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Porphyrins as Photoredox Catalysts - Experimental and Theoretical studies

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ABSTRACT: Metalloporphyrins are not only vital in biological systems but also valuable catalysts in organic synthesis. On the other hand, catalytic properties of free base porphyrins are less explored. They are mostly known as efficient photosensitizers for the generation of singlet oxygen via photoinduced energy transfer processes but under light irradiation, they can also participate in electron transfer processes. Indeed, we have found that free-base tetraphenylporphyrin (H₂TPP) is an efficient photoredox catalyst for the reaction of aldehydes with diazo compounds leading to α -alkylated derivatives. The performance of a porphyrin-catalyst can be optimized by tailoring various substituents at the periphery of the macrocycle at both the β - and *meso*-positions. This allows for the fine tuning of their optical and electrochemical properties, hence their catalytic activity.

INTRODUCTION

Efficient C-C bond formation in a green, non-toxic and inexpensive way has always been a challenge. To this end, the development of visible light-promoted methodologies is one of the means to achieve such a goal.¹⁻⁵ Photoredox catalysis is based on a photo-induced electron transfer process (PET) between a substrate and a photoredox catalyst, commonly Ru- or Ir-complexes.⁶⁻⁸ Though organic dyes have been well known for their ability to participate in photo-induced electron transfer processes, their use as catalysts in such reactions is less explored.⁹ The replacement of Ir- and Ru-complexes with known organic dyes is not always possible but a recent comprehensive review by Romero and Nicewicz compiles a list of organic photoredox catalysts including: xanthenes, cyanoarenes, benzophenones, quinones, and thiazines, to name few.¹⁰ *Surprisingly, porphyrinoid compounds, though known as pigments of life, are not mentioned.*

These beautiful macrocycles are vital for our life, playing a key role in energy and electron transfer processes notably including photosynthesis, transport and storage of respiratory gases, methyl transfer, rearrangement reactions, etc.^{11,12} Among them, porphyrins are of particular importance due to their 18 π -electron aromatic ring, small singlet-triplet splitting, high quantum yield for intersystem crossing, and long triplet state lifetime making them perfectly suited for being robust electron mediators.^{13,14} Under light irradiation porphyrins can absorb photons and in the excited state they are able to transfer energy

(photosensitization) or electrons (photoredox catalysis).^{13,15}

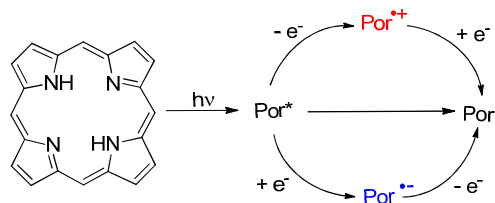
There are numerous reports describing the use of metalloporphyrins as artificial photosynthesis models and enzyme mimics as well as in catalyzing chemical reactions.¹⁶⁻¹⁸ Particular attention has been paid to the aliphatic C-H hydroxylation reaction which in nature is catalyzed by the heme-containing enzyme, cytochrome P450.^{19,20} Other developed reactions include amination, alkylation, olefin epoxidation, cyclopropanation, olefination, oxidative amine coupling, oxidative Mannich reaction, Diels-Alder reactions, and functional group transformations.²¹⁻²³

Conversely, in organic synthesis free-base porphyrins have been mainly applied as photosensitizers for singlet oxygen generation.²⁴ Under light irradiation porphyrins are excited to a singlet state, after which they can undergo ISC to produce a triplet state, and as such via energy transfer, singlet oxygen is formed or electron transfer leads to the formation of reactive oxygen species.²⁵ Using this methodology various compounds including olefins, aromatic compounds, amines, enamines, and aldehydes were oxidized.²⁶ For example, Nagata and coworkers reported photooxidation of alcohols to aldehydes via photoinduced electron transfer from a porphyrin (free-base or zinc) to the quinone.²⁷ Moreover, free-base porphyrins were shown to catalyze photooxidative hydroxylation of arylboronic acids, although in this case the corresponding Zr-organic framework containing substituted-porphyrin groups turned out to be more efficient. This reaction is

believed to proceed via a reductive quenching mechanism.²⁸

We envisaged that following photooxidation-like pathways, porphyrins could be broadly used as photoredox catalysts for C-C bond forming reactions. After light absorption, in the excited state they could then serve as oxidants by accepting electrons from a substrate or transform into a long-lived radical cation, enabling reduction of the starting material (Scheme 1).^{29,30}

Scheme 1. Energy and electron transfer processes



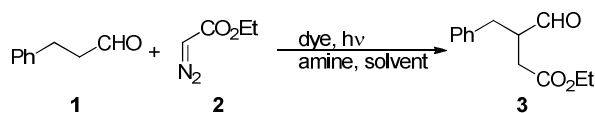
RESULTS AND DISCUSSION

There are only a few reports describing photoinduced electron transfer from free-base porphyrins in polymerization processes.³¹ To the best of our knowledge, the only successful example of free-base porphyrin catalyzing a C-C bond forming reaction, has been recently described by Kanai and co-workers.³² They found that tetra(4-diethylaminophenyl)porphyrin is effective in promoting C(3)-H arylation of coumarins with aryl diazonium salts. The porphyrin reduces aryl diazonium tetrafluoroborate affording an aryl radical and nitrogen. The resulting porphyrin radical cation then oxidizes the benzyl radical intermediate. Interestingly, the reaction is not affected by the presence or absence of light.

The seminal work on photoredox catalysis describes photoinduced functionalization (trifluoromethylation³³, benzylation³⁴, alkylation³⁵) of aldehydes in the presence of well-known photoredox catalysts – ruthenium or iridium metal complexes. As an alternative to transition metal complexes, organic dyes have been also applied in photoredox catalysis,^{36–38} with eosin Y being the most common.³⁹

Recently, we have reported light induced α -alkylation of aldehydes with diazoesters catalyzed by Ru(bpy)₃Cl₂ (Scheme 2).⁴⁰

Scheme 2. Light-induced reaction of aldehydes with EDA



Under the developed conditions, other photoredox catalysts – organic dyes such as eosin Y, methylene blue, fluoresceine, and rose bengal were tested, but only eosin Y and rose bengal gave the desired product **3** in reasonable yields. However, in general, it is not always possible to replace Ir- and Ru-complexes with known organic dyes and therefore the search for new, suitable catalysts is ongoing. Given the promising optical and electrochemical

properties of porphyrins as well as their simple synthesis, we wondered whether under light-irradiation free base porphyrins could be employed as photoredox catalysts under light-irradiation.

We have found that under light irradiation porphyrins are indeed able to participate in both energy and electron transfer processes generating an enamine cation radical and a carbene in the triplet state, thus facilitating functionalization of aldehydes at the α -position. To the best of our knowledge, this is the first example of the use of porphyrins as photoredox catalysts in C-C bond forming reactions.

Electrochemical studies. Given that the crucial step in all light-induced reactions involves absorption of a photon by a photocatalyst to transform it into high energy excited state, it is the reduction potential of the excited state that should be taken into account. This potential cannot be directly measured but it can be estimated from cyclic voltammetry (CV) and spectroscopic data. An approximation of excited-state potentials (both in the singlet and triplet state) of a catalyst relates to a ground state potential and its zero-zero excitation energy ($E_{0,0}$).^{6a,15}

Available data and our experiments suggested that in the studied reaction, porphyrin acts as a photoredox catalyst. The electroreduction of tetraphenylporphyrin (**4**, H₂TPP) and **Zn-4** were investigated in both DMSO and DMSO:buffer (pH = 4) solvents containing TBAP as a supporting electrolyte and potentials are reported vs. saturated calomel electrode (SCE). The reduction of H₂TPP (**4**) is located at $E_{1/2} = -1.03$ and -1.46 V while the oxidation at 1.03 V. For ZnTPP (**Zn-4**) the respective potentials are slightly higher, at $E_{1/2} = -1.32$, -1.71 V and 0.86 , and 1.06 V. In DMSO:buffer (pH = 4) solution, the reaction medium, we have only observed peaks corresponding to the reduction of buffer. Therefore, data from experiments in DMSO were used for calculations of approximate reduction potentials of H₂TPP (**4**) and ZnTPP (**Zn-4**) in both excited states:

Oxidative Quenching:

$$E_{\text{ox}}^*[\text{Por}^{\bullet+}/\text{Por}^*] = E_{\text{ox}}[\text{Por}^{\bullet+}/\text{Por}] - E_{0,0}$$

in the singlet state

$$E_{\text{ox}}^*[\text{TPP}^{\bullet+}/\text{TPP}^*] = 1.03 \text{ V} - 1.94 \text{ V} = -0.91 \text{ V}$$

$$E_{\text{ox}}^*[\text{ZnTPP}^{\bullet+}/\text{ZnTPP}^*] = 0.86 \text{ V} - 2.04 \text{ V} = -1.18 \text{ V}$$

in the triplet state¹⁵

$$E_{\text{ox}}^*[\text{TPP}^{\bullet+}/\text{TPP}^*] = 1.03 \text{ V} - 1.45 \text{ V} = -0.42 \text{ V}$$

$$E_{\text{ox}}^*[\text{ZnTPP}^{\bullet+}/\text{ZnTPP}^*] = 0.86 \text{ V} - 1.59 \text{ V} = -0.73 \text{ V}$$

Reductive Quenching:

$$E_{\text{red}}^*[\text{Por}^*/\text{Por}^{\bullet-}] = E_{\text{red}}[\text{Por}/\text{Por}^{\bullet-}] + E_{0,0}$$

in the singlet state

$$E_{\text{red}}^*[\text{TPP}^*/\text{TPP}^{\bullet-}] = -1.03 \text{ V} + 1.94 \text{ V} = 0.91 \text{ V}$$

$$E_{\text{red}}^*[\text{ZnTPP}^*/\text{ZnTPP}^{\bullet-}] = -1.32 \text{ V} + 2.04 \text{ V} = 0.79 \text{ V}$$

in the triplet state¹⁵

$$E_{\text{red}}^*[\text{TPP}^*/\text{TPP}^{\cdot-}] = -1.03 \text{ V} + 1.45 \text{ V} = \mathbf{0.42 \text{ V}}$$

$$E_{\text{red}}^*[\text{ZnTPP}^*/\text{ZnTPP}^{\cdot-}] = -1.32 \text{ V} + 1.59 \text{ V} = \mathbf{0.27 \text{ V}}$$

In the excited state H₂TPP (**4**, singlet 0.91 V, triplet 0.42 V) and Zn-**4** (singlet 0.79 V, triplet 0.27 V) reduction potentials in DMSO are similar to those calculated for Ru(bpy)₃²⁺ (0.67 V) and eosin Y (0.83 V),⁶ but apparently both are strong enough to act as efficient catalysts in our model reaction. It is well documented that, once excited, H₂TPP (**4**) can function as both an oxidant and a reductant and its redox properties can be tuned by electronic effects of the substituents on the macrocycle.^{41,42} This suggests that porphyrins can also be used as photoredox catalysts and their catalytic properties can be improved if required.

Moreover, Rehm-Weller formalism allows for estimating the thermodynamic driving force, $-\Delta G_{\text{PET}}^{(o)}$, for PET between the enamines and the excited-state porphyrins (see SI). Because of the irreversible electrochemical oxidation of the enamines, and solvents used (DMSO:buffer), we do not have exact values for the potentials for their oxidation. For acetonitrile, the voltammograms show peak potentials between about 0.3 and 0.6 V vs. SCE for oxidation of enamines.⁴³ For irreversible oxidation the inflection points, rather than the peak potential, are representative for the standard reduction potentials.⁴⁴ Therefore, we can assume that the reduction potentials for oxidation of enamines ranges between about 0.2 and 0.6 V vs. SCE. Furthermore, an increase in the media polarity causes negative shifts in the potentials of oxidation, making the enamines better electron donors; there are also positive shifts in the potentials of reduction, making the porphyrins better electron acceptors.⁴⁵ Therefore, for PET initiated from the singlet-excited state of the porphyrins, ΔG most likely assumes negative values of a tens of electronvolts, making it thermodynamically favorable. Conversely, the triplet excited states of the sensitizers lie about half an electron volt below their singlet states, which may or may not results in positive values for the $\Delta G_{\text{PET}}^{(o)}$ estimates. Therefore, we cannot necessarily claim a triplet manifold for PET.

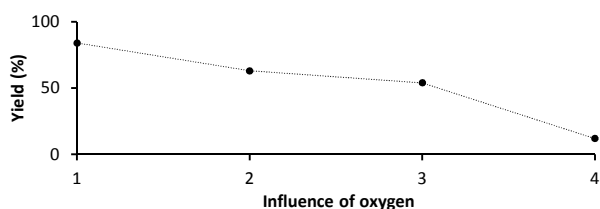
Optimization studies. In a preliminary experiment we tested free base tetraphenylporphyrin (**4**) and the Zn-complex as photoredox catalysts for the reaction of 3-phenylpropanal (**1**) with ethyl diazoacetate (**2**, EDA) under conditions developed for the Ru-catalyzed reaction.⁴⁰ Notably, both reactions gave the desired product **3** in 84 and 88% respectively (Table 1, entries 1, 2). Control experiments confirmed that all reaction components are essential as the exclusion of any of them halted the reaction completely (entries 3-5), the aldehyde remained intact while EDA decomposed or polymerized. Thus, contrary to the arylation of cumarins, the alkylation reaction is indeed induced by white visible light.

Table 1. The reaction of aldehyde **1** with EDA (**2**) – background reactions^a

entry	catalyst ^b	amine	yield (%) ^b
1	H ₂ TPP (4)	morpholine	84
2	Zn- 4	morpholine	88
3	no	morpholine	o
4	H ₂ TPP (4) or Zn- 4	no	o
5 ^c	H ₂ TPP (4) or Zn- 4	morpholine	o

^aReaction conditions: aldehyde **1** (0.5 mmol), morpholine (0.4 equiv.), catalyst (1 mol%, $c = 1.25 \times 10^{-3}$ M), EDA (**2**, 1 equiv.), DMSO:buffer pH = 4 (5 mL, 9:1 mixture), 5 h. ^bYields were determined by GC. ^cNo light

Moreover, as porphyrins are able to generate singlet oxygen and/or reactive oxygen species ROS from oxygen, their presence should diminish the reaction yield.



1 - degassed, under Ar 2 - only degassed 3 - open to air 4 - under O₂

Figure 1. Influence of oxygen on the yield of the reaction to give functionalized aldehyde **3**^a

^aReaction conditions: aldehyde **1** (0.5 mmol), morpholine (0.4 equiv.), H₂TPP (**4**, 1 mol%), EDA (**2**, 1 equiv.), DMSO:buffer pH = 4 (5 mL, 9:1 mixture), 5 h. Yields were determined by GC.

Indeed, the reaction open to air gave functionalized aldehyde **3** in much lower yield (Fig. 1).

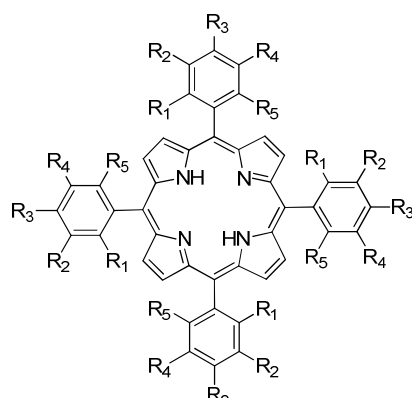
In the next step, the reaction conditions were optimized with respect to the photocatalyst, amine⁴⁶, pH of the buffer used, as well as reaction time and solvents utilized.

The nature of substituents at the periphery of the macrocycle greatly affects the value of the half-wave potentials as well as the magnitude of the HOMO-LUMO gap.^{41,42,47} Hence porphyrins possessing both electron-withdrawing and electron-donating substituents were tested as catalysts. Almost all of the free-base porphyrins studied, **4**, **6**-**13**, catalyzed the model reaction of 3-phenylpropanal (**1**) with EDA (**2**), leading to desired the product **3** (Table 2). However, due to solubility issues (porphyrins are, to a large extend, poorly soluble in the utilized reaction medium), a direct correlation between reaction yield and electronic nature of the substituents was not unequivocal. Free base porphyrin **4** and its zinc complex were found to be the most effective in catalyzing the model reaction.

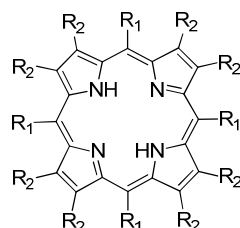
As seen in Table 2, the influence of porphyrin ring substituents Zn-**6**, Zn-**7**, and Zn-**9** series is clear; as the macrocycle became more electron rich (-CO₂Me, Me, -OMe) the catalytic efficacy of the porphyrin increases (entries 5, 8, 11). The β -substituted protoporphyrin IX, derivative **13**, furnished the product with a reasonable yield of 54%.

Zinc complex **Zn-4** exhibiting the best solubility, allowed for the use of very low catalytic loading (0.1 mol%) with only a slight decrease in yield (Table 3, entries 7, 13). This fact also emphasizes the advantage of porphyrins over Ru- and Ir- complexes.

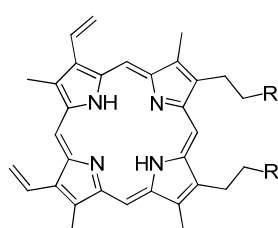
Table 2. Porphyrins tested in alkylation reaction.



- 4** $R_1 = R_2 = R_3 = R_4 = H$, H_2TPP
5 $R_1 = R_2 = R_3 = R_4 = F$
6 $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = CO_2Me$
7 $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Me$
8 $R_2 = R_4 = H$, $R_1 = R_2 = R_3 = Me$
9 $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = OMe$



- 10** $R_1 = C_6H_{19}$, $R_2 = H$
11 $R_1 = H$, $R_2 = Et$



- 12** $R = CO_2H$, PPIX
13 $R = CO_2Et$

entry	catalyst	yield (%) ^b
1	H_2TPP (4)	84
2	5	traces
3	6	44
4	7	14
5	8	10
6	9	60
7	10	8
8	11	15
9	PP-IX, 12	15
10	PP-IX diethyl ester, 13	54
11	Zn-4	88
12	Zn-6	0
13	Zn-7	54
14	Zn-9	75

^aReaction conditions: aldehyde **1** (0.5 mmol), morpholine (0.4 equiv.), porphyrin (1 mol%), EDA (**2**, 1 equiv.), DMSO:buffer pH = 4 (5 mL, 9:1 mixture), 5 h. ^bYields were determined by GC.

Subsequently, various amines were studied (Table 4). Only in the presence of secondary amines did the reaction furnish the desired product **3**. DABCO and NEt_3 did not catalyze the reaction, thus confirming the proposed role of an amine in the catalytic cycle e.g. the formation of enamine (entries 6, 7). Surprisingly, among the secondary amines tested, morpholine proved to be the best with respect to the reaction yield although it is pyrrolidine that furnishes more reactive enamines.

Table 3. Optimization of the catalyst loading^a

entry	catalyst	loading, mol%	yield, % ^b
1	H_2TPP (4)	1.5	73
2	H_2TPP (4)	1.0	84
3	H_2TPP (4)	0.7	63
4	H_2TPP (4)	0.4	65
5	H_2TPP (4)	0.1	61
6	Zn-4	2.0	84
7	Zn-4	1.5	90
8	Zn-4	1.0	88
9	Zn-4	0.8	86
10	Zn-4	0.4	86
11	Zn-4	0.1	80

^aReaction conditions: aldehyde **1** (0.5 mmol), morpholine (0.4 equiv.), porphyrin (1 mol%), EDA (**2**, 1 equiv.), DMSO:buffer pH = 4 (5 mL, 9:1 mixture), 5 h. ^bYields were determined by GC.

Table 4. The influence of an amine used^a

entry	catalyst	amine	pK_b^{48}	yield, % ^b
1	H_2TPP (4)	pyrrolidine	2.89	57
2	H_2TPP (4)	piperidine	2.73	59
3	H_2TPP (4)	piperazine	4.19	26
4	H_2TPP (4)	<i>N</i> -methylpiperazine	4.87	24
5	H_2TPP (4)	morpholine	5.6	84
6	H_2TPP (4)	DABCO	5.2	0
7	H_2TPP (4)	NEt_3	3.3	0
8	Zn-4	pyrrolidine	2.89	68
9	Zn-4	piperidine	2.73	83
10	Zn-4	piperazine	4.19	79
11	Zn-4	<i>N</i> -methylpiperazine	4.87	73
12	Zn-4	morpholine	5.6	88

^aReaction conditions: aldehyde **1** (0.5 mmol), morpholine (0.4 equiv.), porphyrin (1 mol%), EDA (**2**, 1 equiv.), DMSO:buffer pH = 4 (5 mL, 9:1 mixture), 5 h. ^bYields were determined by GC.

We confirmed that the addition of buffer at pH = 4 assured the highest yield and any deviation from this value

diminished the amount of product formed (Fig. 2). The tendency was even more pronounced for the ZnTPP-catalyzed reactions, which is understandable as demetalation can occur in acidic conditions.

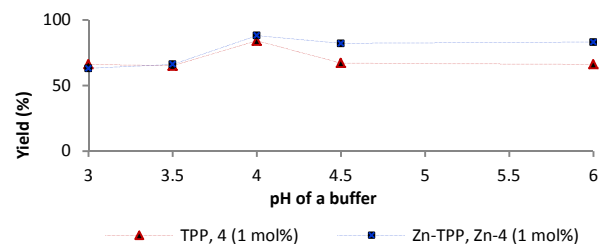


Figure 2. Influence of pH buffer used in the reaction^a
^aAldehyde **1** (0.5 mmol), morpholine (0.4 equiv.), H₂TPP, (**4**, 1 mol%), EDA (**2**, 1 equiv.), DMSO: buffer pH = 4 (5 mL, 9:1 mixture), 5 h. ^cYields were determined by GC.

As the reactions are pH dependent, the final step in our study involved examining Brønsted and Lewis acids as co-catalysts (for details see SI). The addition of common Brønsted acids lowered the reaction yield, in the case of ascorbic acid, which is a known radical scavenger, and no product formation was observed. Gratifyingly, the addition of LiBF₄ led to further increase in the yield up to 90%.

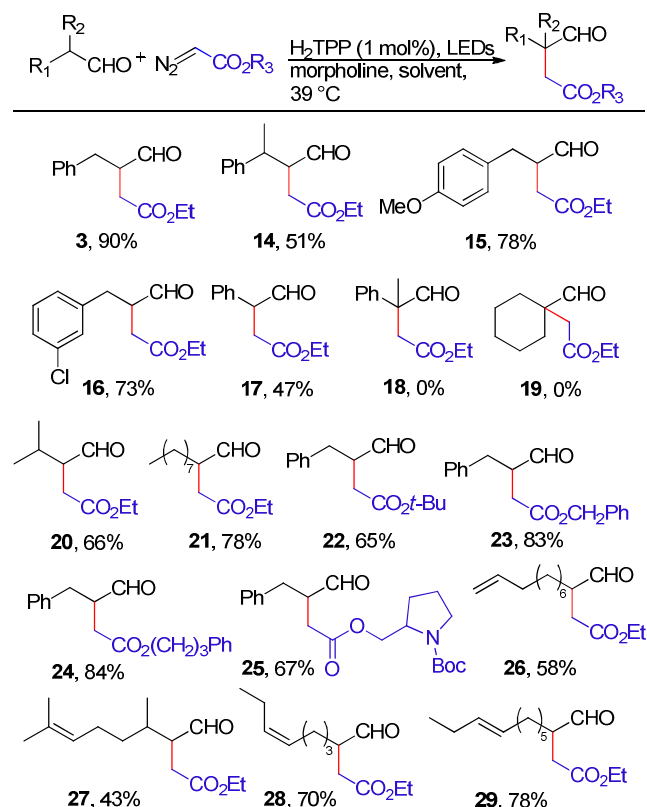
Scope and limitations studies. Under the described conditions: aldehyde (1 mmol), morpholine (0.4 mmol), H₂TPP (**4**) (1 mol%), LiBF₄ (20 mol%), EDA (**2**, 1 mmol), a mixture of DMSO/buffer (9:1, 10 mL, buffer pH = 4, c = 0.1 M), 5 h, 4 'household' LEDs, the scope and limitations of α-alkylation of aldehydes with diazoesters were explored (Scheme 3). In general, the reactions gave good yields in C-H alkylation of aldehydes with diazoesters with different functional groups being well tolerated (-Cl and -OMe). It is noteworthy that unsaturated aldehydes furnished only C-H alkylated compounds (**26-29**) with no cyclopropane product being formed. The observed chemoselectivity creates great possibilities for further functionalization of compounds possessing double bonds. However, generation of a quaternary center proved difficult under the developed conditions and requires further studies.

Mechanistic Considerations

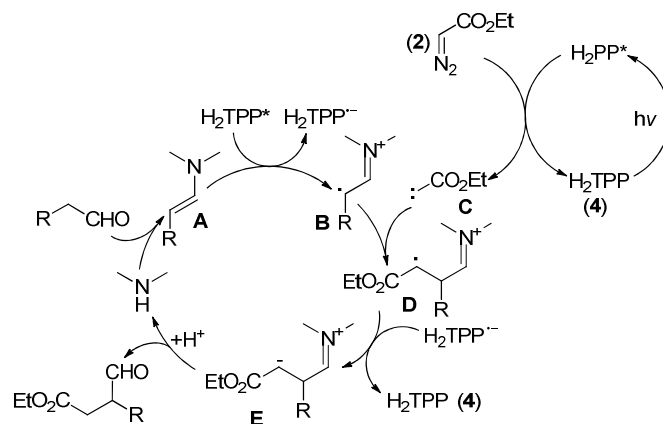
A proposed mechanism for the functionalization of aldehydes involves two interrelated catalytic cycles as shown in Scheme 4. Each reaction component, the amine, photocatalyst and light, play an important role (Table 1, entries 3-5). It is assumed that the porphyrin acts as both a photosensitizer and photoredox catalyst. Firstly, H₂TPP (**4**) under light irradiation is excited from the singlet ground state to the excited state and as such it can transfer energy to EDA (**2**) forming carbene in the triplet state (biradical C) with simultaneous extrusion of nitrogen. It is known that in the presence of light, carbenes in a singlet ground state are generated via direct photolysis, while in the presence of triplet-sensitizers less reactive triplet carbenes are formed.⁴⁹ As porphyrins are known triplet

photosensitizers we assumed that such a carbene is formed.

Scheme 3. Scope and limitations of α-functionalization of aldehydes



Scheme 4. Proposed mechanism for light-induced functionalization of aldehydes with EDA in the presence of porphyrin (**4**)



Moreover, EDAs quench porphyrin luminescence as demonstrated by the Stern-Volmer analysis (Fig. 3). The reaction yields are inversely proportional to the EDA quenching rates. This feature is consistent with the proposed mechanism, which requires two parallel processes involving the sensitizer: 1) the PET for forming the oxidized enamine and 2) the intersystem crossing (ISC) for the energy transfer needed for the formation of a triplet carbene. As such, neither of these processes should have rates which are too fast. If PET is fast and outcompetes

the processes, energy transfer will not occur efficiently and the C-C bond cannot be formed (no carbene). On the other hand, if ISC is too fast, PET will not occur hence the enamine will not be oxidized.

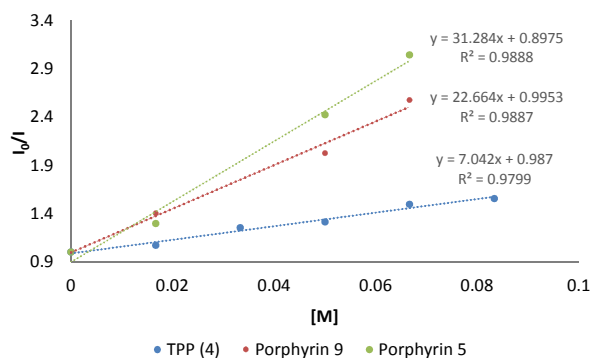


Figure 3. Stern-Volmer quenching experiments for porphyrins^a

^aExperimental conditions: for EDA samples were prepared by adding solutions of substrates to porphyrins **4**, **5**, and **9** in DMSO (total volume 2 mL) and degassed with Ar. The concentration of porphyrins **4**, **5**, and **9** in DMSO were 3.6×10^{-5} M, 3.8×10^{-5} M, 3.4×10^{-5} M respectively. For H₂TPP $\tau_0 = 9.95$ ns, $k_q = 7.3 \cdot 10^8$ [M⁻¹s⁻¹], for porphyrin **9** $\tau_0 = 8.6$ ns, $k_q = 2.61 \times 10^9$ [M⁻¹s⁻¹], for porphyrin **5** $\tau_0 = 10.1$ ns, $k_q = 1.0 \times 10^9$ [M⁻¹s⁻¹] (for calculations see SI).

When both the singlet and triplet excited porphyrin (**4**) were quenched with benzoquinone, the model reaction stopped completely, thus confirming the involvement of a carbene in the triplet state.^{49,50} It can react with other molecules such as radicals or undergo ISC. Concomitantly an aldehyde reacts with a secondary amine furnishing an intermediary enamine **A** which was detected by ESI-MS and ¹H NMR analyses. In MS, the corresponding peak at 204.14 Da [M+H]⁺ was observed not only when aldehyde **1** was treated with morpholine but also in the reaction mixture. The ¹H NMR spectrum clearly showed characteristic proton resonances for enamine at 5.95 and 4.56 ppm. Subsequently, H₂TPP (**4**) in its excited state oxidizes enamine **A** to form a porphyrin (**4**) radical anion and an active cation radical **B** which reacts with biradical **C** furnishing the new radical **D**. After electron transfer from the porphyrin radical anion and protonation, the final product of the reaction is formed. In addition, chain propagation reactions may likely be also involved.⁵¹ The presence of cation radical **B** was confirmed by EPR experiments and Stern-Volmer quenching experiments.

The Stern-Volmer analyses for each of the reaction components clearly shows that enamine **A** and EDA (**2**) exhibit strong, in comparison with morpholine and 3-phenylpropanal (**1**), quenching of H₂TPP (Fig. 4). This indicates that the reaction of H₂TPP with enamine and ethyl diazoacetate play a crucial role in the mechanism of the α -alkylation reaction. Furthermore, the highly efficient quenching of the porphyrin luminescence by enamines, i.e., the bimolecular quenching constants are comparable with diffusion-limited rates, indicating suffi-

ciently fast PET steps. For the concentrations used in this study, the rates of PET are comparable to the nanosecond decay times of the singlet-excited porphyrins.

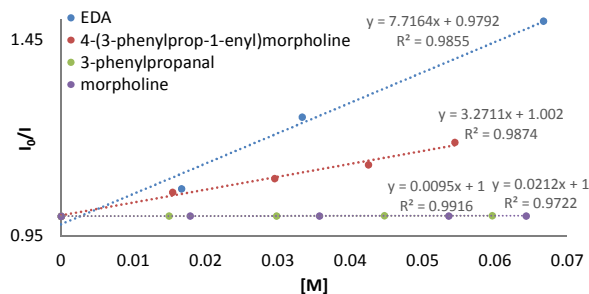


Figure 4. Stern-Volmer quenching experiment for H₂TPP^a

^aExperiment conditions: for 3-phenylpropanal (**1**), EDA, enamine (4-(3-phenylprop-1-enyl)morpholine), and morpholine samples were prepared by adding solutions of substrates to H₂TPP (**4**) in DMSO (total volume 2 mL) and degassed with Ar. The concentration of H₂TPP (**4**) in DMSO was 3.6×10^{-5} M.

Conversely, for these types of sensitizers, ISC is the principal pathway of non-radiative deactivation of their singlet-excited states. Still, because of the inherently long lifetimes of the triplet excited states, even small quantum yields of porphyrin triplets will prove sufficient for the bimolecular energy transfer essential for the formation of the carbenes for the proposed mechanism. That is, while the PET, occurring in the nanosecond time domain from the singlet-excited states of the sensitizers, generates the oxidized enamines; the triplet energy transfer from the sensitizer, occurring with considerably smaller rates, provides the carbenes.

In accordance with the proposed mechanism reactive radicals are formed. To confirm their presence, EPR spectroscopy experiments were performed.

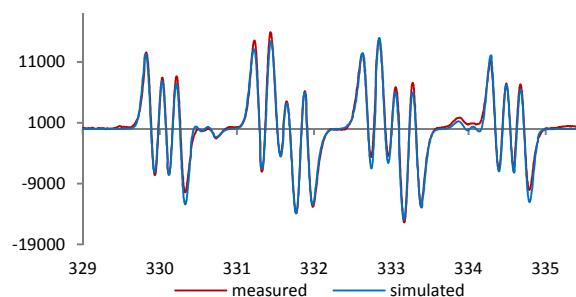


Figure 5. EPR spectra of the reaction mixture in the presence of DMPO^a

^aReaction conditions: aldehyde **1** (1 equiv., 1 mmol), morpholine (0.4 equiv.), H₂TPP (**4**, 1 mol%), EDA (**2**, 1 equiv.), DMSO:buffer pH = 4 (10 mL, 9:1 mixture), spin trap DMPO after 10 min of irradiation with LED.

As the concentration of free radicals in the reaction mixture was too low to be detected directly, EPR measurements were performed with two spin traps *N-tert*-butyl- α -

phenylnitron (PBN) and 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO). The spectra were also simulated using the EasySpin package in Matlab. First, EPR spectra of the reaction mixture were recorded after 10 min of irradiation (Fig. 5 for DMPO, Fig. S1 for PBN in SI). Spectral simulations indicate the presence of three paramagnetic species with the intensity ratio of the two corresponding components being very similar (See SI Fig. S4). To identify these radical species present, the EPR spectrum of H₂TPP (**4**), morpholine, and aldehyde (**1**) with no EDA added was registered in the presence of spin traps after light irradiation (Fig. 6 and SI Fig. S10).

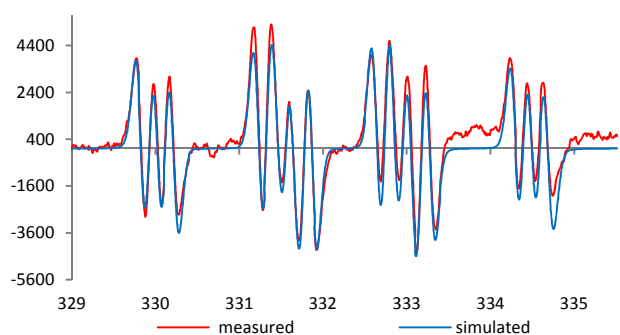


Figure 6. EPR spectra for the mixture of porphyrin (**4**) with aldehyde (**1**) and morpholine in DMSO: buffer with DMPO^a

^aReaction conditions: aldehyde **1** (1 equiv., 1 mmol), morpholine (0.4 equiv.), H₂TPP (**4**, 1 mol%), DMSO:buffer pH = 4 (10 mL, 9:1 mixture), spin trap DMPO after 10 min of irradiation with LED.

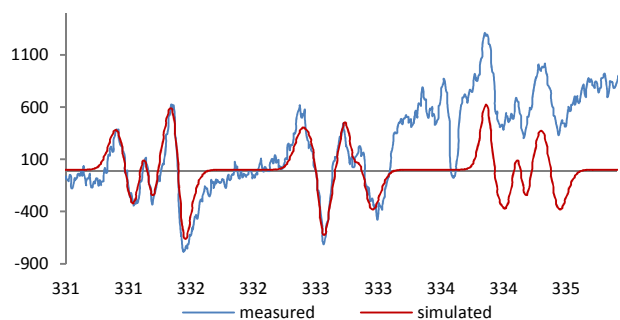


Figure 7. EPR spectra of the mixture of TPP (**4**) with EDA (**2**) and PBN

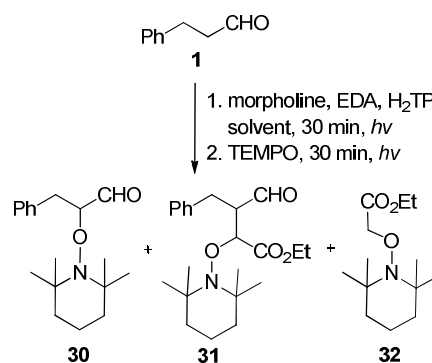
^aReaction conditions: H₂TPP (**4**, 1 mol%), EDA (**2**, 1 mmol), DMSO:buffer pH = 4 (10 mL, 9:1 mixture), spin trap PBN after 10 min of irradiation with LED.

Two components are present in the simulated EPR spectrum. The first one, responsible for 63% of intensity in the presence of DMPO ($a_N = 1.40$ mT, $a_{H\beta} = 1.47$ mT and $a_{H\gamma} = 0.20$ mT), corresponds to a carbon-centered radical adduct as indicated by the value of $a_{H\beta}$ higher than a_N value and a small difference between them suggests the bulkiness of a radical. It can be ascribed as an enamine radical **B**.

Subsequently the EPR spectrum was measured for a mixture of H₂TPP (**4**) and EDA (**2**) in the presence of PBN

(Fig. 7). Two components are present in the simulated EPR spectrum. It is known that the thermal decomposition of diazo compounds leads to the formation of carbon-centered radicals that with PBN give adducts with $a_N = 1.54$ mT and $a_H = 0.4$ mT.⁵² Our measured parameters of a dominating component ($a_N = 1.49$ mT and $a_H = 0.4$ mT) are very similar thus suggesting that the signal corresponds to a radical formed during photolysis of EDA (**2**), e.g. radical **C**. Its hyperfine splitting constants are also similar to those obtained for PBN-benzoyl radical adduct in DMSO solution ($a_N = 1.45$ mT and $a_H = 0.47$ mT)⁵³, so its presence can be considered as an alternative.

Scheme 5. Experiment with TEMPO



Hence, the use of two different spin-traps in the EPR experiments proved beneficial, allowing the detection of two paramagnetic species **B** and **C**, thus supporting the proposed mechanism. We were not able to detect the radical **D** using this technique but the addition of TEMPO, a radical scavenger, to the reaction mixture stopped the reaction completely, providing evidence for the formation of three radical species (**B**, **C**, **D**) as TEMPO-adducts (**30**, **31**, **32**) in the reaction mixture as detected by MS (Scheme 5).

CONCLUSIONS

We have demonstrated that porphyrins are effective in catalyzing the reaction of aldehydes with diazo compounds under light irradiation. Mechanistic studies confirmed that the effective reaction requires a dual catalytic system composed of a photocatalyst and an organocatalyst. It is assumed that the porphyrin acts both as a photoredox catalyst and as a photosensitizer.

Porphyrins can now be added to the list of photoredox catalysts that are suitable for photoredox catalysis. As these compounds are easy to synthesize and their optical and electrochemical properties can be tuned by placing a variety of electron-donating or electron-withdrawing substituents at the periphery of the macrocycle, they are perfectly suited for this role. These findings demonstrate unexplored venues in both porphyrin chemistry and photocatalysis.

ASSOCIATED CONTENT

Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>.

Full description of optimization and mechanistic studies, general procedure, for the α -alkylation of aldehydes, compound characterization (NMR, HRMS, AE), copies of NMR and EPR spectra

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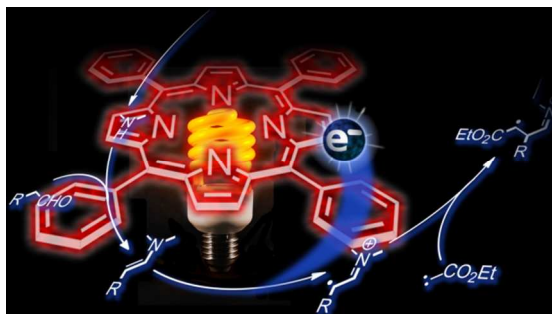
Dedicated to Prof. Jonathan S. Lindsey on his 60th birthday. The authors greatly acknowledge prof. V. Vullev for helpful discussions.

REFERENCES

- (1) Fontecave, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 6946.
- (2) Peña-López, M.; Rosas-Hernández, A.; Beller, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 5006.
- (3) Angnes, R. A.; Li, Z.; Correia, C. R. D.; Hammond, G. B. *Org. Biomol. Chem.* **2015**, *13*, 9152.
- (4) Meggers, E. *Chem. Commun.* **2015**, *51*, 3290.
- (5) Brimiouille, R.; Lenhart, D.; Maturi, M. M.; Bach, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 2.
- (6) a) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. b) Douglas, J. J.; Sevrin, M. J.; Stephenson, C. R. J. *Org. Process. Res. Dev.* **2016**, *20*, 1134. c) Staveness, D.; Bosque, I. B.; Stephenson, C. R. J. *Acc. Chem. Res.* **2016**, *49*, 2295-2306. d) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. *Org. Process Res. Dev.* **2016**, *20*, 1156. e) Demissie, T. B.; Ruud, K.; Hansen, J. H. *Organometallics* **2015**, *34*, 4218.
- (7) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.
- (8) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035-10074.
- (9) a) Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355. b) Fukuzumi, S.; Ohkubo, K. *Org. Biomol. Chem.* **2014**, *12*, 6059. c) Pitre, S. P.; McTiernan, C. D.; Scaiano, J. C. *ACS Omega* **2016**, *1*, 66.
- (10) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075-10166.
- (11) Kadish, K. M.; Smith, K. M.; Guillard, R. Handbook of porphyrin science. Vol. 4. Phototherapy, radioimmunotherapy and imaging, World Scientific, **2010**, Singapore.
- (12) Imahori, H.; Mori, Y.; Matano, Y. *J. Photochem. Photobiol. C* **2003**, *4*, 51.
- (13) Whitten, D. G. *Rev. Chem. Intermed.* **1978**, *2*, 107.
- (14) Fukuzumi, S.; Honda, T.; Kojima, T. *Coord. Chem. Rev.* **2012**, *256*, 2488.
- (15) a) Seely, G. R. *Photochem. Photobiol.* **1978**, *27*, 639. b) Rillema, D. P.; Nagle, J. K.; Barringer, L. F.; Meyer, T. J. *J. Am. Chem. Soc.* **1981**, *103*, 56.
- (16) Gust, D.; Moore, T. A.; Moore, A. L. *Acc. Chem. Res.* **2009**, *42*, 1890.
- (17) a) Fukuzumi, S. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 177. b) Fukuzumi, S.; Mizuno, T.; Ojiri, T. *Chem. Eur. J.* **2012**, *18*, 15794. c) Fukuzumi, S.; Ohkubo, K.; Suenobu, T. *Acc. Chem. Res.* **2014**, *47*, 1455.
- (18) Chang, C.-H.; Hu, Y.-T.; Lo, C.-F.; Luo, L.; Lin, H.-M.; Lin, C.-Y.; Diao, E. W.-G.; Wu, T.-K. *Int. J. Biol. Sci.* **2011**, *7*, 1203.
- (19) Liu, W.; Groves, J. T. *Acc. Chem. Res.* **2015**, *48*, 1727.
- (20) Maldotti, A.; Andreotti, L.; Molinari, A.; Carassiti, V. *JBC* **1999**, *4*, 154.
- (21) a) Zhou, C.-Y.; Lo, V. K.-Y.; Che, C.-M. Handbook of porphyrin science. Vol. 21, Chapter 101: Metalloporphyrin-Catalyzed C-C Bond Formation, World scientific, **2012**, Singapore. b) Rybicka-Jasińska, K.; Ciszewski, E. W.; Gryko, D. *J. Porphyrins Phtalocyanines* **2016**, *20*, 76-95. c) Barona-Castaño, J. C.; Carmona-Vargos, C. C.; Brocksom, T. J.; de Oliveira, K. T. *Molecules* **2016**, *21*, 310. d) Lu, H.-J.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899. e) Anding, B. J.; Woo, L. K. Handbook of porphyrin science. Vol. 21, Chapter 100: An overview of Metalloporphyrin-Catalyzed Carbon and Nitrogen Group Transfer Reactions, World scientific, **2012**, Singapore.
- (22) a) Subbarayan, V.; Jin, L.-M.; Cui, X.; Zhang, X. P. *Tetrahedron Lett.* **2015**, *56*, 3431. b) Lu, H.-J.; Jiang, H.-L.; Hu, Y.; Wojtas, L.; Zhang, X. P. *Chem. Sci.* **2011**, *2*, 2361.
- (23) Du, G.; Mirafzal, G. A.; Woo, L. K. *Organometallics* **2004**, *23*, 4230.
- (24) Clennan, E. L.; Pace, A. *Tetrahedron* **2005**, *61*, 6665.
- (25) DeRosa, M. C.; Crutchley, R. J. *Coord. Chem. Rev.* **2002**, *351*.
- (26) Berlicka, A.; König, B. *Photochem. Photobiol. Sci.* **2010**, *9*, 1359.
- (27) Nagasawa, T.; Allakhverdiev, S. I.; Kimura, Y.; Nagata, T. *Photochem. Photobiol. Sci.* **2009**, *8*, 174.
- (28) Toyao, T.; Ueno, N.; Miyahara, K.; Matsui, Y.; Kim, T.-H.; Horiuchi, Y.; Ikeda, H.; Matsuoka, M. *Chem. Commun.* **2015**, *51*, 16103.
- (29) Lazarides, T.; Sazanovich, I. V.; Simaan, A. J.; Kafentazi, M. C.; Delor, M.; Mekmouche, Y.; Faure, B.; Reglier, M.; Weinstein, J. A.; Coutsolelos, A. G.; Tron, T. *J. Am. Chem. Soc.* **2013**, *135*, 3095.
- (30) Inisan, C.; Saillard, J.-Y.; Guillard, R.; Tabard, A.; Le Mest, Y. *New. J. Chem.* **1998**, *823*.
- (31) a) Xu, J.; Shanmugam, S.; Boyer, C. *ACS Macro Lett.* **2015**, *4*, 926. b) Shanmugam, S.; Xu, J.; Boyer, C. *J. Am. Chem. Soc.* **2015**, *137*, 9174. c) Xu, J.; Shanmugam, S.; Fu, C.; Aguey-Zinsou, K.-F.; Boyer, C. *J. Am. Chem. Soc.* **2016**, *138*, 3094.
- (32) Kojima, M.; Oisaki, K.; Kanai, M. *Chem. Commun.* **2015**, *51*, 9718.
- (33) Nagib, D. A.; Scott, M. E.; McMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875.
- (34) Shih H.-W.; Vander, M. N.; Wal, R. L.; Grange; MacMillan D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600.
- (35) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77-80.
- (36) Neumann, M.; Földner, S.; König B.; Zeitler K. *Angew. Chem. Int. Ed.* **2011**, *50*, 951.
- (37) Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750-756.
- (38) Silvi, M.; Arceo, E.; Jurberg, I. D.; Cassni, C.; Melchiorre, P. *J. Am. Chem. Soc.* **2015**, *137*, 6120.

- (39) a) Hari, D. P.; König, B. *Chem. Commun.* **2014**, 50, 6688.
b) Hari, D. P.; König, B. *Org. Lett.* **2011**, 13, 3852.
- (40) Rybicka-Jasińska, K.; Ciszewski, Ł. W.; Gryko, D. *Adv. Synth. Catal.* **2016**, 358, 1671.
- (41) Kadish, K. M.; Morrison, M. M. *Bioinorg. Chem.* **1977**, 7, 107.
- (42) a) Kadish, K. M.; Van Caemelbecke, E. J. *Solid State Electrochem.* **2003**, 7, 254. b) Williams, R. F. X.; Hambright, P. *Bioinorg. Chem.* **1978**, 9, 537. c) Cui, Y.; Zeng, L.; Fang, Y.; Zhu, J.; Devillers, C. H.; Lucas, D.; Desbois, N.; Gros, C. P.; Kadish, K. M. *ChemElectroChem* **2016**, 3, 228. d) Tu, Y.-J.; Cheng, H. C.; Chao, I.; Cho, C.-R.; Cheng, R.-J.; Su, Y. O. *J. Phys. Chem. A* **2012**, 116, 1632. e) Xue, S.; Ou, Z.; Ye, L.; Lu, G.; Fang, Y.; Jiang, X.; Kadish, K. M. *Chem. Eur. J.* **2015**, 21, 2651. f) Fang, Y.; Bhyrappa, P.; Ou, Z.; Kadish, K. M. *Chem. Eur. J.* **2014**, 20, 524.
- (43) Schoeller, W. W.; Niemann, J.; Rademacher, P. *J. Chem. Soc. Perkin Trans 2* **1988**, 369.
- (44) a) Espinoza, E. M.; Larsen, J. M.; Vullev, V. L. *J. Phys. Lett.* **2016**, 7, 758; b) Larsen, J. M.; Espinoza, E. M.; Hartman, J. D.; Lin, Ch-K.; Wurch, M.; Maheshwari, P.; Kaushal, R. K.; Marsella, M. J.; Beran, G. J. O.; Vullev, V. L. *Pure Appl. Chem.* **2015**, 87, 779.
- (45) a) Bao D.; Ramu, S.; Contreras, A.; Upadhyayula, S.; Vasquez, J. M.; Beran, G.; Vullev, V. *J. Phys. Chem. B* **2010**, 114, 14467; b) Bao D.; Millare, B.; Xia, W.; Steyer, B. G.; Gerasimenko, A. A.; Ferreira, A.; Contreras, A.; Vullev, V. I. *J. Phys. Chem. A* **2009**, 113, 1259.
- (46) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, 9, 2209.
- (47) Morrison, M. M.; Kadish, K. M. *J. Am. Chem. Soc.* **1976**, 98, 3326.
- (48) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, 107, 5471.
- (49) L'Esperance, R. P.; Ford, T. M.; Jones, M. *J. Am. Chem. Soc.* **1988**, 110, 209.
- (50) Osuka, A.; Maruyama, K. *J. Chem. Research* **1987**, 2401.
- (51) Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, 6, 5426.
- (52) Hiramoto, K.; Johkoh, H.; Sako, K.; Kikugawa, K. *Free Radic. Res. Commun.* **1993**, 19, 323.
- (53) Janzen, E.G.; Coulter, G.A.; Oehler, U.M.; Bergsma, J.P. *Can. J. Chem.* **1982**, 60, 2725.

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