EDGE ARTICLE

Check for updates

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

Sadhan Jana, (ID) Ajay Verma, (ID) Rahul Kadu (ID) and Sangit Kumar (ID) *

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 photoredox catalyst, CF_3SO_2Na, and phenanthrene-9,10-dione (**PQ**), Langlois' reagent (CF_3SO_2Na) and water as the oxygen source. This benign protocol allows for access to various CF_3-containing C_3-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 CF_3 radical from CF_3SO_2Na. The generated CF_3 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 CF_3-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 C_3-aryloyl/acylated heterocycles.

Introduction

C_3-Aryloylated benzofurans, benzothiophenes, indoles, and related fused polyheterocycles are privileged structures with numerous applications in materials, drugs, and biology (Fig. 1).[1–5] Benzbromarone[2] is being used for the treatment of gout as a urate lowering drug (ULD) and amiodarone[3] is a potent inhibitor of the human cytochrome P-450 $(CYP)_2C_{19}$ responsible for metabolizing commonly prescribed drugs. The C_3-aryloylated benzothiophenes,[4] raloxifene and tubulin, which are antimitotic agents, act as an estrogen receptor and inhibitor for the polymerization of tubulin and growth of tumour cells, respectively. Similarly, 2-methyl-C_3-aryloylated indoles,[5] namely pravadoline, WIN55212-2, and clometacin, are nonsteroidal anti-inflammatory drugs, which are used against pain and inflammation. However, the construction of C_3-aryloylated benzofuran, indole, and thiophene scaffolds is still challenging (*vide infra*) despite the availability of advanced synthetic strategies.[15–17]

Department of Chemistry, Indian Institute of Science Education and Research (IISER) Bhopal, Bhopal By-pass Road, Bhauri, Bhopal-462066, India. E-mail: sangitkumar@iiserb.ac.in; Web: http://home.iiserbhopal.ac.in/~sangitkumar/

The incorporation of a trifluoromethyl group ($-CF_3$) into drug molecules can dramatically change their properties, such as their solubility, lipophilicity, metabolic stability, *etc.*[6] As a result, several trifluoromethylated heterocycles, such as efavirenz and celecoxib, are used as potential drugs for the treatment of various diseases.[7] It is worth noting that the synthesis of trifluoromethylated C_3-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
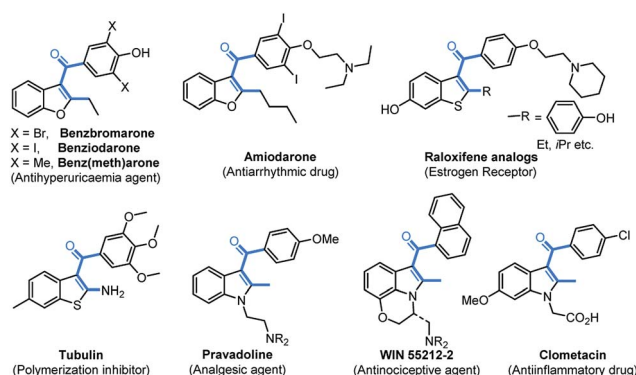

X = Br, **Benzbromarone**
X = I, **Benziodarone**
X = Me, **Benz(meth)arone**
(Antihyperuricaemia agent)

Amiodarone
(Antiarrhythmic drug)

Raloxifene analogs
(Estrogen Receptor)
—R = Et, *i*Pr etc.

Tubulin
(Polymerization inhibitor)

Pravadoline
(Analgesic agent)

WIN 55212-2
(Antinociceptive agent)

Clometacin
(Antiinflammatory drug)

Fig. 1 C_3-Aryloylated heterocyclic drugs.

oxygen as the oxidant and/or transition metal catalytic system (Scheme 1, eqn (1)).[8–14] Although different valuable approaches appear to have been incorporated into the –CF$_3$ 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 C$_3$-aryloyl/acylated heterocycles (Scheme 1, eqn (2)).[15–17] 1,6-Enyne substrates under transition metal (TM)-catalyzed reaction conditions are rearranged to benzofuran,[15] benzothiophene[16] and indole[17] heterocycles, and thus restrict the use of TM to access the desired C$_3$-aryloylated heterocycles. On the other hand, the use of oxidants such as hypervalent iodine reagents, peroxides, and oxygen, which are required for the generation of the CF$_3$ radical and as a source of oxygen under TM-free conditions, led to the cleavage of the vinylic carbon–heteroatom (oxygen, sulfur, nitrogen, etc.)[8c] bond and thus provided undesired phenol, thiophenol 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.[8f] 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.[18,19] Although several photocatalyzed trifluoromethylation reactions viz. aromatic trifluoromethylation,[20a] conversion of alkynes into tetra-substituted trifluoromethylated alkenes,[20b] and radical trifluoromethylation/cyclization cascade for CF$_3$-containing pyrazolines and isoxazolines[20c] 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.[21]

In the continuation of our research interest in TM-free C–C and C–heteroatom coupling reactions,[22] here, we disclose a photocatalyzed reaction that not only activates CF$_3$SO$_2$Na for the generation of the CF$_3$ 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.

Results and discussion

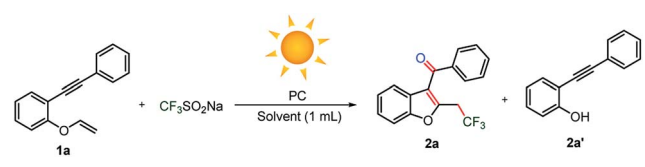### Initial screening and photo-initiated conditions with and without oxidants

Initially, 1-(phenylethynyl)-2-(vinyloxy)benzene substrate **1a** was reacted with an economical amount of trifluoromethylating Langlois' reagent (CF$_3$SO$_2$Na) under an oxygen atmosphere and heated conditions (Table 1). Disappointingly, cleavage of the vinylic carbon–oxygen bond occurred, which yielded undesired 2-(phenylethynyl)phenol **2a′** instead of C$_3$-aryloylated-2-trifluoromethylated benzofuran **2a** (Table 1, entry 1). Similarly, various oxidants, such as hydrogen peroxide, benzyl peroxide, tert-butyl hydroperoxide, di-tert butyl peroxide, iodine, (diacetoxyiodo)benzene, persulfate salts, oxone, ceric ammonium nitrate, 2,3-dichloro-5,6-dicyano-p-benzoquinone and the radical initiators azobisisobutyronitrile and azobis(2,4-dimethylvaleronitrile), provided the undesired phenol **2a′** as a major product and **2a** was noticed as a minor product (<20% yields, see ESI, page S3 and S4†). Next, we performed the reaction at room temperature using oxygen, and the reaction provided **2a** and **2a′** in <10 and 15% yields, respectively (Table 1, entry 2). However, poor conversion was observed despite the continuation of the reaction for a longer time (24 h) and 70% of substrate **1a** was recovered from the reaction.

Next, we envisaged that the UV-visible irradiation of the reaction system in the presence of diketones would bring about oxy-trifluoromethylation in 1,6-enyne as n → π* triplet-excited ketones have been successfully exploited in several photoinduced chemical transformations.[23] Consequently, α-diketones
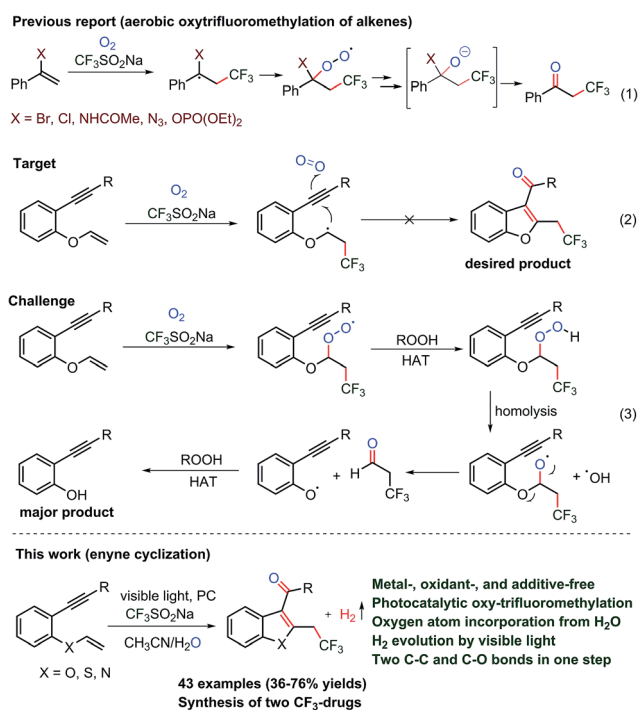
**Scheme 1** Oxy-trifluoromethylation of alkenes.

Table 1 Optimization of the reaction conditions[a]

Entry	PC (mol%)	Gas	Solvent	Yield[b] 2a/2a′
1	−(90 °C)	O$_2$	DMSO	Trace/74
2	−(25 °C)	O$_2$	DMSO	<10/15
3	—	O$_2$	Acetone	Trace/20
4	**A**	O$_2$	Acetone	Trace/15
5	**B**	O$_2$	Acetone	nd/10
6	**C**	O$_2$	Acetone	5/15
7	**D**	O$_2$	Acetone	5/15
8	**PQD**	O$_2$	Acetone	3/25
9	**PQ**	O$_2$	Acetone	9/30
10	**PQ**	Ar	Acetone	Trace/—
11	**PQ**	Ar	Acetone : H$_2$O (9 : 1)	20/8
12	**PQ**	Ar	EtOH : H$_2$O (9 : 1)	13/5
13	**PQ**	Ar	DMF : H$_2$O (9 : 1)	35/10
14	**PQ**	Ar	DMSO : H$_2$O (9 : 1)	48/12
15	**PQ**	**Ar**	**CH$_3$CN : H$_2$O (9 : 1)**	**76/trace**
16	**PQ**	Ar	THF : H$_2$O (9 : 1)	32/5
17[c]	**PQ**	Ar	CH$_3$CN : H$_2$O (9 : 1)	69/trace
18	**PQ**	O$_2$	CH$_3$CN : H$_2$O (9 : 1)	24/40

[a] The reactions were carried out using 0.1 mmol of **1a**, 0.3 mmol of CF$_3$SO$_2$Na and 0.01 mmol of photocatalyst (PC) in 1 mL of solvent at 30 °C in a 5 mL round bottom flask under O$_2$ 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)[24] 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.[25] 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"
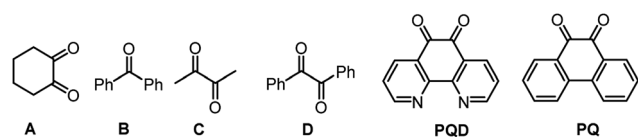
characteristic of carbonyl in **PQ**, its reduction is enabled[26] by the abstraction of an electron from CF$_3$SO$_2$Na and the generation of a CF$_3$ radical, which can indeed initiate a cascade reaction.

The reaction system under UV-irradiation in acetone, which acts as a solvent and radical initiator,[20m] 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,[27] 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**)[28] 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 hetero-aromatics pyridyl and thiophenyl and other aromatic naphthyl, as the ethynyl ring containing substrates **1k–1m**, were also amenable to the reaction and transformed into the respective benzofurans **2k–2m**. 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%).
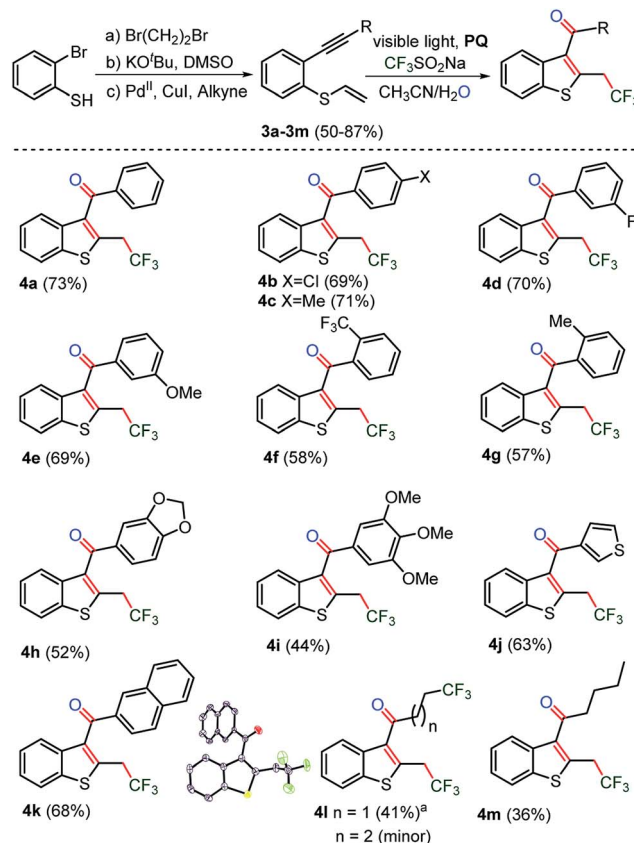
Substrate scope with regard to thiophenolic 1,6-enynes

In order to explore the synthesis of trifluoromethylated C$_3$-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

Fig. 2 Screened diketones and *ortho*-quinones.
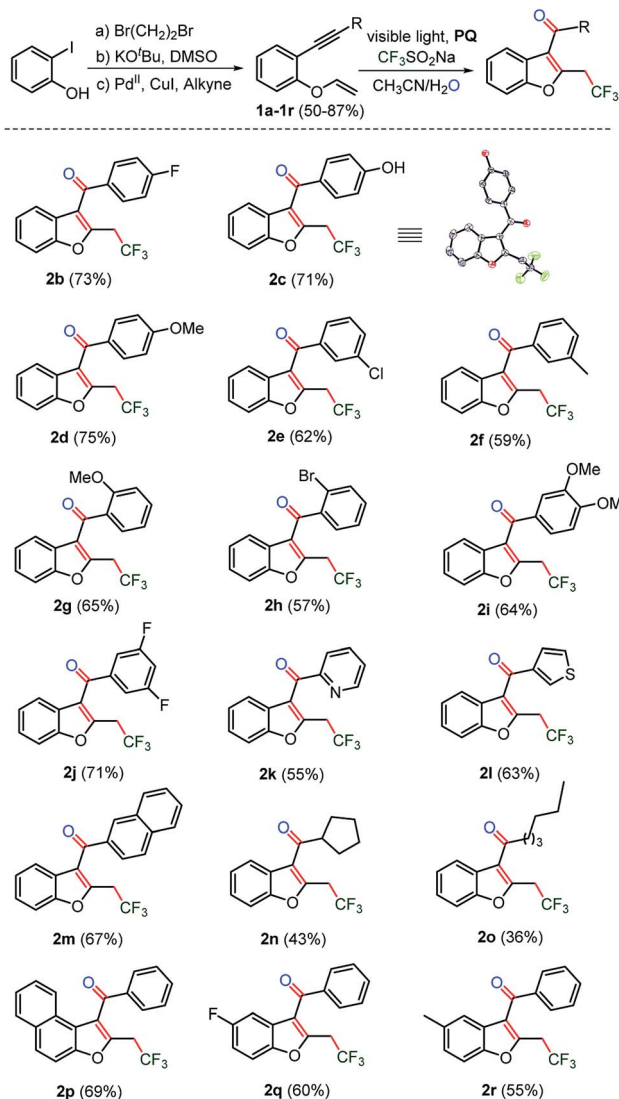
Scheme 2 CF$_3$-Benzo[b]furans: the scope with regards to the ethynyl and vinyloxy rings; the reactions were carried out at 0.1 mmol of **1a** using 0.3 mmol of CF$_3$SO$_2$Na and 0.01 mmol of photocatalyst **PQ** in CH$_3$CN + H$_2$O (0.9 + 0.1 mL) under Ar, and the progress of the reaction was monitored by TLC for 4–8 h.

Scheme 3 Synthesis of CF$_3$-benzo[b]thiophenes. The reaction of 0.1 mmol of **3a**, 0.3 mmol of CF$_3$SO$_2$Na and 0.01 mmol of photocatalyst **PQ** in CH$_3$CN and H$_2$O was irradiated under Ar and the progress of the reaction was monitored by TLC. **4l** was obtained from cyclopropane substituted substrate **3l**, as the major along with the minor (n = 1) product (see the ESI, page S56 and S57, and the spectra on pages S203–S207†).

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 sulfoxide in the presence of high loading of the Au, Hg and Pd-catalysts.[16d,e] To our delight, a TM-free cyclization reaction yielded C$_3$-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 CF$_3$ and F and also naphthyl, thiophenyl, and n-butyl substituents provided unaltered yields of 2-tri-fluoromethyl C$_3$-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[29] substrates were prepared to construct tri-fluoromethylated C$_3$-aryloyl indoles, which are prevalent heterocycles in many drugs and materials (Scheme 4).[5a,b] 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 C$_3$-aryloyl indoles **6a–6g** in 67–56% yields. Next, we sought for the synthesis of N-protected trifluoromethylated C$_3$-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 oxy-trifluoromethylation reactions. A more
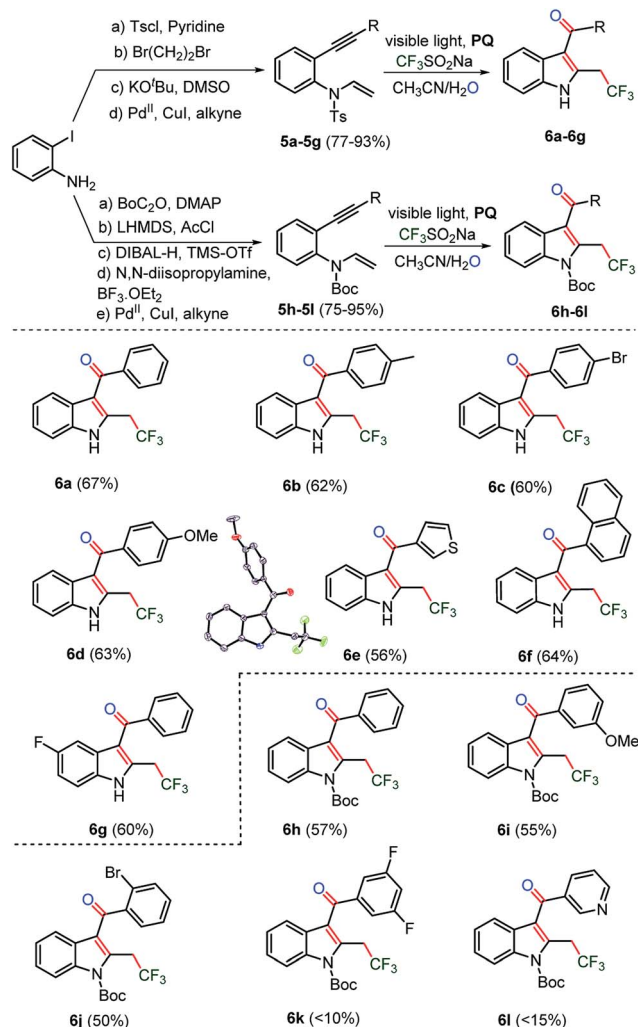
Scheme 4 Synthesis of CF$_3$-indoles. The reaction of **5a** (0.1 mmol), 0.3 mmol of CF$_3$SO$_2$Na and 0.01 mmol of photocatalyst **PQ** in CH$_3$CN and H$_2$O was irradiated for 4–8 h under argon atmosphere.

efficient electron delocalization occurs with the *N*-protected carbonyl group of carbamate rather than the sufonyl 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.[30] 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 C$_3$-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 CF$_3$-bearing drugs

The synthesis of trifluoromethylated drug molecules was explored from synthesized 2-trifluoromethyl-C$_3$-aryloyl benzofuran **2c** and indole **6f** by late-stage functionalization (Scheme 5). The bromination of benzofuran **2c** using *N*-bromosuccinimide afforded novel trifluoromethylated benzbromarone **7a** in
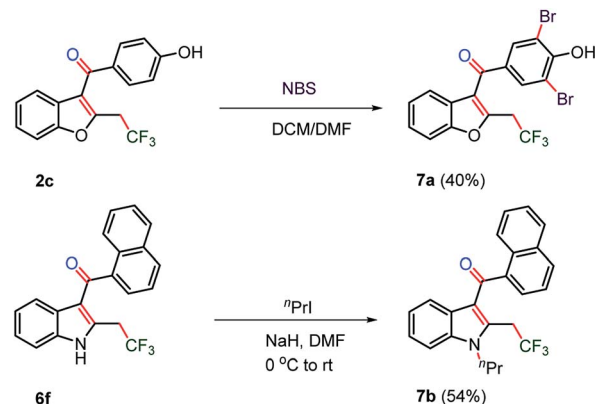
Scheme 5 CF$_3$-bearing drugs by post-modification. NBS (0.40 mmol) and **2c** (0.20 mmol) were used for **7a**. ^{n}PrI (0.12 mmol) and **6f** (0.16 mmol) in DMF were used for **7b**.

40% yield. The *N*-alkylation of the synthesized oxy-trifluoromethylated indole **6f** was observed to be difficult by known methods using KOH in DMSO, Cs$_2$CO$_3$ in DMSO or K$_2$CO$_3$ in DMF and failed to yield *N*-alkylated indole **7b** and instead a decomposed product was realized.[31] 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 ^{1}H NMR experiments

A labelling experiment was performed using H$_2$O^{18} under the optimized reaction conditions (Scheme 6). Mass analysis revealed the formation of O^{18}-labelled trifluoromethylated C$_3$-aryloyl benzofuran **2a** (M + H$^+$ = 307.0821; calcd 307.0851).

^{1}H NMR experiments were performed on the reaction mixture to gain further insights. ^{1}H NMR spectroscopy of the reaction mixture shows a peak (δ = 4.57 ppm) indicative of
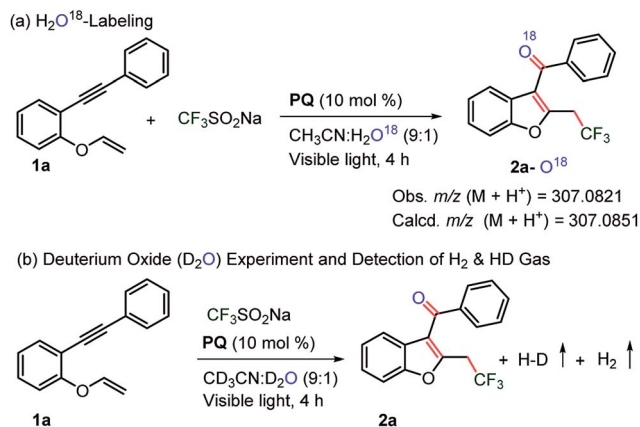
Scheme 6 Labelling experiments. (a) 0.1 mmol of **1a**, 0.3 mmol of CF$_3$SO$_2$Na and 0.01 mmol of **PQ** in CH$_3$CN + H$_2$^{18}O (900 + 100 μL). (b) The reaction was performed in an NMR tube at 0.05 mmol of **1a** using 0.15 mmol of CF$_3$SO$_2$Na and 0.005 mmol of **PQ** in CH$_3$CN + D$_2$O (450 + 50 μL).
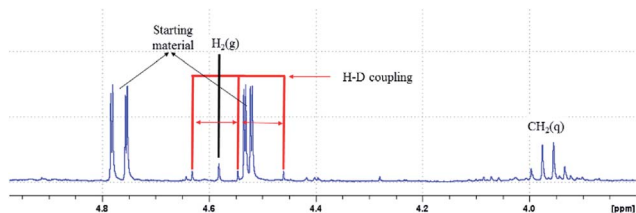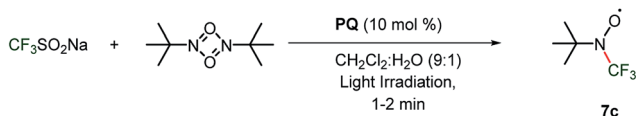
Fig. 3 ^{1}H NMR spectrum of the reaction showing H_2 & HD evolution.

hydrogen evolution in the reaction mixture (see the ESI, page S7–S8 for details†).[32] Next, a reaction was carried out in CH_3CN-d_3 to study the role of the solvent. Expectedly, ^{1}H NMR spectroscopy shows the formation of H_2, which suggests that acetonitrile does not participate in the reaction. When D_2O was used in the reaction, the formation of H–D ($\delta = 4.55$ ppm, $J = 42.8$ Hz) and H_2 was realized in the ^{1}H NMR spectrum, revealing the involvement of water in the hydrogen gas evolution (Fig. 3 and Scheme 6). The formation of H_2 gas is attributed to H_2O 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 CF_3 radical in the reaction was trapped by the 2-methyl-2-nitrosopropane (MNP) dimer, and its EPR spectrum was monitored (Scheme 7).

CF_3SO_2Na and MNP in the presence of CH_3CN/H_2O 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 CH_2Cl_2/H_2O 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.[33] A reaction mixture of MNP, CF_3SO_2Na 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 CF_3 radical to achieve maximum conversion.
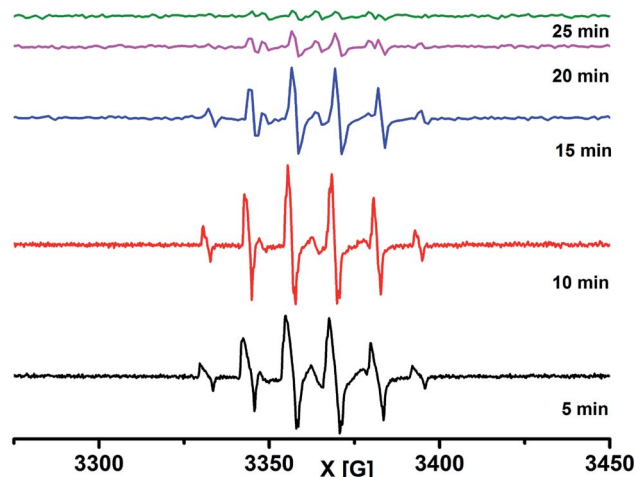

Fig. 4 EPR spectra of the reaction mixture with MNP at different time intervals.

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 CH_3CN and H_2O (9 : 1) mixtures (Fig. 5). An equimolar mixture of **PQ** and CF_3SO_2Na did not lead to any change in the absorption spectrum under dark conditions.

The reaction mixture of **PQ**, CF_3SO_2Na 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,

Scheme 7 The reaction with a radical trapping reagent. The reaction was carried out using CF_3SO_2Na (0.3 mmol), **1a** (0.1 mmol) and MNP (0.2 mmol) in an EPR tube in CH_2Cl_2/H_2O.
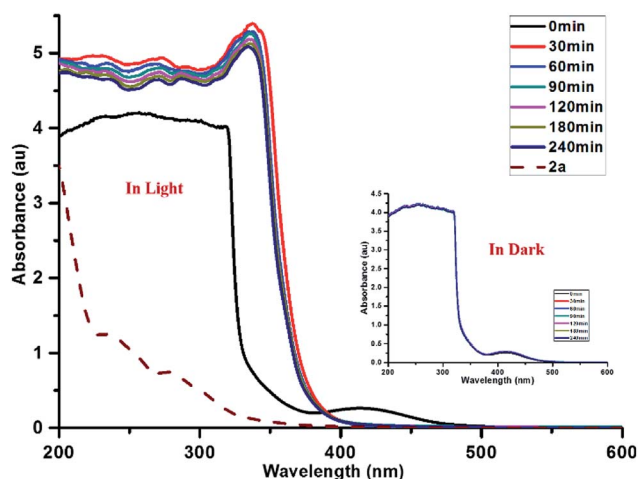

Fig. 5 Absorption spectra of **PQ** : CF_3SO_2Na : **1a** = 0.1 : 3 : 1 under visible light and dark conditions at different time intervals.

presumably phenanthrene-9,10-diol (**PQH$_2$**), 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 ^{13}C 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 ($E_{1/2}^{red}$) 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·H** and diol **PQH$_2$**. 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 V.[36a] Thus, the excited state reduction potential $E_{1/2}^{red}*$ (^{3}**PQ***/**PQ·$^-$**) of **PQ** is 1.6 V (ref. 27f and 36b) 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 CF_3SO_2Na 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 CF_3SO_2Na 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

Fig. 6 The cyclic voltammogram of **PQ** in CH_3CN/H_2O (9 : 1) vs. SCE.
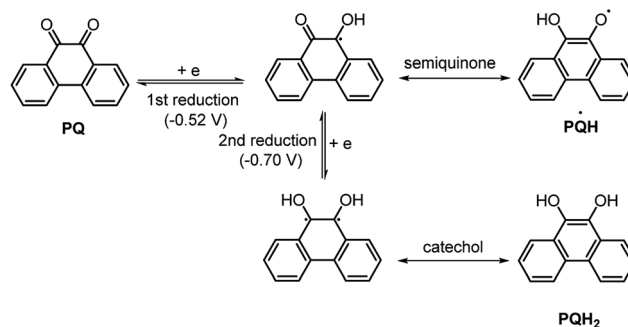
Scheme 8 The electrochemical reduction of **PQ** in CH_3CN/H_2O (9 : 1).
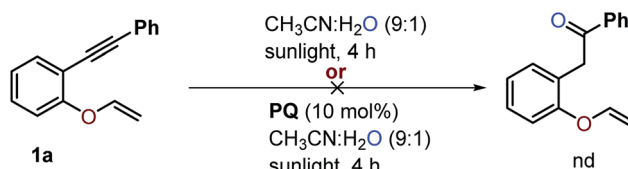
Scheme 9 The attempted hydroxylation of 1,6-enyne **1a**. The reaction was carried out using 0.1 mmol of **1a**, 0.3 mmol of CF_3SO_2Na and 0.01 mmol of **PQ** in CH_3CN and H_2O in a 5 mL round bottom flask.

not undergo photohydration of the alkynes[34] to provide 1-phenyl-2-(2-(vinyloxy)phenyl)ethan-1-one, which is suggestive of the reaction procession 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 CF_3 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 CF_3SO_2Na by single electron transfer to produce a CF_3 radical and SO_2 (Scheme 10). The trifluoromethylated radical would add to the vinylic carbon–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 carbocation **III** and **PQH$_2$**. Although, vinylic carbocations have low thermodynamic stability due to the sp-hybridization of the carbenium centre and as a consequence show poor S_N^1-reactivity. However, the sp–sp^2 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 carbocation **III**.

Alternatively, the alkyl ether radical **I** may transfer an electron to **PQ·H** intermolecularly and convert into carbocation **IIb**, which may proceed by an intramolecular cationic cyclization to provide vinylic carbocation **III**.[39]
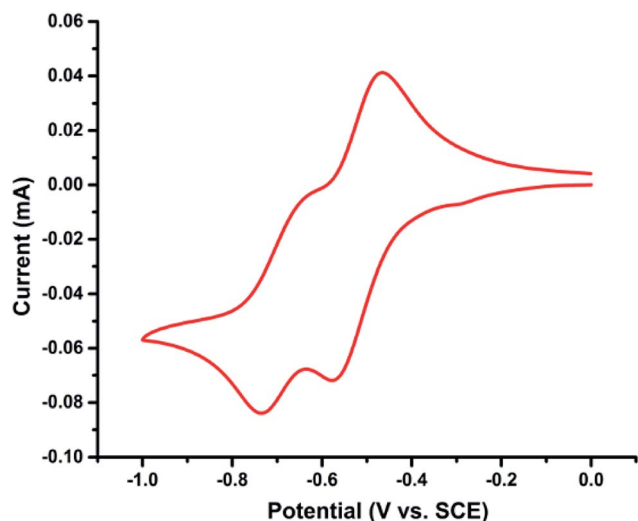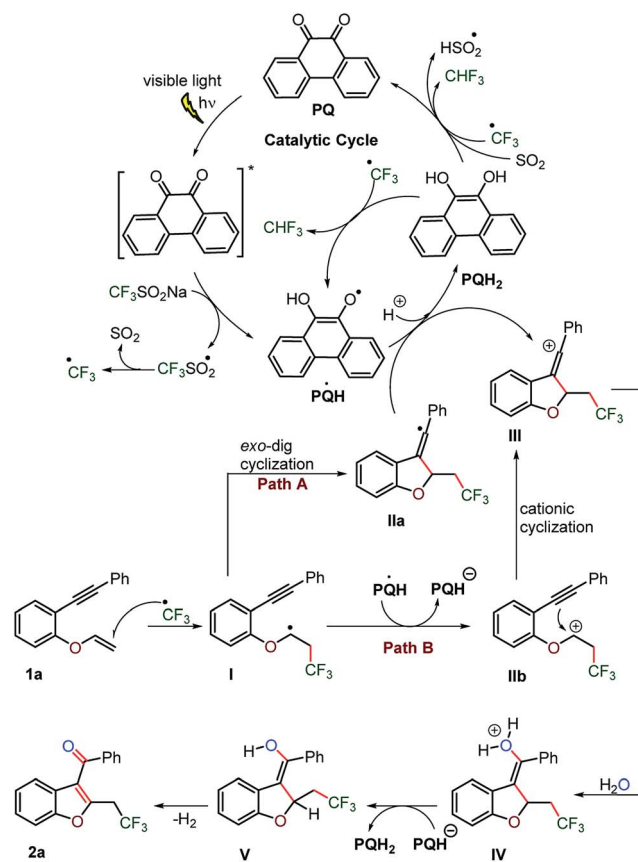
Scheme 10 Proposed mechanism for C$_3$-aryloyl benzofuran.

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 photo-aromatization of enol **V** would furnish 2-trifluromethylation C$_3$-aryloyl benzofuran **2a** along with the concomitant release of hydrogen gas.[40] As inferred from the UV-visible study (*vide supra*), **PQH$_2$** would be the predominant species in the catalytic cycle. **PQH$_2$** could regenerate to **PQ** by the transfer of its electrons to sulfur dioxide[37] and/or the trifluoromethyl radical to form a HSO$_2$ 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 $\varphi = 27$ (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 HSO$_2$ radical propagates the radical chain by reacting with Langlois' reagent, which again provides a CF$_3$ 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 CH$_3$CN (see the ESI, page S65–S80†). The Gibbs free energy of the reaction suggests that the proposed intermediates **I–V** are
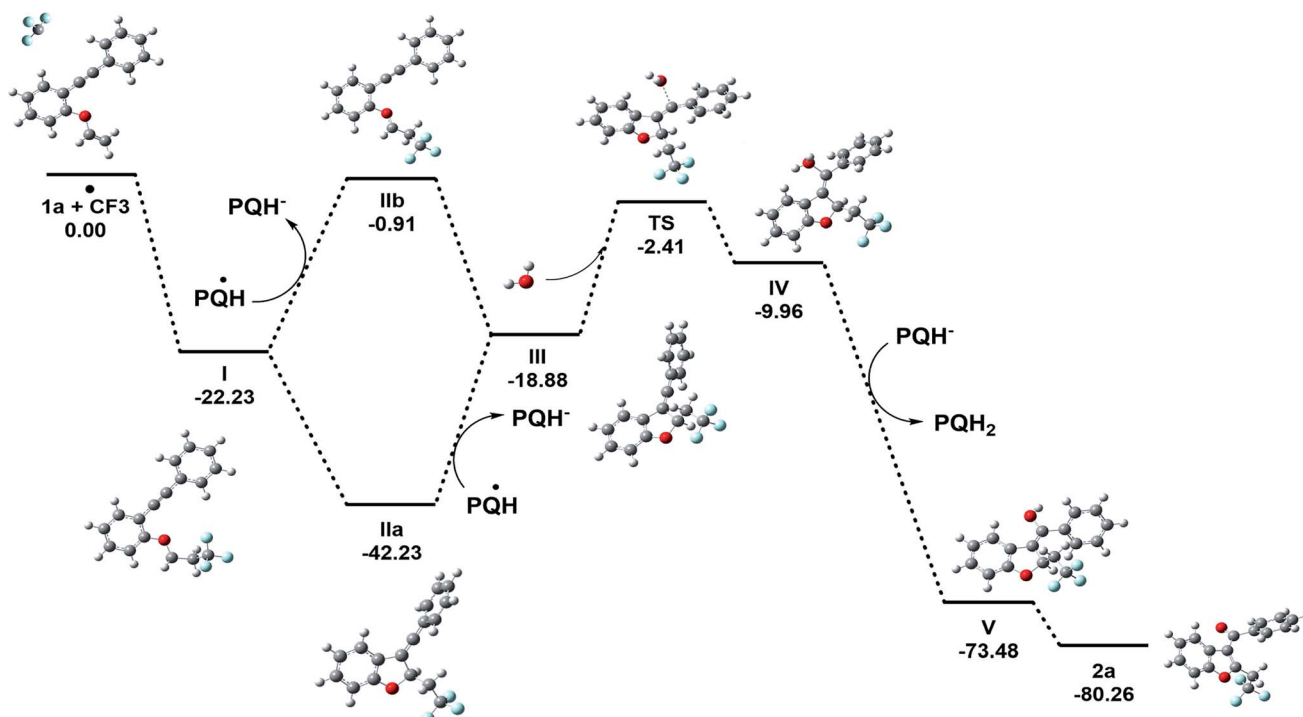

Fig. 7 The calculated relative Gibbs' free energy of the reaction (ΔG° in kcal mol^{-1}) obtained at a DFT-B3LYP/6-31+G(d)/CPCM(acetonitrile) level of theory.

stable under the reaction conditions.[38] The vinylic cation **III** 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 vinylic cation **III** could be the key step in the transformation and may occur through a transition state **TS**. The energy barrier ($\Delta G^{\#}$) 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 **PQH**$^-$ 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 ethynylic or vinylic arene, and as a consequence the methyl group in benzbromarone 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-phenanthrequinone 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 advance heterocyclic molecules under atom and step economical pathways.

Acknowledgements

Notes and references

1 T. Liu, *et al.*, *Org. Lett.*, 2016, **18**, 4044.
2 (*a*) C. W. Locuson, H. Suzuki, A. E. Rettie and J. P. Jones, *J. Med. Chem.*, 2004, **47**, 6768; (*b*) M. F. Wempe, *et al.*, *J. Med. Chem.*, 2011, **54**, 2701.
3 (*a*) T. A. Theodossiou, M. C. Galanou and C. M. Paleos, *J. Med. Chem.*, 2008, **51**, 6067; (*b*) A. N. Snead, M. Miyakawa, E. S. Tan and T. S. Scanlan, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5920.
4 (*a*) T. A. Grese, *et al.*, *J. Med. Chem.*, 1998, **41**, 1272; (*b*) R. Romagnoli, *et al.*, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5041.
5 (*a*) T. E. D'Ambra, *et al.*, *J. Med. Chem.*, 1992, **35**, 124; (*b*) O. Mazzoni, *et al.*, *Chem. Biol. Drug Des.*, 2010, **75**, 106.
6 (*a*) K. Muller, C. Faeh and F. Deiderich, *Science*, 2007, **317**, 1881; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*c*) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315; (*d*) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422.
7 (*a*) S. D. Young, *et al.*, *Antimicrob. Agents Chemother.*, 1995, **39**, 2602; (*b*) T. D. Penning, *et al.*, *J. Med. Chem.*, 1997, **40**, 1347.
8 Oxy-trifluoromethylation of alkenes by Langlois' reagent: (*a*) A. Deb, S. Manna, A. Modak, T. Patra, S. Maity and D. Maiti, *Angew. Chem., Int. Ed.*, 2013, **52**, 9747; (*b*) X. Y. Jiang and F. L. Qing, *Angew. Chem., Int. Ed.*, 2013, **52**, 14177; (*c*) Q. Lu, C. Liu, Z. Huang, Y. Ma, J. Zhang and A. Lei, *Chem. Commun.*, 2014, **50**, 14101; (*d*) X.-Z. Luo, H.-Q. Luo, Z.-P. Zhang and W. Dong, *Synlett*, 2014, **25**, 1307; (*e*) Y. Yang, Y. Liu, Y. Jiang, Y. Zhang and D. A. Vicic, *J. Org. Chem.*, 2015, **80**, 6639; (*f*) C. Liu, Q. Lu, Z. Huang, J. Zhang, F. Liao, P. Peng and A. Lei, *Org. Lett.*, 2015, **17**, 6034; (*g*) T. Kawamoto, R. Sasaki and A. Kamimura, *Angew. Chem., Int. Ed.*, 2017, **56**, 1342.
9 Oxy-trifluoromethylation of alkenes by different CF$_3$-sources: (*a*) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu and J.-C. Xiao, *Chem. Commun.*, 2011, **47**, 6632; (*b*) Y. Li and A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8221; (*c*) R. Zhu and S. L. Buchwald, *J. Am. Chem. Soc.*, 2012, **134**, 12462; (*d*) H. Egami, R. Shimizu and M. Sodeoka, *Tetrahedron Lett.*, 2012, **53**, 5503; (*e*) C. Feng and T.-P. Loh, *Chem. Sci.*, 2012, **3**, 3458; (*f*) Y. Yasu, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2012, **51**, 9567; (*g*) P. G. Janson, I. Ghoneim, N. O. Ilchenko and K. J. Szado, *Org. Lett.*, 2012, **14**, 2882; (*h*) D.-F. Lu, C.-L. Zhu and H. Xu, *Chem. Sci.*, 2013, **4**, 2478; (*i*) E. Kim, S. Choi, H. Kim and E. J. Cho, *Chem.–Eur. J.*, 2013, **19**, 6209; (*j*) R. Zhu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 12655; (*k*) Y.-T. He, H.-L. Li, Y.-F. Yang, Y.-Q. Wang, J.-Y. Luo, X.-Y. Liu and Y.-M. Liang, *Chem. Commun.*, 2013, **49**, 5687; (*l*) Q. Yu and S. Ma, *Chem.–Eur. J.*, 2013, **19**, 13304; (*m*) Photoredox-catalyzed: Y. Yasu, Y. Arai, R. Tomita, T. Koike and M. Akita, *Org. Lett.*, 2014, **16**, 780; (*n*) H. Egami, R. Shimizu, Y. Usui and M. Sodeoka, *J. Fluorine Chem.*, 2014, **167**, 172; (*o*) S. Jana, A. Ashokan, S. Kumar, A. Verma and S. Kumar, *Org. Biomol. Chem.*, 2015, **13**, 8411; (*p*) N. Yi, H. Zhang, C. Xu, W. Deng, R. Wang, D. Peng, Z. Zeng and J. Xiang, *Org. Lett.*, 2016, **18**, 1780; (*q*) J. Ye, *et al.*, *Angew. Chem., Int. Ed.*, 2016, **55**, 10022; (*r*) Y.-B. Wu, G.-P. Lu, T. Yuan, Z.-B. Xu, L. Wan and C. Cai, *Chem. Commun.*, 2016, **52**, 13668.

10 Oxy-trifluoromethylation of alkynes by CF_3SO_2Na: (a) Z. He, R. Zhang, M. Hu, L. Li, C. Ni and J. Hu, *Chem. Sci.*, 2013, **4**, 3478; (b) A. Maji, A. Hazra and D. Maiti, *Org. Lett.*, 2014, **16**, 4524.

11 Various initiators for trifluoromethylation: (a) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond and P. S. Baran, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 14411; (b) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95; (c) R. Gianatassio, S. Kawamura, C. L. Eprile, K. Foo, J. Ge, A. C. Burns, M. R. Collins and P. S. Baran, *Angew. Chem., Int. Ed.*, 2014, **53**, 9851; (d) Y. Ye, S. A. Künzi and M. S. Sanford, *Org. Lett.*, 2012, **14**, 4979; (e) Y. Ye, S. H. Lee and M. S. Sanford, *Org. Lett.*, 2011, **13**, 5464; (f) A. T. Parsons and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 9120; (g) Z. Li, Z. Cui and Z.-Q. Liu, *Org. Lett.*, 2013, **15**, 406.

12 Cascade trifluoromethylation: (a) L. Zhang, Z. Li and Z. Q. Liu, *Org. Lett.*, 2014, **16**, 3688; (b) Y. Q. Wang, Y. T. He, L. L. Zhang, X. X. Wu, X. Y. Liu and Y. M. Liang, *Org. Lett.*, 2015, **17**, 4280; (c) Y.-T. He, *et al.*, *Adv. Synth. Catal.*, 2015, **357**, 3069; (d) Q. Wang, H. Song, Y. Liu, H. Song and Q. Wang, *Adv. Synth. Catal.*, 2016, **358**, 3435; (e) L.-Z. Yu, Q. Xu, X.-Y. Tang and M. Shi, *ACS Catal.*, 2016, **6**, 526.

13 Reviews on trifluoromethylation: (a) H. Egami and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 8294; (b) E. Merino and C. Nevado, *Chem. Soc. Rev.*, 2014, **43**, 6598; (c) C. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 2895; (d) C. Alonso, E. Martinez de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847; (e) C. Ni and J. Hu, *Chem. Soc. Rev.*, 2016, **45**, 5441.

14 Cascade oxy-trifluoromethylation: H. Fu, S.-S. Wang and Y.-M. Li, *Adv. Synth. Catal.*, 2016, **358**, 3616.

15 C_3-aryloyl benzofurans: (a) Y. Liao, M. Reitman, Y. Zhang, R. Fathi and Z. Yang, *Org. Lett.*, 2002, **4**, 2607; (b) Y. Hu, Y. Zhang, Z. Yang and R. Fathi, *J. Org. Chem.*, 2002, **67**, 2365; (c) A. Furstner, E. K. Heilmann and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 4760; (d) Y. Liu, J. Qian, S. Lou and Z. Xu, *J. Org. Chem.*, 2010, **75**, 6300; (e) J. U., L.-Y. Wu, X.-C. Wang, Y.-Y. Hu, Y.-N. Niu, X.-Y. Liu, S. Yang and Y.-M. Liang, *Adv. Synth. Catal.*, 2010, **352**, 351; (f) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464; (g) N. Aljaar, C. C. Malakar, J. Conrad, S. Strobel, T. Schleid and U. Beifuss, *J. Org. Chem.*, 2012, **77**, 7793; (h) S. Ngwerume, W. Lewis and J. E. Camp, *J. Org. Chem.*, 2013, **78**, 920; (i) S. Bensulong, J. Boonsombat and S. Ruchirawat, *Tetrahedron*, 2013, **69**, 9335; (j) M. Hu, R. J. Song and J. H. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 608.

16 C_3-aryloyl benzothiophenes: (a) D. Fréhel, R. Boigegrain and J. Maffrand, *Heterocycles*, 1984, **22**, 1235; (b) S. Dadiboyena, *Eur. J. Med. Chem.*, 2012, **51**, 17; (c) S. Kim, N. Dahal and T. Kesharwani, *Tetrahedron Lett.*, 2013, **54**, 4373; (d) C. H. Lin, C. C. Chen and M. J. Wu, *Chem.–Eur. J.*, 2013, **19**, 2578; (e) A. Acharya, S. V. Kumar and H. Ila, *Chem.–Eur. J.*, 2015, **21**, 17116.

17 C_3-aryloyl indole synthesis: (a) M. A. Eissenstat and J. D. Weaver III, *Tetrahedron Lett.*, 1995, **36**, 2029; (b) M. J. Earle, K. R. Seddon and P. B. McCormac, *Green Chem.*, 2000, **2**, 261; (c) I. Nakamura, Y. Sato, S. Konta and M. Terada, *Tetrahedron Lett.*, 2009, **50**, 2075; (d) T. Back and D. Gao, *Synlett*, 2013, **24**, 389; (e) F. Huang, P. Wu, L. Wang, J. Chen, C. Sun and Z. Yu, *J. Org. Chem.*, 2014, **79**, 10553; (f) T.-J. Gong, W.-M. Cheng, W. Su, B. Xiao and Y. Fu, *Tetrahedron Lett.*, 2014, **55**, 1859; (g) S. Prathapan, S. Radhamani, R. Natarajan, J. Rappai and P. Unnikrishnan, *Synlett*, 2015, **26**, 2467; (h) H. Johansson, A. Urruticoechea, I. Larsen and D. Sejer Pedersen, *J. Org. Chem.*, 2015, **80**, 471; (i) A. Arcadi, M. Chiarini, L. Del Vecchio, F. Marinelli and V. Michelet, *Chem. Commun.*, 2016, **52**, 1458; (j) P. Sharma and R. S. Liu, *Org. Lett.*, 2016, **18**, 412.

18 Recent photocatalytic reactions: (a) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875; (b) A. E. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 4986; (c) P. V. Pham, K. Ashton and D. W. C. MacMillan, *Chem. Sci.*, 2011, **2**, 1470; (d) P. V. Pham, D. A. Nagib and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2011, **50**, 6119; (e) S. B. Jones, B. Simmons, A. Mastracchio and D. W. C. MacMillan, *Nature*, 2011, **475**, 183; (f) S. Maity and N. Zheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 9562; (g) D. P. Hari, T. Hering and B. König, *Org. Lett.*, 2012, **14**, 5334; (h) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (i) U. Wille, *Chem. Rev.*, 2013, **113**, 813; (j) B. N. Laforteza, M. Pickworth and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2013, **52**, 11269; (k) I. Ghosh, T. Ghosh, J. I. Bardagi and B. König, *Science*, 2014, **346**, 725; (l) L. Chu, C. Ohta, Z. Zuo and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 10886; (m) N. A. Romero and D. A. Nicewicz, *J. Am. Chem. Soc.*, 2014, **136**, 17024; (n) J. D. Griffin, M. A. Zeller and D. A. Nicewicz, *J. Am. Chem. Soc.*, 2015, **137**, 11340; (o) L. Li, W. Liu, H. Zeng, X. Mu, G. Cosa, Z. Mi and C.-J. Li, *J. Am. Chem. Soc.*, 2015, **137**, 8328; (p) C. C. Nawrat, C. R. Jamison, Y. Slutskyy, D. W. C. MacMillan and L. E. Overman, *J. Am. Chem. Soc.*, 2015, **137**, 11270; (q) P. D. Morse and D. A. Nicewicz, *Chem. Sci.*, 2015, **6**, 270; (r) C. L. Cavanaugh and D. A. Nicewicz, *Org. Lett.*, 2015, **17**, 6082; (s) A. Joshi-Pangu, F. Lévesque, H. G. Roth, S. F. Oliver, L.-C. Campeau, D. Nicewicz and D. A. DiRocco, *J. Org. Chem.*, 2016, **81**, 7244; (t) E. Brachet, L. Marzo, M. Selkti, B. König and P. Belmont, *Chem. Sci.*, 2016, **7**, 5002; (u) X. Q. Hu, X. Qi, J. R. Chen, Q. Q. Zhao, Q. Wei, Y. Lan and W. J. Xiao, *Nat. Commun.*, 2016, **7**, 11188; (v) L. Li, W. Liu, X. Mu, Z. Mi and C.-J. Li, *Nat. Protoc.*, 2016, **11**, 1948; (w) I. Ghosh, L. Marzo, A. Das, R. Shaikh and B. König, *Acc. Chem. Res.*, 2016, **49**, 1566; (x) T. Hering, A. U. Meyer and B. König, *J. Org. Chem.*, 2016, **81**, 6927; (y) H. Bartling, A. Eisenhofer, B. König and R. M. Gschwind, *J. Am. Chem. Soc.*, 2016, **138**, 11860; (z) A. U. Meyer, A. Wimmer and B. König, *Angew. Chem., Int. Ed.*, 2017, **56**, 409; (aa) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18566; (ab)

L. J. Allen, P. J. Cabrera, M. Lee and M. S. Sanford, *J. Am. Chem. Soc.*, 2014, **136**, 5607.

19 Photoredox catalysis reviews: (*a*) J. M. Narayanam and C. R. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102; (*b*) S. Barata-Vallejo, S. M. Bonesi and A. Postigo, *Org. Biomol. Chem.*, 2015, **13**, 11153; (*c*) M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898; (*d*) N. Corrigan, S. Shanmugam, J. Xu and C. Boyer, *Chem. Soc. Rev.*, 2016, **45**, 6165; (*e*) E. Brachet, L. Marzo, M. Selkti, B. König and P. Belmont, *Chem. Sci.*, 2016, **7**, 5002; (*f*) N. Corrigan, S. Shanmugam, J. Xu and C. Boyer, *Chem. Soc. Rev.*, 2016, **45**, 6165; (*g*) S. P. Pitre, C. D. McTiernan and J. C. Scaiano, *Acc. Chem. Res.*, 2016, **49**, 1320; (*h*) J. R. Chen, X. Q. Hu, L. Q. Lu and W. J. Xiao, *Acc. Chem. Res.*, 2016, **49**, 1911; (*i*) D. Staveness, I. Bosque and C. R. Stephenson, *Acc. Chem. Res.*, 2016, **49**, 2295; (*j*) T. Chatterjee, N. Iqbal, Y. You and E. J. Cho, *Acc. Chem. Res.*, 2016, **49**, 2284; (*k*) T. Koike and M. Akita, *Acc. Chem. Res.*, 2016, **49**, 1937; (*l*) J. Goddard, C. Ollivier and L. Fensterbank, *Acc. Chem. Res.*, 2016, **49**, 1924; (*m*) M. Majek and A. Wangelin, *Acc. Chem. Res.*, 2016, **49**, 2316; (*n*) K. A. Margrey and D. A. Nicewicz, *Acc. Chem. Res.*, 2016, **49**, 1997; (*o*) J. J. Douglas, M. J. Sevrin and C. R. Stephenson, *Org. Process Res. Dev.*, 2016, **20**, 1134; (*p*) X. Pan, H. Xia and J. Wu, *Org. Chem. Front.*, 2016, **3**, 1163.

20 Photo-induced trifluoromethylation: (*a*) D. A. Nagib and D. W. C. MacMillan, *Nature*, 2011, **480**, 224; (*b*) Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2012, **134**, 9034; (*c*) D. J. Wilger, N. J. Gesmundo and D. A. Nicewicz, *Chem. Sci.*, 2013, **4**, 3160; (*d*) S. P. Pitre, C. D. McTiernan, H. Ismaili and J. C. Scaiano, *ACS Catal.*, 2014, **4**, 2530; (*e*) R. Tomita, Y. Yasu, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2014, **53**, 7144; (*f*) A. Carboni, G. Dagousset, E. Magnier and G. Masson, *Org. Lett.*, 2014, **16**, 1240; (*g*) N. Noto, K. Miyazawa, T. Koike and M. Akita, *Org. Lett.*, 2015, **17**, 3710; (*h*) Q. Wei, J.-R. Chen, X.-Q. Hu, X.-C. Yang, B. Lu and W.-J. Xiao, *Org. Lett.*, 2015, **17**, 4464; (*i*) J. W. Beatty, J. J. Douglas, K. P. Cole and C. R. J. Stephenson, *Nat. Commun.*, 2015, **6**, 7919; (*j*) R. Tomita, T. Koike and M. Akita, *Angew. Chem., Int. Ed.*, 2015, **54**, 12923; (*k*) N. Noto, T. Koike and M. Akita, *J. Org. Chem.*, 2016, **81**, 7064; (*l*) Y. Arai, R. Tomita, G. Ando, T. Koike and M. Akita, *Chem.–Eur. J.*, 2016, **22**, 1262; (*m*) Q. Lefebvre, N. Hoffmann and M. Rueping, *Chem. Commun.*, 2016, **52**, 249; (*n*) L. Li, X. Mu, W. Liu, Y. Wang, Z. Mi and C.-J. Li, *J. Am. Chem. Soc.*, 2016, **138**, 5809; (*o*) X. L. Yu, J. R. Chen, D. Z. Chen and W. J. Xiao, *Chem. Commun.*, 2016, **52**, 8275; (*p*) L. Jarrige, A. Carboni, G. Dagousset, G. Levitre, E. Magnier and G. Masson, *Org. Lett.*, 2016, **18**, 2906; (*q*) W. Fu, X. Han, M. Zhu, C. Xu, Z. Wang, B. Ji, X.-Q. Hao and M.-P. Song, *Chem. Commun.*, 2016, **52**, 13413; (*r*) T. Koike and M. Akita, *Org. Chem. Front.*, 2016, **3**, 1345; (*s*) H. Xiang, Q. Zhao, Z. Tang, J. Xiao, P. Xia, C. Wang, C. Yang, X. Chen and H. Yang, *Org. Lett.*, 2017, **19**, 146; (*t*) H.-T. Qin, S.-W. Wu, J.-L. Liu and F. Liu, *Chem. Commun.*, 2017, **53**, 1696.

21 Photocatalytic oxidative activation of H_2O for oxygenation: (*a*) S. Fukuzumi, T. Kishi, H. Kotani, Y. M. Lee and W. Nam, *Nat. Chem.*, 2011, **3**, 38; (*b*) G. Zhang, X. Hu, C. W. Chiang, H. Yi, P. Pei, A. K. Singh and A. Lei, *J. Am. Chem. Soc.*, 2016, **138**, 12037; (*c*) X. Hu, G. Zhang, F. Bu and A. Lei, *ACS Catal.*, 2017, **7**, 1432; (*d*) K. Ohkubo, A. Fujitomo and S. FuKuzumi, *J. Am. Chem. Soc.*, 2013, **135**, 5368.

22 (*a*) B. S. Bhakuni, A. Yadav, S. Kumar, S. Patel, S. Sharma and S. Kumar, *J. Org. Chem.*, 2014, **79**, 2944; (*b*) S. Kumar, *et al.*, *Org. Lett.*, 2015, **17**, 82; (*c*) A. Verma, *et al.*, *Chem. Commun.*, 2015, **51**, 1371; (*d*) A. Verma and S. Kumar, *Org. Lett.*, 2016, **18**, 4388; (*e*) A. Verma, S. Jana, C. D. Prasad, A. Yadav and S. Kumar, *Chem. Commun.*, 2016, **52**, 4179; (*f*) V. Rathore, M. Sattar, R. Kumar and S. Kumar, *J. Org. Chem.*, 2016, **81**, 9206; (*g*) C. D. Prasad, M. Sattar and S. Kumar, *Org. Lett.*, 2017, **19**, 774; (*h*) S. Kumar, *et al.*, *Angew. Chem., Int. Ed.*, 2016, **55**, 3729.

23 (*a*) N. C. Yang and D.-D. H. Yang, *J. Am. Chem. Soc.*, 1958, **80**, 2913; (*b*) N. Hoffmann, *Chem. Rev.*, 2008, **108**, 1052; (*c*) J. D. Coyle and H. A. Carless, *Chem. Soc. Rev.*, 1972, **1**, 465.

24 9,10-Phenanthroline UV-visible study: (*a*) D. M. Togashi, S. M. B. Costa and D. E. Nicodem, *J. Mol. Struct.*, 2001, **565**, 93; (*b*) D. M. Togashi and D. E. Nicodem, *Spectrochim. Acta, Part A*, 2004, **60**, 3205; (*c*) R. S. Becker and L. V. Natarajan, *J. Phys. Chem.*, 1993, **97**, 344.

25 Umpolung of aromatic ketones: (*a*) P. Wagner and B. S. Park, Photoinduced Hydrogen Atom Abstraction Reaction by Carbonyl Compounds, in *Organic Photochemistry*, ed. A. Padwa, Marcel Dekker, New York, 1991, pp. 227–366; (*b*) V. R. Kumar, N. Rajkumar, F. Ariese and S. Umapathy, *J. Phys. Chem. A*, 2015, **119**, 10147.

26 P. A. Carapellucci, H. P. Wolf and K. Weiss, Photoreduction of, *J. Am. Chem. Soc.*, 1969, **91**, 4635.

27 **PQ** is readily available, air stable, and has low molecular weight and an arbitrary absorption maximum at 420 nm. Nonetheless, however, this has not been explored in synthetic transformations other than its applications in H_2 activation with $B(C_6H_5)_3$,[27a] in organic materials.[27b,c]: (*a*) L. E. Longobardi, L. Liu, S. Grimme and D. W. Stephan, *J. Am. Chem. Soc.*, 2016, **138**, 2500; (*b*) Y. X. Yu, *ACS Appl. Mater. Interfaces*, 2014, **6**, 16267; (*c*) K. Urakawa, M. Sumimoto, M. Arisawa, M. Matsuda and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2016, **55**, 7432; Organic dyes as photoredox catalysts: (*d*) E. Yoshioka, S. Kohtani, T. Jichu, T. Fukazawa, T. Nagai, A. Kawashima, Y. Takemoto and H. Miyabe, *J. Org. Chem.*, 2016, **81**, 7217; (*e*) S. P. Pitre, C. D. McTiernan and J. C. Scaiano, *ACS Omega*, 2016, **1**, 66; (*f*) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075.

28 1-(Alkyl/arylethynyl)-2-(vinyloxy)benzene substrates **1a–1r** were prepared by following the reported procedure: N. Sakiyama, K. Noguchi and K. Tanaka, *Angew. Chem., Int. Ed.*, 2012, **51**, 5976.

29 (*a*) J. Zhu, Y.-J. Cheng, X.-K. Kuang, L. Wang, Z.-B. Zheng and Y. Tang, *Angew. Chem., Int. Ed.*, 2016, **55**, 9224; (*b*) W.-I. Lee,

J.-W. Jung, J. Sim, H. An and Y.-G. Suh, *Tetrahedron*, 2013, **69**, 7211.

30 I. Chataigner, C. Panel, H. Gerard and S. R. Piettre, *Chem. Commun.*, 2007, 3288.

31 *N*-alkylated indole: (*a*) T. Back and D. Gao, *Synlett*, 2013, **24**, 389; (*b*) T.-J. Gong, W.-M. Cheng, W. Su, B. Xiao and Y. Fu, *Tetrahedron Lett.*, 2014, **55**, 1859; (*c*) P. Sharma and R. S. Liu, *Org. Lett.*, 2016, **18**, 412.

32 For the detection of hydrogen gas in the reaction by ^{1}H NMR spectroscopy: (*a*) D. P. Ojha, K. Gadde and K. R. Prabhu, *Org. Lett.*, 2016, **18**, 5062; Synthetic photocatalytic hydrogen evolution: (*b*) G. Zhang, C. Liu, H. Yi, Q. Meng, C. Bian, H. Chen, J. X. Jian, L. Z. Wu and A. Lei, *J. Am. Chem. Soc.*, 2015, **137**, 9273; (*c*) C.-J. Wu, Q.-Y. Meng, T. Lei, J.-J. Zhong, W.-Q. Liu, L.-M. Zhao, Z.-J. Li, B. Chen, C.-H. Tung and L.-Z. Wu, *ACS Catal.*, 2016, **6**, 4635; (*d*) K. Luo, Y. Z. Chen, W. C. Yang, J. Zhu and L. Wu, *Org. Lett.*, 2016, **18**, 452; (*e*) G. Zhang, L. Zhang, H. Yi, Y. Luo, X. Qi, C. H. Tung, L. Z. Wu and A. Lei, *Chem. Commun.*, 2016, **52**, 10407; (*f*) H. Wang, Q. Lu, C.-W. Chiang, Y. Luo, J. Zhou, G. Wang and A. Lei, *Angew. Chem., Int. Ed.*, 2017, **56**, 595; (*g*) H. Yi, L. Niu, C. Song, Y. Li, B. Dou, A. K. Singh and A. Lei, *Angew. Chem., Int. Ed.*, 2017, **56**, 1120.

33 Because the reaction mixture provides an EPR signal only for dissociated MNP; *tert*-buyl nitroxide radical in CH_3CN: H_2O solvent. Therefore, the reaction mixture along with the MNP dimer was conducted in a CH_2Cl_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.

34 Hydration of alkynes: (*a*) P. Wan, S. Culshaw and K. Yates, *J. Am. Chem. Soc.*, 1982, **104**, 2509; (*b*) C.-J. Li, *Acc.Chem. Res.*, 2010, **43**, 581; (*c*) E. H. Hill, S. Goswami, D. G. Evans, K. S. Schanze and D. G. Whitten, *J. Phys. Chem. Lett.*, 2012, **3**, 1363.

35 M. W. Lehmann and D. H. Evans, *J. Electroanal. Chem.*, 2001, **500**, 12.

36 (*a*) Triplet exited state energy ($E_{o,o}^T$) 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 $E_{1/2}^{red}*$ (^{3}**PQ***/**PQ**$^{\bullet-}$) of PQ was calculated by following ref. 27*f*: ground state $E_{1/2}^{red}$ (**PQ/PQ**$^{\bullet-}$) + triplet excited state ($E_{o,o}^T$); $-0.52 + 2.1161 = +1.60$ V. $E_{1/2}^{red}$ (**PQ/PQ**$^{\bullet-}$) is determined experimentally.

37 J.-B. Tommasino, A. Brondex, M. Médebielle, M. Thomalla, B. R. Langlois and T. Billard, *Synlett*, 2002, **10**, 1697.

38 P. A. Byrne, S. Kobayashi, E.-U. Würthwein, J. Ammer and H. Mayr, *J. Am. Chem. Soc.*, 2017, **139**, 1499.

39 W. S. Johnson, G. W. Daub, T. A. Lyle and M. Niwa, *J. Am. Chem. Soc.*, 1980, **102**, 7800.

40 (*a*) M. Bettoni, T. D. Giacco, C. Rol and G. V. Sebastiani, *J. Phys. Org. Chem.*, 2006, **19**, 359; (*b*) R. K. Saunthwal, M. Patel and A. K. Verma, *Org. Lett.*, 2016, **18**, 2200.

41 M. A. Cismesia and T. P. Yoon, *Chem. Sci.*, 2015, **6**, 5426.