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Synthetic Chameleon Turns into Oximes, Nitrones, and Hydroxylamines when Exposed to Blue Light

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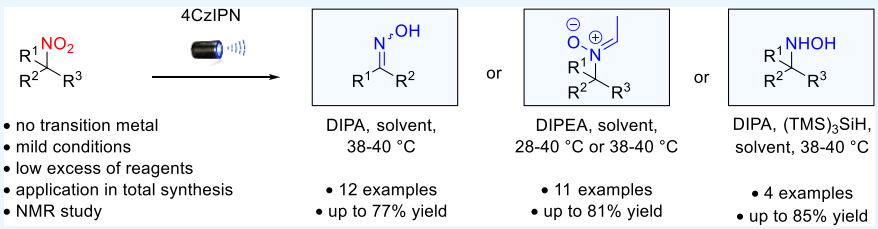

ABSTRACT: A metal-free, user-friendly photochemical transformation of nitroalkanes to oximes, nitrones, and hydroxylamines has been developed. The visible-light-induced reactions are catalyzed by the readily available photoredox organocatalyst 4CzIPN and use inexpensive amines as reductants. Broad in scope and tolerant of multiple functional groups and heterocycles, the transformation proceeds under mild conditions. Its synthetic potential was demonstrated in the formal total synthesis of amathaspiramide F. A basic insight into the reaction mechanism was gained with the help of an NMR study.

1. INTRODUCTION

The dawn of modern organic synthesis was marked by Victor Meyer's preparation of nitroalkane from alkyl halides.[1] Ever since the significance of nitroalkanes evolved alongside organic synthesis, they gradually became an irreplaceable bulk feedstock to fine chemicals. Their ready commercial and synthetic accessibility and fascinating reactivity reaches enabled the development of countless reliable methodologies.[2] Already in 1979, Dieter Seebach, in his comprehensive review, labeled nitroaliphatic compounds as "ideal intermediates in organic synthesis?"[3] and later on described the nitro group as having "chameleon qualities".[4] Although competing for the nickname with organic sulfones,[5] the nitro group is frequently loosely associated with the term "synthetic chameleon".[6] Many transformations involving the synthetic chameleon, such as the Henry reaction[7] and the Nef reaction,[8] became cornerstones of organic synthesis. Apart from the already classical transformation, the nitro group has recently found application in modern reactions such as C−H functionalization[9] and cross-couplings.[10] Further reactivity patterns and utilizations were identified when external forces and technologies were involved in their chemical reactions. Thus, flow chemistry,[11] crystallization,[12] electrochemistry,[13] mechanochemistry,[14] and photochemistry[15] assisted in developing novel transformations of nitroalkanes.

Driven by the sustainability demands and yet unexplored photochemistry of nitroalkane, we have become particularly interested in photochemical transformation employing visible light. Recently reported visible-light-promoted photochemical reactions of nitroalkanes **1** opened attractive access to oximes **2** and nitrones **3** (Scheme 1, part B).[15b−d] Transition-metal-containing photoredox catalysts and additives were utilized in the process described by Wang and Hong (Scheme 1, part B). Considering the ready accessibility of redox-active organocatalysts and redox-active amines, we believed that metal-free divergent photoredox transformations of nitroalkanes were possible. We have envisaged that photochemical transformations of nitroalkanes operating under mild conditions could provide access to a wider variety of functional groups[16] and thus significantly enhance the rapidly expanding field of sustainable photochemistry (Scheme 1, part C).[17] With this goal in mind, we began our investigations.

2. RESULTS AND DISCUSSION

Intending to develop a user-friendly protocol applicable to academic research and industry, we initially searched for a robust, readily accessible, and powerful photoredox-active organocatalyst.[18] Due to its photoredox activity, easy accessibility, and increasing popularity, we chose 4CzIPN (**4**) as the catalyst.[19] When searching for a suitable reductant in the transformation of nitroalkanes, we considered the availability,

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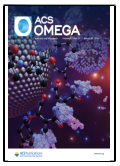
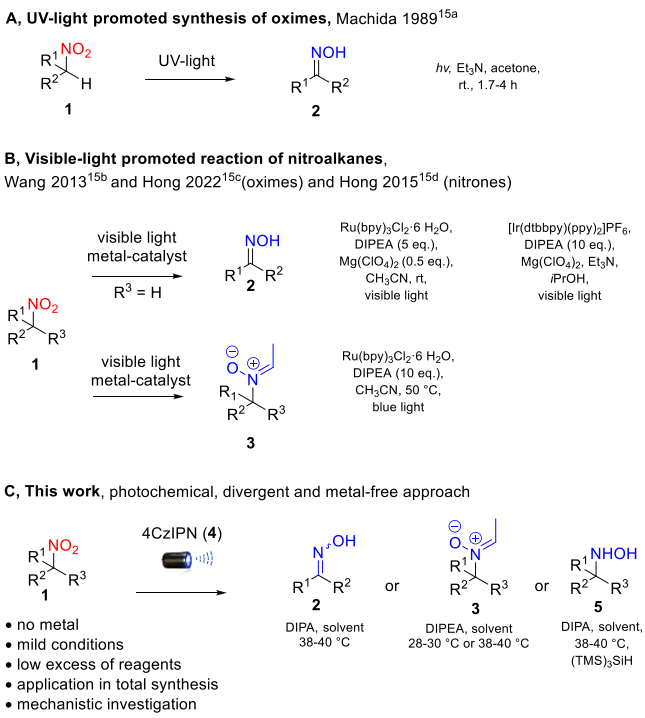
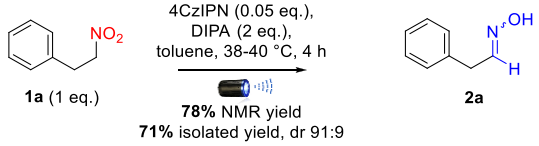


Scheme 1. Selected Photochemical Transformation of Nitroalkanes



Scheme 2. Visible-Light-Promoted Transformation of Nitroalkane to Oxime—Initial Experiment



price, and environmental character as decisive parameters. All set criteria were met in readily available diisopropylamines (DIPA and DIPEA), which function as single-electron reductants.

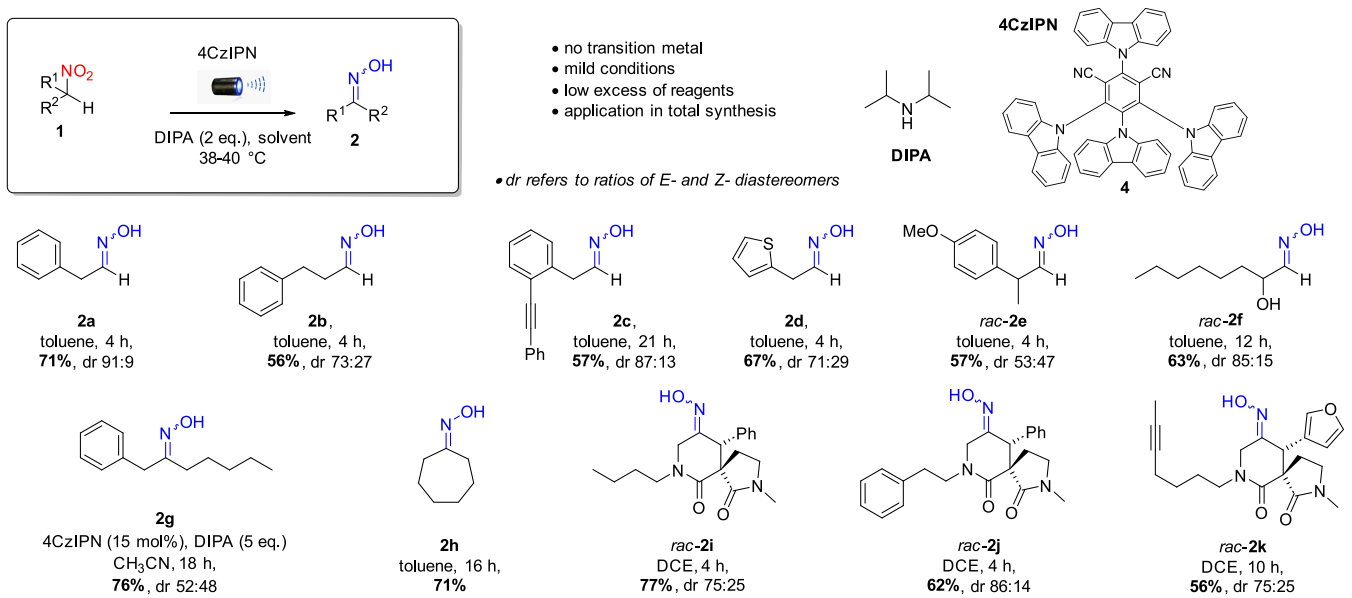
Our hypothesis was initially tested in the reduction of unfunctionalized nitroalkane **1a** to oxime **2a**. To our delight, 4CzIPN (**4**) facilitated the envisaged photochemical transformation under mild conditions, yielding a diastereomeric mixture of oximes (Scheme 2). The reaction retained all intended attractive features as it proceeded within 4 h at a slightly elevated temperature with readily available DIPA. Moreover, the reaction proceeded without an inert atmosphere or transition-metal-containing photocatalyst.

With the proof of concept established, we investigated the reaction scope. Initially, a set of primary nitroalkanes was tested. Pleasingly, nitroalkanes containing phenyl, functionalized phenyl, and thiophene were smoothly transformed to the corresponding oximes **2a**–**2d** (Scheme 3). The reaction tolerated a substitution at the α-position next to the nitro group. The corresponding oximes **2e** and **2f** bearing methyl and hydroxyl groups at the α-position were isolated in good chemical yields. As demonstrated in the synthesis of unfunctionalized acyclic and cyclic oximes **2g** and **2h,** the discovered reaction conditions were suitable even for secondary nitroalkanes. Once the method was verified on structurally relatively simple substrates, we contemplated testing it on more complex and functionalized molecules. For this purpose, we selected a set of decorated nitropiperidinones accessed via the multicomponent nitro-Mannich reaction/lactamization cascade discovered by Jain and Mühlstädt.[20] Spirocyclic functionalized nitropiperidinones reacted under standard conditions within hours and yielded a set of spirocyclic oximes **2i**–**2k**. We consider the synthesis of oxime **2k** to be especially valuable, where both the internal alkyne and furane substituent remained intact during the photochemical reaction.

We speculated that a structural tuning of the single-electron reductant (DIPA) might allow for more extensive reduction of the nitro group.

Simultaneously, the SET process of the reductant should generate *in situ* a more reactive electrophilic species capable of

Scheme 3. Photochemical Synthesis of Oximes



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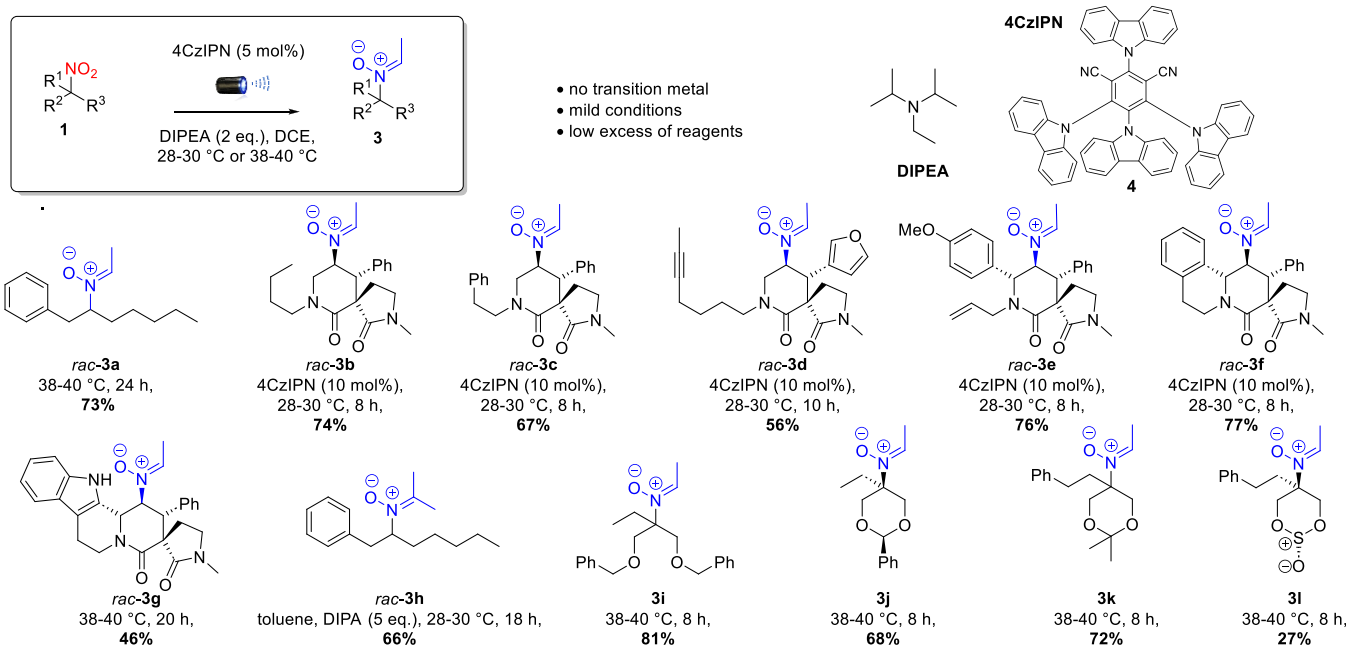
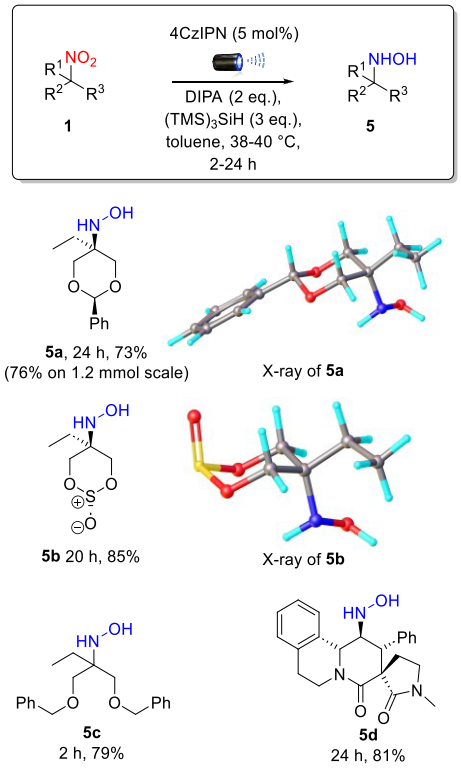
Scheme 4. Photochemical Synthesis of Nitrones

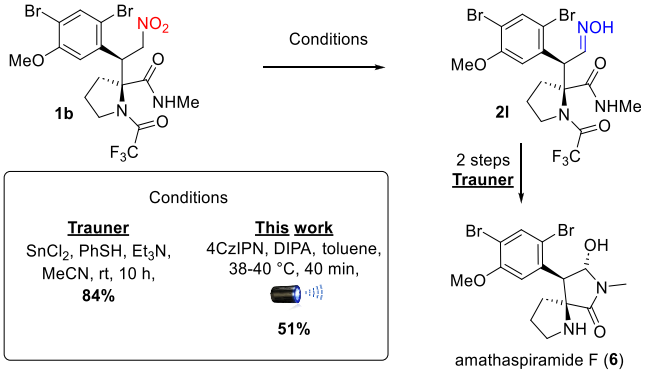


Scheme 5. Photochemical Synthesis of Hydroxylamines[a]



[a]Compounds **5a**, **5b**, and **5d** were isolated as single diastereomers.

Scheme 6. Formal Synthesis of Amathaspiramide F (6)



reacting with the product of the nitroalkane reduction. Thus, targeting a transformation of nitroalkane **1** to nitrone **3**, we replaced DIPA with DIPEA in the established set of reagents (Scheme 4). Indeed, this subtle change in the structure of the redox-active amine had an anticipated impact on the course of the reaction. The reaction of an acyclic unfunctionalized nitroalkane with DIPEA yielded nitrone **3a** in good chemical yield. Having established a proof of concept for the photochemical, metal-free transformation of nitroalkane **1** to nitrones **3**, we investigated the applicability of the reaction. Again, a set of heavily functionalized nitropiperidinones was selected as substrates (Scheme 4). The reaction proceeded smoothly within hours at ambient or slightly elevated temperatures, providing nitrones **3** in good to moderate yields. Most of the tested nitropiperidinones successfully underwent the transformation and afforded functionalized nitrones **3b**−**3g** (Scheme 4).[21] Noteworthy is the tolerance of the methodology toward important functional groups and heterocycles. Thus, an internal alkyne, substituted furan, PMP group, tetrahydroisoquinoline, and tetrahydrocarboline remained intact in the isolated nitrones **3d**−**3g**. During the initial optimization process, we encountered a unique formation of isopropylidene nitrone **3h** when the reaction was performed in toluene instead of DCE, and DIPA was used instead of DIPEA. Due to our limited effort to prepare isopropylidene nitrones from other substrates, **3h** remains only a rare, substrate-specific example in our initial disclosure. On the other hand, nitrone **3h** represents a promising lead for future investigation toward nitrones bearing an extended alkylidene chain on the nitrogen atom.

The method's scope was further extended when several tertiary nitroalkanes were confirmed as suitable substrates for

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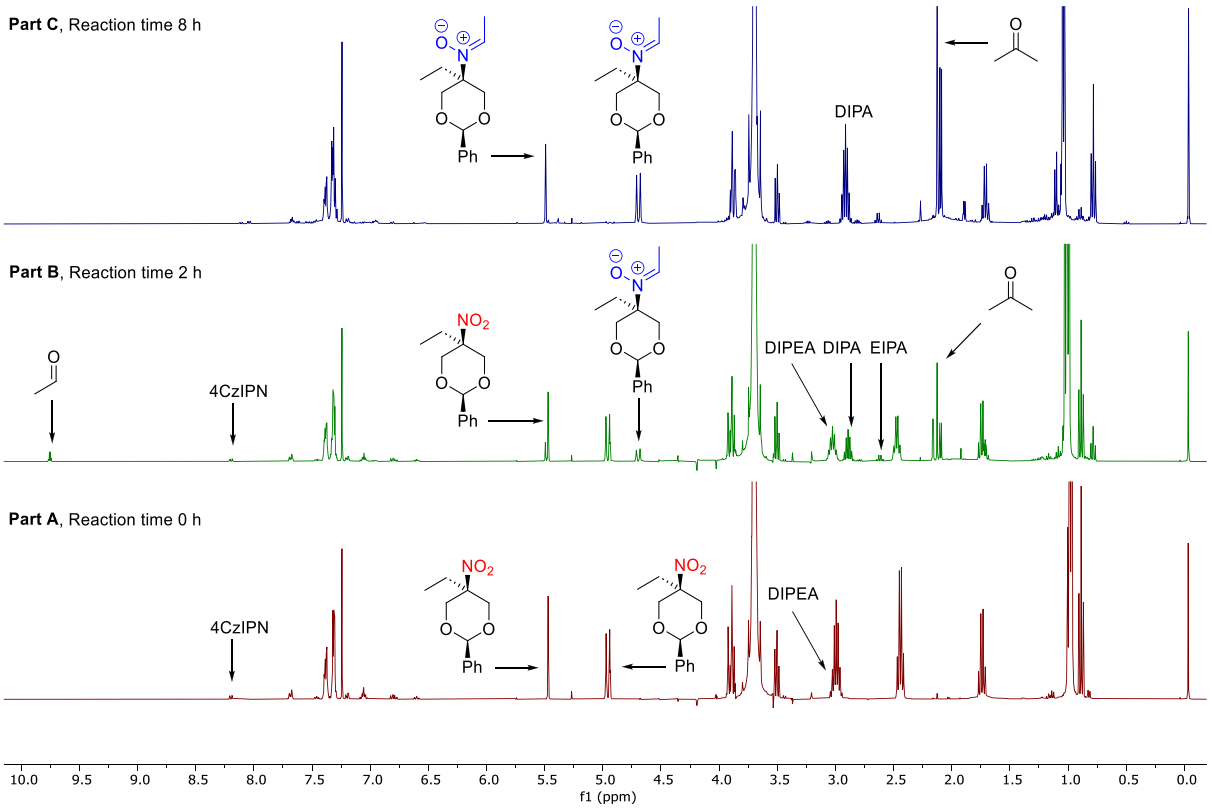
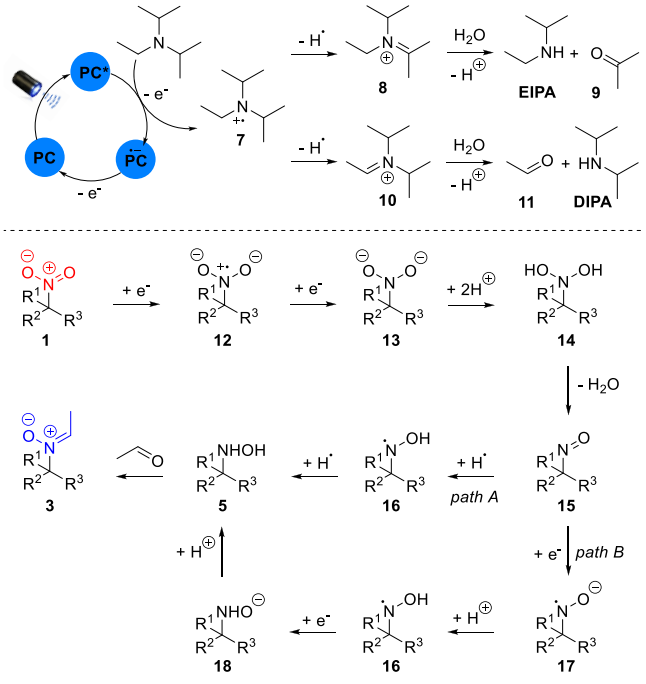


Figure 1. ^{1}H NMR spectra of the reaction mixture during transformation of nitroalkane (1 equiv, 0.2 mmol) to nitrone **3j** using DIPEA (2 equiv) and 4CzIPN (0.05 equiv). The reaction was performed in DCE (0.2 M solution). DIPEA, diisopropylethylamine; DIPA, diisopropylamine; EIPA, ethylisopropylamine; DCE, 1,2-dichloroethane. Only key signals of some of the present components are highlighted.

Scheme 7. Proposed Mechanism of Nitrone 3 Formation



nitrone formation. Acyclic and cyclic nitrone **3i**–**3l** were isolated after convenient 8 h-long reactions.

In this series of new compounds, the nitrone **3l** stands out as an important example highlighting tolerance toward reactive sulfite. Having established access to oximes and nitrones, we assumed that a process leading to hydroxylamines[22] was also plausible.

Our idea was based on the hypothesis that hydroxylamines and an iminium ion are formed due to photochemical redox processes (see Scheme 7 for a mechanistic proposal). If the reactive electrophile (iminium) were reduced fast enough, the process would not produce nitrone, and hydroxylamine should become the primary product instead. This hypothesis led us to add $(TMS)_3SiH$ as a readily accessible and popular reductant to the standard set of reagents (4CzIPN, DIPA, and solvent). Although the exact mechanism of the reduction requires further studies, we were able to prove the concept on a small number of tertiary and secondary nitroalkanes by preparing hydroxylamines **5a**–**5d** (Scheme 5). The structure of **5a** and **5b** and the relative configuration of substituents was unambiguously confirmed by single-crystal X-ray analysis.[18] Encouraged by the development, we decided to scrutinize one of the novel, user-friendly methodologies and perform a more challenging test in the total synthesis of natural products.

Arguably, the utilization of the basic amines and the reductive nature of the process might be harmful to base-labile functional groups and substituents prone to reduction. Therefore, we selected a step in a total synthesis of natural products employing a base-labile protective group and a reduction-sensitive functional group.

The stereoselective reduction of nitroalkane **1b** to oxime **2l** was crucial in Trauner's elegant total synthesis of amathaspiramide F (**6**) (Scheme 6).[23] To achieve the necessary formation of oxime **2l** from precursor **1b**, Trauner utilized a combination of thiophenol and anhydrous tin chloride in acetonitrile. After a 10 h reaction at room temperature, the desired oxime **2l** was

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obtained in an excellent yield, and the total synthesis was then completed in just two more steps. The presence of two halogen substituents in a substrate prone to photochemical hydrodehalogenation[24] and the base-labile trifluoroacetyl protective group made molecule **1b** a suitable candidate for testing the applicability of our method. To our delight, nitroalkane **1b** underwent the desired transformation to oxime **2l** within 40 min, and the oxime was isolated in 51% yield as a single isomer. By achieving the formal synthesis of amathaspiramide F (**6**), we have demonstrated the synthetic utility of the method in a programmed, target-oriented synthesis.

To gain basic insight into the mechanism, we followed the formation of nitrone **3j** from nitroalkane by ^{1}H NMR (Figure 1). To avoid unnecessary interference with the reaction mixture and possible undesired chemical reactions during a workup, samples of the homogeneous reaction mixture were taken in specific time intervals and then, after being diluted with $CDCl_3$, directly analyzed by ^{1}H NMR. Such an approach allowed us to observe even volatile intermediates and side products and collect precious information about the composition of the reaction mixtures. In 0 h, before exposure to blue light irradiation, the NMR analysis confirmed that all introduced components were present. Thus, the presence of the nitroalkane, catalyst 4CzIPN (**4**), reductant DIPEA, and solvent DCE were positively confirmed (Figure 1, part A). Within 2 h of exposure to blue light, the composition of the mixture dramatically changed and became more complex (Figure 1, part B). Apart from the starting materials and catalyst, desired products **3j**, acetone (**9**), acetaldehyde (**11**), and DIPA and EIPA (ethylisopropylamine) were present. Analysis after 8 h (Figure 1, part C) confirmed complete consumption of the nitroalkane and formation of the desired nitrone **3j**. Based on the observed progress of the reaction, previously suggested mechanisms of photochemical formation of nitrones and oximes,[15] and generally accepted mechanism of photochemical reactions with 4CzIPN,[19] we propose the following mechanism for the formation of nitrones **3** (Scheme 7).

After visible-light stimulation, the photocatalyst **4** enters the excited state when it receives an electron from DIPEA and forms the anion radical $PC^{\bullet-}$. Then, this electron is transferred into a nitro group, and the catalyst returns to the ground state. After the initial electron transfer, DIPEA forms cation radical **7**, which, upon losing hydrogen atoms, forms either iminium ion **8** or **10**. These highly reactive intermediates undergo hydrolysis, forming acetone (**9**) and acetaldehyde (**11**) alongside EIPA and DIPA. The nitroalkane serves as an electron acceptor and, after receiving two electrons, forms dianion **13**. Consequently, double protonation and dehydration enable the formation of nitroso compound **15**. This reactive intermediate is further reduced to hydroxylamine **5** by two HATs. The final stage in the formation of nitrone **3** involves a condensation of *in situ*-formed hydroxylamine **5** and acetaldehyde (**11**). An alternative SET and proton transfer mechanism instead of HAT might operate in some of the depicted steps (Scheme 7, path B).[25]

In conclusion, this paper describes a visible-light-induced, organocatalyzed transformation of nitroalkanes to three different types of organic molecules: oximes, nitrones, and hydroxylamines. The metal-free methodologies generally operate under mild reaction conditions with low catalyst loading and low excess of reductants (amines and $(TMS)_3SiH$). The described methodologies are usually broad in scope and tolerate multiple functional groups and heterocycles. The applicability and high tolerance toward reactive functional groups were demonstrated in the formal synthesis of the natural product amathaspiramide F. With the help of the performed NMR study, some reactive intermediates were identified, and a plausible reaction mechanism was proposed. We have observed that a subtle change of reaction conditions had a dramatic impact on the structure of isolated products. Therefore, further advances in the photochemistry of nitroalkanes can be anticipated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c10041.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

Crystallographic data of compounds (CIF)

Accession Codes

CCDC 2302280 and 2302281 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(16) In due course, further visible-light-promoted photochemical transformations of nitroalkanes will be disclosed.

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