Visible-light-induced oxidant and metal-free dehydrogenative cascade trifluoromethylation and oxidation of 1,6-enynes with water†

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Generally, oxy-trifluoromethylation in olefins is achieved using oxidants and transition metal catalysts. However, labile olefins remain unexplored due to their incompatibility with harsh reaction conditions. Here, unprecedented light-induced oxidant and metal-free tandem radical cyclization–trifluoromethylation and dehydrogenative oxygenation of 1,6-enynes have been achieved using a photocatalyst, CF₃SO₂Na, and phenanthrene-9,10-dione (PQ). Langlois’ reagent (CF₂SO₂Na) and water as the oxygen source. This benign protocol allows for access to various CF₃-containing C₃-aryloyl/acylated benzofurans, benzothiophenes, and indoles. Moreover, the oxidized undesired products, which are inherently formed by the cleavage of the vinylic carbon and heteroatom bond, have been circumvented under oxidant free conditions. The mechanistic investigations by UV-visible and ESR spectroscopy, electrochemical studies, isotope labelling and density functional theory (DFT) suggest that light induced PQ produced a CF₃ radical from CF₂SO₂Na. The generated CF₃ radical adds to the alkene, followed by cyclization, to provide a vinylic radical that transfers an electron to PQ and generates a vinylic cation. Alternatively, electron transfer may occur from the CF₃-added alkene moiety, forming a carbocation, which would undergo cationic cyclization to generate a vinylic carbocation. The subsequent addition of water to the vinylic cation, followed by the elimination of hydrogen gas, led to the formation of trifluoromethylated C₃-aryloyl/acylated heterocycles.

The incorporation of a trifluoromethyl group (-CF₃) into drug molecules can dramatically change their properties, such as their solubility, lipophilicity, metabolic stability, etc. As a result, several trifluoromethylated heterocycles, such as efa-virenz and celecoxib, are used as potential drugs for the treatment of various diseases. It is worth noting that the synthesis of trifluoromethylated C₃-aryloyl heterocycles (shown in Fig. 1) has not been reported to date.

The trifluoromethylation and oxygenation of alkene and alkyne substrates have been achieved using various trifluoromethylating reagents and peroxides, persulfates, hypervalent iodine salts and...
oxygen as the oxidant and/or transition metal catalytic system (Scheme 1, eqn (1)).

Although different valuable approaches appear to have been incorporated into the –CF3 group, still there is demand for mild and sustainable synthetic methods that avoid oxidants and heavy metals and are applicable to sensitive substrates for the construction of functionalized advanced heterocycles.

The cyclization of 1,6-enynes can be a powerful transformation that allows for the construction of C3-aryloylated heterocycles (Scheme 1, eqn (2)). On the other hand, the use of TM-catalyzed reaction conditions are rear-

Results and discussion

Initial screening and photo-initiated conditions with and without oxidants

Initially, 1-(phenylethynyl)-2-(vinloxy)benzene substrate 1a was reacted with an economical amount of trifluoromethylating Langlois’ reagent (CF3SO2Na) under an oxygen atmosphere and heated conditions (Table 1). Disappointingly, cleavage of the vinylic carbon–oxygen bond occurred, which yielded undesired phenol, thiphenoil and aniline as the main side products, respectively (eqn (3)). It is a natural inherent property of oxygen (bi-radical) to form a peroxide that leads to the cleavage of the labile carbon–heteroatom bond and thus imposes a major challenge to functionalize such a vinylic carbon–carbon double bond.

Consequently, keeping the ether linkage intact throughout the trifluoromethylation of the vinylic C–C double bond adjacent to the heteroatom has not been reported to date, despite the presence of this skeleton in various molecules of pharmaceuticals, agrochemicals, materials, and fine chemicals.

Photocatalyzed cascade radical reactions have gained much attention in recent times as these reactions provide access to complex molecules in one pot with step and atom economy.

Although several photocatalyzed trifluoromethylation reactions viz. aromatic trifluoromethylation,20 conversion of alkenes into tetra-substituted trifluoromethylated alkenes,20b and radical trifluoromethylation/cyclization cascade for CF3-containing pyrazolines and isoxazolines20m have been described, cascade oxy-trifluoromethylation has not been explored. Water is the most abundant reactant that can be used as an oxygen source in photocatalytic reactions. The incorporation of water for the oxygenation of substrates requires a strong one-electron oxidant. Alternatively, water can be added as a nucleophile to an organic substrate followed by its oxidation by weaker oxidants under light-driven conditions, which could lead to the oxygenation of organic molecules.

In the continuation of our research interest in TM-free C–C and C–heteroatom coupling reactions,21 here, we disclose a phocatalyzed reaction that not only activates CF3SO2Na for the generation of the CF3 radical but also facilitates water towards the oxygenation of organic molecules. This approach enables the oxygenation of labile 1,6-enyne substrates along with the generation of hydrogen gas under oxidant-free conditions, which circumvents an undesired, over-oxidized product. The mechanistic investigations by labelling experiments, UV-visible and ESR spectroscopy and cyclic voltammetry studies, corroborated by DFT calculations, have been carried out to understand the role of the photoredox catalyst (PC) in the oxy-trifluoromethylation reaction of 1,6-enynes under oxidant and metal-free conditions.
characteristic of carbonyl in PQ, its reduction is enabled by the abstraction of an electron from CF₃SO₂Na and the generation of a CF₃ radical, which can indeed initiate a cascade reaction.

The reaction system under UV-irradiation in acetone, which acts as a solvent and radical initiator, and under oxygen atmosphere provided only traces of 2a (Table 1, entry 3). Similar results were obtained with A-C under UV-irradiation and also with D, PQD and PQ under visible light and oxygen atmosphere (Table 1, entries 4–9). In the absence of oxygen, no product formation was realized, as expected (Table 1, entry 10). Surprisingly, when the reaction was performed in the absence of oxygen in a mixture of an organic and water solvent system, a noticeable increase in the yield of the desired product 2a was observed, moreover, the formation of undesired side product was minimized to <10% yield (Table 1, entries 11–16). The reactions presented here were optimized under sun-light irradiation. In a separate experiment, a household CFL bulb (23 W) was used, which provided nearly the same yield of 2a (69% vs. 76% in sunlight) although a longer time (6 h for sunlight vs. 16 h for one 23 W CFL bulb) is required (Table 1, entry 17). A trifluoromethylation reaction under oxygen atmosphere, instead of argon, under optimized conditions, afforded 24% yield of the desired product 2a (Table 1, entry 18). Among the various diketones screened (A–D, PQD, PQ) (Table 1, entries 3–17), PQ, which has been explored for the first time, provided optimum yield of the desired oxy-trifluoromethylated benzofuran 2a under sunlight irradiation.

The substrate scope of the light-induced oxy-trifluoromethylation reaction to phenolic 1,6-enynes

Next, the substrate scope was studied on phenolic 1,6-enynes (1a–1r) under the optimized reaction conditions (Table 1, entry 15). Substrates 1b–1j, with electron donating as well as electron withdrawing substituents on the ethynyl ring, showed compatibility with the optimized reaction conditions and afforded respective trifluoromethylated benzofurans 2b–2j in 57–75% yields (Scheme 2). Moreover, the phenolic-1,6-enyne substrate 1c with OH functionality and an acidic proton was tolerated to provide hydroxyl benzofuran 2c in good yield. The heteroaromatics pyridyl and thiophenyl and other aromatic naphthyl, as well as phenolic ring was also explored under the optimized conditions (Table 1, entry 15). Similar results were obtained with other aromatic, naphthyl containing substrates we and were amenable to the reaction and transformed into the respective benzofurans 2k–2r. Next, the n- and sec-alkyl substituted substrates 1n–1o underwent an oxy-trifluoromethylation reaction to afford the acyl-benzofurans 2n–2o, albeit in low yields. Substitution on the phenolic ring was also explored under the optimized conditions. Substrate 1p, containing a naphthyl ring, and substrates 1q–1r, having fluoro and methyl substituents on the phenolic ring, afforded respective trifluoromethylated benzofurans 2p and 2q–2r without any noticeable loss in the yields (55–69%).

Substrate scope with regard to thienophenolic 1,6-enynes

In order to explore the synthesis of trifluoromethylated C₃-aryloyl benzothiophenes, thio-linked 1,6-enyne substrates 3a–3m were prepared from 2-bromo-benzenethiols in moderate yields (Scheme 3, for details see the ESI, page S28 and S29†). In

- Table 1: Optimization of the reaction conditions

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\(^a\) The reactions were carried out using 0.1 mmol of 1a, 0.3 mmol of CF₃SO₂Na and 0.01 mmol of photocatalyst (PC) in 1 mL of solvent at 30 °C in a 5 mL round bottom flask under O₂ or Ar atmosphere, unless otherwise stated; the progress of the reaction was monitored by TLC. \(^b\) Percentage isolated yield. \(^c\) Under a household CFL bulb (23 W). nd = not detected.

(A–D) and ortho-quinones 1,10-phenanthroline-5,6-dione (PQD) and phenanthrene-9,10-dione (PQ) were investigated for their UV-visible absorption properties (Fig. 2). A–D show strong absorption in the ultraviolet range below 380 nm, whereas ortho-quinones PQD and PQ exhibit absorption bands in the visible range (380–420 nm). The absorption bands for PQ appeared in the visible light region (420 and 505 nm) in acetone solvent, which shows a slight red shift in acetonitrile (ESI, page S12 and S13†). The electronic excitation would lead to a first triplet excited state (T1) of the carbonyl group having a diradicaloid nature. The triplet states of aromatic ketones are long-lived, and also the electronic character and reactivity of the lowest triplet state can be tuned by the solvent polarity. \(^d\) 9,10-Phenanthrenequinone PQ shows an n → π* transition of an aromatic ketone that could reverse the charges on the C=O group, thus making the oxygen atom electron deficient. Due to the electron-deficient oxygen atom and “radical-like”

Fig. 2 Screened diketones and ortho-quinones.
general, the sulfur-containing substrates showed sluggish reactivity under TM-catalyzed reaction conditions due to the poisoning of the catalyst by sulfur. Earlier synthetic methods involve inter or intramolecular coupling of alkynyl and sulf-oxide in the presence of high loading of the Au, Hg and Pd-catalysts.

To our delight, a TM-free cyclization reaction yielded C3-aryloyl trifluoromethylated benzothiophenes 4a–4m in nearly the same yields (73–36%) as those obtained for benzofurans. Moreover, a similar substrate scope was realized as thio-linked 1,6-enyne substrates 3b–3m with electron donating methyl, methoxy, [1,3]-dioxole, and tri-methoxy and electron withdrawing CF3 and F and also naphthyl, thiophenyl, and n-hexyl substituents provided unaltered yields of 2-trifluoromethyl C3-aryloyl/acylated benzothiophenes 4b–4m. The cyclopropyl substituted substrate 3l also underwent ring opening of the cyclopropyl ring by the trifluoromethyl radical to yield an unexpected di-trifluoromethylated benzothiophene 4l as the major product and a di-trifluoromethylated product as the minor product.

### Substrate scope with regard to anilinic 1,6-enynes

Next, N-tosyl (Ts) and N-tert-butyloxycarbonyl (Boc) protected 1,6-enyne substrates were prepared to construct trifluoromethylated C3-aryloyl indoles, which are prevalent heterocycles in many drugs and materials (Scheme 4).

Indeed, N-tosylated substrates 5a–5g underwent an oxy-trifluoromethylation reaction. Moreover, the removal of the tosyl (Ts) group was realized in the same pot leading to N-unprotected trifluoromethylated C3-aryloyl indoles 6a–6g in 67–56% yields. Next, we sought for the synthesis of N-protected trifluoromethylated C3-aryloyl indoles. Substrates 5h–5l, which were protected by a N-tert-butyloxycarbonyl (Boc) group, provided trifluoromethylated indoles in moderate (10–57%) yields. Both N-Ts and Boc-protected 1,6-enyne substrates, having bromo, fluoro, difluoro, methoxy, methyl and pyridyl, naphthyl and thiophenyl rings, were amenable to the oxidant and metal-free o xo-trifluoromethylation reactions. A more
efficient electron delocalization occurs with the N-protected carbonyl group of carbamate rather than the sulfonyl moiety of the tosyl group. The weak mesomeric effect indicates that the sulfur-centered group had increased electron density on the nitrogen, which reflected the higher aromaticity of the indole.

As a consequence, tosyl becomes a better leaving group than carbamate. Thus the deprotection of the tosyl protecting group under the optimized reaction conditions is attributed to its labile nature. The C3-aryloyl trifluoromethylated indoles 6c and 6d, benzofuran 2c, and benzothiophene 4k are also characterized by X-ray single crystal structure analysis (for details, see ESI, pages S80–S106†).

**Synthesis of CF3-bearing drugs**

The synthesis of trifluoromethylated drug molecules was explored from synthesized 2-trifluoromethyl-C3-aryloyl benzofuran 2c and indole 6f by late-stage functionalization (Scheme 5). The bromination of benzofuran 2c using N-bromosuccinimide afforded novel trifluoromethylated benz bromarone 7a in 40% yield. The N-alkylation of the synthesized oxy-trifluoromethylated indole 6f was observed to be difficult by known methods using KOH in DMSO, Cs2CO3 in DMSO or K2CO3 in DMF and failed to yield N-alkylated indole 7b and instead a decomposed product was realized.21 The addition of NaH in DMF along with n-propyl iodide at 0 °C provided the trifluoromethylated JWH-105 7b drug in moderate yield (54%).

**Mechanistic study**

**Labelling and 1H NMR experiments**

A labelling experiment was performed using H2O18 under the optimized reaction conditions (Scheme 6). Mass analysis revealed the formation of O18-labelled trifluoromethylated C3-aryloyl benzofuran (M + H+ = 307.0821; calcd 307.0851).

1H NMR experiments were performed on the reaction mixture to gain further insights.1H NMR spectroscopy of the reaction mixture shows a peak (δ = 4.57 ppm) indicative of...
hydrogen evolution in the reaction mixture (see the ESI, page S7–S8 for details†). Next, a reaction was carried out in CH3CN-d3 to study the role of the solvent. Expectedly, 1H NMR spectroscopy shows the formation of H2, which suggests that acetonitrile does not participate in the reaction. When D2O was used in the reaction, the formation of H–D (δ = 4.55 ppm, J = 42.8 Hz) and H2 was realized in the 1H NMR spectrum, revealing the involvement of water in the hydrogen gas evolution (Fig. 3 and Scheme 6). The formation of H2 gas is attributed to H2O in deuterated solvents and it is the result of hydrogen and deuterium exchange (page S8†).

ESR investigation

To investigate the reaction pathways, EPR experiments were conducted on the reaction mixture. For this purpose, the generated reactive CF3 radical in the reaction was trapped by the 2-methyl-2-nitrosopropane (MNP) dimer, and its EPR spectrum was monitored (Scheme 7).

CF3SO2Na and MNP in the presence of CH3CN/H2O under light irradiation provided a triplet centred at 3364.5 G with a coupling constant 14.7 G, which is attributed to the dissociation of MNP to a tert-butyl nitroxide radical (see the ESI, Fig. S6†). The formation of the tert-butyl nitroxide radical is largely suppressed in CH2Cl2/H2O and the formation of the tert-butyl-trifluoromethyl nitroxide radical 7c (Scheme 7) is observed predominantly as the EPR spectrum shows a sextet centered at g = 2.0054 with a coupling constant 12.27 G. A reaction mixture of MNP, CF3SO2Na and 1a under dark conditions was realized to be EPR silent. Upon light irradiation, the reaction mixture shows a similar well-resolved sextet centered at g = 2.0089 with a coupling constant 12.38 G (Scheme 7 and Fig. 4). The intensity of the EPR signals gradually decreased with time and completely diminished after 25 minutes. The second time irradiation of the same reaction mixture again showed a sextet signal in the EPR spectrum. This suggests that continuous irradiation of the reaction mixture is necessary for the generation of the CF3 radical to achieve maximum conversion.

Absorption spectra

UV-visible spectroscopic studies were performed on the reaction mixture to understand the role of PQ. The spectra of PQ shows well-resolved absorption maxima at 420 and 510 nm in CH3CN and H2O (9 : 1) mixtures (Fig. 5). An equimolar mixture of PQ and CF3SO2Na did not lead to any change in the absorption spectrum under dark conditions.

The reaction mixture of PQ, CF3SO2Na and substrate 1a provided a similar absorption spectrum under dark conditions. Further, the impact of light on the reaction progress was studied for 3 h at 30 min time intervals. Upon sunlight irradiation (30 min) of the reaction mixture, the characteristic peaks of PQ completely disappeared (Fig. 5) suggesting the involvement of PQ in the oxy-trifluoromethylation reaction.

The absorption spectra of the standard reaction mixture remained nearly unchanged at various time intervals. It seems that photocatalyst PQ is transformed into another species,
presumably phenanthrene-9,10-diol (PQH₂), which might be the dominant species observable by UV-visible spectroscopy under the reaction conditions (Fig. S13, see the ESI page S14†). A slight increase in the absorption at 420 nm was observed with an increase in time, which could be attributed to the partial regeneration of PQ after the completion of the reaction. Further, the regeneration of PQ is confirmed by ¹³C NMR spectroscopy and mass spectrometry (ESI, page S16 and S17†).

Cyclic voltammetric study

To gain insights into the redox behaviour of photocatalyst PQ, a cyclic voltammetry study was performed (Fig. 6). The cyclic voltammogram (CV) of PQ shows reversible two-electron reduction processes at −0.52 and −0.70 V (E½ red) attributed to the quinone → semiquinone and semiquinone → catechol redox couples, respectively (Scheme 8) 35.

The considerably lower reduction potentials of PQ, presumably due to the presence of conjugation adjacent to the 9 and 10-positions of the C=O group, provide stability to the radical PQ⋅* and diox PQH₂. Also, photocatalyst PQ exhibited high stability under the electrochemical redox process as it underwent 12-cycles without any loss in the redox activity.

Photocatalyst PQ has a triplet excited state energy of 2.116 eV, 36 thereby the excited state reduction potential E½ red(−0.52 V) of PQ is 1.6 V (ref. 27f and 36h) and Langlois’ reagent exhibits an oxidation potential of 1.05 V (vs. SCE), 37 which suggests that PQ is strong enough for the oxidation of CF₃SO₂Na by single electron transfer (ΔG_{PET} = −12.7 kcal mol⁻¹).

Control experiments

To study whether water alone is enough to initiate the reaction, substrate 1a was treated with water in the absence of CF₃SO₂Na under optimized reaction conditions (Scheme 9). The hydroxylation of the alkene or alkyne was not observed and 1,6-enyne 1a was recovered quantitatively. It seems that the substrate does not undergo photohydration of the alkynes 34 to provide 1-phenyl-2-(2-(vinyloxy)phenyl)ethan-1-one, which is suggestive of the reaction process being less likely via oxygenation followed by trifluoromethylation of substrate 1a.

When the reaction was performed in the presence of a radical scavenger, TEMPO, the formation of 2a was not observed. Instead, the coupling between CF₃ and TEMPO was realized (see ESI, S11†).

Mechanism, quantum yield and DFT calculations

Based on the control and labelling experiments, it is reasonable to assume that the photoredox catalyst PQ, excited by visible light, activates CF₃SO₂Na by single electron transfer to produce a CF₃ radical and SO₂ (Scheme 10). The trifluoromethylated radical would add to the vinyl carbonyl–carbon double bond of the substrate 1a, forming a radical species I, which intramolecularly translocated to the alkyne bond via 5-exo-dig cyclization and thus rearranged to the vinylic radical IIa. The electron transfer from vinylic radical IIa to PQ would lead to vinylic carboxation III and PQH₂. Although, vinylic carbocations have low thermodynamic stability due to the sp-hybridization of the carbene resonance centre and as a consequence show poor S₄N-reactivity. However, the sp–sp² rehybridization in the high energy state could account for its electrophilic nature. 38 The second electron accepting ability of the photoredox catalyst PQ would facilitate the formation of vinylic carboxation III.

Alternatively, the alkyl ether radical I may transfer an electron to PQH⁺ intermolecularly and convert into carboxation IIb, which may proceed by an intramolecular cationic cyclization to provide vinylic carboxation III 39.
The slow addition of water to vinylic carbocation III shall provide aquated intermediate IV, which upon release of the proton converts into enol intermediate V. Further, the photoaromatization of enol V would furnish 2-trifluoromethylation C₃-arylloy benzofuran 2a along with the concomitant release of hydrogen gas.⁴⁰ As inferred from the UV-visible study (vide supra), PQH₂ would be the predominant species in the catalytic cycle. PQH₂ could regenerate to PQ by the transfer of its electrons to sulfur dioxide³⁷ and/or the trifluoromethyl radical to form a HSO₂ radical and/or fluoroform, respectively.

The quantum yield (QY) can in particular provide valuable insight into the mechanistic understanding of the photocatalytic reaction, which involves radical chain propagation. The QY of the developed reaction, substrate 1a to product 2a, was studied using the photodecomposition of potassium ferrioxalate, which is a well-explored chemical actinometer.⁴¹ The determined QY is ϑ = 27 (for details, see the ESI page S17†) which suggests that 27 equivalents of product 2a are formed for every photon absorbed by the photocatalyst PQ. Therefore, the reaction may proceed via a chain mechanism. The generated HSO₂ radical propagates the radical chain by reacting with Langlois’ reagent, which again provides a CF₃ radical, thus continuing the radical chain reaction.

DFT calculations were explored to examine the mechanism of the reaction (Fig. 7 and Scheme 10). The thermodynamic feasibility of the intermediates and oxygenation by water were computed using DFT-B3LYP/6-31+G(d) in a Gaussian 09 suite in CH₃CN (see the ESI, page S65-S80†). The Gibbs free energy of the reaction suggests that the proposed intermediates I-V are
stable under the reaction conditions. The vinylc cation could be obtained from radical I by two paths A and B (Fig. 7) as the energy difference between them is 2.03 kcal mol\(^{-1}\). The attack of a water molecule on vinylc cation III could be the key step in the transformation and may occur through a transition state TS. The energy barrier (\(\Delta G^e\)) for the step is +16.47 kcal mol\(^{-1}\), which could be feasible under the reaction conditions. Further, the abstraction of the proton from the hydronium ion IV by POH\(_2\) provides a stabilization to intermediate V by the energy difference of 63.52 kcal mol\(^{-1}\) and the subsequent removal of hydrogen gas from the intermediate V lowers the energy by 6.78 kcal mol\(^{-1}\).

Conclusions

In summary, we have unveiled an oxidant and TM-free visible light induced oxy-trifluoromethylation of enynes that enables access to biologically important carboxy-trifluoromethylated benzofurans, thiophenes, and indoles. The mild reaction conditions tolerate electronically diverse substrates, regardless of the substitution pattern on either ethynlic or vinylic arene, and as a consequence the methyl group in benzboramone and JWH015 drugs has been substituted by a trifluoromethyl group. This protocol relies on the universal solvent as a source of oxygen for the oxygenation of enynes. The use of a highly practical 9,10-phenanthroquinone photoredox catalyst, which has a two electron redox property, seems crucial for the transformation as it not only generates trifluoromethyl radicals from the Langlois’ reagent by an electron transfer, but it also brings about one electron oxidation of enynes by a second electron transfer, which in turn facilitates oxygenation utilizing water followed by hydrogen gas evolution under oxidant and TM-free mild conditions. Moreover, we have shown that the di-functionalization of the vinylic double bond adjacent to the heteroatom, which is a formidable task due to the cleavage of the labile carbon–heteroatom bond, can be achieved under the developed conditions. The finding of oxy-trifluoromethylation of enyne substrates under metal and oxidant-free conditions opens a new avenue for the synthesis of trifluoromethylated advanced heterocyclic molecules under atom and step economical pathways.

Acknowledgements

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Notes and references


1-(Alky/arylthethyl)-2-(vinyllyoxy)benzenes substrates 1a-1r were prepared by following the reported procedure: N. Sakiyama, K. Noguchi and K. Tanaka, *Angew. Chem., Int. Ed.*, 2012, **51**, 5976.


33 Because the reaction mixture provides an EPR signal only for dissociated MNP; tert-butyl nitroxide radical in CH$_3$CN: H$_2$O solvent. Therefore, the reaction mixture along with the MNP dimer was conducted in a CH$_2$Cl$_2$ : water solvent system for EPR study. (a) Z. Li, Y. Zhang, L. Zhang and Z.-Q. Liu, *Org. Lett.*, 2014, 16, 382; (b) Z. Hang, Z. Li and Z.-Q. Liu, *Org. Lett.*, 2014, 16, 3648.


36 (a) Triplet exited state energy ($E^T_{o,o}$) of PQ is 48.8 kcal mol$^{-1}$ or 2.116 V, please see: J. J. Bohning and K. Weiss, *J. Am. Chem. Soc.*, 1966, 88, 2893; (b) Excited state reduction potential $E^\text{red}_{1/2}$ of PQ was calculated by following ref. 27: ground state $E^\text{red}_{1/2}$ (PQ/PQ$^\text{-}$) + triplet excited state ($E^T_{o,o}$) = 0.52 + 2.1161 = +1.60 V. $E^\text{red}_{1/2}$ (PQ/PQ$^\text{-}$) is determined experimentally.


