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The Photocatalyzed Aza-Henry Reaction of *N*-Aryltetrahydroisoquinolines – Comprehensive Mechanism, $H^{\bullet}$- versus H^{+}-Abstraction and Background Reactions

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KEYWORDS photoredox catalysis, NMR study, reaction mechanism, C-H functionalization, oxidative coupling

ABSTRACT: The cross-dehydrogenative coupling (CDC) reaction of *N*-aryltetrahydroisoquinolines (THIQ) is one of the most exploited photocatalytic transformation and a test reaction for an exceptional variety of catalysts. However, its mechanism remained unclear concerning involved intermediates, reactive pathways of the amine radical cation and the influence of oxygen and the light source. Therefore, NMR-, ESR- and synthetic methods were combined to provide a comprehensive picture of the reaction mechanism using $Ru(bpy)_3Cl_2$ as a photocatalyst under aerobic and anaerobic conditions. The reaction profiles and involved intermediates were monitored and analyzed by NMR spectroscopy. Several intermediates contributing to product formation were identified, the iminium ion, the hydroperoxide and dimer of THIQ, and a new ring opened intermediate, cleaved at the benzylic C-N bond. Mechanistic evidence is given that under anaerobic conditions preferentially the α-amino radical is formed by deprotonation, in contrast to the formation of iminium ions via $H^{\bullet}$-abstraction in the presence of oxygen. Further, the light-induced background reaction in the absence of the catalyst was studied in detail, revealing that the product formation rate is correlated to the intensity and wavelength of the light source and that oxygen is essential for an efficient conversion. The reaction rate and efficiency is comparable to previously reported photocatalytic systems, performed under aerobic conditions in combination with intense blue light sources. Thus, the multitude of reaction parameters investigated reveals the preference for hydrogen atom or proton abstraction in photoreactions and allows to assess the influence of experimental conditions on the mechanistic pathways.

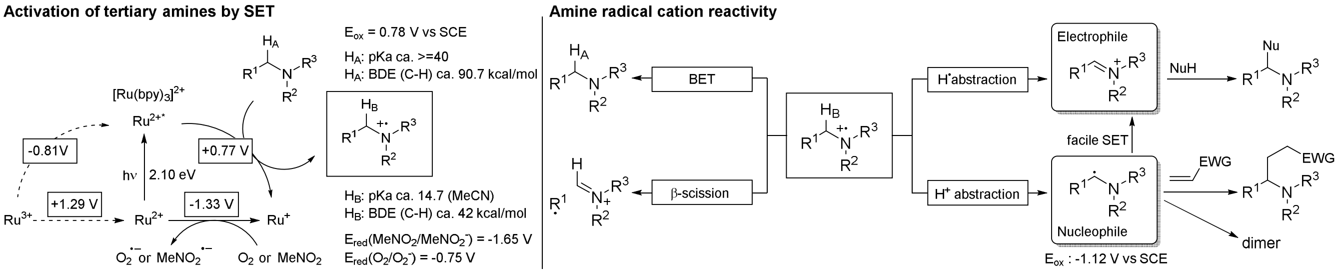
INTRODUCTION

The direct and efficient transformation of C-H groups into C-C bonds under mild reaction conditions is of high interest in organic synthesis.[1–3] In the last decade, visible-light photoredox catalysis developed into a powerful method for the activation of C-H bonds under mild conditions.[4–16] In this context, the visible light photocatalytic C-H functionalization of tertiary amines adjacent to nitrogen atoms became a valuable extension of transition-metal-catalyzed,[17] electrochemical[18–20] and DDQ-mediated reactions,[21–24] and for UV-light-induced photochemical approaches.[25–27] Since in 2010 Stephenson *et al.*[28] published an efficient concept for the visible-light mediated photocatalytic aza-Henry reaction of nitromethane with *N*-aryl-tetrahydroisoquinolines (THIQ) using air as terminal oxidant several synthetic applications emerged. [7,11,15,16] The aza-Henry reaction of THIQ represents one of the most exploited photocatalytic transformations and an exceptional variety of visible-light absorbing photocatalysts has been applied for the CDC of the THIQ substrate with nitromethane: metal complexes containing ruthenium,[29,30] iridium,[28,31] palladium,[32] platinum,[33] cobalt[34] or copper,[35] organic dyes,[36–43] and heterogeneous photocatalysts like TiO_2,[44] Cu_2O,[45] CdS,[46] or mpg-C_3N_4,[47] metal-organic frameworks,[48,49] or cross-linked polymers.[50–54]

Despite the plethora of different catalytic systems, a mechanistic overlap exists in the initial electron transfer step from the lone pair of the amine substrate to the photoexcited catalyst generating an amine radical cation.[55] Mechanistic evidence was given by early studies of Whitten *et al.* by luminescence quenching of the frequently used photocatalyst $Ru(bpy)_3Cl_2$ (tris(bipyridine) ruthenium(II)chloride hexahydrate) with triethylamine. [56,57] Recent spectroscopic investigations confirmed a reductive quenching of the photoexcited state of the respective catalyst by THIQ substrates for a series of catalytic systems described above.[28,37,38,58,59] In addition, Wu *et al.* could prove the existence of the THIQ **1**$^{+\bullet}$ by transient absorption spectroscopy in combination with the spectroelectrochemical absorption spectrum of THIQ **1**$^{+\bullet}$.[58,60]

The amine radical cation provides unique properties for the α-C-H functionalization. Compared with the neutral amine the bond dissociation energy and the pKa value[61] are reduced significantly, which opens different mechanistic pathways dependent on the reaction conditions (Scheme 1).[11,15]

Scheme 1. Activation of tertiary amines by photoredox catalysis and amine radical cation modes of reactivity. Values for the bond dissociation energy (BDE) and oxidation potentials (vs. SCE) are given for triethylamine (R^1=-CH$_3$, R^2=R^3= -CH$_2$-CH$_3$). (SET = single electron transfer, BET = back electron transfer)[11,15,56,57,62–66]

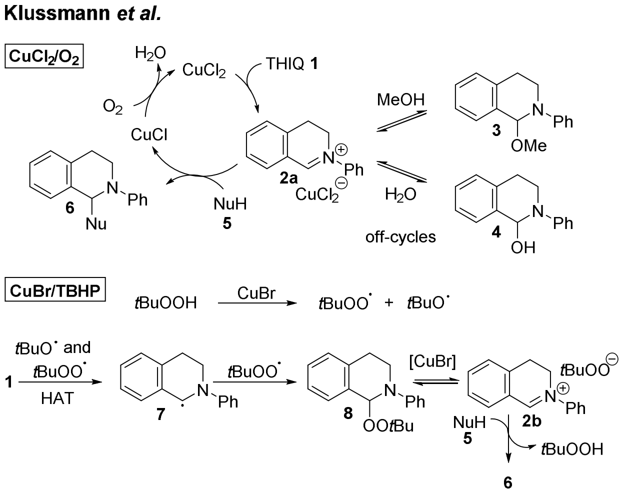


Oxidative coupling reactions of tertiary amines are generally supposed to proceed via the electrophilic iminium ion, which is formed from the amino radical cation and can be intercepted by nucleophiles. The intermediacy of iminium ions was confirmed for transition-metal[67] and DDQ-catalyzed reactions,[22] as well as for photocatalyzed systems using BrCCl$_3$ as terminal oxidant.[29,68]

However, for the photocatalytic aza-Henry reaction mechanistic evidence is missing, if the iminium ion is directly formed via hydrogen atom abstraction from the amine radical cation or by deprotonation generating the α-amino radical followed by a subsequent electron transfer. Investigations of the influence of the terminal oxidant on those reaction pathways are lacking. Furthermore, the question remains, whether the iminium species **2** is the only intermediate, which contributes to the product formation or if other mechanistic pathways are operating. In some cases intermediates have been observed, but their role within the catalytic cycle remained unclear.[37,41] The existence of the α-amino radical of THIQ **7** was proven by Xiao and Lu for the α-allylation of amines in a dual catalytic approach, by ESR spectroscopy.[69] Whitten *et al.* detected the respective α-amino radical of triethylamine with a spin trap by ESR spectroscopy.[57]

The question of reactive key intermediates and the active pathways also remains a topic of debate for the related transition-metal catalyzed reaction. Previous studies of Murahashi, Li, Che, Klussmann and Doyle led to divergent mechanistic models.[70] Mechanistic studies of Klussmann *et al.* demonstrated that varying the oxidant/catalyst pair from CuCl$_2$·2H$_2$O/O$_2$ to CuBr/*tert*-butyl hydroperoxide (TBHP) in the oxidative coupling of THIQ **1** lead to major changes in the catalytic cycle (Scheme 2).[71–73] For CuCl$_2$·2H$_2$O/O$_2$ the iminium ion **2a** was found as the key intermediate, which originate from a direct oxidation of THIQ **1** by the Cu-catalyst. The role of oxygen was limited to the reoxidation of the catalyst. The solvent methanol stabilized the iminium ion **2a** by formation of stable reservoirs in an off-cycle equilibrium,[74] which provides the active iminium species **2a** in a controlled fashion. The roles of the oxidant and the catalyst change for the CuBr/TBHP system. CuBr converts TBHP in a Kharasch type reaction to the *tert*-butyl peroxy radical and the respective *tert*-butyloxy radical, which activates THIQ **1** by a hydrogen atom transfer (HAT). Radical recombination formed the THIQ peroxy species **8** as a true intermediate, which is converted to the iminium ion **2b** assisted by CuBr acting as a Lewis acid.

Scheme 2. Mechanistic proposals of Klussmann *et al.* for the Cu-catalyzed oxidative coupling of THIQ 1 using oxygen or *tert*-butyl hydroperoxide (TBHP) as oxidant.[71–73]



In light of transition metal-catalyzed studies the question arises, if in the photocatalyzed system similar off-cycle equilibria are operative and to what extent the terminal oxidant influences the mechanism. Notwithstanding the variety of elaborated spectroscopic and mechanistic studies, that have been performed under different conditions – all dealing with photocatalyzed CDC reactions of *N*-arylamines and with the aza-Henry reaction in particular – to the best of our knowledge no comprehensive study regarding the pathways of the amine radical cation and involved intermediate species with respect to the terminal oxidant of the photocatalyzed reaction of THIQ **1** with nitromethane **5a** has been reported so far.

Herein, we present our mechanistic study of the CDC reaction of THIQ **1** with nitromethane investigating the reaction profiles, (elusive) intermediates and the necessity of the photocatalyst, together with the role of oxygen and light in different reaction setups by NMR and ESR spectroscopy. Furthermore, the role of the reaction intermediates within the catalytic cycle is discussed and background reactions are investigated. Based on our results we divided the reaction into different pathways, which are presented in detail.

RESULTS AND DISCUSSION

In order to elucidate the reactive pathway ($H^{\bullet}$- vs. H^{+}-abstraction) of the photocatalytically generated amine radical cation and the involved intermediates dependent on the reaction conditions, we systematically studied different reaction parameters. The aza-Henry reaction stands out from the photocatalyzed CDC reactions as the nucleophile nitromethane itself is feasible of regenerating the catalyst and can act as a terminal oxidant albeit with a reduced reaction rate compared to oxygen. Thus, no external terminal oxidant is required (Scheme 1).[28,37,41] This enabled us to investigate the role of oxygen separately with respect to $H^{\bullet}$- vs. H^{+}- abstraction pathways. First, the influence of the terminal oxidant – in particular the presence or absence of oxygen – on the catalytic cycle and the correlation to involved intermediate species and the reaction profiles were investigated by NMR spectroscopy.

Setup The control of the oxygen concentration was accomplished by a variation of the reaction setups, which are depicted schematically in Figure 1 and are referred to as *in situ* and *ex situ*. Almost anaerobic conditions were achieved with the *in situ* technique developed by Feldmeier *et al.*,[75] which allows the illumination of the sample with an LED inside the spectrometer. This setup provides a unique possibility monitoring reaction profiles as well as for the detection and characterization of elusive intermediates and products of photochemical reactions. However, due to the conditions of the setup (closed system, no boundary layer to air, only diffusion) the corresponding aerobic sample cannot be monitored with this technique. Therefore, the aerobic sample was irradiated open to air outside of the spectrometer (*ex situ* strategy). While the reaction proceeded, aliquot samples were taken and the reaction profile was monitored by NMR spectroscopy.

Aerobic and Anaerobic Reaction Profiles For both kinetics, THIQ **1** (200 mM) and 1 mol% of $Ru(bpy)_3Cl_2$ in deuterated nitromethane-d3 **5a** were irradiated with blue LEDs (for specification see SI) at room temperature (Figure 1a,b). The nucleophile nitromethane was used as solvent. The *in situ* experiment was repeated with 50 mM THIQ **1** and an increased catalyst loading of 10 mol% of $Ru(bpy)_3Cl_2$ (Figure 1c). The intermediates THIQ dimer **9** and THIQ-nitrone **10** showed the same profiles and relative intermediate ratios, but with 10 mol% of $Ru(bpy)_3Cl_2$ a reduced reaction time and an increased absolute amount of intermediates was observed (Figure 1b,c). To facilitate the assignment and to reduce measurement time the following *in situ* experiments were conducted at these conditions.

Under anaerobic conditions (*in situ*), two main intermediates were observed, the dimerization product **9** of the THIQ substrate and a THIQ-nitrone **10** cleaved at the benzylic C-N bond (for NMR data and assignment see SI). The dimer **9** and the ring opened intermediate **10** could also be observed as intermediates for the aerobic sample, but the main intermediate constitutes the THIQ hydroperoxide **11**, reaching a maximum of 20%. All detected THIQ species showed maxima in their reaction profile under photocatalytic conditions, indicating their role as intermediate or as off-cycle resting state in the reaction mechanism. The ^{1}H reaction profiles of the dimer **9** and ring opened intermediate **10** of the *ex situ* illuminated reaction basically follow the same pattern as the reaction under *in situ* conditions.

In the initial minutes of the *ex situ* and *in situ* reaction THIQ iminium ion **2**[76] was detected. In addition, traces of THIQ-OOH **11** were observed in the *in situ* ^{1}H NMR reaction profile due to residual oxygen. However, these species are not depicted in Figure 1a-1c because of concentrations below 2% and fast decrease within 30 minutes. For NMR spectra under *in situ* conditions showing all detected THIQ species, please refer to Figure 3 and SI.

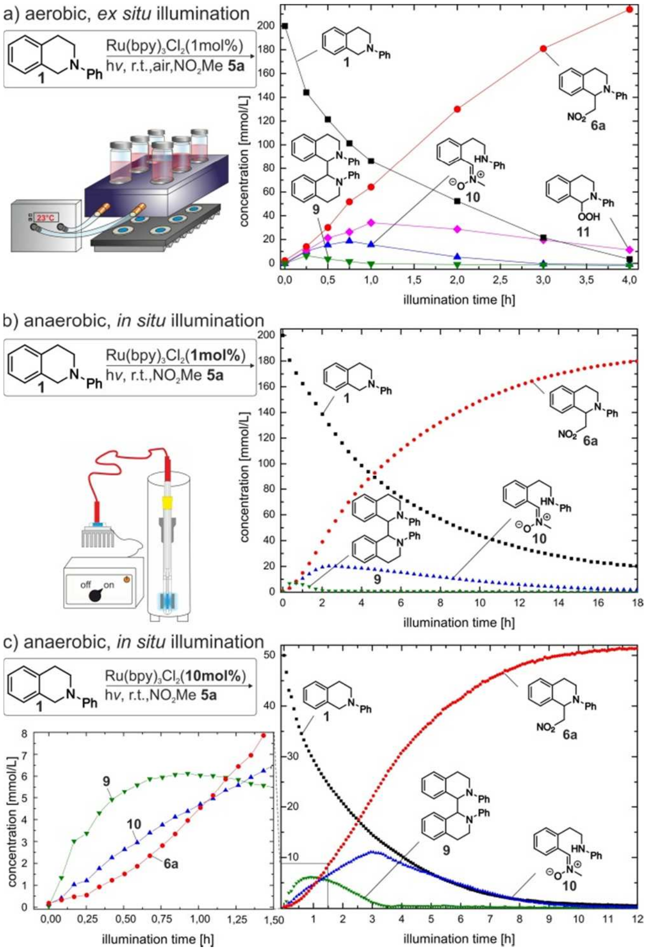


Figure 1. Reaction conditions, setups and ^{1}H NMR kinetics of the photocatalytic coupling reaction of THIQ **1** and nitromethane-d3 **5a** shown for aerobic *ex situ* (a) and anaerobic *in situ* illumination with 1 mol% (b) and 10 mol% (c) catalyst loading.

The aerobic reaction proceeds significantly faster, which is in agreement with literature reports.[28,37,41] After 3 h, 90% of product **6a** were obtained compared to 18 h of reaction time in the *in situ* system. This indicates that oxygen plays an important role in the reaction process, either by accelerating the efficiency of the catalyst turnover or by involvement in follow up reactions of the amine radical cation or by a combination of both.

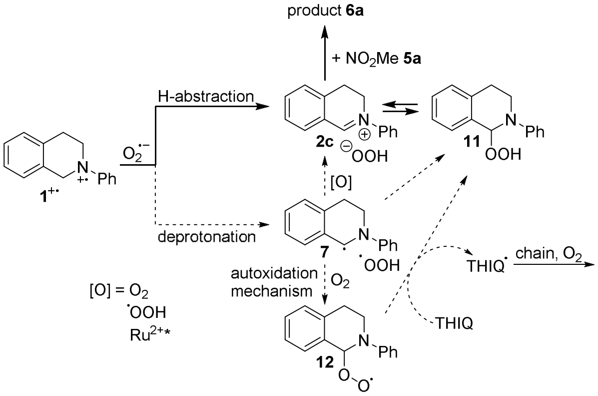
THIQ starting material **1** decreased exponentially under aerobic and anaerobic conditions. While the product curve showed a linear increase for the aerobic (*ex situ*) experiment (for additional proof refer to SI), a sigmoidal shape was obtained for the *in situ* measurement. The latter indicates the product formation from (transient) species, which are accumulated during the reaction. A possible explanation for this sigmoidal reaction progression would be that the nitromethane nucleophile requires activation to the tautomeric, but thermodynamically unfavorable aci-form for the nucleophilic attack.[77–81] Klussmann *et al.* reported increasing pH values with reaction progress.[72] Higher pH values result in an increased formation of the reactive deprotonated aci-form of nitromethane and finally lead to an increased product formation rate. This would be in good accordance with the observed sigmoidal curve of product formation. However, if the delayed product formation can exclusively be ascribed to the activation of nitromethane the aerobic and the dimer **9** kinetic (see Figure 2c and text below) should also exhibit a sigmoidal shape. As for both of them a linear product formation rate was observed, we explain the disparity of the curves by different underlying reaction mechanisms.

Intermediate Formation Mechanisms

THIQ Dimer 9 The intermediate providing the first maximum during the course of the reaction is the dimerization product **9** of THIQ, which is commonly accepted to occur via a radical pathway by homocoupling of two amine radicals **7**.[82,83] König *et al.* developed a method for the radical homocoupling of THIQ on polycrystalline CdS.[46] The formation of the THIQ dimer **9** gives evidence, that the deprotonation pathway proceeds under aerobic and anaerobic conditions (see Scheme 1). This is remarkable as amino radicals are very strong reducing agent and are thus prone to oxidation. Even molecular oxygen ($E_{red}(O_2/O_2^{\bullet-}) = -0.75$ V vs. SCE)[65] is able to oxidize α-amino radicals ($E_{ox}(Et_2N\text{-}^{\bullet}CHCH_3/\ Et_2N^{+}{=}CHCH_3) = -1.12$ V vs. SCE) thermodynamically.[63] Therefore, synthetic applications of the α-amino radical are conducted under inert atmosphere conditions e.g. the addition to electron-deficient alkenes.[82–84] However, Jiang and coworkers recently published a radical cascade reaction between the α-amino radical of THIQ **7** and *N*-itaconimides under aerobic conditions, which is in line with our observations.[85–88]

THIQ-OOH 11 The elucidation of the mechanistic pathway for the formation of THIQ-OOH **11** is more challenging. The intermediate species THIQ-OOH **11** was anticipated by Wu *et al.*, but no full characterization was provided.[37] The formation of the THIQ hydroperoxide species **11** requires an incorporation of oxygen. Based on the amine radical cation of THIQ $\mathbf{1}^{+\bullet}$ different mechanistic pathways are possible (see Scheme 3). As discussed above, the amine radical cation can undergo hydrogen atom abstraction or deprotonation. Superoxide radical anion $O_2^{\bullet-}$, which is formed after regeneration of the photocatalyst, can initiate both pathways as $O_2^{\bullet-}$ is reported in literature as $H^{\bullet}$- and H^{+}-acceptor.[65,89–98] The intermediate superoxide radical anion was confirmed by ESR spectroscopy after trapping with the radical probe DMPO (see SI). The attributed role of the superoxide radical anion varies also within the suggested mechanism reported for the aza-Henry reaction.[28,37,99,100] The product of the $H^{\bullet}$-abstraction pathway is the iminium ion **2**, which can be intercepted by the generated OOH^{-} to form THIQ-OOH **11**. The hydroperoxide is in a pH-dependent equilibrium with the iminium species **2**, which was shown by Klussmann *et al.* for the THIQ-iminium **2b**/THIQ-*tert*-butyl hydroperoxide **8** couple (Scheme 2).[72] Nevertheless, also the amino radical **7**, formed via the deprotonation pathway, could deliver the respective amino peroxide **11** by a radical coupling with •OOH.[101] Furthermore, it is known that α-amino radicals **7** can react very fast with atmospheric molecular oxygen in an autoxidation type mechanism (see Scheme 3 and SI).[73,102–105] The formed oxygen centered peroxyl radical adduct **12** can provide the THIQ-OOH **11** in a chain propagation step together with another amino radical **7**.

Scheme 3. Possible pathways for the formation of THIQ hydroperoxide 11.

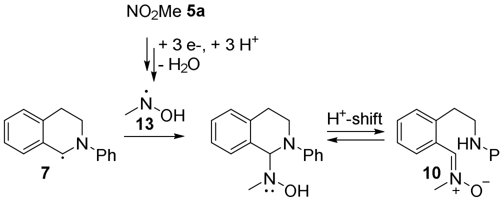


To probe if THIQ-OOH **11** is formed via the iminium **2** ($H^{\bullet}$-abstraction pathway) or the amino radical **7** (deprotonation pathway) the reaction profiles were investigated in the presence of the radical inhibitor TEMPO.

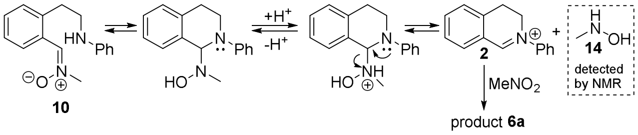
The addition of TEMPO slowed down the aerobic reaction (for details see SI). However, due to extensive line broadening – indicating the presence of radical species – no reliable reaction yields could be achieved. The reaction profiles elucidate that the formation of the dimer **9** and the nitrone **10** are completely suppressed, whereas the THIQ-OOH **11** could be observed throughout the kinetic, increasing within the first hour of the reaction (for details see SI). This specific suppression of two intermediates strongly indicates that both the dimer **9** and the open intermediate **10** are formed via a radical pathway. The formation of THIQ-OOH intermediate **11** in the presence of TEMPO also corroborates the existence of an additional productive reaction pathway, not occurring via the amino radical **7**.[106] Based on these results we propose that the superoxide radical anion acts preferentially as a hydrogen atom acceptor leading to iminium ion **2c**. This hydrogen abstraction pathway was later supported by the detection of both iminium ion **2** and THIQ-OOH **11** in the photocatalyst free studies (see Effective Background Reaction with Light and Figure 5). We further suggest that THIQ hydroperoxide **11** is formed in an off-cycle equilibrium from the iminium ion **2c** (Scheme 3, bold line).

Ring opened Intermediate 10 The intermediate **10** is detected for the first time and only one previous publication anticipated a C-N cleavage within the route to product formation.[66] The mechanistic evidence for radical species involved in the formation of the ring opened intermediate **10** under aerobic conditions (see above) was corroborated by the addition of TEMPO under anaerobic conditions. Again, the reaction was slowed down and the formation of the dimer **9** and the open intermediate **10** were completely suppressed. Based on this observation in conjunction with the product structure determined by NMR (see SI) we propose a radical coupling between the α-amino radical **7** and a hydroxylamine radical **13** (Scheme 4). The formation of the hydroxylamine radical **13** is reported for a stepwise reduction of nitromethane by metal catalysts,[107] electrochemically[108] or via dissociation or disproportionation of nitromethane.[109] Here, the electrons come from the reoxidation of the photocatalyst (see Scheme 1 left). The initial strong formation of dimer **9** (see Figure 1c) supports this mechanistic proposal, since three electrons are required for the formation of one hydroxylamine radical **13**. Furthermore, we assume that the ring opened intermediate **10** is in a pH-dependent equilibrium with the reactive iminium species **2** and thus constitutes a true, productive intermediate (Scheme 5). This assumption is supported by a formation of *N*-methylhydroxylamine **14**, which was detected in the NMR spectra with progressing reaction (Scheme 5 and SI).[110]

Scheme 4. Proposed radical mechanism for the formation of the ring opened intermediate 10.



Scheme 5. Proposed reaction mechanism for the formation of the coupling product 6a and *N*-methylhydroxylamine 14 from the ring opened intermediate 10.

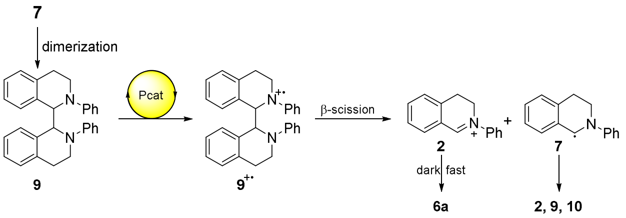


Light On-Off Studies and Identification of Productive Intermediates The role of the intermediates was further investigated by light on-off studies to address the question which intermediates are directly involved in the product formation and the influence of light for the transformation. Therefore, the intermediates were accumulated during an irradiation period (*in situ* and *ex situ*) followed by the measurement of the NMR reaction profiles in the dark (see Figure 2a,b). The reaction kinetic of the dark period for the *in situ* (anaerobic) light on-off study showed that the ring opened intermediate **10** is a direct precursor of the aza-Henry product **6a**. Even in the dark, the gradient of the product **6a** formation remains unchanged, as long as the intermediate **10** is present. After the intermediate **10** is fully consumed the rate of the product formation drops to zero. In contrast, the concentration of the dimer **9** is constant in the dark (Figure 2a).

The light on-off studies of the externally irradiated aerobic system (see Figure 2b) are in accordance with the *in situ* observation considering the behavior of the ring opened intermediate **10** and the dimer **9** in the dark. In addition, the hydroperoxide species **11** also contributes to the product formation in the absence of light. This is in agreement with Klussmann *et al.*; they observed a similar trend for the conversion of THIQ-OO^{t}Bu **8** to the product in the absence of the respective metal catalyst albeit with a reduced rate. This was explained by a Lewis acid activation by the CuBr catalyst (Scheme 2).[72] The accumulation of intermediates, which can be converted to the product in the dark is in line with the report of Wu *et al.* for the TBA-eosin Y catalyzed reaction of THIQ and nitromethane. They observed an increase in yield of the aza-Henry product from 75% to 92% when they continued stirring for 12 h in the dark after irradiation for 4 h. They assumed the intermediacy of THIQ-OOH **11**, but no structural proof was given.[37]

In both systems, the concentration of dimer **9** remains unchanged in the dark (see Figure 2a and 2b). However, the kinetic profile showed a reversible behavior under photocatalytic conditions without decomposition as the mass balance is almost 100% (see Figure 1c).

Scheme 6. Proposed mechanism for the photocatalytic C-C cleavage of dimer 9.



This observation incited us to investigate the influence of light on the reversibility of the dimer **9** formation. For that reason, the dimer **9** was prepared according to a literature-known procedure[46] and subjected to *in situ* NMR measurements. The illumination of dimer **9** in nitromethane-d3 **5a** only led to a slow product formation in the absence of the catalyst (see Figure 2c). The addition of $Ru(bpy)_3Cl_2$ (10 mol%) to the reaction mixture drastically increased the reaction rate and gave 80% of product **6a** after 2 h. The ring opened intermediate **10** was detected, but its formation was considerably delayed with respect to the product **6a** formation and only a maximum amount of 10% was reached (see Figure 2c). Based on the

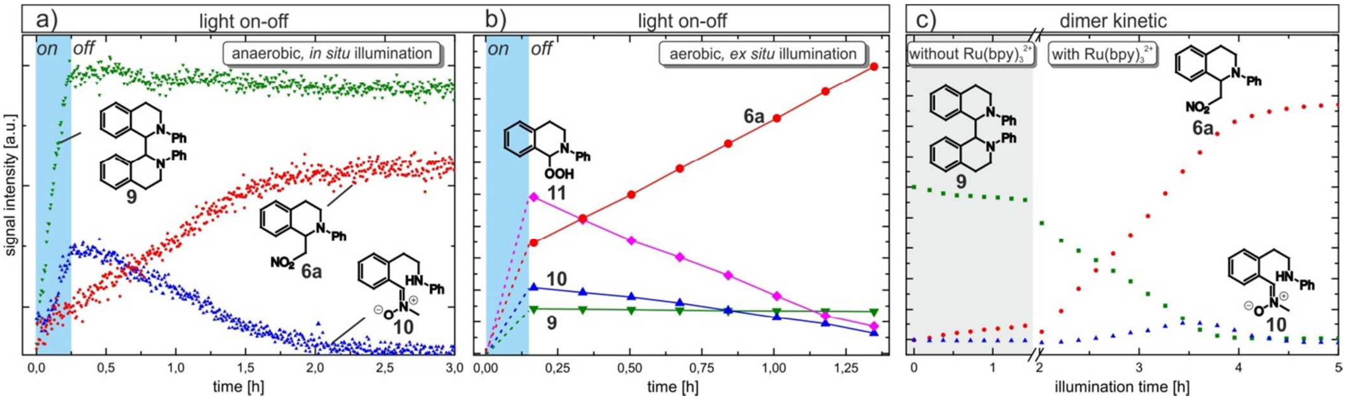


Figure 2. Product **6a** formation from intermediates **10** and **11** in the dark (a,b) and light and photocatalyst dependent product **6a** formation from THIQ dimer **9** (c). The ^{1}H NMR reaction profiles of the photocatalyzed CDC reaction of THIQ **1** and nitromethane **5a**, irradiated for 15 minutes (a) anaerob or (b) aerob were monitored regarding their contribution to the product formation **6a** in the dark. c) ^{1}H NMR kinetic of THIQ dimer **9** and nitromethane **5a** under continuous illumination with blue LEDs at 300 K in the absence and presence of $Ru(bpy)_3Cl_2$ as photocatalyst.

results we assume that the amino radical cation of the dimer **9**$^{+\cdot}$ is generated by an electron transfer to the catalyst, which can undergo homolytic C-C bond cleavage resulting in a α-amino radical **7** and the iminium ion **2** (Scheme 6).[111–113]

Remarkably, in contrast to the *in situ* kinetic no sigmoidal product formation curve was observed. Instead, a linear curve with a high product formation rate was detected (compare Figure 1c and Figure 2c). We ascribe the linear product formation rate to the iminium species **2**, irreversibly formed by β-scission of the dimer radical cation **9**$^{+\cdot}$. This observation gives further evidence that the sigmoidal shape and thus the delayed product formation under anaerobic conditions is not caused by the accumulation of the reactive aci-nitromethane species (see above). Furthermore, the differences in the initial product formation curves (sigmoidal vs. linear) of the *in situ* ^{1}H kinetic of the photocatalytic aza-Henry reaction (Figure 1c) with the photocatalytic dimer **9** cleavage (Figure 2c) rule out the direct formation of THIQ iminium **2** from THIQ **1** under anaerobic conditions. Based on these results the participation of the H$^{\cdot}$-abstraction pathway under anaerobic conditions is unlikely. Further support comes from the change of the sigmoidal shape of the curve to a linear slope at the maximum dimer **9** concentration of the *in situ* kinetic (Figure 1c). The offset between the maximum of the dimer **9** and the maximal slope of the product formation (Figure 1b,c) is due to the additional contribution of the ring opened intermediate **10**. The absence of the iminium ion **2** during the initial hour also excludes a fast oxidation of the α-amino radical **7** under *in situ* conditions. The α-amino radical is sufficiently stable to react under the applied conditions by radical recombination.

On the basis of the experimental results we propose that the dimer **9** is a productive intermediate and not an undesired byproduct for the iminium ion **2** generation, as described in literature[82]. In addition, these data indicate that the reduced nitromethane species MeNO2$^{\cdot-}$ solely functions as base and not as hydrogen atom acceptor.

In summary, the two terminal oxidants lead to different intermediate distributions and pathways. A radical pathway, opened by MeNO2$^{\cdot-}$, generates the amino radical **7**, a precursor of the intermediates **9** and **10**. After formation of a certain concentration of **9** and **10**, these intermediates were converted to product **6a** via the iminium ion **2**, leading to an increase in the reaction rate over time and thus to a sigmoidal product curve. Under anaerobic conditions this pathway is exclusively operating. In addition to the radical pathway an iminium pathway is opened by O2$^{\cdot-}$ under aerobic conditions. Besides the formation of **9** and **10**, the main intermediate now constitutes the THIQ-OOH **11** in equilibrium with iminium ion **2**, latter directly resulting from the radical cation **1**$^{+\cdot}$ not taking the detour via **9** and **10**. The dominance of the iminium pathway is reflected in the linear product formation and the accelerated reaction rate.

Slow Background Reaction in the Dark After mixing THIQ **1**, $Ru(bpy)_3Cl_2$ (10 mol%) and nitromethane **5a** under *in situ* conditions we observed the THIQ iminium ion **2** accompanied by a delayed formation of the THIQ hydroperoxide species **11**.[114] The first ten minutes of the photocatalyzed reaction are depicted by a row of stacked proton spectra in Figure 3. After initiation of the reaction by visible light, dimer **9** arises followed by product **6a** and the ring opened THIQ species **10**. The reaction profiles of the iminium THIQ **2** and THIQ hydroperoxide **11** are correlated, which indicates that the iminium ion **2** is converted into the amino hydroperoxide species **11** directly.

Surprisingly, the maximum amount of THIQ iminium ion **2** is already generated in the dark (indicated with 0 s of irradiation in Figure 3) and rapidly decreases below the detection limit after irradiation.

Control measurements showed that the initial formation of the iminium ion **2** upon mixing THIQ **1** with nitromethane **5a** in the dark is independent of the presence or absence of photocatalyst or air. Up to 2% of THIQ iminium ion **2** were already detected in the dark, even if the sample is prepared directly at the spectrometer (elapsed time before measurement 60-90 s). However, the efficiency of the background reaction in the dark is low, as only negligible yields were obtained under anaerobic conditions in the presence of 10 mol% Ru(bpy)$_3^{2+}$ (6% after 18 h) and without catalyst in air (2% after 20 h). Therefore, we investigated the origin of the background reaction in the dark. Upon mixing the pure white THIQ **1** and colorless nitromethane **5a** a color change to fade pale yellow was observed. The THIQ iminium **2** as well as the color change could not be detected when nitromethane was substituted by CDCl$_3$, DMF-d7 or MeCN-d3. The formation does not require light, air or a photocatalyst, but nitromethane **5a**. Therefore, we assume a direct interaction of nitromethane **5a** and THIQ **1** in form of redox or acid-base equilibria. However, a comparison of the pKa values [115] and measured redox potentials by cyclic voltammetry[116] (for detailed considerations see SI) show that the equilibria reside strongly on the side of the neutral species explaining the ineffectiveness of the background reaction.

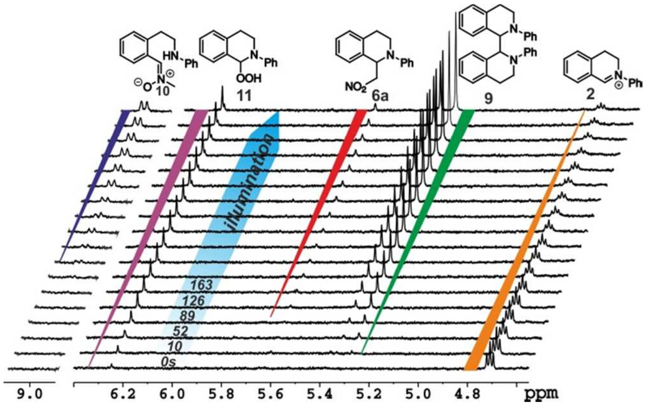


Figure 3. The formation of iminium ion **2** in the dark and subsequent formation of THIQ-OOH **11** is shown by a row of stacked ^{1}H-NMR spectra (initial 10 min, 50 mM THIQ **1** and nitromethane **5a** with Ru(bpy)$_3$Cl$_2$ (10 mol%) in nitromethane-d$_3$ under continuous irradiation with blue LEDs at 300 K).

Effective Background Reaction with Light More control experiments addressing the light-induced background reaction were performed. Surprisingly, reactions without photocatalyst but under air in combination with an intense visible light source (blue LEDs) gave 80% of the coupling product after 24 h.

Stephenson *et al.* already reported a slow background reaction in the absence of the catalyst by irradiation with a fluorescent bulb, but prolonged reaction times were required. The product of the aza-Henry reaction was obtained with 83% conversion after 180 h in contrast to 92% yield after 10 h when Ir(ppy)$_2$(dtbbpy)PF$_6$ was applied as photocatalyst.[28] However, we observed a remarkable increase of the reaction rate for the light-induced “background” reaction, by changing the irradiation setup to use high power LEDs with defined emission spectra, see Table 1. Upon mixing of the pure white crystalline THIQ **1** with nitromethane, a solution possessing a stable fade pale yellow color was obtained. We assume the formation of an electron donor acceptor (EDA) complex between THIQ **1** and nitromethane **5a**. Literature evidence is given by spectroscopic studies for similar systems. Andrabi *et al.*[117] proposed CT complexes of aromatic amines with nitromethane. They described the formation of weak 1:1 molecular CT complexes of nitromethane with different *N,N*-dialkylanilines (N,N-diethylaniline: λ_{CT} = 377 nm, K(25°C) = 0.31 l mol^{-1}), a structural motif, which is present in THIQs. The color change upon addition of tertiary amines to nitromethane was also reported by Constantinou *et al.*; they assigned it to the formation of charge transfer complexes.[118] For THIQ systems significant light-induced background reactions were detected in some cases.[68,85,119] Rovis and coworkers observed a high background reaction in the absence of catalyst for the α-acylation of THIQ with aldehydes using *m*-DNB (*m*-dinitrobenzene) as terminal oxidant. They propose the formation of an EDA complex between *m*-DNB and THIQ.[119] Zeitler *et al.* recently published a photocatalyst-free method for the α-C-H functionalization of THIQ; mechanistically they assume the involvement of EDA complexes between THIQ and BrCCl$_3$, which was added as terminal oxidant.[68]

When the reaction was carried out under an argon atmosphere only a low yield of the desired cross-coupling product **6a** was obtained (7% after 20 h). This shows, that oxygen is essential for the visible light induced aza-Henry reaction, in contrast to the photocatalyzed reaction. In order to elucidate the role of oxygen and the involved reactive oxygen species ESR spectroscopic measurements were performed.[120] DMPO (5,5-dimethyl-1-pyrroline-N-oxide) was employed as a probe for superoxide radical anion confirming the formation of O2$^{\cdot-}$ by the characteristic signal of the superoxide-DMPO adduct (Figure 4). Superoxide radical anion was exclusively formed upon irradiation with blue LEDs and the presence of both reaction partners (THIQ **1** and nitromethane **5a**). By exclusion of light or THIQ **1** no O2$^{\cdot-}$ was detected.

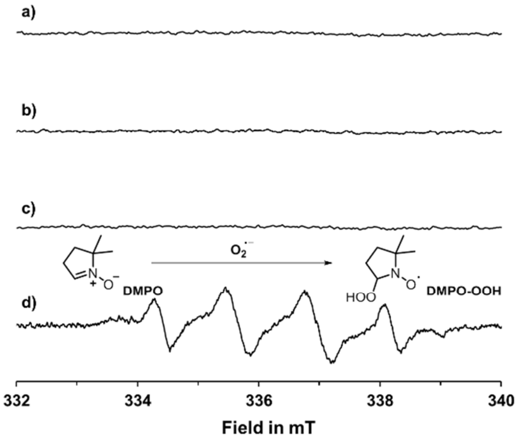


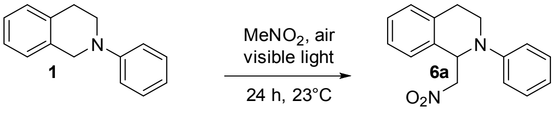
Figure 4. Detection of O2$^{\cdot-}$ using DMPO as radical trap by ESR. (a) and (b): ESR spectra of DMPO (2.0 x 10^{-2} molL^{-1}) in air-saturated nitromethane in the dark (a) and under the irradiation of blue LEDs (b); c) and d): ESR spectra of a solution of THIQ **1** (1.5 x 10^{-3} molL^{-1}) and DMPO (2.0 x 10^{-2} molL^{-1})

in air-saturated nitromethane in the dark (c) and under the irradiation of blue LEDs (d).

The influence of intensity and wavelength of the light source on the reaction rate was further investigated. For that reason, we examined high power LEDs with different wavelengths. In order to have a comparable value to the literature reported photo-background reaction of Stephenson *et al.*[28] we also applied a household energy-saving bulb as irradiation source (Table 1).

The reactions were performed under aerobic conditions and the conversions were compared after 24 h. The expected β-nitroamine coupling product **6a** was obtained for all investigated light sources (Table 1, entries 1-4). In agreement with the literature reported values, we observed low conversion of THIQ **1** when an energy-saving bulb was used as irradiation source (Table 1, entry 4). By changing the light source to high power LEDs a significant acceleration of the reaction rate was observed. Almost full conversion of the THIQ **1** was achieved after 24 h using LEDs with a peak wavelength λ_{max} of 400 nm or 440 nm providing the desired cross coupling product **6a** with good yields in reasonable reaction times. Applying LEDs with longer wavelength the product formation decreases (Table 1, entry 3). Further experiments were conducted with blue LEDs (440 nm) as they are most suitable for an efficient product formation.

Table 1. Wavelength dependence of the light-induced aza-Henry reaction without photocatalyst.[121]



Entry	Light source[a]	Recovered THIQ **1**[b]	Yield **6a** [%][b]
1	400 nm LED	3	74
2	440 nm LED	8	80
3	520 nm LED	62	38
4	Energy saving bulb	85	15

[a] For a detailed specification see Supporting Information.

[b] Based on NMR analysis using 2,5-dimethylfuran as an internal standard.

Using filters with different transmission values (25-75%) we further examined the impact of the light intensity on the reaction rate (see SI). As expected a decrease in product formation was observed by reduced transmission. The influence of wavelength and intensity on the product formation clearly proofs the importance of the reaction parameter light on the background reaction.

In analogy to the photocatalyzed *ex situ* studies ^{1}H-NMR kinetics were recorded to gain mechanistic insights and to elucidate the involved intermediates. The conditions are identical to the *ex situ* study described above, apart from the exclusion of the photocatalyst. In contrast to the aerobic photocatalyzed reaction (see Figure 1a) no dimer **9** and intermediate **10** were detected during the kinetic measurement (see Figure 5). THIQ hydroperoxide **11** constitutes the main intermediate, with constant amount of 10-15% over the reaction time. A moderate amount of iminium ion **2** is detected. The differences in the reaction profile - the absence of dimer **9** and open intermediate **10**, which we assume is derived from the α-amino radical **7** - indicate that the iminium pathway is operative and gave evidence that O2$^{\cdot-}$ exclusively act as an hydrogen atom acceptor.

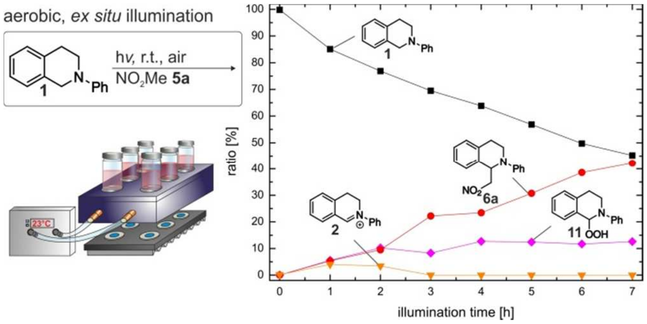


Figure 5. The photocatalyst free ^{1}H NMR kinetic shows the intermediates iminium ion **2** and THIQ hydroperoxide **11**, indicating an iminium pathway.

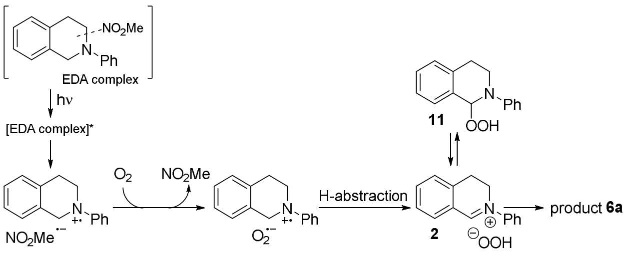
In analogy to the results of the photocatalyzed studies, light on-off studies revealed that THIQ hydroperoxide **11** is build up photo-induced. The reaction from THIQ-OOH **11** to the product **6a** and hydrogen peroxide also proceeds independent from light and catalyst in the dark (see SI).

However, the involvement of the amino radical **7** or other radical species cannot be completely excluded as BHT[122] (2,6-di-tert-butyl-4-methylphenol), a radical inhibitor, decreased the rate of product formation from 62-65% (without BHT) to 31-33% (with 1.3 equiv. BHT) after 15 h of irradiation.[123] Due to this effect an autoxidation mechanism[105,124,125] for the formation of THIQ-OOH **11** as reported for the acetic acid promoted[104] and sulfuryl chloride initiated[103] CDC of THIQ **1** with nucleophiles cannot be excluded (for detailed mechanism of the autoxidation see SI).

Despite the suppressing effect of the radical inhibitor, the reaction profile and the absence of intermediates formed on the radical pathway (e.g. dimer **9**) suggest that THIQ hydroperoxide **11** is predominantly generated via the iminium ion **2** and not via the amino radical **7**. This topic is also discussed for the metal-catalyzed CDC reaction of THIQ **1** with different nucleophiles using *tert*-butyl hydroperoxide as terminal oxidant. Doyle *et al.*[70] suggested the formation of the respective *tert*-butyl peroxide species in analogy to our proposal via iminium ions, whereas Klussmann *et al.*[72] proposed a radical pathway for the formation of amino *tert*-butyl hydroperoxide **8** (see Scheme 2) for a similar reaction system.

On the basis of these results we propose the following mechanism for the light induced background reaction presented in Scheme 7. THIQ **1** and nitromethane **5a** form an EDA complex. Upon irradiation with visible light the electron transfer from the lone pair of THIQ **1** to nitromethane is promoted, which provides a pair of radical ions. Oxygen is anticipated to prevent back electron transfer to the neutral components by accepting the electron from the radical anion of nitromethane ($E_{red}(MeNO_2/MeNO_2^{\cdot-})$ = -1.65 V vs. SCE, $E_{red}(O_2/O_2^{\cdot-})$ = -0.75 V vs. SCE)[65] making the process efficient. The resulting superoxide radical anion abstracts a hydrogen atom to produce the iminium ion **2**, which can be intercepted by nucleophiles including the formed peroxide anion.

Scheme 7. Proposed mechanism of the light induced reaction of THIQ 1 and nitromethane 5a in the presence of oxygen.



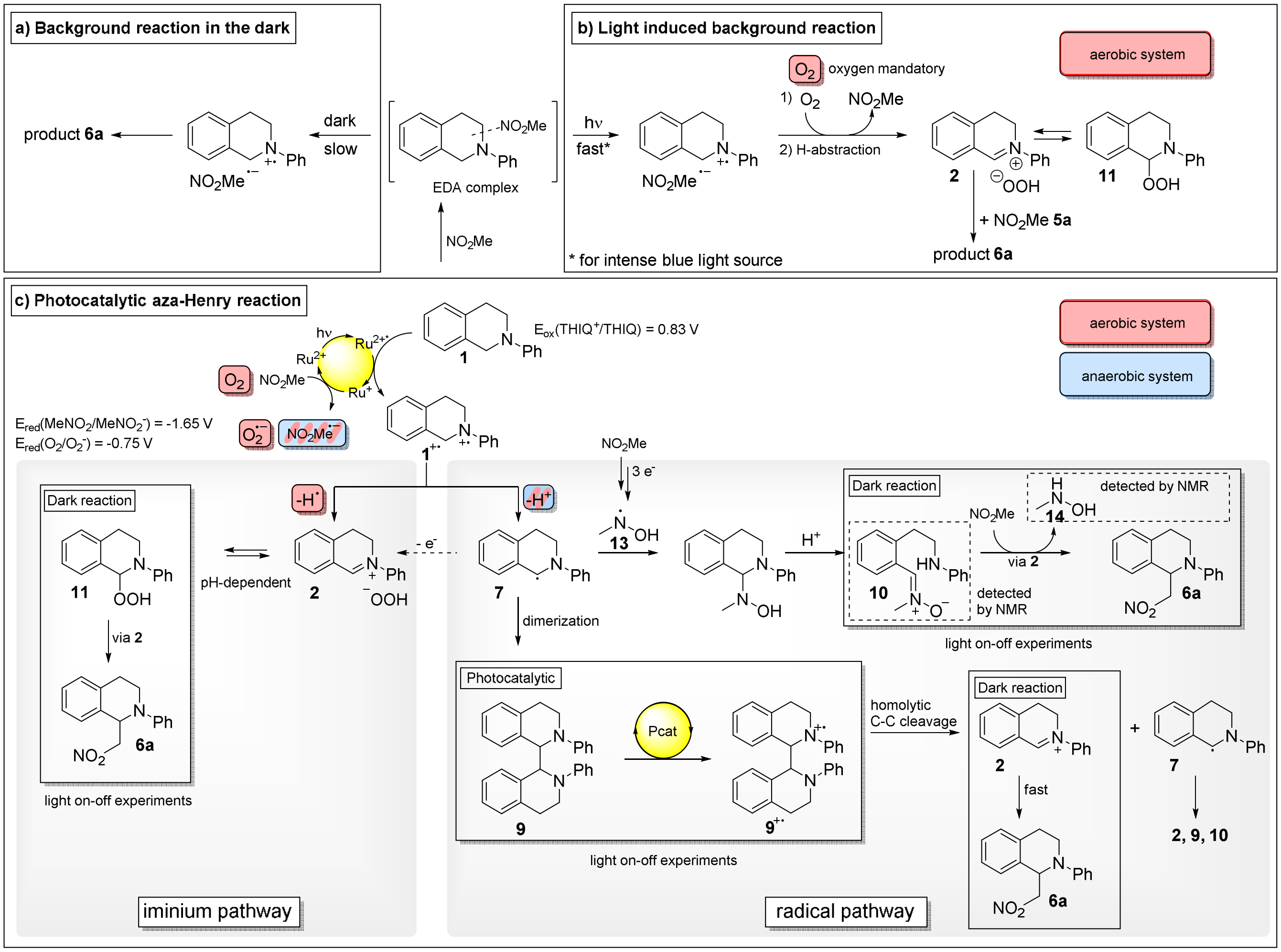
Summary of the Mechanistic Proposal and Conclusion The results are summarized in a mechanistic proposal depicted in Scheme 8. The photocatalyzed aza-Henry reaction is initiated by a reductive quenching of the photoexcited state of $Ru(bpy)_3Cl_2$ upon irradiation with visible light generating the THIQ amine radical cation $1^{+\bullet}$(Scheme 8c). The subsequent reactive mode of $1^{+\bullet}$ depends on the nature of the terminal oxidant regenerating the photocatalyst. Under anaerobic conditions, nitromethane acts as terminal oxidant exclusively. The resulting $MeNO2^{\bullet-}$ is assumed to deprotonate THIQ $1^{+\bullet}$ initiating the radical pathway via the α-amino radical **7**, characterized by a sigmoidal product formation. On this pathway, dimer **9** and a new ring opened species **10** are detected as intermediates, which are found to be productive towards **6a** in the dark (**10**) or light dependent (**9**). In the presence of radical inhibitors the intermediates **9** and **10** cannot be observed and the reaction is slowed down. Further experiments starting from dimer **9** show a very effective linear product formation via an iminium ion intermediate **2** under anaerobic conditions. All of these data indicate that $MeNO2^{\bullet-}$ acts as a base and opens an effective radical pathway, while $H^{\bullet}$- abstraction followed by the iminium ion pathway is negligible.

Under aerobic conditions O_2 as well as nitromethane operate as terminal oxidants in the photocatalyzed reaction. Now, the $MeNO2^{\bullet-}$ based radical pathway is active (see above). In addition, THIQ hydroperoxide **11** is detected as intermediate and a fast and linear product formation is observed. THIQ hydroperoxide **11** is an off cycle resting state of the iminium ion pathway. In studies without photocatalyst ($O2^{\bullet-}/1^{+\bullet}$ interaction) the intermediates **9** and **10** of the radical pathway are not detected. With the radical inhibitor TEMPO only the iminium ion pathway is observed. All of these data indicate that $O2^{\bullet-}$ functions mainly as radical species and initiates via $H^{\bullet}$- abstraction the highly effective iminium ion pathway.

Even without photocatalyst a productive light dependent reaction is observed with rates comparable to previously reported photocatalyzed systems (Scheme 8b). A correlation between the rate of product formation, the light intensity and the wavelengths was found. With strong light sources (blue LEDs) and O_2 after 24 h full conversion is reached (compared to 4 h with $Ru(bpy)_3Cl_2$ and O_2 as well as 12 h with $Ru(bpy)_3Cl_2$ and without O_2). Oxygen proved to be mandatory and exclusively $O2^{\bullet-}$ as well as THIQ hydroperoxide **11** and the iminium ion **2** intermediates were found. This is in accordance with the photocatalytic iminium pathway and corroborates that $O2^{\bullet-}$ acts mainly via $H^{\bullet}$- abstraction. We assume that three features promote this light dependent background reaction to become effective. First, light excitation facilitates the charge transfer in an electron-donor-acceptor (EDA)-complex between nitromethane and THIQ **1** to generate the respective radical ion pair. Second, back electron transfer is prevented by electron transfer from $MeNO2^{\bullet-}$ to dissolved oxygen providing $O2^{\bullet-}$. Third, $O2^{\bullet-}$ initiates an effective product formation via $H^{\bullet}$-abstraction and iminium pathway. In the absence of light the charge transfer is inefficient (2% yield after 20h). With light but without oxygen, the combination of BET and less reactive radical pathway leads to only 7% after 20h (Scheme 8a).

The comprehensive picture of the aza-Henry reaction presented herein reveals the influence of reaction conditions on the mechanistic pathways in photocatalytic reactions in detail. The possibility to switch between the operative reaction pathways (H^{+}-or $H^{\bullet}$-abstraction) provides a more accurate prediction and planning of the experimental setup in photoreactions.

Scheme 8. Overview of the proposed mechanism of the aza-Henry reaction, divided into three parts: the photocatalyzed aza-Henry reaction (c), the light induced reaction in the absence of a photocatalyst (b) and the background reaction of THIQ and nitromethane in the dark (a). The respective reactions were investigated in the presence (aerobic, red) and absence (anaerobic, blue) of oxygen. The pathways active under both conditions are dashed in red and blue. (c) The under photocatalytic conditions stated iminium and radical pathways are highlighted in grey.



ASSOCIATED CONTENT

Supporting Information. NMR, ESR, CV and UV data, preparation procedures and additional experiments are included in the SI. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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ABBREVIATIONS

LED, light emitting diode; NMR, nuclear magnetic resonance; ESR, electron spin resonance; SET, single electron transfer; BET, back electron transfer; SCE, saturated calomel electrode.

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requirement to obtain reliable QY describing a photoreaction is that the QY has to be independent of the experimental boundary conditions. Depending on the investigated process the QY can be influenced by different physical quantities. For the investigated light-induced aza-Henry reaction, we expect an almost wavelength independent QY as an extension of Kasha's rule. However, for certain systems QYs can be strongly dependent on the wavelength. For examples and detailed information, refer to: (c) Klán, P.; Wirz, J. *Photochemistry of Organic Compounds: From Concepts to Practice*; Wiley-Blackwell, **2009**.; (d) Riedle, E.; Wenninger, M. In *Chemical Photocatalysis*; König, B., Ed.; De Gruyter, Berlin **2013**; pp 319–378. Thus, the determination of QYs for different wavelengths of irradiation for the here discussed reaction cannot provide additional information. In order to compare the light-induced reaction at different wavelength and to strengthen the importance of control experiments by variation of the light source, we chose product yields.

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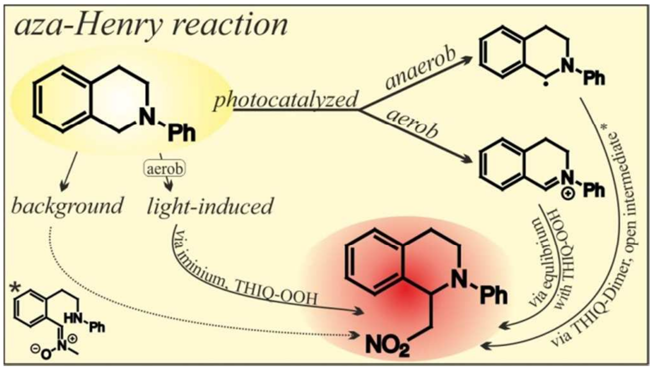
aza-Henry reaction
photocatalyzed
anaerob
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N
Ph
aerob
background
light-induced
via iminium, THIQ-OOH
via equilibrium with THIQ-OOH
via THIQ-Dimer, open intermediate *
NO2
*
HN
Ph