-6c** with **2a** in standard condition furnished expected products **7a-7c** in 42-52% yields.

Scheme 4. Substrate scope of cyclopentanone and cyclohexanone oxime esters

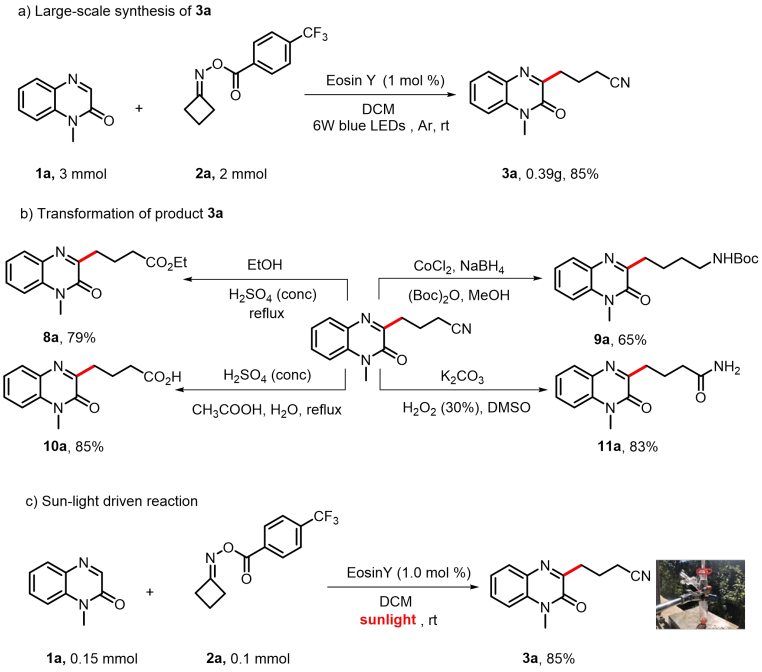


Scheme 5. Substrate scope of other significant heteroarenes



To evaluate the prospective utility of the methodology, a large-scale reaction, the transformation of the product and a sunlight-driven experiment were performed (Scheme 6). Notably, the scalability of this procedure was demonstrated by a 2 mmol of **2a** with 3 mmol of **1a**, which proceeded smoothly to deliver the product **3a** in 85% yield. It is worthy noted that the cyano group was a synthetically versatile precursor. We then selected several key transformations to highlight the potential of the product. Conversion of **3a** into ester **8a** or carboxylic acid **10a** could be easily achieved with good yields by hydrolysis in the presence of acid. Moreover, selective reduction of the nitrile group could be achieved by using $NaBH_4$ to afford the secondary amine **9a** in 65% yield. In addition, the oxidation of **3a** with H_2O_2 delivered amides **11a** in 83% yield. To our delight, the reaction was also proceeded well in the sunlight, gave the product **3a** in 85 % yield.

Scheme 6. Synthetic Utility of the Methodology [a]

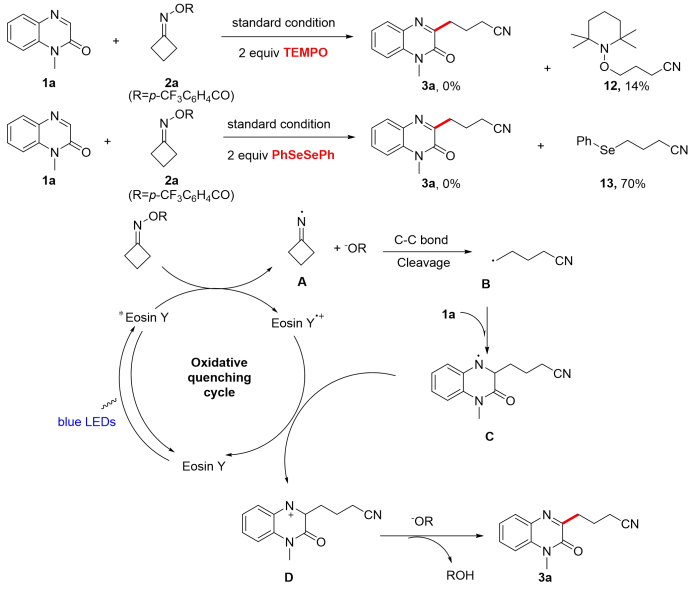


[a] The image in the scheme 6 was photographed by Yu-Liang Pan

In order to gain more insight into the mechanism of this reaction, some experiments were carried out (Scheme 7). The reaction was obviously suppressed when 2 equiv of radical scavenger TEMPO or PhSeSePh were added under the standard conditions. Instead, the radical trapping adducts were obtained in 14% and 70% yields, respectively. These evidence implied that iminyl radical-mediated C-C bond cleavage and formation of cyanoalkyl radical might be involved in the reaction. Stern-Volmer fluorescence quenching experiments clearly demonstrated that the excited state of the photocatalyst can be quenched by the cyclobutanone oxime derivatives (Figure S2). Based on the above results and previous related literature, a possible mechanism was proposed (Scheme 7). Initially, the photocatalyst Eosin Y is irradiated to the excited states Eosin Y * (E_{ox}= - 1.58V vs Ag/AgCl),[16e] which is oxidatively quenched by *O*-acyl oxime (E_{2a}= - 1.60V vs Ag/AgCl) [7e] with the generation of a Eosin Y $^{\cdot+}$ complex, a iminyl radical A and alkoxy anion. This process is similar to the Xiao's work using *fac*-Ir(ppy)$_3$ as the photocatalyst. [7e] Subsequently, the iminyl radical **A** undergoes a ring-opening by homolytic C-C bond cleavage to form a highly reactive cyanoalkyl radical **B**. Addition of **B** to 1-methylquinoxalin-2(1*H*)-one **1a** produces radical intermediate **C**, which undergoes single-electron oxidation by Eosin Y $^{+}$

complex with the regeneration of ground-state Eosin Y, closing the photocatalytic cycle. Finally, intermediate **D** by loss of H^+ assisted with alkoxy anion to afford the product **3a**.

Scheme 7. Experiment for mechanistic study and a proposed mechanism



Conclusions

In summary, cyanoalkylation of quinoxalin-2(1*H*)-ones or other heteroarenes has been achieved with organic photoredox catalysis. This reaction provides a green and efficient approach to construct long-chain nitriles moieties, which are valuable in pharmaceutical chemistry. The reaction shows good functional group tolerance and wide substrate scope, accessing to a wide range of 3-cyanoalkylated quinoxalin-2(1*H*)-ones, which could be a potential biological and pharmaceutically active molecule. Notably, the established methodology is also applicable for the cyanoalkylation of other heteroarenes, such as benzothiazole, benzoxazole and isoquinoline. The products can be easily converted to some significant organic compounds. Preliminary mechanistic evidence suggests that the cyanoalkyl radicals are involved in the process.

Experimental Section

General Experimental Procedures. Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. The purchased solvents were degassed by three cycles of freeze-pump-thaw before use in the reaction. ^{1}H NMR spectra were recorded in on 400 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m). ^{13}C NMR were recorded on 100 MHz with complete proton decoupling spectrophotometer. Mass spectra were measured using agilent 6520 Q-TOF micro spectrometer. The light source in detail and the material of the irradiation vessel see the SI (Figure S1).

Most substrates **1** and **2** were synthesized according to the reported literatures. [7, 10-15] In addition, **1b** and **1j** were new compounds.

General Experimental Procedure for the Synthesis of product 3

1 (0.15 mmol), **2** (0.1 mmol) and Eosin Y (1 mol %) were dissolved in DCM (1 mL). Then, the resulting mixture was degassed via 'freeze-pump-thaw' procedure (3 times). After that, the solution was stirred at a distance of ~5 cm from a 6 W blue LEDs (450-460 nm) at room temperature about 10-24 h until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethylacetate 3:1~2:1) directly to give the desired

product **3.**

4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3a***) yellow solid, 22 mg, 97% yield; mp 98-100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57-7.53 (m, 1H), 7.37-7.30 (m, 2H), 3.70 (s, 3H), 3.08 (t, *J* = 6.8 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.22 (m, 2H); ^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$) δ158.5, 154.7, 133.1, 132.5, 130.1, 129.8, 123.8, 119.6, 113.6, 32.3, 29.1, 22.0, 16.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{13}N_3ONa$:250.0951, , found:250.0954.

*4-(4,8-dimethyl-3-oxo-3,4-dihydroquinoxalin-2-yl)*butanenitrile (***3b***) yellow solid, 21.1 mg, 88% yield; mp 120-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.43 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 3.69 (s, 3H), 3.10 (t, *J* = 6.8 Hz, 2H), 2.67 (s, 3H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.25 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ156.4, 154.7, 138.5, 133.1, 131.0, 129.7, 125.0, 119.7, 111.6, 32.1, 29.2, 21.9, 17.5, 16.6; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{15}N_3ONa$: 264.1107, found: 264.1110.

4-(7-chloro-4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3c***) yellow solid, 25.2 mg, 96% yield; mp 106-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.83 (d, *J* = 2.4 Hz, 1H), 7.51 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 3.71 (s, 3H), 3.11 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.24 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 160.0, 154.4, 133.0, 131.8, 130.0, 129.2, 129.1, 119.5, 114.8, 32.3, 29.2, 21.8, 16.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{12}ClN_3ONa$: 284.0561, found:284.0565.

4-(7-bromo-4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3d***) yellow solid, 30.5mg, 99.9% yield; mp 96-98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.67-7.65 (m, 1H), 7.46-7.43 (m, 2H), 3.66 (s, 3H), 3.05 (t, *J* = 6.8 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.20 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ158.9, 154.4, 134.1, 131.3, 131.0, 127.0, 124.1, 119.5, 116.8, 32.3, 29.2, 21.9, 16.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{12}BrN_3ONa$: 328.0056, found:328.0060.

4-(6-bromo-4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3e***) yellow solid, 29.1 mg, 95% yield; mp 87-89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m,

1H), 7.47-7.44 (m, 2H), 3.66 (s, 3H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.53 (t, *J* = 7.6 Hz, 2H), 2.21 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ158.9, 154.4, 134.1, 131.3, 131.0, 127.0, 124.1, 119.5, 116.8, 32.3, 29.2, 21.9, 16.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{12}BrN_3ONa$: 328.0056, found:328.0058.

4-(7-fluoro-4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3f***) yellow solid, 22 mg, 90% yield; mp 93-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.53 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.34-7.26 (m, 2H), 3.71 (s, 3H), 3.10 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.22 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ160.1, 158.7 (d, *J* = 244.8 Hz), 154.4, 133.1 (d, *J* = 11.1 Hz), 129.7 (d, *J* = 2.2 Hz), 119.5, 117.8 (d, *J* = 23.9 Hz), 115.3 (d, *J* = 22.7 Hz), 114.8 (d, *J* = 8.9 Hz), 32.4, 29.4, 21.8, 16.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{12}FN_3ONa$: 268.0857, found:268.0860

4-(6,7-dichloro-4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3g***) yellow solid, 20.7 mg, 70% yield; mp 135-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.39 (s, 1H), 3.65 (s, 3H), 3.07 (t, *J* = 6.8 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.19 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ160.1, 154.1, 134.1, 132.5, 131.5, 130.6, 127.5, 119.4, 115.2, 32.3, 29.4, 21.7, 16.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{11}Cl_2N_3ONa$: 318.0171, found:318.0175.

4-(4-methyl-6-nitro-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3h***) yellow solid, 17.8 mg, 65% yield; mp 132-134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.20 (m, 2H), 8.00 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 3.18 (t, *J* = 7.2 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.27 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ162.8, 154.2, 147.7, 135.8, 133.5, 130.9, 119.3, 118.3, 109.7, 32.6, 29.6, 21.6, 16.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{12}N_4O_3Na$: 295.0802, found: 295.0804.

3-(3-cyanopropyl)-1-methyl-2-oxo-1,2-dihydroquinoxaline-6-carbonitrile (***3i***) yellow solid, 21.4 mg, 85% yield; mp 133-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.92-7.90 (m, 1H), 7.61-7.59 (m, 2H), 3.71 (s, 3H), 3.13 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.23 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ162.2, 154.2, 134.6, 133.5, 130.8, 126.7, 119.4, 118.1, 117.9, 113.2, 32.5, 29.3, 21.7, 16.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{12}N_4ONa$: 275.0903, found:275.0906.

4-(7-methoxy-4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3j***) yellow solid, 24.9 mg, 97% yield; mp 136-138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.33 (d, *J* = 2.8 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.21 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.93 (s, 3H), 3.73 (s, 3H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.26 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ159.0, 156.0, 154.4, 133.3, 127.3, 119.6, 119.2, 114.6, 111.2, 55.8, 32.5, 29.2, 22.1, 16.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{15}N_3O_2Na$: 280.1056, found:280.1060.

4-(4-methyl-3-oxo-3,4-dihydrobenzo[g]quinoxalin-2-yl)butanenitrile (***3k***) yellow solid, 25.8 mg, 93% yield; mp 138-140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.93 (dd, *J* = 26.4, 8.4 Hz, 2H), 7.63-7.53 (m, 2H), 7.51-7.47 (m, 1H), 3.75 (s, 3H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.25 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ159.0, 154.6, 133.5, 131.8, 131.6, 129.7, 128.9, 128.4, 127.9, 127.2, 125.4, 119.6, 110.1, 32.4, 29.1, 22.0, 16.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{15}N_3ONa$: 300.1107, found:300.1111.

4-(4-allyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3l***) yellow solid, 23.2 mg, 92% yield; mp 77-79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.83 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.53-7.49 (m, 1H), 7.36-7.32 (m, 1H), 7.29 (dd, *J* = 8.4, 0.4 Hz, 1H), 5.98-5.88 (m, 1H), 5.27 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.16 (dd, *J* = 17.2, 0.4 Hz, 1H), 4.90 (dt, *J* = 5.2, 1.8 Hz, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.24 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ158.5, 154.3, 132.7, 132.3, 130.5, 130.0, 129.9, 123.7, 119.6, 118.2, 114.3, 44.5, 32.3, 22.0, 16.8; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{15}N_3ONa$: 276.1107, found:276.1112.

4-(3-oxo-4-propyl-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3m***) yellow solid, 24.2 mg, 95% yield; mp 79-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.83 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.53 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.36-7.30 (m, 2H), 4.23-4.19 (m, 2H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.23 (m, 2H), 1.84-1.74 (m,2H), 1.05 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 158.5, 154.5, 132.8, 132.3, 130.0, 129.9, 123.5, 119.6, 113.7, 43.9, 32.3, 22.1, 20.6, 16.8, 11.4; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{17}N_3ONa$: 278.1264, found:278.1266.

4-(4-benzyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3n***) yellow solid, 29 mg, 96% yield; mp 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.84 (d, *J* = 8.0, 1H), 7.45-7.40 (m, 1H), 7.34-7.22 (m, 7H), 5.50 (s, 2H), 3.15 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.27 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ158.6, 154.8, 135.1, 132.8, 132.4, 130.0, 129.9,129.0, 127.8, 126.9, 123.8, 119.7, 114.5, 46.0, 32.4, 22.1, 16.8; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{17}N_3ONa$: 326.1264, found:326.1268.

4-(3-oxo-4-pentyl-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3o***) yellow solid, 28.2 mg, 99% yield; mp 77-79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54 (ddd, *J* = 16.0, 7.3, 1.6 Hz, 1H), 7.35-7.30 (m, 2H), 4.25-4.18 (m, 2H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 2.22 (m, 2H), 1.79-1.71 (m, 2H), 1.47-1.35 (m, 4H), 0.92 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ158.5, 154.4, 132.8, 132.3, 130.0, 129.9, 123.5, 119.7, 113.6, 42.4, 32.2, 29.1, 27.0, 22.4, 22.1, 16.8, 14.0; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{21}N_3ONa$: 306.1577, found:306.1579.

4-(3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3p***) yellow solid, 12.7 mg, 60% yield; mp 181-183 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ12.37 (s, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.50 (td, *J* = 7.7, 1.4 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.1 Hz, 2H), 2.05 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, DMSO-*d*$_6$) δ 160.2, 154.6, 131.8, 131.5, 129.5, 128.1, 123.0, 120.6, 115.2, 31.3, 21.6, 15.9; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{12}H_{11}N_3ONa$: 236.0794, found:236.0797.

(R)-4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)-5-phenylpentanenitrile (***3aa***) yellow solid, 31.4 mg, 99% yield; mp 95-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.83 (m, 1H), 7.58-7.52 (m, 1H), 7.39-7.26 (m, 6H), 7.21-7.16 (m, 1H), 3.86-3.84 (m, 1H), 3.71 (s, 3H), 3.27-3.20 (m, 1H), 2.39-2.22 (m, 3H), 2.03-1.98 (m, 1H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 160.4, 154.6, 139.3, 133.0, 132.5, 130.3, 130.0, 129.2, 128.5, 126.4, 123.8, 119.7, 113.7, 42.6, 39.3, 29.2, 27.1, 15.1; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{19}N_3O$: 340.1420, found:340.1425.

(S)-4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)pentanenitrile (***3ab***) yellow solid, 20.7 mg, 86% yield; mp 80-82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.83 (dd, *J* = 8.0, 1.2

Hz, 1H), 7.55 (ddd, *J* = 16.0, 7.3, 1.5 Hz, 1H), 7.38-7.30 (m, 2H), 3.71 (s, 3H), 3.67-3.58 (m, 1H), 2.47-2.32 (m, 3H), 2.04-1.94 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 161.8, 154.5, 133.0, 132.5, 130.1, 130.0, 123.7, 119.8, 113.7, 35.5, 29.6, 29.2, 18.5, 15.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_3O$: 242.1288, found: 242.1290.

(R)-4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)hept-6-enenitrile (***3ac***) yellow oil, 17.8 mg, 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.56 (ddd, *J* = 16.0, 7.3, 1.6 Hz, 1H), 7.38-7.33 (m, 2H), 5.83-5.75 (m, 1H), 5.08-4.99 (m, 2H), 3.71 (s, 3H), 3.69-3.62 (m, 1H), 2.66-2.58 (m, 1H), 2.41-2.30 (m, 4H), 2.13-2.04 (m, 1H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 160.5, 154.6, 135.4, 132.9, 132.5, 130.2, 130.0, 123.7, 119.8, 117.4, 113.7, 40.2, 37.3, 29.3, 27.4, 15.1; HRMS (EI): m/z $[M + Na]^+$ calcd for $C_{16}H_{17}N_3O$: 290.1264, found: 290.1266.

2-((4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)methyl)succinonitrile (***3ad***) yellow solid, 22.2 mg, 88% yield; mp 139-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.87 (d, *J* = 8.0, 1H), 7.61 (t, *J* = 7.6, 1H), 7.41-7.34 (m, 2H), 3.81 (m, 1H), 3.72 (s, 3H), 3.51-3.34 (m, 2H), 2.97 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ154.3, 153.8, 133.2, 132.1, 131.0, 130.1, 124.1, 118.9, 115.7, 113.9, 34.7, 29.3, 25.1, 20.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{13}N_4O$: 253.1084, found:253.1087.

tert-butyl 3-cyano-2-((4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)methyl)propanoate (***3ae***) yellow solid, 32.7 mg, 99% yield; mp 117-119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.55 (ddd, *J* = 8.5, 7.2, 1.2 Hz, 1H), 7.36-7.31 (m, 2H), 3.70 (s, 3H), 3.44-3.38 (m, 2H), 3.30-3.23 (m, 1H), 2.88-2.74 (m, 2H), 1.41 (s, 9H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ171.1, 156.7, 154.6, 133.1, 132.2, 130.2, 129.7, 123.8, 118.0, 113.7, 81.9, 39.3, 34.5, 29.1, 27.9,19.2; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{18}H_{21}N_3O_3Na$: 350.1475, found:350.1478.

ethyl 3-cyano-2-((4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)methyl)propanoate (***3af***) brown solid, 24.8 mg, 83% yield; mp 75-77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.56 (ddd, *J* = 16.0, 7.3, 1.6 Hz, 1H), 7.36-7.31 (m, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 3.51-3.45 (m, 2H), 3.31 (dd, *J* = 19.2, 8.8 Hz,

1H), 2.93-2.80 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ172.0, 156.4, 154.6, 133.1, 132.2, 130.3, 129.8, 123.8, 117.9, 113.7, 61.5, 38.5, 34.3, 29.1, 19.1, 14.1; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{18}N_3O_3$: 300.1343, found:300.1345.

3-(benzyloxy)-4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (***3ag***) brown oil, 14 mg, 42% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57 (ddd, *J* = 15.6, 8.4, 1.6 Hz, 1H), 7.39-7.35 (m, 1H), 7.31-7.26 (m, 3H), 7.22-7.19 (m, 3H), 4.73-4.66 (m, 2H), 4.43-4.40 (m, 1H), 3.65 (s, 3H), 3.42 (dd, *J* = 15.2, 6.4 Hz, 1H), 3.18 (dd, *J* = 15.2, 6.5 Hz, 1H), 2.78 (qd, *J* = 16.8, 4.8 Hz, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ156.4, 154.7, 137.4, 133.2, 132.5, 130.3, 130.0, 128.3, 128.1, 127.8, 123.8, 117.7, 113.7, 72.4, 72.1, 38.6, 29.1, 23.7; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{20}H_{19}N_3O_2Na$: 356.1369, found:356.1375.

4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)-3-phenylbutanenitrile (***3ah***) yellow solid, 23 mg, 76% yield; mp 143-145 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ7.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57-7.53 (m, 1H), 7.40-7.29 (m, 6H), 7.27-7.23 (m, 1H), 3.92-3.85 (m, 1H), 3.69 (s, 3H), 3.48-3.34 (m, 2H), 2.88-2.75 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 157.4, 154.8, 141.6, 133.1, 132.5, 130.2, 129.9, 128.9, 127.5, 127.4, 123.8, 118.5, 113.7, 38.9, 38.6, 29.7, 29.2, 24.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{18}N_3O$: 304.1444, found:304.1448.

3-methyl-4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)-3-phenylbutanenitrile (***3ai***) yellow solid, 16.5 mg, 52% yield; mp 119-121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.56-7.51 (m, 1H), 7.44-7.41 (m, 2H), 7.35-7.26 (m, 4H), 7.25-7.20 (m, 1H), 3.64 (s, 3H), 3.52-3.37 (m, 2H), 3.25-3.10 (m, 2H), 1.69 (s, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 157.3, 155.1, 144.6, 133.0, 132.2, 130.3, 129.9, 128.5, 126.9, 125.6, 123.7, 118.6, 113.6, 42.9, 41.1, 29.6, 29.3, 26.0; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{20}N_3O$: 318.1601, found:318.1605.

3-methyl-4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)-3-(p-tolyl)butanenitrile (***3aj***) yellow oil, 21.6 mg, 57% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.77 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.56-7.52 (m, 1H), 7.35-7.28 (m, 4H), 7.13 (d, *J* = 8.0 Hz, 2H), 3.65 (s, 3H),

3.50-3.36 (m, 2H), 3.22-3.08 (m, 2H), 2.30 (s, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 157.5, 155.2, 141.8, 136.5, 133.0, 132.3, 130.2, 130.0, 129.2, 125.5, 123.7, 118.7, 113.6, 42.9, 40.8, 29.6, 29.3, 26.0, 20.9; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{21}N_3ONa$: 354.1577, found:354.1581.

tert-butyl4-(cyanomethyl)-4-((4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)methyl)piperidine-1-carboxylate (***3ak***) yellow oil, 26 mg, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.57 (ddd, *J* = 16.0, 7.2, 1.6 Hz, 1H), 7.38-7.30 (m, 2H), 3.71 (s, 3H), 3.63-3.50 (m, 4H), 3.19 (s, 2H), 2.78 (s, 2H), 1.77-1.72 (m, 2H), 1.67-1.61 (m, 2H), 1.45 (s, 9H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ157.2, 147.3, 133.0, 132.3, 130.9, 130.5, 130.0, 128.8, 123.8, 113.7, 79.7, 38.7, 37.7, 36.0, 34.4, 29.4, 28.4, 26.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{29}N_4O_3$: 397.2234, found: 397.2237.

benzyl (cyanomethyl)((4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)methyl)carbamate (***3al***) yellow solid, 34.4 mg, 95% yield; mp 109-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.81 (m, 1H), 7.62-7.56 (m, 1H), 7.45-7.32 (m, 4H), 7.20 (d, *J* = 0.8 Hz, 3H), 5.27-5.15 (m, 2H), 4.88-4.85 (m, 2H), 4.54-4.43 (m, 2H), 3.70 (s, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 156.1, 153.4, 135.8, 133.1, 132.2, 130.7, 130.3, 128.6, 128.4, 128.1, 127.8, 124.0, 115.7, 113.7, 68.1, 49.3, 37.0, 28.9; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{20}H_{18}N_4O_3Na$: 385.1271, found:385.1275.

2-((4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)methoxy)acetonitrile (***3am***) yellow solid, 15.6 mg, 68% yield; mp 109-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 0.4 Hz, 1H), 7.64-7.60 (m, 1H), 7.42-7.35 (m, 2H), 4.97 (s, 2H), 4.59 (s, 2H), 3.73 (s, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 154.1, 153.9, 133.2, 132.4, 131.0, 130.5, 124.1, 115.8, 113.8, 70.0, 56.6, 29.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{12}N_3O_2$: 230.0924, found:230.0927.

2-((4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)methyl)benzonitrile (***3an***) white solid, 27.5 mg, 99% yield; mp 142-144°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.78 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.56-7.49 (m, 2H), 7.44-7.43 (m, 1H), 7.37-7.29 (m, 3H), 4.51 (s, 2H), 3.70 (s, 3H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 157.3, 154.5,

140.9, 133.3, 133.0, 132.6, 132.6, 130.5, 130.3, 130.2, 127.1, 123.7, 118.2, 113.9, 113.6, 39.0, 29.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{17}H_{14}N_3O$: 276.1131, found: 276.1135.

1,5-dimethylquinoxalin-2(1H)-one (***1b***) ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.27-7.16 (m, 2H), 3.70 (s, 1H), 2.69 (s, 3H); ^{13}C NMR{^1H} (100 MHz, $CDCl_3$) δ155.0, 148.3, 139.2, 133.4, 132.0, 130.8, 125.1, 111.7, 28.9, 17.6. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{10}H_{10}N_2NaO$: 197.0685, found: 197. 0685.

6-methoxy-1-methylquinoxalin-2(1H)-one (**1j**) ^1H NMR (400 MHz, $CDCl_3$) δ 8.32-8.31 (m, 1H), 7.38-7.36 (m, 1H), 7.27-7.21 (m, 2H), 3.90 (s, 3H), 3.70 (s, 3H); ^{13}C NMR{^1H} (100 MHz, $CDCl_3$) δ 156.1, 150.5, 134.0, 127.5, 120.4, 114.7, 113.0, 111.7, 55.8, 29.0. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{10}H_{10}N_2NaO_2$: 213.0634, found: 213. 0645.

General procedure for synthesis of products 5

1a (0.15 mmol), **4** (0.1 mmol) and Eosin Y (1 mol %) were dissolved in DCM (1 mL). Then, the resulting mixture was degassed via 'freeze-pump-thaw' procedure (3 times). After that, the solution was stirred at a distance of ~5 cm from a 6 W blue LEDs (450-460 nm) at room temperature until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethylacetate 5:1~2:1) directly to give the desired product **5.**

5-methyl-5-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)hexanenitrile (***5a***) colorless oil, 24.2 mg, 90% yield; ^1H NMR (400 MHz, $CDCl_3$) δ7.88-7.86 (m, 1H), 7.58-7.53 (m, 1H), 7.38-7.29 (m, 2H), 3.71 (s, 3H), 2.34 (td, *J* = 7.2, 1.8 Hz, 2H), 2.18-2.13 (m, 2H), 1.62-1.54 (m, 2H), 1.50 (s, 6H); ^{13}C NMR{^1H} (100 MHz, $CDCl_3$) δ 163.5, 153.7, 133.2, 132.1, 130.2, 130.0, 123.4, 119.8, 113.4, 42.5, 39.3, 28.9, 26.1, 21.6, 17.7; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{19}N_3ONa$: 292.1420, found:292.1426.

(R)-6-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)-6-phenylhexanenitrile (***5b***) yellow solid, 17.2mg, 52% yield; mp 102-104 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.55-7.51 (m, 1H), 7.45-7.43 (m, 2H), 7.38-7.34 (m, 1H),

7.30-7.25 (m, 3H), 7.21-7.17 (m, 1H), 4.67 (t, *J* = 7.6 Hz, 1H), 3.63 (s, 3H), 2.38-2.29 (m, 3H), 2.13-2.04 (m, 1H), 1.75-1.67 (m, 2H), 1.53-1.39 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 160.7, 154.5, 141.1, 133.0, 132.7, 130.1, 129.9, 128.6, 128.5,126.8, 123.5, 119.7, 113.5; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{21}N_3ONa$: 354.1577, found:354.1580.

2-((3S)-2,2,3-trimethyl-3-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)cyclopentyl)acetonitrile (***5c***) colorless oil, 14.2mg, 46% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.87(dd, *J* = 8.0, 1.5 Hz, 1H), 7.56-7.52 (m,1H), 7.37-7.27 (m,2H), 3.70 (s, 3H), 3.37 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.45 (d, *J* = 14.2 Hz, 1H), 2.39-2.22 (m,2H), 2.00-1.95 (m,1H), 1.93-1.90 (m,2H), 1.58 (s, 3H), 1.02 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 163.6, 153.8, 133.3, 131.8, 130.2, 129.8, 123.4, 119.8, 113.4, 53.5, 47.0, 45.3, 42.4, 41.0, 28.9, 28.8, 27.8, 23.8, 17.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{24}N_3O$: 310.1914, found: 310.1914.

General procedure for synthesis of products 7

6 (0.15 mmol), **2a** (0.1 mmol) and Eosin Y (1 mol %) were dissolved in DCM (1 mL). Then, the resulting mixture was degassed via 'freeze-pump-thaw' procedure (3 times). After that, the solution was stirred at a distance of ~5 cm from a 6 W blue LEDs (450-460 nm) at room temperature until the reaction was completed as monitored by TLC analysis. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethylacetate 5:1~3:1) directly to give the desired product **7.**

*4-(benzo[d]thiazol-2-yl)butanenitrile (**7a**)* colorless oil, 10.5mg, 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.50-7.46 (m,1H), 7.41-7.36(m,1H), 3.28 (t, J = 7.2 Hz, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.33-2.26 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 168.8, 153.2, 135.0, 126.2, 125.1,122.7, 121.6, 119.0, 32.5, 24.8, 16.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{11}N_2S$: 203.0637, found:203.0640.

*4-(benzo[d]oxazol-2-yl)butanenitrile (**7b**)* colorless oil, 7.8mg, 42% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 1H), 7.52-7.48 (m, 1H), 7.35-7.31 (m, 2H), 3.12 (t, J = 7.2 Hz, 2H), 2.60 (t, J = 7.2 Hz, 2H), 2.29 (m, 2H); ^{13}C NMR{^{1}H} (100 MHz,

$CDCl_3$) δ 164.7, 150.8, 141.1, 124.9, 124.4, 119.8, 118.8, 110.5, 27.1, 22.4, 16.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{11}N_2O$: 187.0866, found:187.0863.

4-(isoquinolin-1-yl)butanenitrile (***7c***) yellow oil, 8.9mg, 47%, ^1H NMR (400 MHz, $CDCl_3$) 8.45 (d, *J* = 5.6 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.74-7.70 (m, 1H), 7.67-7.63 (m,1H), 7.58 (d, *J* = 5.6 Hz, 1H), 3.49 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.31 (m, 2H); ^{13}C NMR{^1H} (100 MHz, $CDCl_3$) δ 159.1, 141.2, 136.4, 130.4, 127.7, 127.6, 127.0, 124.8, 120.0, 119.7, 32.8, 24.4, 17.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{13}N_2$: 197.1073, found:197.1073.

Conversation of **3a** into ester **8a**

To a solution of 4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (**3a**, 22.7 mg, 0.1 mmol) in EtOH (1 mL) in a 10 ml two-neck flask were added H_2O (5 drops) and H_2SO_4 (conc., 0.4 mL). The reaction mixture was heated at 90 °C for 9 h. After cooling to room temperature, the reaction mixture was slowly quenched with saturated aqueous $NaHCO_3$ to pH 8 and extracted with DCM (10 mL × 3). The combined organic phases were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using hexane/ethyl acetate (2:1) to afford the pure product **8a**.

ethyl 4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanoate (***8a***) colorless oil, 21.6 mg, 79% yield; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.81 (m, 1H), 7.55-7.50 (m, 1H), 7.36-7.27 (m, 2H), 4.11 (q, *J* = 7.2Hz, 2H), 3.70 (s, 3H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.17 (p, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR{^1H} (100 MHz, $CDCl_3$) δ 173.4, 160.0, 154.8, 133.0, 132.6, 129.7, 129.7, 123.5, 113.6, 60.3, 33.9, 33.2, 29.0, 21.6, 14.2; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{18}N_2NaO_3$: 297.1210, found:297.1214.

Conversation of **3a** into secondary amine **9a**

To a solution of 4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (**3a**, 22.7 mg, 0.1 mmol), $(Boc)_2O$ (43.6 mg, 0.2 mmol) and $CoCl_2$ (26 mg, 0.2mmol) in MeOH(1mL) was cooled to 0°C and was added in portions. The reaction was stirred for 12 h at room temperatureand then quenched with water and filtered over celite

(washings with DCM). The crude product was purified by column chromatography to afford the pure product **9a**.

tert-butyl (3-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)propyl)carbamate (***9a***) colorless oil, 21.2 mg, 64% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.36-7.29 (m, 2H), 4.80 (s, 1H), 3.70 (s, 3H), 3.19 (q, *J* = 5.6 Hz, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 1.84 (p, *J* = 7.2 Hz, 2H), 1.62 (p, *J* = 7.2 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 160.6, 156.0, 154.9, 133.1, 132.7, 129.7, 123.6, 113.6, 99.9, 79.0, 40.4, 33.6, 29.7, 29.1, 28.4, 23.6; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{18}H_{25}N_3NaO_3$: 354.1788, found:354.1793.

Conversation of **3a** into carboxylic acid **10a**

A 25 ml two-neck flask was charged with 4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (**3a**, 22.7 mg, 0.1 mmol) and a mixture of acetic acid, concentrated sulfuric acid and H_2O (3/3/1, 2ml), The solution was heated under reflux for 4 h. After cooling to room temperature the mixture was diluted with water and extracted 5 times with 5 mL of CH_2Cl_2. The combined organic phases were washed with 5 mL of a saturated aqueous NaCl-solution, dried over Na_2SO_4 and concentrated under reduced pressure The residue was subjected to column chromatography to afford the pure product **10a**.

4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanoic acid (***10a***) yellow oil, 20.9 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.55-7.50 (m, 1H), 7.37-7.28 (m, 2H), 3.70 (s, 3H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.6 Hz, 2H), 2.16 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ 178.6, 159.9, 154.9, 133.1, 132.6, 129.8, 129.7, 123.7, 113.6, 33.5, 33.0, 29.1, 21.4; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{14}N_2NaO_3$: 269.0897, found:269.0901.

Conversation of **3a** into amide **11a**

To a solution of ethyl 4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanenitrile (**3a**, 22.7 mg, 0.1 mmol), 7.0 mg K_2CO_3 (0.05 mmol) and 1 mL DMSO. Then, 0.6 mL aq. H_2O_2 (0.6 mmol, 30%) was dropped in room temperature. The mixture was then stirred for 6 h, after that the reaction mixture was added 0.5 mL sat. $Na_2S_2O_3$ and 5

mL sat. $NaHCO_3$ at 0 °C, the resulting mixture was subjected to extraction with ethyl acetate (2 x 15 mL). The combined organic phase was washed with brine (2 x 10 mL), dried over Na_2SO_4, concentrated in vacuo, and the residue was subjected to flash chromatography (Eluent: ethyl acetate/petroleum ether 1:2) to give amide **11a**.

4-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)butanamide (***11a***) colorless oil, 20.3 mg, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.0 Hz, 1H), 7.60-7.56 (m, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.73 (s, 1H), 3.61 (s, 3H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.14 (t, *J* = 7.2 Hz, 2H), 1.91 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$) δ174.5, 160.3, 154.6, 133.4, 132.4, 130.2, 129.3, 123.8, 115.1, 35.1, 33.3, 29.4, 22.4; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{15}N_3NaO_2$: 268.1056, found:268.1060.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: .

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Notes

The authors declare no competing financial interest.

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(19) CCDC 1869210 contains the supplementary crystallographic data for compound **3a**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre.