Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 3735

Highly chemoselective deoxygenation of N-heterocyclic *N*-oxides under transition metal-free conditions†

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Received 9th February 2021,
Accepted 26th March 2021

DOI: 10.1039/d1ob00260k

rsc.li/obc

Because their site-selective C–H functionalizations are now considered one of the most useful tools for synthesizing various N-heterocyclic compounds, the highly chemoselective deoxygenation of densely functionalized N-heterocyclic *N*-oxides has received much attention from the synthetic chemistry community. Here, we provide a protocol for the highly chemoselective deoxygenation of various functionalized *N*-oxides under visible light-mediated photoredox conditions with Na_2-eosin Y as an organophotocatalyst. Mechanistic studies imply that the excited state of the organophotocatalyst is reductively quenched by Hantzsch esters. This operationally simple technique tolerates a wide range of functional groups and allows high-yield, multigram-scale deoxygenation.

Introduction

N-Heterocycles are arguably one of the most prevalent structural motifs found in various compounds, such as natural products, bioactive compounds, pharmaceutically relevant compounds, agrochemicals, chiral and achiral ligands, and advanced functional materials. In particular, they have played a pivotal role in drug discovery and medicinal chemistry.[1]

Over the past several decades, extensive efforts have been continuously devoted to synthesizing these privileged derivatives through the development of efficient and versatile synthetic methods and strategies.[2] Direct functionalization of ubiquitous carbon–hydrogen (C–H) bonds has emerged as a reliable and sustainable method to construct complex molecules.[3] However, regiospecific C–H bond activation and functionalization of N-heterocyclic compounds, such as pyridine, quinoline, isoquinoline, quinoxaline, and pyrazine derivatives, have achieved limited success, mainly because of the low reactivity and instability of the organometallic species derived from these N-heterocycles.[4]

In 2005, Fagnou reported on palladium-catalysed direct C–H arylation of pyridine *N*-oxides with aryl bromides.[5] More importantly, Fagnou's work has triggered extensive investigation of a diverse range of catalytic regioselective C–H functionalization reactions of N-heteroaryl *N*-oxides. Consequently, researchers have reported numerous examples of useful catalytic procedures in the past 15 years, which has led to the straightforward and controlled formation of carbon–carbon and carbon–heteroatom bonds at the specific position of the heterocyclic cores.[6,7]

In most of these procedures, after the desired functional group is added, a highly chemoselective removal of the oxygen atom in the *N*-oxides is necessary to obtain the corresponding deoxygenated N-heteroaromatic compounds.[8] The deoxygenation of N-heteroaromatic *N*-oxide derivatives is among the most fundamental reactions in organic synthesis, and a vast number of reduction methods have been developed,[9–15] including the several recent successful implementations.[16] However, chemoselective deoxygenation of highly functionalized *N*-oxides often proved to be challenging or sometimes nearly impossible because of the undesirable reduction of the other functional group(s) present in the same molecule. Given the importance of synthesizing highly functionalized N-heterocyclic derivatives, the development of new protocols that enable highly chemoselective deoxygenation of the corresponding *N*-oxides would be highly desirable.

To this end, we hypothesized that a hydroxyl radical (HO$^{\bullet}$) could be conveniently generated *in situ via N*-hydroxy species intermediate **A** through the reductive scission of the N–O bond of oxygenated N-heterocycles **1** with an appropriate reductant, which provides an opportunity to gain access to deoxygenated N-heteroaromatic **3** through visible-light-driven photoredox catalysis (Scheme 1).[17] We recently reported a simple photocatalytic protocol that enables the deoxygenation of *N*-oxides with hydrazine hydrate as the stoichiometric reductant along

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†Electronic supplementary information (ESI) available: Experimental details, characterization and spectroscopic data for all compounds and mechanistic studies. See DOI: 10.1039/d1ob00260k

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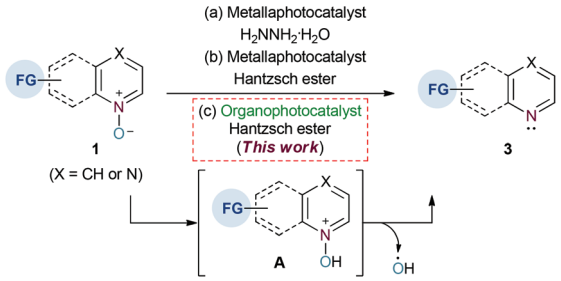


Scheme 1 Visible-light-mediated photocatalytic deoxygenation of N-heterocyclic *N*-oxides.

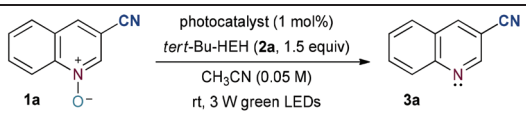
with a transition metal (Ru or Ir) polypyridyl complex as the catalyst.[18a,19] However, the increased nucleophilicity of hydrazine hydrate limits the functional group compatibility (Scheme 1a). More recently, by employing 1,4-dihydropyridine-3,5-dicarboxylate esters [Hantzsch esters (HEHs)] as mild reducing agents, we also developed a highly chemoselective deoxygenation method that is applicable to a wide range of functionalized N-heterocyclic *N*-oxides *via* visible-light-mediated metallaphotoredox catalysis (Scheme 1b).[18b] We anticipated that replacing precious metallaphotocatalysts with less expensive and less toxic organic dyes would be possible and more advantageous for a greener and more practical deoxygenation protocol, especially for large-scale applications.

Herein, we describe a convenient method that allows highly chemoselective deoxygenation of diversely functionalized N-heteroaromatic *N*-oxides *via* a visible-light-mediated photoredox catalysis reaction under mild and transition-metal-free conditions (Scheme 1c).

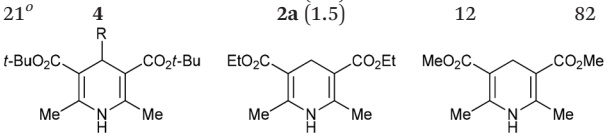
Results and discussion

To test the feasibility of a more sustainable and practical strategy, we first sought to explore the deoxygenation of quinoline-3-carbonitrile *N*-oxide (**1a**) with commercially available organophotocatalysts. Organic dyes have emerged as an attractive alternative to transition metal polypyridyl complexes in visible-light-mediated photoredox catalysis since they are much cheaper, less toxic, easy to handle, and even superior to transition metal counterparts in some cases.[21j,w,ah,aq] After much experimentation, we found that our previous deoxygenation conditions using hydrazine hydrate as the reductant were incompatible with transition-metal-free photocatalysts, such as eosin Y, methylene blue, rose bengal, rhodamine B, and rhodamine 6G. Next, we turned our attention to the use of HEH **2** as the reductant. We were already aware that *tert*-Bu-HEH **2a**, presumably because of its high solubility in CH_3CN, works as a suitable photoreductant in the related deoxygenation reaction under a metallaphotoredox catalyst.[18b] Naturally, we screened several organic dyes (1 mol%) alongside **2a** (1.5 equiv.) in acetonitrile (0.05 M) at room temperature under irradiation with two 3 W green LEDs (Table 1). Under these conditions, methylene blue and rhodamines 6G and B gave deoxygenated

Table 1 Optimization of the reaction parameters[a]



Entry	Photocatalyst	HEH **2** (equiv.)	Time (h)	Yield[b] (%)
1	Methylene blue	**2a** (1.5)	5	28
2	Rhodamine 6G	**2a** (1.5)	12	58
3	Rhodamine B	**2a** (1.5)	12	72
4	Eosin Y	**2a** (1.5)	12	87
5	Rose bengal	**2a** (1.5)	1	90
6	Na_2-eosin Y (**4**)	**2a** (1.5)	1	95
7[c]	**4**	**2a** (1.5)	2	90
8[c,d]	**4**	**2b** (1.5)	22	77
9[e]	**4**	**2c** (1.5)	2.5	76
10[f]	**4**	**2d** (1.5)	4	67
11	**4**	**2a** (1.2)	1	90
12	**4**	**2a** (1.0)	5	91
13[g]	**4**	**2a** (1.5)	0.5	89
14[h]	**4**	**2a** (1.5)	12	64
15[i]	**4**	**2a** (1.5)	1	83
16[j]	**4**	**2a** (1.5)	1	44
17[k]	**4**	**2a** (1.5)	2	44
18[l]	**4**	**2a** (1.5)	3	73
19[m]	**4**	**2a** (1.5)	1	18
20[n]	**4**	**2a** (1.5)	12	8
21[o]	**4**	**2a** (1.5)	12	82



[a] Unless otherwise noted, a mixture of **1a** (0.20 mmol), **2a** (0.30 mmol, 1.5 equiv.) and a photocatalyst (1.0 mol%) in CH_3CN (4 mL, 0.05 M) was irradiated with 3 W green LEDs at room temperature. [b] Isolated yields of **3a**. [c] In 0.1 M CH_3CN. [d] Using **2b** (0.30 mmol, 1.5 equiv.). [e] Using **2c** (0.30 mmol, 1.5 equiv.). [f] Using **2d** (0.30 mmol, 1.5 equiv.). [g] Under the irradiation of 3 W blue LEDs. [h] Under the irradiation of 40 W CFL. [i] DMSO (0.05 M) as the solvent. [j] DMF (0.05 M) as the solvent. [k] CH_3OH (0.05 M) as the solvent. [l] 2-Me-THF (0.05 M) as the solvent. [m] THF (0.05 M) as the solvent. [n] H_2O (0.05 M) as the solvent. [o] EtOAc (0.05 M) as the solvent.

product **3a** in low to moderate yields (entries 1–3). An improved isolated yield of **3a** was attained with eosin Y as the catalyst, albeit with a prolonged reaction time of 12 h (entry 4). Switching to rose bengal significantly reduced the reaction time to 1 h, even with a slightly better isolated yield of 90% (entry 5). Eventually, we were pleased to find that Na_2-eosin Y (**4**) led to quite promising results in terms of both the reaction rate and the isolated yield of the deoxygenated product (entry 6). Hence, we were eager to investigate the other reaction parameters by fixing Na_2-eosin Y as the photocatalyst. Interestingly, increasing the reaction concentration led to a detrimental effect on both the reaction rate and the isolated yield of **3a** (entry 7). The use of other HEH derivatives (entries 8–10) and reducing the loading of **2a** led to inferior results (entries 11 and 12). We also found that the source of visible light profoundly affects the reaction outcomes. Green LEDs (3 W) were more efficient than other sources. Indeed, the use of 3 W blue

LEDs resulted in a somewhat lower yield of **3a** (entry 13) and using 40 W compact fluorescent lamps (CFL) was far less efficient (entry 14). A thorough screening of solvents revealed that acetonitrile was vastly superior to others, such as DMSO, DMF, CH_3OH, 2-methyltetrahydrofuran (2-Me-THF), THF, H_2O, and ethyl acetate (EtOAc) (entries 15–21). It is worth mentioning that this operationally convenient procedure does not require rigorous drying of the solvent and any other additional reagents, such as a sacrificial single-electron donor, a coreductant, and a base. However, the newly developed conditions require stoichiometric quantities of HEHs, which significantly affects the atom economy.

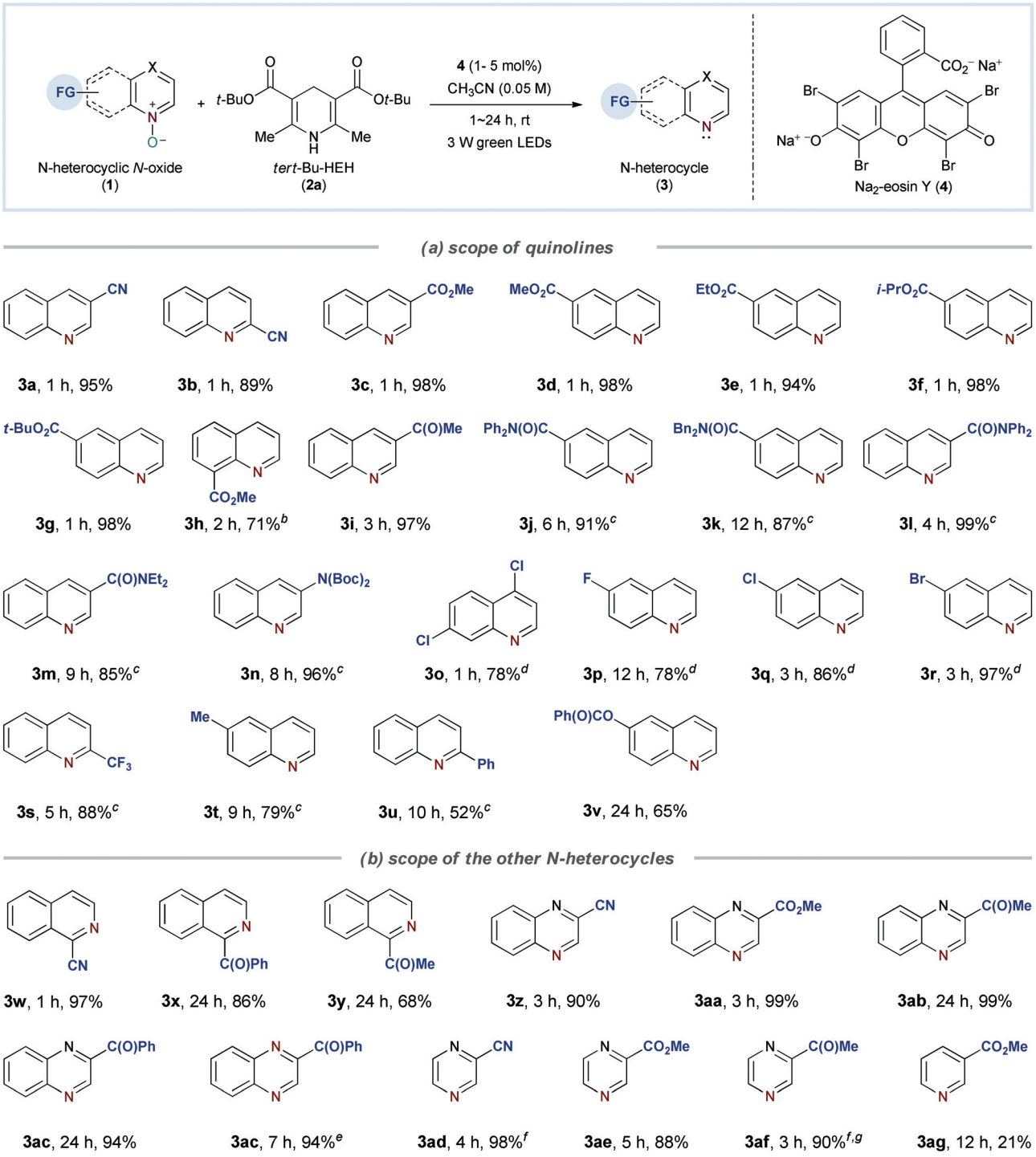
Having optimized the conditions for the deoxygenation of **1a** (Table 1, entry 6), we became interested in determining whether this protocol would also be applicable to other N-heterocyclic *N*-oxides with labile functional group(s). First, we evaluated the scope of this visible light-mediated photocatalytic deoxygenation reaction with functionalized quinoline *N*-oxides (Scheme 2a). A wide range of functional groups embedded in the quinoline *N*-oxide core (**1a–1v**) were compatible, leading to deoxygenated N-heterocyclic products **3** in moderate to excellent yields (52–99% yields). In particular, quinoline *N*-oxides (**1a–1i**) bearing a strong electron-withdrawing group, such as a cyano, an alkoxy carbonyl, or an acetyl group, smoothly underwent photocatalytic deoxygenation to provide access to the corresponding quinolines in good to excellent yields (89–98%) within 1–3 hours. Notably, neither the functional group position nor the alkyl substituent in the ester functionality affected the deoxygenation outcomes. The only exception was *N*-oxide **1h**, which had a methoxycarbonyl group at the 8-position and resulted in the formation of **3h** in a moderate yield of 71%. Various amide groups and a carbamate group embedded at the 3- or 6-position of the quinoline *N*-oxide core were also tolerated well, albeit with a prolonged reaction time and a higher loading of catalyst **4**, leading to deoxygenated products **3j–3n** in good to excellent yields (85–99%). Moreover, a range of oxygenated quinolines bearing halogen substituent(s) and a trifluoromethyl group furnished quinolines **3o–3s** in good to excellent yields (78–97% yield). In comparison, deoxygenation of quinoline *N*-oxides bearing a weakly electron-donating group, such as 6-methyl (**1t**), 2-phenyl (**1u**), and 6-benzoyloxy (**1v**), led to the desired products in moderate yields (52–79%).

Next, we turned our attention to deoxygenation of the other oxygenated N-heterocycles, such as isoquinoline, quinoxaline, pyrazine, and pyridine, that had a synthetically fruitful functional group (Scheme 2b). A series of isoquinoline *N*-oxides with electron-withdrawing cyano groups (**1w**), phenyl ketones (**1x**), and methyl ketones (**1y**) underwent deoxygenation under standard conditions without any noticeable overreduction of these labile functionalities. Previously, we observed that our photocatalytic deoxygenation of quinoxaline *N*-oxide using hydrazine hydrate as the reductant was hampered by a severe overreduction of the N-heterocycle by the *in situ*-generated diimide, presumably because of its weak aromaticity.[18a] Gratifyingly, we found that various quinoxaline *N*-oxides **1z–1ac** bearing nitrile, ester, and ketone functionalities at the 3-position all undergo facile deoxygenation, which provides access to the desired quinoxalines in excellent yields without any observed overreduction of both the heteroaromatic core and other functionalities that are present in the same molecules. Moreover, we found that quinoline bis-*N*-oxide **1ac′** was also amendable to this photocatalytic deoxygenation to yield 2-benzoylquinoxaline (**3ac**) in 94% yield. Finally, the other N-heteroaromatic *N*-oxides were evaluated in visible-light-mediated photocatalytic deoxygenation, including several pyrazine *N*-oxides and a pyridine *N*-oxide. While functionalized pyrazine *N*-oxides **1ad–1af** were successfully deoxygenated in high yields, pyridine *N*-oxide **1ag** unfortunately exhibited an extremely low reactivity, which probably occurred due to its higher N–O bond strength compared to the other *N*-oxides.[18]

Next, we carried out a series of control experiments to shed light on the reaction mechanism of this transition-metal-free deoxygenation (Scheme 3). We did not observe any deoxygenation of standard *N*-oxide **1a** when visible light was excluded from this protocol, which suggests that a photoredox mechanism could operate in this reaction (Scheme 3a). According to our observations and independent observations from others,[18b,16m] omitting a photocatalyst under otherwise identical conditions did not interrupt the deoxygenation of **1a**, albeit with a diminished yield of the desired quinoline **3a** (Scheme 3b).[19] We observed a marginal kinetic deuterium isotope effect (k_H/k_D) of 1.3 in the deoxygenation of *N*-oxide **1c** bearing a methoxycarbonyl group at the 3-position (Scheme 3c). The inclusion of an oxygen-centred radical TEMPO (4 equiv. to **2a**) in this protocol efficiently suppressed the deoxygenation of *N*-oxide **1f**, which led to only a tiny amount of deoxygenated product **3f** (Scheme 3d). Furthermore, an experiment on the on–off switching of the light source confirms the requirement for continuous irradiation with visible light, although we cannot completely rule out the radical chain propagation mechanism in this reaction manifold (Scheme 3e).

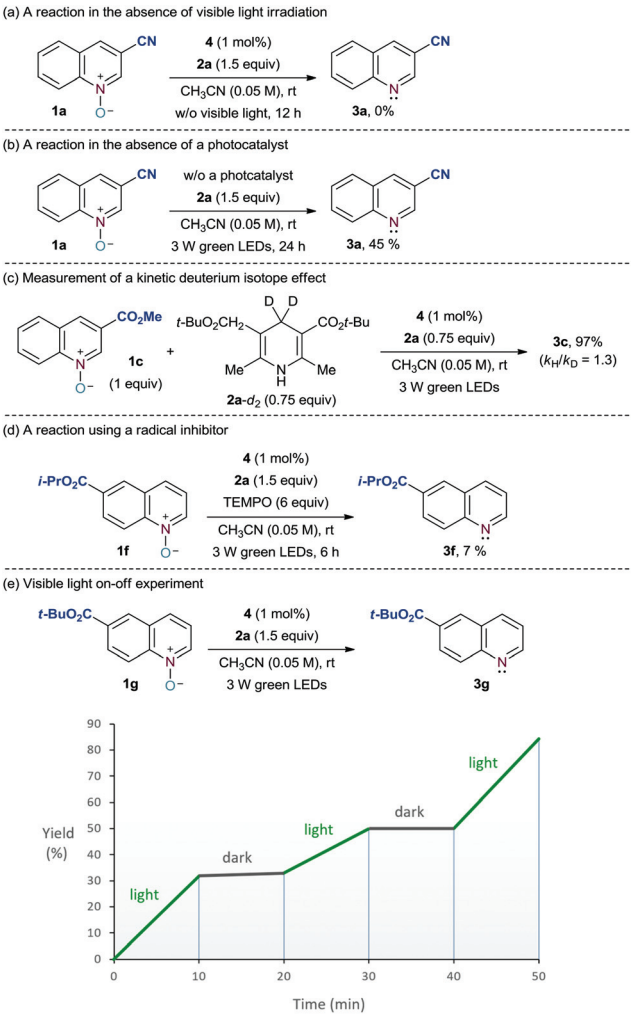
Moreover, we conducted a series of Stern–Volmer fluorescence-quenching experiments to gain further insight into the pathway of this photoredox-catalysed deoxygenation. Intriguingly, not only *tert*-Bu-HEH **2a** but also several quinoline *N*-oxides, such as **1e**, **1q**, and **1t**, regardless of the electronic properties of the attached functionalities, can quench the excited state of photocatalyst **4** (Fig. 1). However, given the high oxidation potential of N-heterocyclic *N*-oxides,[20] we reasonably presume that reductive quenching of HEH **2a** is operative.

Based on the results of the control and fluorescence-quenching experiments as well as precedents in the literature,[21] we have proposed a plausible mechanism for transition-metal-free deoxygenation (Fig. 2). Because *tert*-Bu-HEH **2a** cannot undergo direct photoexcitation at $\lambda > 445$ nm,[22] only Na_2-eosin Y (**4**) can be excited to generate excited-state Na_2-eosin Y* (**5**) under green LED (530–535 nm) irradiation. Based on Stern–Volmer studies (Fig. 1) as the starting point of the photoredox catalytic cycle, we propose that **5** can then be reductively quenched by **2a** *via* a single electron transfer (SET) process to give Na_2-eosin $Y^{\bullet-}$ (**6**) and N-centred radical cation **7** ($HEH^{\bullet+}$). Subsequent deprotonation of electrophilic **7** by the



Scheme 2 Scope of N-heterocyclic *N*-oxides. Conditions: **1** (0.20 mmol), **2a** (0.30 mmol, 1.5 equiv.), Na_2-eosin Y (1.0 mol%), CH_3CN (4.0 mL, 0.05 M) and 3 W green LEDs at room temperature for 1–24 h. [a] 1.0 mol% of Na_2-eosin Y and 2.0 equiv. of **2a** were used. [b] 5.0 mol% of Na_2-eosin Y and 2.0 equiv. of **2a** were used. [c] 2.0 mol% of Na_2-eosin Y and 1.5 equiv. of **2a** were used. [d] Bis-*N*-oxide **1ac** (0.20 mmol) and 3.0 equiv. of **2a**. [e] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [f] 1.0 mol% of Na_2-eosin Y and 2.0 equiv. of **2a** were used.

anionic oxygen atom of N-heterocyclic *N*-oxide **1** would achieve equilibrium with a mixture consisting of *N*-hydroxy species **A** and HEH radical (HEH$^{\bullet}$) **8**, which presumably occurs *via* a hydrogen-bonding intermediate.[18b] Next, the N–O bond of **A** can be reductively cleaved by **6** *via* a second SET process to generate a hydroxyl radical (HO$^{\bullet}$) and the desired N-heterocycle **3**, which completes the photocatalytic cycle with the regeneration of ground-state photocatalyst **4**.[23] Subsequently, hydrogen atom transfer (HAT) from **8** to the hydroxyl radical delivers pyridine **9** and water as byproducts



Scheme 3 Control experiments for a mechanistic study.

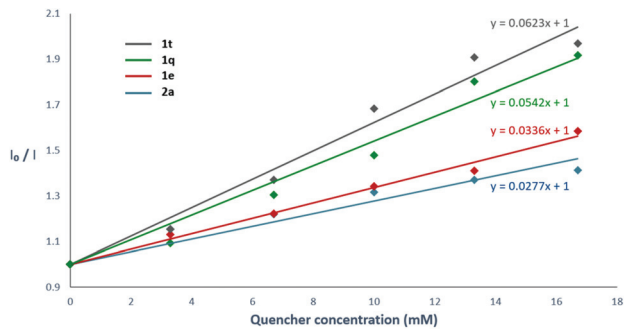


Fig. 1 Stern–Volmer fluorescence quenching experiments.

(Fig. 2). As suggested by the marginal kinetic deuterium isotope effect (Scheme 3c), it seems likely that the HAT process might not be the rate-limiting step of the overall deoxygenation process. We reasoned that the formation of highly stable heteroaromatic compound **9** might be the driving force for this HAT process.

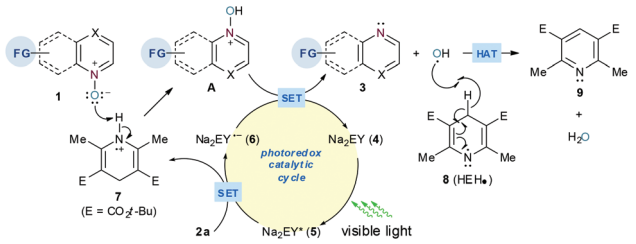
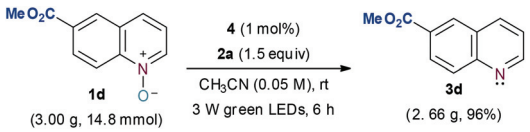


Fig. 2 Plausible mechanism for transition-metal-free deoxygenation.



Scheme 4 Multigram-scale deoxygenation.

Finally, we performed multigram-scale deoxygenation of **1d** (3.00 g, 14.8 mmol) under standard conditions (1.5 equiv. of **2a**, 1.0 mol% **4**, 0.05 M in CH_3CN, room temperature, and under irradiation with two 3 W green LEDs) to demonstrate the scalability and practicability of the newly developed protocol. We obtained deoxygenated product **3d** in a comparable excellent yield of 96% (2.66 g product, *cf.* Scheme 2a, 98% yield), albeit with a prolonged reaction time of 6 hours (Scheme 4).

Conclusions

In conclusion, we developed a practical method that enables the highly chemoselective removal of oxygen atoms in a diverse range of N-heterocyclic *N*-oxides *via* visible-light-mediated photoredox catalysis under ambient and transition-metal-free conditions. Various N-heterocycles, such as quinolines, isoquinolines, quinoxalines, and pyrazines, bearing synthetically valuable functional groups, including nitrile, ester, ketone, amide, carbamate, halogen(s), trifluoromethyl, alkyl, and aryl groups, were obtained in good to excellent yields (an average of 86.6% yield for 34 examples) *via* this transition-metal-free deoxygenation protocol employing *tert*-Bu-HEH and commercially available Na_2-eosin Y as the reductant and photocatalyst, respectively. Other additives, dried solvents, and any special, expensive laboratory equipment are unnecessary for this operationally simple protocol. Finally, this technique also supports high-yielding multigram-scale deoxygenation.

Experimental

General procedure for the visible light-mediated photoredox-catalysed deoxygenation of N-heterocyclic *N*-oxides under transition-metal-free conditions

A 10 mL test tube equipped with a small magnetic stir bar was charged with N-heterocyclic *N*-oxide (**1**, 0.200 mmol,

1.00 equiv.), *tert*-Bu-HEH (**2a**, 92.8 mg, 0.300 mmol, 1.50 equiv.), and Na_2-eosin Y (**4**, 1.4 mg, 2.0 μmol, 1.0 mol%). The flask was fitted with a rubber septum, and CH_3CN (4.0 mL, 0.05 M) was added *via* a syringe under an atmosphere of N_2. After degassing by N_2 bubbling at room temperature for 10 min, the reaction mixture was then irradiated at room temperature with two MR16 3 W green LED spotlight lamps (12 V, 530–535 nm) from a distance of approximately 3 cm for the indicated time (see Scheme 2). Upon completion of the reaction as determined by TLC, the reaction mixture was concentrated using a rotary evaporator. The resulting residue was directly purified by flash column chromatography on silica gel (hexanes and EtOAc) to afford the corresponding deoxygenated N-heterocycle **3**.

Author contributions

S.H.K. and J.H.A. performed the experiments and analysed the data. S.H.K., J.H.A., and J.H.L. designed the experiments. J.H.L. supervised the project and prepared the original manuscript. All authors proofread, commented on, and approved the final manuscript for submission.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We dedicate this paper to Prof. Kyo Han Ahn (POSTECH) for his invaluable contribution to the Korean Chemical Society on the occasion of his honourable retirement. We gratefully acknowledge Professors Jaiwook Park, Young Ho Rhee, Seung Hwan Cho (POSTECH), and Duckhyung Lee (Sogang University) for their generous support and helpful discussions. This research was supported by the National Research Foundation (NRF) of the Korea-Basic Science Research Program (no. NRF-2017R1D1A1B03029926 and NRF-2020R1F1A1076460) and the Dongguk University Research Fund of 2020.

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