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Water-Mediated Rhenium-Catalyzed Photodeoxygenation of Polyfunctional Organic *N*-oxides

Nicolas Joly^{a,‡} Marianne Kjellberg^{a,‡} Alexis Bouchet,^a Emmanuel Nicolas,^a Thibault Cantat,^a Lucile Anthore-Dalio^{*a}

[a] Université Paris-Saclay, CEA, CNRS, NIMBE, 91191 Gif-sur-Yvette, France. E-mail: lucile.anthore@cea.fr; [‡] equal contributions

Abstract

The oxidation of *N*-heterocycles is key to their functionalization since it enhances their reactivity in the ortho position. However, an efficient post-reduction is often required to access the targeted compound. Here, an air-stable rhenium(I)-based photocatalyst enables the fast deoxygenation of *N*-heterocyclic and alkyl *N*-oxides, avoiding sacrificial oxophilic reagents. We demonstrate that adding H₂O dramatically accelerates the reaction rate. The system tolerates air contamination, is scalable, and shows a high functional group tolerance towards other reducible functions (free alcohol, carboxylic acid, ester, nitrile, halogen,...) and light-sensitive *N*-heterocycles.

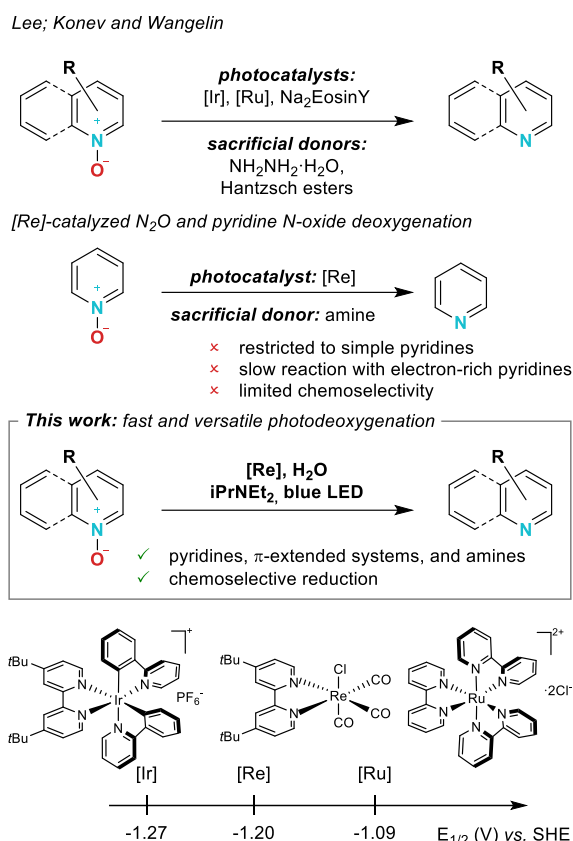
Introduction

Found in DNA, vitamin B6, or the co-factor NADP, *N*-heterocycles are essential to life and ubiquitous in natural products, agrochemicals, and pharmaceutical compounds.^[1] The selective C–H functionalization of the parent heterocycles is thus critical to accessing useful and reactive compounds. Their *N*-oxidation enhances the nucleophilicity and electrophilicity of the ortho carbon atom while introducing a directing group, thereby enabling efficient and selective functionalization at this position.^[2] However, subsequent deoxygenation is often required to access the targeted *N*-heterocycle.^[3] Accordingly, thermal, electrochemical, and photochemical methods for reducing *N*-oxide compounds have been developed.^[4] Most of these methods use an excess of low-valent transition metals or strongly oxophilic reagents such as phosphine,^[5] borane,^[6] and silicon^[7] derivatives in the presence or absence of an organometallic catalyst.

As early as the 1960s, the photolability of *N*-heterocyclic *N*-oxides under UV irradiation was recognized. However, the highly energetic UV light irradiation mainly leads to skeletal rearrangements, and the parent *N*-heterocycles were identified only as minor products.^[8]

Recent advancements in photocatalysis have demonstrated successful selective *N*-oxide deoxygenations under visible light irradiation. Lee et al. described the deoxygenation of π -extended *N*-oxide derivatives using [Ru(bpy)₃]Cl₂^[9] (bpy=2,2'-bipyridine) and Na₂Eosin Y^[10] as photocatalysts in the presence of sacrificial electron and proton donors such as hydrazines^[9a] or Hantzsch esters.^[9b] Under these

conditions, pyridine *N*-oxides with a stronger N–O bond could hardly be reduced, and a more reductive Ir-based photocatalyst ($E_{1/2}(\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}) = -1.27 \text{ V}$ and $E_{1/2}(\text{Ru}^{\text{II}}/\text{Ru}^{\text{I}}) = -1.09 \text{ V}$ vs. SHE)^[11] proved necessary.^[9] The same group recently disclosed a visible-light-induced Meerwein-Ponndorf-Verley reduction of quinoline *N*-oxides using a strongly oxidizing acridinium photocatalyst. Pyridine *N*-oxides were also reduced, albeit after prolonged reaction times.^[4] Interestingly, the group of Konev and Wangelin demonstrated that the photocatalyst was not required for deoxygenation when Hantzsch esters were used as the electron donor, although the kinetics were slower. The authors suggested that an electron donor-acceptor complex formed between the *N*-heterocyclic *N*-oxide and the Hantzsch ester and was responsible for the observed reactivity (Scheme 1).^[12]



Scheme 1 Visible-light photodeoxygenation of *N*-heterocyclic *N*-oxides in the absence of sacrificial oxophilic reagents

In our search for an efficient catalytic system able to deoxygenate the low reactive N₂O, we have recently discovered that Re(I)-carbonyl photocatalyst [(dtbpy)Re(CO)₃Cl] (**1**) ($E_{1/2}(\text{Re}^{\text{I}}/\text{Re}^{\text{0}}) = -1.20 \text{ V}$ vs SHE, dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) could also reduce pyridine *N*-oxide (**2a**) without the use of an oxophilic reagent.^[13] The reaction occurred in the presence of Hünig's base (diisopropyl ethyl amine, DIPEA) as the electron and proton donor under white LED's (8 W) irradiation. However, the photocatalytic system suffered from several limitations, hampering its synthetic applicability and restricting its use to a few simple pyridine derivatives. For example, the deoxygenation of the electron-rich 4-(dimethylamino)pyridine 1-oxide required more than 5 days to reach full completion on a 0.1 mmol scale. Moreover,

sensitive functional groups were not tolerated. The cleavage of the cyano group of *p*-cyanopyridine *N*-oxide was observed along with its deoxygenation, and light-sensitive products such as quinoline were degraded.

Driven by this intriguing but somewhat limited proof-of-concept, we aimed to reveal the full potential of Re-photocatalyst **1** to deoxygenate N-heterocyclic *N*-oxides for preparative purposes. Herein, we demonstrate that H₂O as an additive combined with the use of powerful blue LEDs (40 W) dramatically accelerates the reaction rate, stabilizes the Re-photocatalyst, and unlocks the fast deoxygenation of polyfunctionalized *N*-oxides with high tolerance towards coordinating or other reducible functional groups.

Realizing that the limits of the catalytic system are primarily due to the slow reaction rate and the degradation of the catalyst, we focused on stabilizing the catalyst and optimizing key parameters in photocatalysis – photon and proton fluxes.

We first evaluated the addition of chloride ions (using 1 equiv. NEt₄Cl) in the reaction mixture since it increased both the catalytic activity and stability in the reduction of CO₂^[14] and N₂O.^[13] The catalyst stability increased in the presence of pyridine *N*-oxide (**2a**), but no significant reaction acceleration was observed (TOF₀ = 6.2 h⁻¹ vs. 5.5 h⁻¹; see ESI section 2.1 for details).

We thus implemented a setup change to increase the photon influx.^[15] Re-complex [(dtbpy)Re(CO)₃Cl] (**1**) presents a maximum of absorption in the near-UV at 364 nm and absorbs mainly in the blue region (see ESI section 2.2). Using a powerful blue light (Kessil®, LED 40 W), with an emission spectrum centered at 440 nm in the presence of complex **1** (5 mol%) as the catalyst and DIPEA (5.7 equiv.) as electron donor led to a significant increase in the catalytic activity, compared to the previous cool white LEDs (8 W). Pyridine *N*-oxide (**2a**) was deoxygenated in 45 % yield after 30 minutes of irradiation (Figure 1, orange curve) *versus* 26 % with the original setup (Figure 1, purple curve).

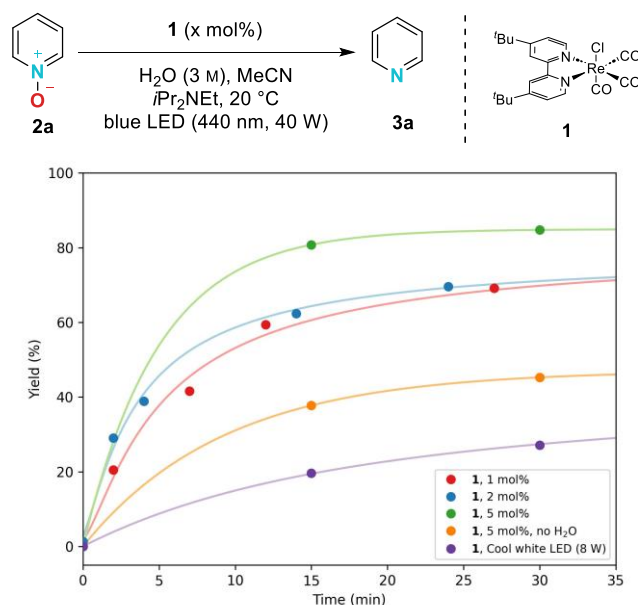
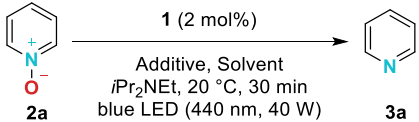


Figure 1 Optimization of the reaction parameters: addition of H₂O, catalyst loading, and influence of the solvent. NMR monitoring of the reaction (internal standard:

mesitylene). Conditions: **2a** (0.1 mmol), **1**, DIPEA (5.7 equiv.), H₂O (3 m), CD₃CN (0.5 mL). Original setup: cool white LEDs (8 W).^[13]

DIPEA is the sacrificial electron donor and proton source in this system.^[16] To improve the proton transfer, we evaluated the influence of proton donor additives. Inspired by previous work on CO₂ photodeoxygenation,^[17] H₂O was chosen as an additive. In the presence of H₂O (3 m), we observed that the reaction speed doubled to reach 85 % yield in pyridine (**2a**) after 30 min (Figure 1, green curve). With such a catalytic performance, we considered lowering the catalyst loading. Both 1 and 2 mol% catalyst loadings led to comparable initial rates (Figure 1, red and blue curves). However, with 1 mol% of photocatalyst **1**, the conversion reached a plateau of 79 % after 2.5 h. In contrast, complete conversion and 87 % yield of pyridine (**2a**) were observed after 2.5 h when 2 mol% of [(dtbpy)Re(CO)₃Cl] (**1**) were used. Decreasing or increasing the amount of H₂O proved detrimental to the catalytic activity (Table 1, entries 1-6), and no product was detected after 30 min in H₂O as solvent (Table 1, entry 7). Replacing H₂O by 4-methoxyphenol (3 m) and isopropanol (3 m) led after 30 min of irradiation to yields in pyridine (**3a**) of 2 % and 36 %, respectively (Table 1, entries 8 and 9). We also probed whether more sustainable solvents^[18] (EtOAc, anisole, dimethyl carbonate) than acetonitrile could be used. However, none proved as efficient as acetonitrile, leading to yields below 20 % after 1 h of reaction (Table 1, entries 10–12). Performing the reaction under air with non-degassed reagents and solvent yielded 56 % of pyridine (**3a**) in 30 min (Table 1, entry 13, see ESI section 3.4 for details), demonstrating the robustness of the photocatalytic system towards oxygen contamination.

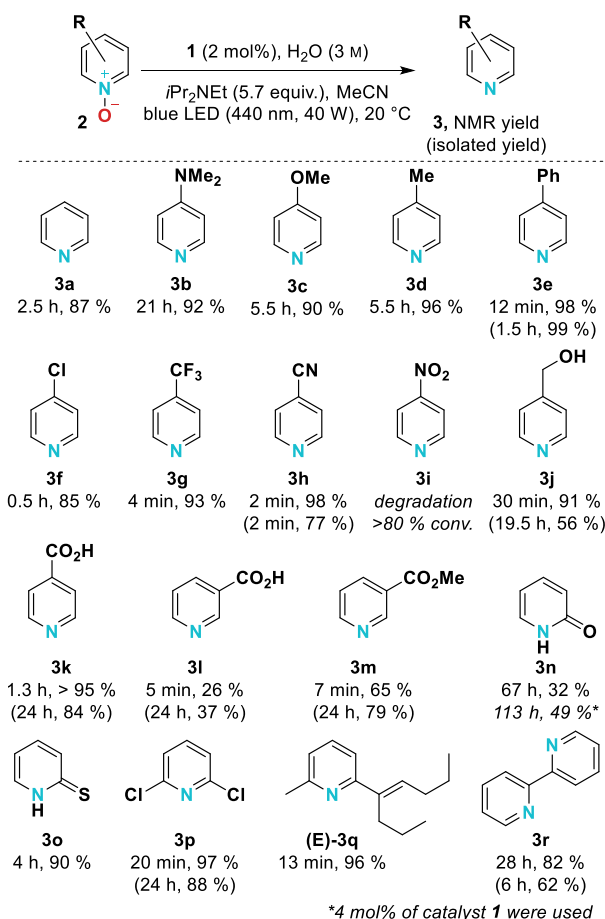
Table 1 Influence of proton donor additives on the reaction.

			
Entry	Additive	Solvent	Yield after 30 min ^c
1	-	MeCN	26 %
2	H₂O (3 m)	MeCN	65 %
3	H ₂ O (1 equiv.)	MeCN	25 %
4	H ₂ O (1.5 m)	MeCN	37 %
5	H ₂ O (6 m)	MeCN	48 %
6	-	MeCN/H ₂ O (1:1)	14 %
7	-	H ₂ O	0 %
8	4-MeOC ₆ H ₄ OH (3 m)	MeCN	2 %
9	<i>i</i> PrOH (3 m)	MeCN	36 %
10 ^a	H ₂ O (3 m)	AcOEt	8 %
11 ^a	H ₂ O (3 m)	Anisole	7 %
12 ^a	H ₂ O (3 m)	DMC	20 %
13 ^b	H ₂ O (3 m)	MeCN	56 %

^a1 h of reaction; ^bReaction was performed under air with non-degassed reagents and solvent; ^cNMR yields measured after 30 min of reaction (internal standard: mesitylene).

The efficiency of the catalytic system was first tested on a large library of *p*-substituted pyridine *N*-oxide **2b-k** to evaluate the influence of the electron density on the reaction (Scheme 2). Both electron-rich and electron-poor pyridines **3b-h** were obtained in 85–98 % yields within 2 min – 21 h. As expected, the more electron-rich the pyridine, the slower the reaction was. Complete conversion of the electron-rich 4-(dimethylamino)pyridine-1-oxide (**2b**) was observed in only 21 h, vs. more than 5 days without H₂O.^[13] *p*-Methoxy and methyl derivatives **2c** and **2d** were deoxygenated after 5.5 h of irradiation in 90 % and 96 % yields, respectively. Despite being a photosensitive compound,^[19] 4-phenylpyridine (**3e**) was obtained in 98 % yield after 12 minutes of irradiation. The electron-poor *p*-chloro and *p*-CF₃ pyridine *N*-oxides (**2f** and **2g**) were deoxygenated within short times (30 and 4 min, respectively) of irradiation in 85 and 93 % yields, respectively. The deoxygenation of *p*-cyanopyridine *N*-oxide (**2h**) required only 2 min of irradiation, and the corresponding pyridine **3c** was obtained in 98 % yield. No significant degradation of the cyano substituent was observed, even on a preparative scale of 100 mg (0.8 mmol), and pyridine **3c** was isolated in 77 % yield.

The nitro derivative **2i** also reacted under the reaction conditions but led to a complex mixture, the nitro group being unselectively reduced under the reaction conditions. 4-Pyridyl carbinol *N*-oxide (**2j**) was deoxygenated in 91 % yield within 30 min, the labile primary alcohol remaining untouched. Isonicotinic acid *N*-oxide (**2k**) was completely converted into the corresponding pyridine **3k** in 1.3 h. However, with its *meta*-substituted isomer, the reaction stopped after 5 min, and nicotinic acid (**3l**) was obtained in a maximum yield of 26 %. The complete conversion was recovered using the corresponding methyl ester **2m**, giving methyl nicotinate (**3m**) in 65 % yield after 7 min. A similar behavior was observed with *N*-oxide **2n**, bearing an alcohol substituent in the 2-position (32 % yield after 67 h). Increasing the amount of catalyst to 4 mol % enabled the reaction to reach 49 % yield after an extended reaction time of 113 h. The plateau of conversion reached for substrates **2i** and **2n** hints at the inhibition of photocatalyst **1** by the products, probably due to the chelation of the latter to the Re-complex. Conversely, pyridine 2-thiol *N*-oxide (**2o**) was converted to the corresponding thioamide **3o** in 90 % yield. C2-chlorinated pyridine *N*-oxides **2p** gave the corresponding pyridine in 97 % yield. When the *E/Z* mixture of the C2-functionalized *N*-oxide **2q** (97:3) was subjected to the reaction conditions, the isomer (*E*)-**2q** was reduced in 96 % yield after 13 min of irradiation, whereas the (*Z*)-isomer was unreactive under the same reaction conditions. This result was also observed in the absence of H₂O.^[13] The slight difference in reactivity may come from the higher steric hindrance around the *N*-oxide in (*Z*)-**2q**, hinting at a possible coordination of the substrate on Re-complex **1** during the catalytic cycle. Bipyridine *N,N'*-dioxide (**2r**) underwent deoxygenation in 85 % yield, albeit in an extended reaction time of 28 h, providing bipyridine (**3r**). The poor solubility of the oxide **2r** certainly explains the slower deoxygenation of this substrate compared to other pyridine derivatives.

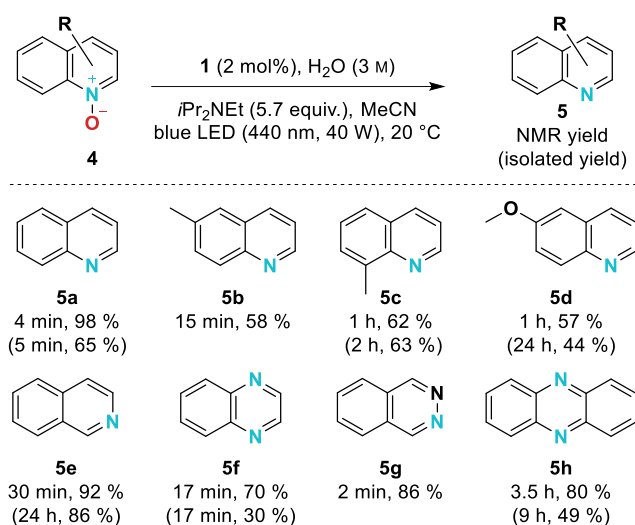


Scheme 2 Scope of the reaction with substituted pyridines. Reaction conditions for NMR yields: substrate (0.1 mmol), **1** (2 mol%), DIPEA (5.7 equiv.), H₂O (3 M), CD₃CN (0.5 mL). Yields were determined by ¹H NMR analysis of the crude reaction mixture (internal standard: mesitylene). Isolated yields were obtained on 0.2–0.8 mmol scales in vials. Reactive centers are highlighted in blue.

Other N-heterocyclic derivatives were also successfully reduced. Quinolines **5a–d** and isoquinoline (**5e**) were obtained in 57–98 % within 4 min–1 h. These results exemplify the efficiency of the rhenium catalyst in the presence of H₂O since light-sensitive quinolines were degraded under our previous reaction conditions.^[13] Quinoxaline *N,N'*-dioxide (**4f**) and phthalazine *N*-oxide (**4g**) were reduced within minutes in 70 % and 86 % yield, respectively, and phenazine (**5h**) was obtained in 80 % yield, albeit with a longer reaction time (3.5 h). Acridine *N*-oxide was, however, unreactive under the same conditions. A Stern-Volmer analysis showed that the rhenium photocatalyst **1** luminescence is quenched in the presence of acridine *N*-oxide, and the rate of excitation decay was measured as being about 10 times faster than with DIPEA (see ESI section 2.3 for more details).

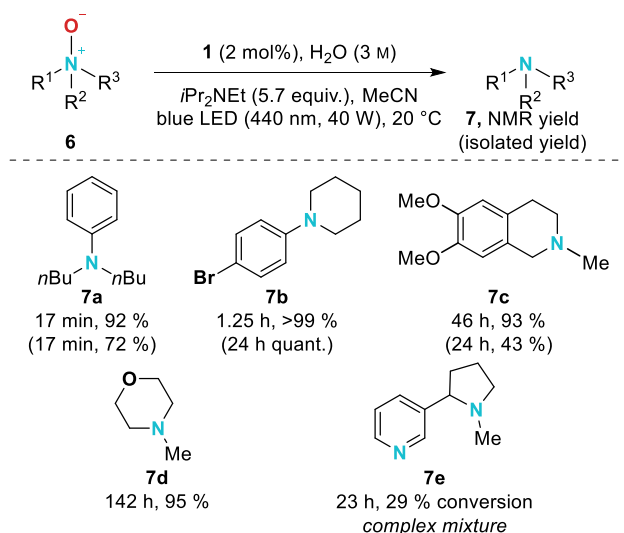
The deoxygenation was successfully scaled up to 2.0 mmol (ca. 400 mg) in vials without any significant reaction conditions change, thus demonstrating the synthetic applicability of the method. H₂O (3 m) was added by opening the vial to air, and the reaction mixture was irradiated without further precautions (see ESI section 4.4 for more details). Although contamination by air could occur, 14 deoxygenated N-

heterocycles (**3e,h,j-m,p,r** and **5a,c-f,h**) were isolated in moderate to excellent yields (30 – 99 %, Scheme 2 and Scheme 3). Small contaminations by oxygen were thus not deleterious to the reaction. Complete conversion was generally obtained under extended reaction times (2 min – 24 h) compared to the 0.1 mmol scale. This phenomenon was ascribed to a decreased photon flux in 1 cm-diameter vials compared to NMR tubes: the light penetration has indeed been estimated at less than 2 mm.^[20] The poorly-soluble bipyridine *N,N'*-dioxide (**2r**) reached faster full conversion in the vial than in the NMR tube (6 h vs. 21 h), certainly due to the active stirring, which helped to solubilize the starting material. In contrast, the scale-up with phthalazine *N*-oxide (**4g**) was ineffective: a gas evolution and complete degradation of the reaction mixture were observed.



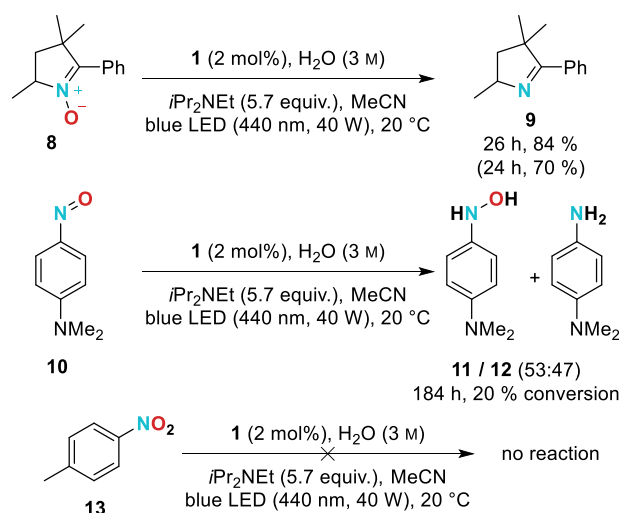
Scheme 3 Scope of the reaction with substituted π -extended aza-heterocycles. Reaction conditions for NMR yields: substrate (0.1 mmol), **1** (2 mol%), DIPEA (5.7 equiv.), H₂O (3 M), CD₃CN (0.5 mL). Yields were determined by ¹H NMR analysis of the crude reaction mixture (internal standard: mesitylene). Isolated yields were obtained on 0.2-0.8 mmol scales in vials. Reactive centers are highlighted in blue.

Aniline *N*-oxides were also deoxygenated under the same reaction conditions and products **7a** and **7b** were obtained in 92 % and quantitative yields, respectively (Scheme 4). The deoxygenation of aliphatic amines was also effective, albeit it required extended reaction times. 1,2,3,4-Tetrahydroisoquinoline **6c** and *N*-methyl morpholine *N*-oxide (**6d**) yielded 93 % and 95 % of their respective reduced products in 46 h and 142 h, respectively. In the case of nicotine *N,N'*-dioxide (**6e**), deoxygenation appeared preferentially on the pyridine ring first, and nicotine (**7e**) was detected by NMR analysis. However, a low conversion and a mixture of products were obtained after 23 h.



Scheme 4 Scope of amine derivatives. Reaction conditions for NMR yields: substrate (0.1 mmol), **1** (2 mol%), DIPEA (5.7 equiv.), H₂O (3 M), CD₃CN (0.5 mL). Yields were determined by ¹H NMR analysis of the crude reaction mixture (internal standard: mesitylene). Isolated yields were obtained on 0.2-2.0 mmol scales in vials.

We finally evaluated the applicability of this photocatalytic deoxygenation method to other *N*-oxide compounds. With nitron **8** complete conversion was achieved, although the reaction required 26 h to complete, and imine **9** was obtained in 84 % yield (70 % on preparative scale). With nitroso derivative **10**, a low conversion rate was observed, and an equimolar mixture of hydroxylaniline **11** and aniline **12** (53:47) was obtained after 184 hours of irradiation. Finally, the deoxygenation of nitroarene **13** proved ineffective (Scheme 5).



Scheme 5 Deoxygenation of other classes of *N*-oxide compounds. (Isolated yield in parenthesis)

Re-complex **1** thus demonstrated its versatility in deoxygenating a large scope of *N*-oxide derivatives. The photocatalytic system proved efficient in reducing both π-extended *N*-heterocyclic derivatives and substituted pyridine *N*-oxides, in contrast to

[Ru(bpy)₃]Cl₂, and without resorting to highly reducing [Ir] photocatalysts.^[9] Hence, we sought to understand how the photons and electrons are transferred and the role of H₂O in the acceleration of the reaction.

First, rhenium carbonyl complexes such as complex **1** act as both photosensitizers and photocatalysts and can absorb photons under light irradiation.^[21] The Stern-Volmer analysis of complex **1** with pyridine *N*-oxide (**2a**) and DIPEA has demonstrated that the luminescence of complex **1** is effectively quenched by DIPEA and not substrate **2a**, suggesting a first electron transfer between DIPEA and Re-complex **1**.^[13]

We were also intrigued by the effect of the solvent since solvents other than MeCN performed poorly (Table 1, entries 10–12). Interestingly, when using a DMC/MeCN (4:1) mixture, the reactivity was equivalent to that of pure MeCN, and pyridine (**2a**) was obtained in 92 % yield after 1 h. The strong influence of MeCN, a coordinating solvent, could be explained by a better solubility of the different species or by the necessity to perform ligand exchanges around the Re-center. A possible coordination of the substrate **2a** to the rhenium center can be envisaged since complex **1** presents a labile chloride ligand. Moreover, since the resulting pyridine is a good ligand, the product could deactivate the catalyst throughout the reaction, as observed with the bidentates pyridines **3l** and **3n**. Using MeCN as the solvent could facilitate the pyridine decoordination, thereby accelerating the catalyst turnover. These considerations and a strong influence of the steric bulk around the *N*-oxide center hint at the coordination of the substrate to Re-complex **1**, and thus at an inner-sphere electron transfer, as already observed for CO₂ and N₂O photo- and electrodeoxygenation with rhenium carbonyl complexes.^[17c,22]

We finally performed a reaction in the presence of D₂O instead of H₂O to get more insight into the role of H₂O. Under the reaction conditions, pyridine (**3a**) was observed in 39 % yield after 30 min of the reaction (vs. 65 % with H₂O; Figure 2a). Kinetic monitoring over 3 min on a reaction twice as diluted also showed a small kinetic isotope effect (<1.2; Figure 2b). These results, combined with the lower efficiency of other proton sources (phenol or isopropanol, Table 1 entries 8 and 9), demonstrated that H₂O is critical for the reactivity and certainly facilitates proton transfers.

In this study, we unveiled a robust and simple Re-based photocatalytic system that enables the deoxygenation of a large scope of *N*-oxide derivatives with a high functional group tolerance towards other reducible functional groups. We demonstrated that the same catalytic system is applicable to polyfunctional alkyl *N*-oxides, π-extended *N*-heterocyclic *N*-oxides, and pyridine *N*-oxides, even though the reductions of the latter are reputed more challenging. The reaction did not require the use of sacrificial oxophilic reagents and occurred rapidly (<5 min in some cases) in the presence of H₂O (3 m) as a simple additive. The transformation tolerated air contamination and was scalable up to at least 2 mmol (ca. 400 mg), demonstrating its synthetic applicability on a preparative scale. Further investigations to get a more precise picture of the ultra-fast phenomena and the overall mechanism, in particular the role of water, are underway using advanced techniques like transient absorption spectroscopy.²³

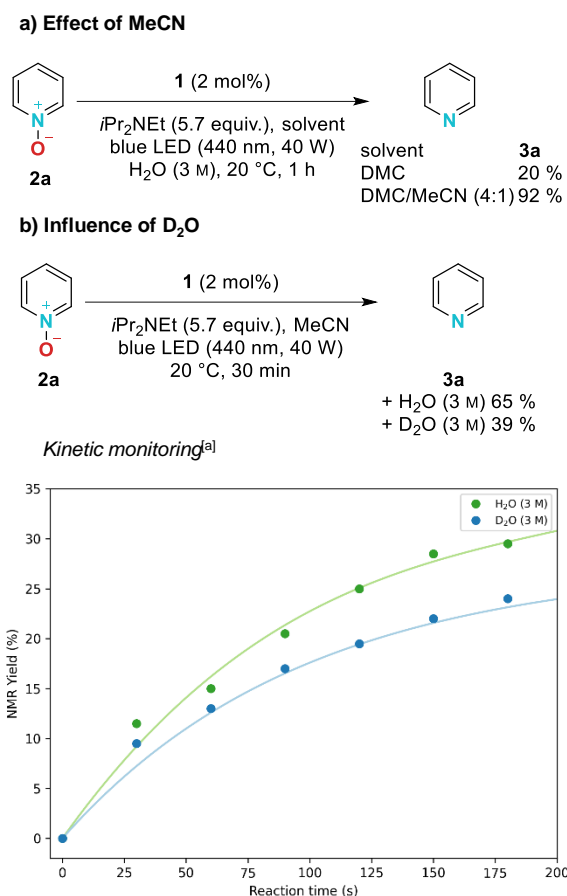


Figure 2 Influence of D₂O on the reaction. [a] NMR monitoring, reaction conditions: **2a** (0.1 mmol), **1** (2 mol%), DIPEA (5.7 equiv.), H₂O or D₂O (3 M), CD₃CN (1 mL).

Detailed procedures can be found in the supporting information, where additional references were cited.²⁴

Procedures

Typical procedure for the reactions in *J. Young* tube: In a glovebox, a 3 mL NMR tube equipped with a *J. Young* valve was charged with rhenium complex **1** (1 mg, 2 μmol, 2 mol%), followed by the desired *N*-oxide (0.10 mmol, 1 eq.), CD₃CN (0.5 mL), DIPEA (0.1 mL), and mesitylene as an internal standard (10 μL). The tube was brought out of the glovebox, and H₂O was added (32 μL, 3.0 m). The tube was sealed, cryo-degassed, put under an argon atmosphere, then left under irradiation at 440 nm with blue Kessil® LED. The conversion rate and pyridine yield were determined by ¹H NMR integration (protons *ortho* to the nitrogen atom) versus mesitylene as an internal standard.

Typical procedure for large-scale reactions: In a glovebox, a 4 mL vial equipped with a stirring bar was charged with the rhenium complex **1** (2.0 mol%), followed by *N*-oxide (1.0 equiv.), MeCN (0.2 M), and DIPEA (5.7 equiv.). The vial was sealed, brought out of the glovebox, opened to air, then H₂O was added (3 m). The content of the vial was not degassed after H₂O was added. The vial was allowed to stir under irradiation at 440 nm with blue Kessil® LED, and the reaction was followed by TLC analysis.

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Conflict of Interest

The authors declare no conflict of interest.

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