Pyridine *N*-oxides as HAT reagents for photochemical C-H functionalization of electron-deficient heteroarenes

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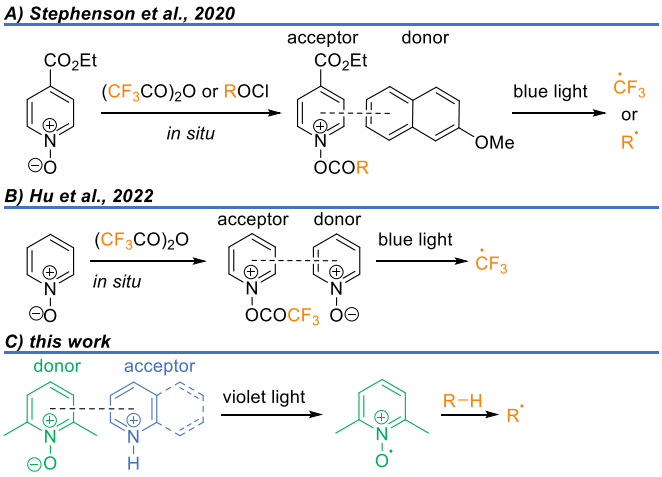
Pyridine *N*-oxides only recenly marked their presence in the photocatalysis outbreak, mainly serving as oxypyridinium salt precursors. Herein, their unique reactivity as a hydrogen atom transfer reagent in photochemical, Minisci-type alkylation of electron-deficient heteroarenes is unveiled. The formation of an EDA complex between a heterocyclic substrate and *N*-oxide precludes the need for a photocatalyst. The developed method allows for a broad range of radical precursors to be used, namely alkanes, alkenes, amides, and ethers, for efficient alkylation of azines.

The relevance of heterocyclic *N*-oxides in various branches of modern organic chemistry is constantly increasing,[1] primarily used as intermediates in the synthesis of the corresponding heterocyclic compounds, they are now investigated as APIs in therapeutics[2] or as energetic materials.[3] Their Lewis basic properties predispose them to be used as organocatalysts,[4] while in transition metal-catalysed C-H activation reactions the constituent oxygen atom serves as a directing group.[5] Furthermore, aromatic *N*-oxides can also be viewed as nitrones that engage as 1,3-dipoles in dipolar cycloadditions, a very useful method for their C-2 selective functionalization.[6]

Over decades photochemistry of pyridine *N*-oxides has been extensively studied.[7] Their direct photolysis leads to ring contraction,[8] expansion,[9] or fragmentation[10] depending on the substituents. They can also either accept[11] or donate electrons.[12,13] In this regard, the photocatalitcally[13] or electrochemically[12] generated pyridine *N*-oxyl radical forms complexes with hydrocarbons, which decompose in the absence of oxygen;[13] otherwise a mixture of the corresponding alcohols and ketones is obtained.[12] Only recently, have *N*-oxides marked their presence in the photoredox catalysis outbreak. They mainly serve as precursors of oxypyridinium salts that act as a source of CF_3 and alkyl radicals (Scheme 1A).[14] Recently, Hu *et. al.* proposed the formation of an electron donor-acceptor complex (EDA) between pyridine *N*-oxide and the corresponding oxypyridinium salt that enables photochemical cascading trifluorometylation-cyclization of cyanamide alkenes (Scheme 1B).[15] Similarly, *N*-alkoxy pyridinium salts proved useful in photochemical α-phosphorylation of aromatic tertiary amines.[16]



Scheme 1 Pyridine *N*-oxide in modern photochemical reactions.

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In 2021 Zhang reported that an electrochemically generated pyridine *N*-oxyl radical cation is capable of abstracting a hydrogen atom from water molecules.[17] Inspired by this result, *we envision pyridine N-oxides as hydrogen atom transfer reagents in C-C bond forming reactions*. To test this hypothesis, we used them in the photocatalytic generation of C(*sp3*) radicals from alkanes, which then engage in a reaction with electron-deficient heteroarenes. Photoinduced Minisci-type azines alkylations with precursors of the C(sp^3)-H radical have already been extensively studied, using various terminal oxidants,[18–20] such as: organic peroxides,[21] persulfates,[22] and recently air.[23] Most of them, however, require a significant excess of the reagent and the use of a photocatalyst. We commenced our studies by performing UV-Vis absorption measurements, since it is well documented that pyridine derivatives easily form EDA complexes,[24–26] (Figure 1). A spectrum of a mixture of lepidine (**1**) and 2,6-lutidine *N*-oxide (**3**) is merely a sum of the absorption of the components; however, upon the addition of an equimolar amount of TFA, an increase in the absorbance of the charge-transfer band was observed around 380 nm (Figure 1A). In fact, the addition of TFA up to 1 equiv. led to a gradual increase in absorption in this region (Figure 1B), suggesting the formation of the EDA complex between protonated lepidine (**1**) and 2,6-lutidine *N*-oxide (**3**). Photoexcitation of the formed complex should generate the *N*-oxyl radical cation, which, according to Zhang's results, should then abstract the hydrogen atom from the C-H bonds generating the corresponding C-centred radical (Scheme 1C).

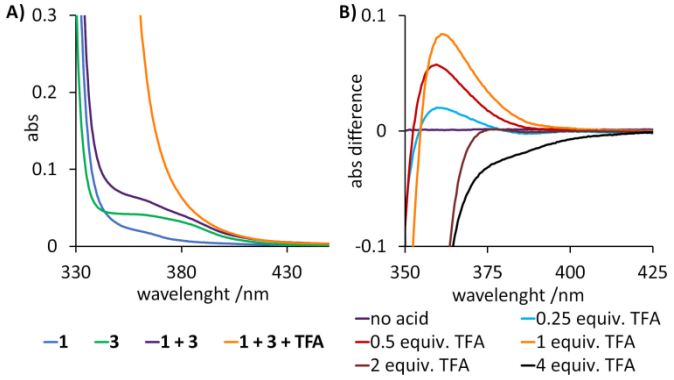
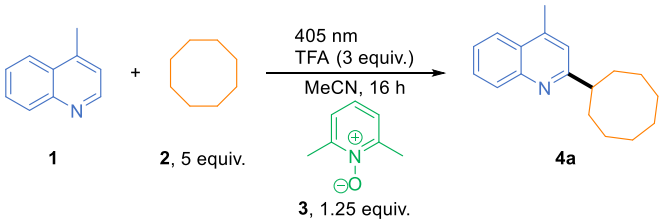


Fig. 1 UV-Vis spectra. **A**) absorption spectra of lepidine (**1**), 2,6 lutidine *N*-oxide (**3**) and their mixture, **B**) difference between the absorbance of a mixture of lepidine (**1**) and 2,6-lutidine *N*-oxide in the presence of varying amounts of TFA.

UV-A irradiation of the model reaction of lepidine (**1**) with cyclooctane (**2**) in the presence of 2,6-lutidine *N*-oxide (**3**) and sulfuric acid in an acetonitrile/water mixture gave alkylated lepidine **4a** in a modest yield (Table 1, entry 1). Less energetic violet light (405 nm, entry 2) induced the reaction as well, without having a negative effect on the yield. Prolonging the reaction time did not improve the conversion; however, an increase in the amount of an acid led to the formation of product **4a** in high yield (entries 3, 4). Among a selection of acids tested, TFA maintained the yield at a high level (entry 5). Lewis acids also promoted the reaction functioning as an alternative activating agent for the heterocyclic substrate, in the presence of $Zn(OTf)_2$ the yield of product **4a** increased up to 81% (entry 7). The energy of the EDA complex charge transfer band corresponds to the difference between the donor ionization energy and the acceptor electron affinity,[27] thus the behaviour of pyridine *N*-oxides with both EWG and EDG as HAT reagents were tested (see SI); however, the initially used 2,6-lutidine *N*-oxide (**3**) was the most efficient.

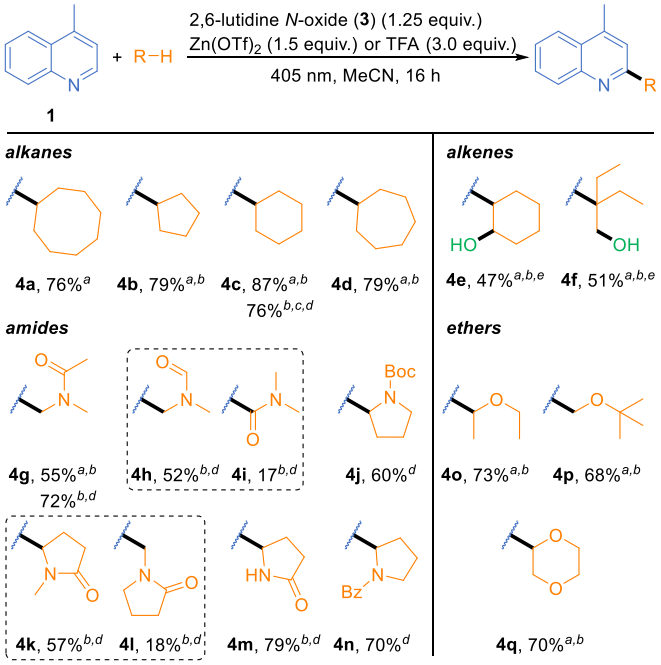
Table 1 Optimization summary.



entry	Deviation from optimal conditions	yield (%)
1	1.5 equiv. of *N*-oxide **3**, 1 equiv. of H_2SO_4 instead of TFA in CH_3CN/H_2O (5:1) irradiated at 365 nm	30
2	1.5 equiv. of *N*-oxide **3**, 1 equiv. of H_2SO_4 instead of TFA in CH_3CN/H_2O (5:1)	37
3	1.5 equiv. of *N*-oxide **3**, 4 equiv. of H_2SO_4 instead of TFA in CH_3CN/H_2O (5:1)	75
4	1.5 equiv. of *N*-oxide **3**, 3 equiv of. H_2SO_4 instead of TFA in CH_3CN/H_2O (5:1)	76
5	1.5 equiv. of *N*-oxide **3**	79
6	**none**	**78**
7	**1.5 equiv. of $Zn(OTf)_2$ instead of TFA**	**81**

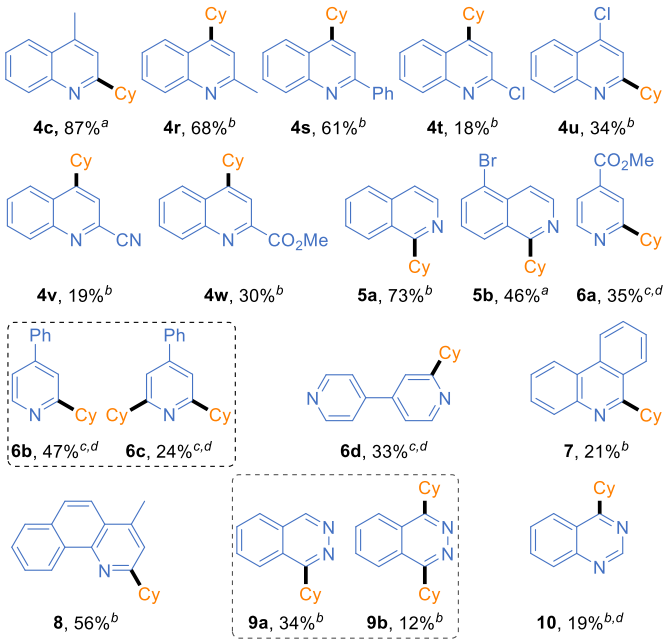
Reaction conditions: lepidine (**1**) 0.2 mmol, cyclooctane (**2**) 1.0 mmol, TFA 0.6 mmol, 2,6-lutidine *N*-oxide (**3**) 0.25 mmol in 2.5 ml of MeCN irradiated with 405 nm LED for 16 h, yield determined by GC.

With the optimized conditions in hand, the scope of nucleophilic radical precursors was investigated (Scheme 2). The method proved to be effective in generating radicals from various types of formal hydrogen atom donors: alkanes, alkenes, amides, and ethers. In particular, the reaction is insensitive to the ring size of secondary alkanes and provided corresponding products **4a**-**d** in good yields (76-87%). The process could be scaled up to 1 mmol, however prolonged reaction time is required to achieve decent yield of the product **4c**. Among alkenes, both cyclohexene and 2-ethyl-but-1-ene furnished mainly hydroxylated products **4e** and **4f**, even when the reaction was carried out under anhydrous conditions. This result suggests that hydroxyl radicals are generated during the reaction course. As far as amides are concerned, the reaction with dimethylacetamide selectively afforded compound **4g** in 52% yield, however, full conversion was not achieved with $Zn(OTf)_2$. These substrates performed best with TFA as an additive, for product **4g** the yield increased to 72%. The use of DMF as a substrate led to a mixture of products **4h** and **4i**. The abstraction of hydrogen atom from the α-position is highly preferred (**4h**, 52%), although the acylation product **4i** was also observed. For 1-Boc-pyrrolidine, the yield decreased slightly (60%), presumably due to steric hindrance. In general, the abstraction of secondary hydrogen atoms is preferred over primary ones, as evidenced by the alkylation with 1-methylpyrrolidone, which gave product **4k** in a yield of 57%. Secondary amides are also well tolerated, and, gratifyingly, substitution at the nitrogen atom was not observed. Aromatic amide (pyrrolidinyl benzamide) gave corresponding product **4n** in good yield. Pyridine *N*-oxides were also effective in generating radicals from ethers under the reaction conditions developed. Alkylation with diethyl ether, methyl-*tert*-butyl ether, and 1,4-dioxane in the presence of $Zn(OTf)_2$ as the activating agent procced in decent yield.



Scheme 2 Scope of radical precursors. Reaction conditions: lepidine (**1**) 0.2 mmol, radical precursor 1 mmol, 2,6-lutidine *N*-oxide (**3**) 0.25 mmol and trifluoroacetic acid 0.6 mmol or $Zn(OTf)_2$ 0.3 mmol in 2.5 ml of MeCN irradiated with 405 nm LED for 16 h, isolated yields given. [a] $Zn(OTf)_2$ as an activating agent, [b]10 equiv. of a radical precursor, [c]1 mmol scale, reaction time 48 h, [d]TFA as an activating agent, [e] anhydrous MeCN.

Next, the scope of electron-deficient heteroarenes was explored using cyclohexane as the alkylating agent (Scheme 3). 2-Methylquinoline, despite its similarity to lepidine, provided C4 alkylation product **4r** in a marginally lower yield (68%), indicating a preference for C2 alkylation. A similar result was obtained for slightly less electron-deficient 2-phenylquinoline (61%). The alkylation of quinolines with electron-withdrawing groups is less efficient. Isoquinolines gave only alkylated products at position 1 (**5a**). However, substitution at position 5 with the halogen atom led to alkylated derivative **5b** in a somewhat diminished yield. For some substrates, fine-tuning of the reaction conditions was required. Increasing the amount of TFA and prolonging the reaction time enabled alkylation of methyl isonicotinate and 4-phenylpyridine, in the first case only a significant amount of monoalkylation product **6a** was isolated, for the latter, both mono- and dialkylation products **6b** and **6c** formed. Similar conditions were used for the monoalkylation of 4,4'-bipyridine (**6d**). The process is feasible for alkylation of highly conjugated azines, 4-methylbenzo[h]quinoline and phenantridine, although product of the latter **7** formed in a low yield. Heteroaromatics with two nitrogen atoms are also suitable starting materials; benzopirazine and benzopyridiazine furnished predominantly monoalkylated products **9a** and **10**.



Scheme 3 Scope of electron-deficient heteroaromatic compounds. Reaction conditions: heteroaromatic compound 0.2 mmol, cyclohexane 2 mmol, 2,6-lutidine *N*-oxide (**3**) 0.25 mmol and trifluoroacetic acid 0.6 mmol or $Zn(OTf)_2$ 0.3 mmol in 2.5 ml of MeCN irradiated with 405 nm LED for 16-48 h, isolated yields given. Cy stands for cyclohexyl. [a]$Zn(OTf)_2$ as an activating agent, [b]TFA as an activating agent, [c]6.0 equiv. (1.2 mmol) of TFA as an activating agent, [d]reaction irradiated for 48 h.

In general, the scope of heteroaromatic substrates seems, as for now, limited to quinolines and isoquinolines with slightly electron-donating substituents, which is inherently connected with the need for efficient formation of an EDA complex between the *N*-oxide and the substrate. Thus, by the proper choice of *N*-oxides with matching electronic properties, the scope can presumably be broadened. Along this line, we reexamined two selected examples to see if the yields of the corresponding products improve when different *N*-oxides are used (Table 2). Indeed, for more electron-rich phenantridine, the yield increased when more electron-deficient 2-cyano-6-methylpyridine *N*-oxide was used. On the contrary, the yield decreased with electron-rich 2,4,6-trimethylpyridine *N*-oxide as an HAT reagent. More electron-deficient substrate 3-(methoxycarbonyl)-quinoline provided the corresponding product **4w** and the yield is virtually independent of the selected *N*-oxide.

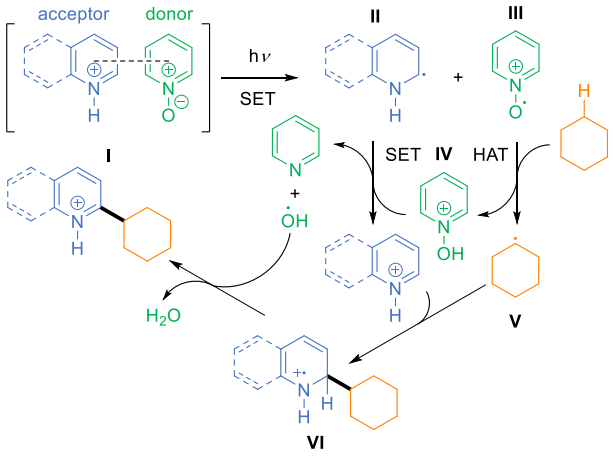
Table 2 Screening of azine *N*-oxides.

entry	*N*-oxide	yield **7** (%)
1	2,6-lutidine *N*-oxide	21
2	2-cyano-6-mehtylpyridine *N*-oxide	41
3	3-(methoxycarbonyl)pyridine *N*-oxide	32
4	isoquinoline *N*-oxide	24
5	lepidine *N*-oxide	25
6	2,4,6-trimethylpyridine *N*-oxide	7

Reaction conditions: phenanthridine 0.1 mmol, cyclohexane 1.0 mmol, TFA 0.3 mmol, *N*-oxide 0.125 mmol in 1.5 ml of MeCN irradiated with 405 nm LED for 18 h, yields determined by GC.

We have proved that *pyridine N-oxides can indeed act as reagents for the activation of inert C-H bonds in the synthetically useful, photochemical Minisci-type alkylation of azines*. Next, we turned our attention to understanding their mode of action. During our initial studies, we confirmed that the formation of EDA complex **I** is a key to this process (Figure 1). The experiment with a radical scavenger confirmed the radical nature of thetransformation. In the presence of TEMPO only traces of the

product were observed but when TEMPO was added after 3 hours of irradiation, peaks with m/z corresponding to adducts of radicals **III** and **V** with TEMPO were detected by ESI-MS. The formation of hydroxylated products **4e** and **4f** in the reaction with alkenes conducted under anhydrous conditions corroborates the formation of the hydroxyl radical in the reaction mixture (Scheme 2). Given that there are no other sources of oxygen atoms and the fact that 2,6-lutidine is a byproduct in this reaction, hydroxyl radicals must originate from the protonated *N*-oxide. Their generation from pyridine *N*-oxides upon photochemical reduction by an NADH analogue has already been suggested.[11] Based on the evidence collected, we propose a plausible mechanism depicted in Scheme 4. The reaction starts from the formation of an EDA complex **I** between protonated lepidine and the *N*-oxide. After irradiation, radical **II** derived from lepidine and *N*-oxyl radical cation **III** is formed. The hydrogen atom is abstracted from a substrate to give corresponding radical **V**, which then reacts with the protonated lepidine. The resultant radical adduct **VI** after hydrogen atom abstraction gives the final product in its protonated form. The reaction requires an overstoichiometric amount of *N*-oxide, and no traces of the reduced product is observed, which imposes the SET process between protonated *N*-oxide **VI** and lepidine-derived radical **II**.



Scheme 4 Mechanistic proposal.

In conclusion, we have discovered that under light irradiation pyridine *N*-oxides can act as an HAT reagent. The EDA complex, formed between protonated azines and pyridine *N*-oxides, provides a *N*-oxyl radical cation, which abstracts a hydrogen atom from alkanes, alkenes, amides, and ethers. The revealed reactivity was tested in a photochemical C-H functionalization of electron-deficient heteroaromatic compounds with formal hydrogen atom donors as alkylating agents. The developed protocol is very simple, as it requires only substrates, a slight excess of *N*-oxide, and a Brønsted or Lewis acid for the activation of an azine. The scope of an alkylating agent is broad, and the yields of the corresponding products are high.

We hope that our discovery will lead to the development of new photochemical methods using pyridine *N*-oxides as a mild and efficient hydrogen atom transfer reagent.

Acknowledgements

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