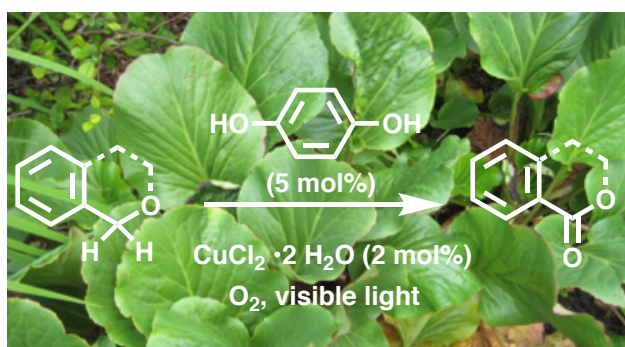# Visible light mediated oxidation of benzylic sp^3 C–H bonds using catalytic 1,4-hydroquinone, or its biorenewable glucoside, arbutin, as a pre-oxidant[†]

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ABSTRACT

Benzylic ethers undergo a visible light induced C–H activation and oxygen insertion to give the corresponding benzoate esters in moderate to good yields. The conditions employ substoichiometric amounts of 1,4-hydroquinone with copper(II) chloride dihydrate as an electron-transfer mediator, oxygen as the terminal oxidant and dimethyl carbonate as solvent under visible light irradiation. The naturally occurring glucoside, arbutin, which is commercially available or can be accessed *via* extraction of the leaves of bearberry (*Arctostaphylos uva-ursi*) or elephant ears (*Bergenia crassifolia*) can be used as a bio-renewable source of 1,4-hydroquinone. The methodology exploits the increase in oxidizing ability of quinones upon irradiation with visible light, and offers a sustainable alternative for the late stage oxidative functionalization of benzylic C–H bonds. It is applicable to a range of cyclic benzylic ethers such as isochromans and phthalans, and simple benzyl alkyl ethers. It

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[†] Electronic Supplementary Information (ESI) available. See: xxxxxxx

can also be applied in the oxidation of benzylic amines into amides, and of diarylmethanes into the corresponding ketones. Mechanistic studies suggest that the reaction proceeds by H-abstraction by the photo-excited triplet benzoquinone to give a benzylic radical that subsequently reacts with molecular oxygen.

Oxidation is a ubiquitous process in the living world, and is fundamental to much of biology and chemistry. In the chemical laboratory, a plethora of methods is available to the chemist, but unfortunately, many of the most commonly used conditions employ stoichiometric quantities of high valent metal salts that pose problems in terms of cost, toxicity and atom economy.[1] For these reasons, stoichiometric metal-mediated reactions have declined in popularity, in favor of using metal or metal salts in catalytic amounts in conjunction with a more benign terminal oxidant,[2] or using organo-oxidation protocols, for example, based on DMSO,[3] or hypervalent iodine compounds.[4]

One of the more important oxidative transformations is the chemoselective oxidation of benzylic sp^3 C–H bonds that can convert simple starting materials into value added synthetic intermediates, and also provide a method for the late stage functionalization of complex molecules by C–H activation.[5] Benzylic oxidation strategies have traditionally centered around the use of stoichiometric quantities of toxic metals, particularly chromium.[6] However, with the increased focus on green and sustainable methodologies, research has moved towards transition-metal catalysis often using oxygen or peroxides as the terminal oxidant.[7] Thus a range of metal catalysts have been deployed in benzylic oxidation reactions, including, for example, those based on copper,[8] manganese,[9] cobalt,[10] rhodium,[11] or iron.[12] Of these, iron based catalysts have come to the fore in recent years, but many of these suffer

from low conversions, and complex, high molecular weight (800-1000 Da) expensive

ligands. There are also a number of non-metal based protocols for benzylic oxidation and

these include photoredox methods,[7a] those based on TEMPO,[13] and combinations of strong

base and oxygen.[14]

Nature also conducts oxidation reactions using both metal-based and metal-free strategies. In

fact, iron is used extensively in biological systems for the activation and oxidation of C–H

bonds by heme-containing oxygenases, and many of the aforementioned iron catalysed

reactions seek to mimic Nature. The metal-free oxidation strategy used by Nature employs

molecules containing a quinone moiety. Thus, plastoquinone and phylloquinone are used as a

terminal electron acceptor and intermediate electron transfer cofactor respectively,[15] in the

light dependent reactions of photosynthesis. Ubiquinone is an antioxidant, but also acts as an

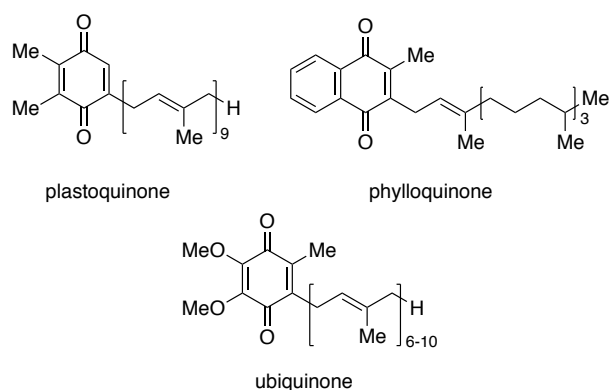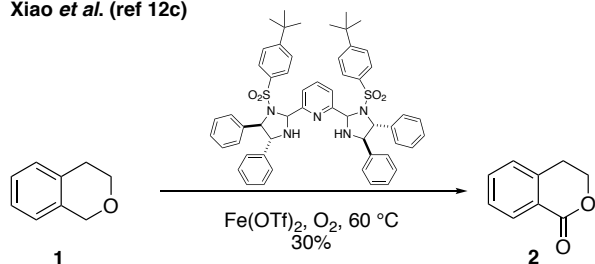electron carrier between the different components of the electron transport chain (Figure 1).[16]

Figure 1. The naturally occurring quinones, plastoquinone, phylloquinone and ubiquinone

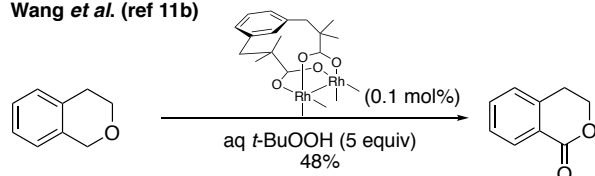that participate in biological redox processes.

Indeed, quinones are well known for their oxidizing ability,[17] and facilitate a range of

oxidation reactions in the laboratory. For many transformations, including benzylic

oxidations,[18] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is routinely used due to its

one-electron reduction potential (E_{red} 0.51 V in MeCN vs SCE).[19] Although DDQ is a versatile organo-oxidant,[20] it suffers from drawbacks such as toxicity, cost and the potential to release HCN on contact with water. Therefore, we,[21] and others[18b, 22] have developed protocols using DDQ in catalytic amounts in the presence of a terminal oxidant. An alternative approach, inspired by Nature's use of lower potential quinones, is to use simpler (and cheaper) quinones such as 1,4-benzoquinone (BQ) itself in oxidation reactions. We now report a new protocol for the oxidation of benzylic sp^3 C–H bonds that, in contrast to some recently reported methods, does not require complex high molecular weight ligands or catalysts that are expensive or difficult to prepare (Scheme 1). Instead it employs catalytic amounts of potentially biorenewable 1,4-hydroquinone (BQH₂), available from its naturally occurring β-D-glucopyranoside arbutin, as a "pre-oxidant" (in place of the toxic BQ) in the presence of a simple copper salt as electron transfer mediator (ETM), and oxygen as the terminal oxidant under visible light irradiation.
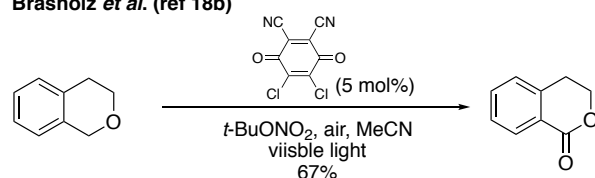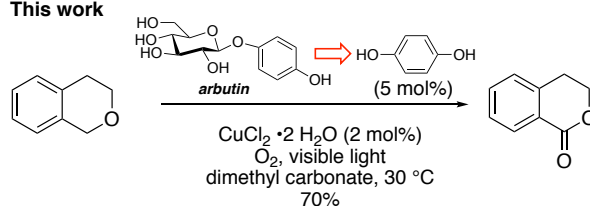
Xiao *et al*. (ref 12c)

Fe(OTf)$_2$, O$_2$, 60 °C
30%

1   **2**

Wang *et al*. (ref 11b)

(0.1 mol%)

aq *t*-BuOOH (5 equiv)
48%

Brasholz *et al*. (ref 18b)

(5 mol%)

t-BuONO$_2$, air, MeCN
viisble light
67%

This work

arbutin   (5 mol%)

CuCl$_2$ ·2 H$_2$O (2 mol%)
O$_2$, visible light
dimethyl carbonate, 30 °C
70%

Scheme 1. Some representative methods for benzylic oxidation as illustrated for the conversion of isochroman **1** into isochromanone **2**.

RESULTS AND DISCUSSION

Upon irradiation with visible light, quinones give a relatively long-lived n → π* triplet by intersystem crossing from the singlet,[23] and this excited state has much stronger oxidizing ability. Thus, for example, photoexcited DDQ (E_{red} 3.18 V vs SCE) is a strong enough oxidant to convert benzene into phenol.[24] Although the increase in redox potential of quinones upon irradiation is documented, it has very rarely been exploited in chemical synthesis, although there are examples of photo-activated anthraquinones being employed in benzylic oxidation reaction using oxygen as terminal oxidant.[25] In addition we demonstrated that photo-activated DDQ can be used in catalytic amounts for the oxidation of benzylic and

allylic alcohols in the presence of oxygen,[21a] and extended the concept to the use of 1,4-benzoquinone (BQ) itself.[26] Although BQ possesses a modest reduction potential, this is considerably enhanced upon visible light irradiation, and the resulting triplet excited state (E_{red} 2.40 V vs SCE),[27] is a more powerful oxidant than ground state DDQ. We therefore set out to investigate the use of visible light activated BQ in the activation of benzylic sp^3 C–H bonds.

1. Preliminary Studies.

Isochroman **1**, a commonly used substrate in benzylic oxidation reactions, was selected for our initial studies. However, rather than use the toxic BQ itself as oxidant, we opted to use the less toxic, and potentially biorenewable (*vide infra*) 1,4-hydroquinone (BQH$_2$) as a "pre-oxidant."[26]   Since BQH$_2$ cannot be oxidized directly by molecular oxygen under neutral reaction conditions,[28] an electron transfer mediator (ETM) is required to facilitate the process. In previous work,[26] we had employed copper nanoparticles (Cu$_{NP}$) as ETM,[29] but now investigated a range of copper catalysts to optimize the reaction with respect to the ETM. Thus isochroman was treated with a catalytic amount of BQH$_2$ (10 mol%) in the presence of a range of copper-based ETM (2 mol%) (Table S1, Supplementary Information) with an oxygen atmosphere in dimethyl carbonate as solvent, chosen for its "green" credentials,[30] under visible light irradiation from a " sunlight mimicking" lamp, a commonly employed light source in commercial glasshouses, with an emission >365 nm (Figure S1, Supplementary Information).

In general, optimal results were achieved with the use of copper(II) salts, when compared with copper nanoparticles, copper(I) salts, or copper metal. No isochroman-1-one was formed in the absence of the ETM. The best results were achieved with the use of copper(II)

triflate and copper(II) chloride dihydrate. However, copper(II) triflate is expensive ($3009/mol – June 2017, SigmaAldrich) when compared with copper(II) chloride dihydrate ($72/mol – June 2017, SigmaAldrich), and made it less economical, particularly as it only offered a marginal improvement in yield. Therefore, for further investigations, copper(II) chloride dihydrate was elected as the ETM of choice. In addition, control reactions established that no reaction occurred in the absence of the hydroquinone or in darkness.

Further optimization with respect to the loadings of both BQH_2 and $CuCl_2 \cdot 2H_2O$ (Table S2) established that the catalytic loadings of BQH_2 could be reduced to 5 mol%. However, further decreasing the catalytic loadings of the hydroquinone led to diminished yields. Likewise, the loading of the copper ETM could not be reduced below 2 mol%. Again, control experiments established that no oxidation occurred in the absence of BQH_2, or of copper(II) chloride, or of oxygen, or in darkness.

It is apparent from the control experiments that the copper salt was essential for the oxidation/reoxidation of BQH_2 into BQ. However, it does not appear to be involved in the subsequent benzylic oxidation reaction itself. Experiments using BQ (5 mol%) in the absence of copper salts resulted in ca. 3% conversion of isochroman into isochromanone. Increasing the amount of BQ to 10 mol%, again in the absence of copper salts, increased the conversion to ca. 10%. Hence photoactivated BQ is a competent oxidant for benzylic C–H bonds in the absence of copper salts, and the experiments suggest that the role of copper salts is solely to facilitate the reoxidation of hydroquinone to benzoquinone, and hence turn over the oxidative catalytic cycle.

Finally, we briefly investigated alternative light sources. The reaction was attempted under visible light irradiation using both a LED flood lamp and block of fan-cooled LED lights with emission >400 nm (Figures S2 and S3) but with no significant improvement in yields. Hence all reactions were subsequently irradiated using the 400 W HQI-T metal halide lamp; this not only gave the products in the highest yield in general, but is also non-specialist, cheap and commercially available equipment. Under these conditions the reaction mixture warms to ca. 30 °C; no reaction occurs in the dark at this temperature.

Notwithstanding the fact that BQH_2 is synthesized on a commercial scale from benzene and propene via oxidation of 1,4-diisopropylbenzene, or in admixture with catechol by oxidation of phenol, a further attraction to its use as a precursor to BQ in benzylic oxidation reaction is that it is potentially biorenewable. Although the concept of bio-renewable platform chemicals has been explored extensively by the scientific community,[31] the use of bio-renewable reagents appears to be largely unexplored. Therefore, we also investigated the use of the naturally occurring β-D-glucopyranoside of 1,4-hydroquinone, arbutin (Figure 2) as a bio-renewable "pre-oxidant" for benzylic oxidation.
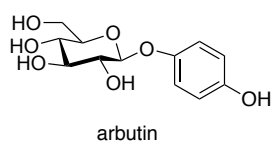

arbutin

Figure 2. Arbutin, the naturally occurring β-D-glucopyranoside of 1,4-hydroquinone.

Arbutin is readily available commercially (it is found in a range of skin lightening treatments), but could not be employed directly our oxidation conditions. Therefore, arbutin was pre-hydrolysed under acidic conditions, and the presence of BQH_2 confirmed by ^{1}H NMR spectroscopic analysis. The hydrolysis mixture was used without purification in the

benzylic oxidation of isochroman, but the yield of isochroman-1-one was low, possibly due to the presence of glucose in the mixture. A simple extraction of the acid hydrolysate (after evaporation) with dimethyl carbonate gave BQH_2 of sufficient purity for direct use as pre-oxidant in the benzylic oxidation of isochroman in yields comparable with the use of commercial BQH_2 (Table S2, Entry 3). Arbutin can be obtained from a variety of plant sources including the leaves of the bearberry plant (*Arctostaphyllos uva-ursi*) and the common garden plant elephant ears (*Bergenia crassifolia*).[32] Although analysis suggest that Bergenia produces higher content of arbutin,[32] in our hands extraction of commercial dried bearberry leaves from Serbia proved a better source than dried bergenia leaves harvested in Nottingham, UK. Following a literature procedure for extraction of arbutin,[33] quantitative HPLC analysis showed that the bearberry extract contained 1 mg of arbutin per mL of extraction solvent (see Supplementary Information). The yield from bergenia was 0.3 mg/mL. The bearberry extract was dried, hydrolysed as above, and evaporated to give a plant residue that, when analysed by ^1H NMR spectroscopy and HPLC, was shown to contain BQH_2. Satisfyingly, this material was shown to facilitate the oxidation of isochroman, albeit in lower yield (26%) compared to commercially sourced arbutin, but it did demonstrate the potential for truly biorenewable reagents in organic synthesis.

2. Oxidation of benzylic ethers.

With the optimized conditions in hand for both the arbutin and commercial BQH_2 protocols, we set out to demonstrate the scope of the reaction, starting with the chemoselective oxidation of isochromans into isochroman-1-ones **2 – 4** (Scheme 2A). Isochroman derivatives were oxidized in moderate to good yields, with both electron releasing and electron withdrawing substituents being tolerated at the 6-position. When the optimized conditions were applied to phthalan derivaties, phthalan itself was oxidized in good yield to phthalide **5**

in the presence of both commercial BQH_2 and that derived from arbutin. Substituted phthalans have two benzylic positions for oxidation, and in the case of 5-methoxyphthalan, the *para* oxidation product **7** was slightly favoured over the isomer **6**, presumably on electronic grounds. On the other hand, oxidation of 4-methoxyphthalan gave the methoxyphthalide **8** as the only observed product, suggesting that steric hindrance at the *peri*-position overrides electronic effects in this case. In all cases the structure of the phthalide products was confirmed by comparison with literature data, and no over-oxidation to the phthalic anhydride was observed. Presumably the introduction of the carbonyl group deactivates the ring towards further oxidation.
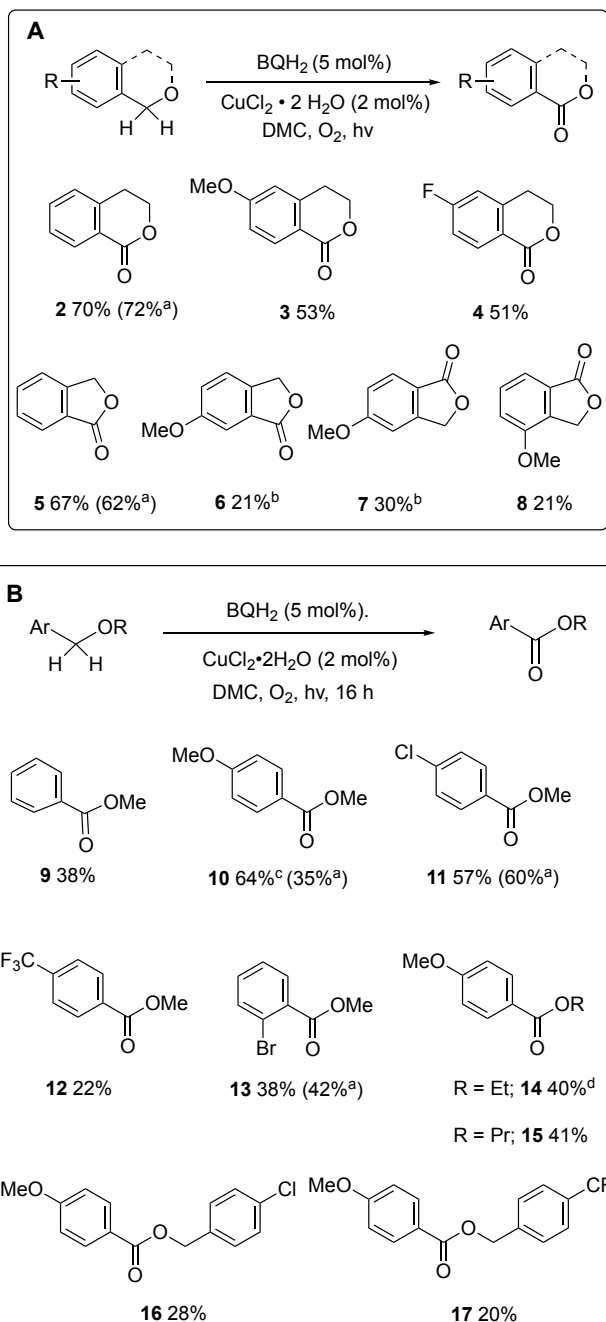
Scheme 2. Benzylic oxidation of ethers. **A** Oxidation of isochromans and phthalans; **B** oxidation of open chain benzylic ethers to benzoate esters.

Experimental conditions: BQH$_2$ (5 mol%), ETM (2 mol%), DMC, O$_2$ atmosphere. All reactions were carried out on 1 mmol scale at a 0.08 M concentration in sealed 25 mL Pyrex tubes, using a 400 W HQI-T metal halide lamp.

[a] Using BQH$_2$ derived from arbutin; [b] BQH$_2$ (5 mol%), CuCl$_2$•2H$_2$O (4 mol%), DMC, hv, O$_2$, rt, 16 h. [c] Combined yield of ester (43%) and acid (21%); [d] Yield by ^{1}H NMR integration

against 1,1,2,2-tetrachloroethane as an internal standard.

The methodology was next applied to the α-oxidation of open chain benzylic ethers to the corresponding benzoate esters **9 – 17**. Both 4-methoxybenzylmethyl ether and 4-chlorobenzylmethyl ether were oxidized in good yield, but the more electron deficient 4-trifluoromethyl derivative was oxidized to ester **12** in low yield. In the case of 4-methoxybenzyl ethyl ether and 4-methoxybenzyl propyl ether a modest reduction in yield was observed compared to the methyl ester. In the case the case of dibenzyl ethers, the oxidation occurred selectively *para*-to the more electron releasing methoxy group to give esters **16** and **17** (Scheme 2B). As with the phthalan derivatives, no over-oxidation at both benzylic positions was observed

3. Other benzylic oxidations.

The α-C–H oxidation of amines is a commonly encountered problem in modern synthesis, and provides a potentially useful route to amide derivatives. A number of metal-mediated methods are available,[34] including those based on copper or iron. Indeed, copper salts are known to facilitate the benzylic oxidation of *N*-phenyltetrahydroisoquinoline into the corresponding isoquinolone.[35] Under our conditions, the oxidation of *N*-phenyltetrahydroisoquinoline also occurred readily but was shown to be mediated by the copper salt alone, and therefore we investigated other *N*-substituted tetrahydroisoquinolines. Although the oxidation of the corresponding *N*-acetyl compound failed, the *N*-tosyltetrahydroisoquinoline and its 7-nitro derivative were oxidized smoothly to the corresponding isoquinolones **18** and **19** in 51 and 63% yield respectively. The oxidation of non-cyclic *N*-tosylbenzylamines, however, was less successful with amide **20** being formed in only poor yield (Scheme 3).
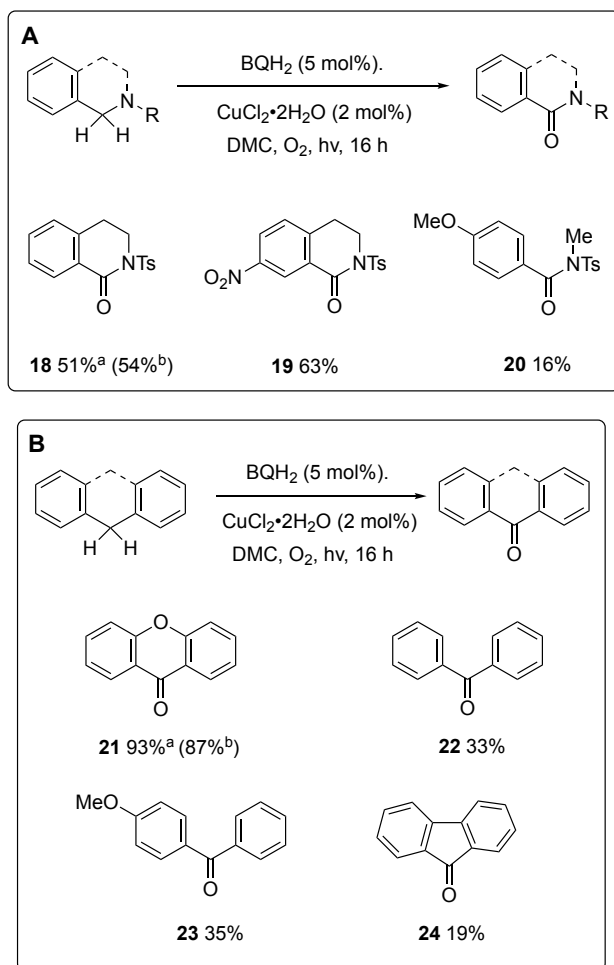
Scheme 3. **A** Oxidation of *N*-tosyl amines; **B** oxidation of diarylmethanes.

Experimental conditions: BQH$_2$ (5 mol%), ETM (2 mol%), DMC, O$_2$ atmosphere. All

reactions were carried out on 1 mmol scale at a 0.08 M concentration in sealed 25 mL Pyrex

tubes, using a 400 W HQI-T metal halide lamp.

[a] BQH$_2$ (5 mol%), CuCl$_2$•2H$_2$O (4 mol%), DMC, hυ, O$_2$, rt, 16 h; [b] In the presence of BQH$_2$

derived from arbutin.

The final reaction investigated was the oxidation of diarylmethanes to the corresponding

diarylketones. Although xanthane was oxidized to xanthone **21** in excellent yield, other biaryl

species gave only moderate yields of the corresponding ketones **22** and **23**. Surprisingly,

fluorene was oxidized to fluorenone **24** in only 19% yield (Scheme 3B). Alkyl benzenes were

only oxidized in very poor yield. Thus toluene gave benzaldehyde and ethylbenzene gave

acetophenone in only 4 and 8% yield respectively. Indan was also oxidized to indanone under

the standard conditions but again the yield was poor (16%). However, this oxidation could be

substantially improved under different conditions as described below (Scheme 5).

4. **Mechanistic Studies**.

In order to gain a greater understanding of the above oxidation reactions, two possible

reaction mechanisms were considered, both based on an initial formation of benzoquinone by

oxidation of the hydroquinone, and its subsequent photo-excitation, as outlined for the

oxidation of isochroman in Scheme 4. Firstly, a direct H-atom abstraction by photo-excited

benzoquinone to give an α-oxy-benzylic radical that subsequently reacts with dioxygen to

give a hydroperoxide intermediate that can collapse to a carbonyl group by further H-

abstraction, or by a heterolytic pathway as shown (Scheme 4, Path A). Alternatively, electron

transfer from the substrate would give a radical cation that can undergo H-atom transfer to

give an oxonium ion that can react with a nucleophile such as water (Scheme 4, Path B). A

key difference between the two pathways is the source of the additional oxygen atom in the

carbonyl group of the product, and although preliminary results suggested that molecular

oxygen was the source (little reaction was observed in its absence), further investigations

were required.
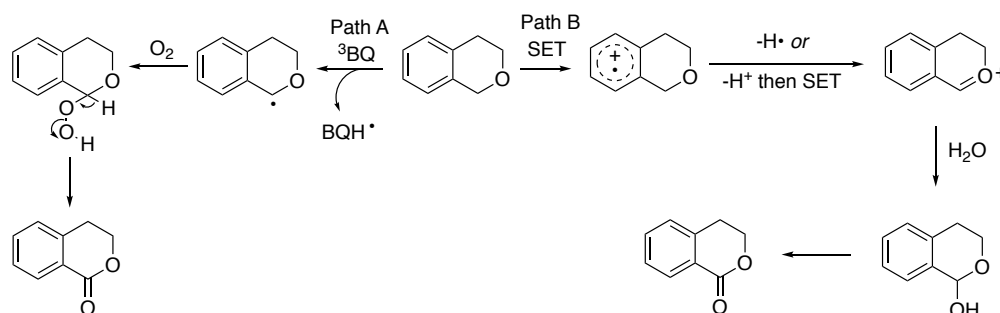
**Scheme 4**. Two possible mechanistic pathways for the light mediated benzylic oxidation. Scheme has been modified

The oxidation of isochroman was therefore performed under an atmosphere of $^{18}O_2$ (98.1%) under anhydrous conditions, alongside a control experiment under $^{16}O_2$ (99.8%). Under isotopically labelled dioxygen, only formation of the ^{18}O-labelled isochroman-1-one was observed, unambiguously identified by IR spectroscopy and HRMS analysis. Analysis of the IR spectrum showed a shift in the carbonyl stretch from 1714 cm^{-1} in the ^{16}O-labelled product to 1691 cm^{-1} in the ^{18}O-product, corresponding to the increase in mass of the ^{18}O atom. HRMS confirmed the presence of a mass ion at 149.0609 (100%) for the ^{16}O-isochromanone, and 151.0653 (100%) for the corresponding ^{18}O-product.

The fact that molecular oxygen was confirmed as the source of the oxygen atom in the product, supports the radical pathway shown in Path A in Scheme 4. Indeed, such photochemical hydrogen abstraction properties of quinones have long been known, and subjected to detailed study.[36] Evidence for a radical pathway was obtained by performing the oxidative functionalization of isochroman in the presence of excess butylated hydroxytoluene (BHT, 2 equiv) as a radical scavenger.[37] In this case, no reaction was observed suggesting that a radical mechanism was plausible, although attempts to intercept the intermediate benzylic radical with TEMPO were unsuccessful. Likewise, attempts to trap the radical in a 5-*exo-trig* radical cyclization using benzyl 3-butenyl ether as a substrate were unsuccessful.

However, when the light-mediated reactions of aromatic hydrocarbons were carried out using benzoquinone itself in stoichiometric quantity in the absence of oxygen, oxidation did occur, although the products were hydroquinone adducts. Thus the aforementioned oxidation of

indan gave the hydroquinone adduct **25** in good yield (70%) (Scheme 5). A similar reaction occurred with diphenylmethane to give the adduct **26** (41%), suggesting that the intermediate benzyl radical, formed by H-abstraction by photoexcited BQ, undergoes radical recombination to form the hydroquinone ether (Scheme 5). The trapping of intermediates formed upon oxidation using quinones with the derived hydroquinone has been observed previously in reactions of 1,4-benzoquinone,[38] and of DDQ.[39]
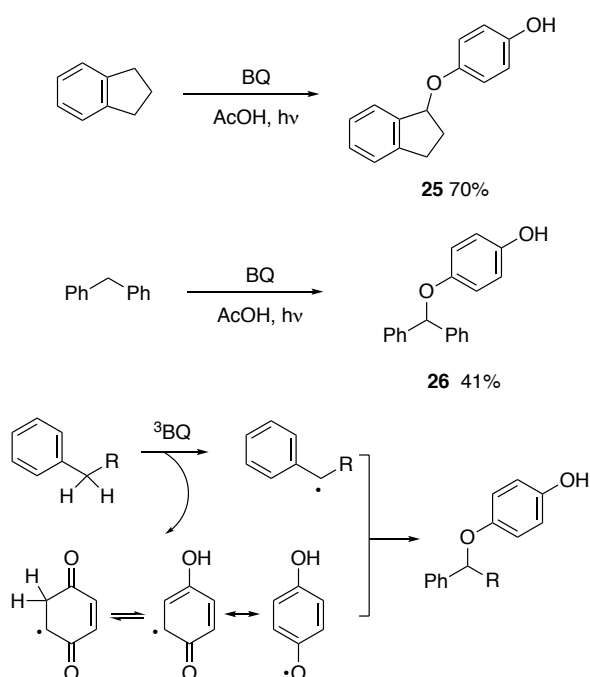
Scheme 5. Formation of hydroquinone ether adducts, and possible mechanism for their formation by radical recombination.

Finally we investigated the deuterium isotope effect in the oxidation of isochroman. Parallel reactions were conducted using isochroman and its known deuterated analogue,[40] 1-d_2-isochroman, prepared from d_2-formaldehyde under acidic conditions using a literature method for formaldehyde itself.[41] The rates of reaction for the two substrates were measured (see Supplementary Information), and a small deuterium isotope effect ($K_H/K_D=1.4$) was observed. When compared to deuterium isotope effects for the radical abstraction of

hydrogen atoms from related compounds, where K_H/K_D ratios are normally in the range ≈ 4–8,[42] the isotope effect is quite small. Nevertheless values as low as 1-2 have also been reported,[43] and therefore a H-abstraction mechanism is not ruled out. Whilst this does not rule out the operation of a radical mechanism, it does suggest that the rate-determining step may not involve benzylic hydrogen abstraction.

CONCLUSION

In summary, we have reported the use of visible-light irradiated BQH_2 in the presence of $CuCl_2 \cdot 2H_2O$ as an ETM, as a sustainable approach to the oxidation of benzylic species. The reaction conditions have been applied to cyclic benzylic ethers and amines, open chain benzylic ethers and diaryl hydrocarbons to give the corresponding carbonyl compounds in moderate to good yields. Mechanistic studies suggest that the reaction proceeds by H-abstraction by the photo-excited triplet benzoquinone to give a benzylic radical that subsequently reacts with molecular oxygen. It has also been demonstrated that arbutin may be used as a bio-renewable source of hydroquinone as pre-oxidant.

EXPERIMENTAL SECTION

All experimental procedures, characterization data for all compounds and copies of the ^{1}H and ^{13}C NMR spectra of new compounds are given in the Electronic Supplementary Information.

ACKNOWLEDGEMENTS

assistance with LED light sources**.**

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