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Solar Photochemical Oxidations of Benzylic and Allylic Alcohols Using Catalytic Organo-oxidation with DDQ: Application to Lignin Models

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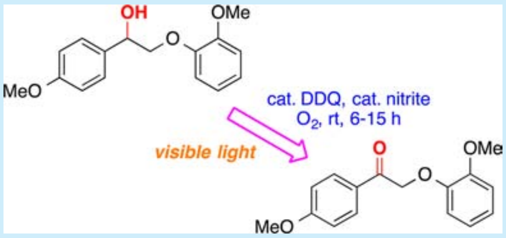
S Supporting Information

ABSTRACT: Visible light has a dramatic effect on the oxidation of benzylic and allylic alcohols, including those deactivated by electron-withdrawing groups, and β-O-4 lignin models, using catalytic amounts of the organo-oxidant 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. Sodium nitrite or *tert*-butyl nitrite is used as cocatalyst, and oxygen is employed as the terminal oxidant.



Oxidation is a fundamental process in chemistry and biology. In chemical synthesis, the oxidation of alcohols to carbonyl compounds is a core transformation,[1−4] and one particular example that has attracted much attention recently is the OH groups in lignin.[5] Lignin is a biopolymer that has been the subject of interest due to its potential as a feedstock.[5−7] The most common connectivity in lignin is the β-O-4 link, which features a primary aliphatic alcohol and a secondary benzylic alcohol and constitutes up to 50% of connectivities in lignin. Recent literature has demonstrated that oxidation of the benzylic position of β-O-4 lignin models results in easier C−C bond cleavage[8−12] and, as a result, allows access to high-value aromatic materials.[13,14]

Oxidation of alcohols is often carried out using high-oxidation-state metal salts usually in excess.[2,3] These metal-based reagents are not ideal since many, such as chromium(VI), lead(IV), and manganese(VII) compounds, are toxic and pose some serious health risks. In addition, they can be expensive, require the use of relatively scarce elements, and produce hazardous waste streams. As a result, considerable efforts have been made to use metals in catalytic amounts or nonmetallic reagents to effect the oxidation of alcohols.[15−18] Examples of the nonmetallic methods, a process that we term *organo-oxidation*, include DMSO-based oxidations, hypervalent iodine reagents, and TEMPO-based protocols.[2,3]

One particular organo-oxidant that is capable of performing a wide variety of oxidative transformations is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[19,20] Examples of its use include oxidative cyclizations,[21,22] aromatizations,[23] and dehydrogenations.[24,25] However, the stoichiometric use of this oxidant results in equimolar quantities of the corresponding hydroquinone ($DDQH_2$) byproduct that makes purification difficult on a large scale. In addition, DDQ is moderately expensive with a cost of \$680/mol (August 2014), and there are some toxicity concerns associated with its use on a large scale; the compound has an LD_{50} of 82 mg/kg and can release HCN on contact with water. Consequently, the use of DDQ in catalytic quantities, alongside a benign terminal oxidant, is an attractive, safer, and more sustainable alternative.[26]

Previous attempts at oxidations using substoichiometric quantities of DDQ have been reported. However, many of these processes have resorted to using an excess of metal-based oxidants, such as $Mn(OAc)_3$,[27] MnO_2,[28] and $FeCl_3$[29] in order to reoxidize the $DDQH_2$, and therefore offer few advantages. In contrast, other reports demonstrate the use of nitrite cocatalysts.[24,30,31] In one example, DDQ and sodium nitrite are utilized for the oxidation of benzylic and allylic alcohols.[32] However, the authors note that the use of alcohols containing electron-withdrawing groups gave unsatisfactory yields (Scheme 1). This is most likely due to the one-electron reduction potential of DDQ (E_{red} = 0.51 V vs SCE),[33] which may be too low to oxidize these electron-poor alcohols. We now report the remarkable effect of visible light on such catalytic DDQ oxidations that allows the oxidation not only of less reactive benzylic and allylic alcohols (Scheme 1) but also of β-O-4 lignin models under mild conditions.

Of the methods that employ substoichiometric amounts of DDQ, the most attractive appeared to be the nitrite-based protocols.[24,30,31] In the presence of oxygen, these generate nitrogen dioxide, a sufficiently strong oxidant to efficiently recycle the $DDQH_2$. However, under these conditions, our test reaction, the oxidation of 1-phenylethanol to acetophenone (Table S1), resulted in only a 13% conversion. Recently, Fukuzumi and co-workers have shown that triplet-excited DDQ

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Scheme 1. Alcohol Oxidations Using Catalytic DDQ

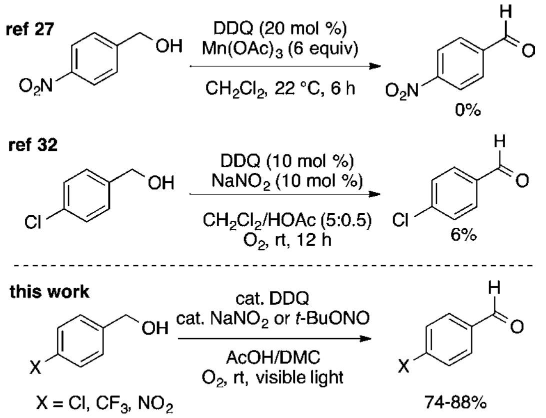
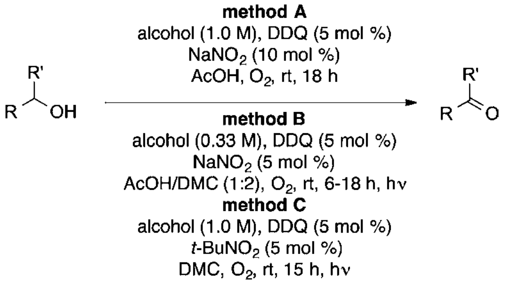
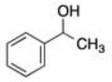
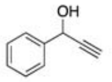
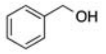
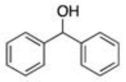
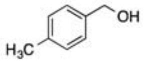
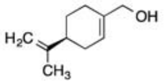
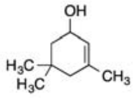
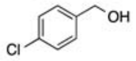
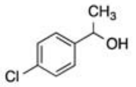
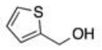
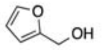
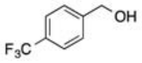
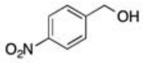
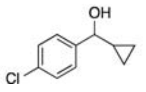


Table 1. Visible-Light-Enhanced Oxidation of Allylic and Benzylic Alcohols with Catalytic Amounts of DDQ (Reactions Carried out on 1 mmol Scale in Pyrex Vessels)



entry	alcohol	dark A conv (%)	light B yield (%)	light C yield (%)
1		13	84	-
2		21	88	-
3		5	77	-
4		36	95	-
5		58	79	-
6		46[a]	81[a]	-
7		71[a]	87[a]	-
8		3	88	-
9		9	94	-
10		51	100[b]	89[c]
11		no reaction	no reaction	51[d]
12		2[a]	28[b,e]	74[e]
13		5[a]	22[a,b]	77[a]
14		4	-	82

[a] 20 mol % of DDQ and nitrite used. [b] Conversion measured by ^{1}H NMR integration. [c] Same result obtained when using 5 mol % of $DDQH_2$ in place of DDQ. [d] 15 mol % of DDQ and nitrite used. [e] 10 mol % of DDQ and nitrite used.

(^{3}DDQ*) has a much stronger oxidizing ability (E_{red} = 3.18 V vs SCE).[34] As a result, we sought to develop a procedure in which benzylic and allylic alcohols could be oxidized under visible light irradiation using catalytic amounts of DDQ and sodium nitrite or *tert*-butyl nitrite as efficient cocatalysts, with oxygen as the terminal oxidant.

For consistency of irradiation, we initially used a "sunlight-mimicking" lamp, a commonly employed light source in commercial glasshouses. The effect was dramatic in that conversion to acetophenone increased to 55% compared to the "dark" reaction. Further experimentation included the screening of catalyst loadings, solvents, and concentrations, as well as a range of control experiments, and the results are summarized in the Supporting Information.

With the photochemical conditions established, we investigated the reactivity of a variety of alcohol substrates (Table 1); reactions under dark conditions (method A) are shown for comparison. Benzylic alcohols were found to give good to excellent yields, such as 1-phenyl-2-propyn-1-ol (entry 2), benzyl alcohol (entry 3), and diphenylmethanol (entry 4). In addition, some improvement in yield was also seen when using allyl alcohols, such as (*S*)-perillyl alcohol (entry 6) and 3,5,5-trimethylcyclo-2-hexen-1-ol (entry 7), which afforded yields of 81 and 87%, respectively. In all cases, conversions were significantly higher and reaction times were lower in comparison with the dark reaction.

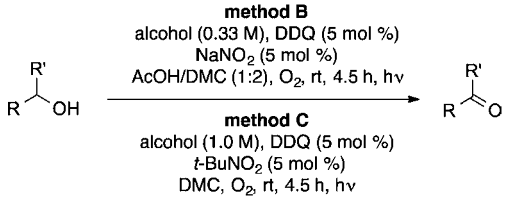
With benzylic alcohols containing electron-withdrawing groups, the effects of light were even more marked. Thus, for 4-chlorobenzyl alcohol (entry 8) and 1-(4-chlorophenyl)-ethanol (entry 9), very little reaction was observed without irradiation, even with stoichiometric quantities of DDQ. However, in 6−10 h, complete conversion was achieved using the visible light source, affording yields of 88 and 94%, respectively. Interestingly, if 4-chlorobenzyl alcohol was left for longer than 6 h, a significant quantity of 4-chlorobenzoic acid was isolated. This process requires no DDQ or $NaNO_2$ and occurs readily when a sample of 4-chlorobenzaldehyde in dimethyl carbonate is irradiated with visible light.

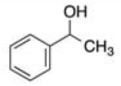
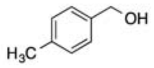
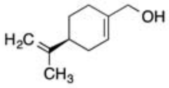
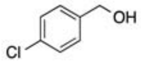
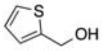
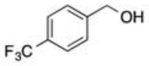
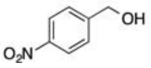
Due to the poor reactivity of some highly electron-deficient alcohols even under irradiation using method B, an alternative set of conditions was developed. In these conditions (method C), the sodium nitrite and acetic acid were replaced with *tert*-butyl nitrite,[30] affording high yields of the corresponding aldehydes. In particular, reactions of 4-(trifluoromethyl)benzyl alcohol (entry 12) and 4-nitrobenzyl alcohol (entry 13), which have been reported as unsuccessful with catalytic DDQ with $Mn(OAc)_3$ (8 equiv) as co-oxidant,[27] afforded yields of 74 and 77%, respectively. Since the conditions are chosen to reoxidize the $DDQH_2$ as it is formed, it is no surprise that the oxidation reaction can be carried out by starting from $DDQH_2$ as reagent in place of DDQ (entry 10) without loss of efficiency or yield.

Given that DDQ is believed to oxidize substrates via a SET mechanism,[35,36] we sought evidence of radical intermediates. When using (4-chlorophenyl)(cyclopropyl)methanol as substrate (entry 14), no cyclopropane ring opening was observed. On the other hand, when butylated hydroxytoluene (BHT) was added, little or no oxidation was observed. For example, with 1-(4-chlorophenyl)ethanol, a conversion of 56% was observed as opposed to 100% when no BHT was added, but with all other examples, including activated benzyl alcohols that ordinarily undergo complete conversion, no conversion was observed.

Subsequently, we explored how the reactions performed in sunlight compared with the visible light source (Table 2). Results demonstrate that even with a relatively low natural illuminance of 32 000 lx, good conversions were observed in just 4.5 h. These results are comparable to the sunlight-mimicking lamp that produced an average of 80 000 lx. Alcohols such as 1-phenylethanol (entry 1) and 4-methylbenzyl alcohol (entry 2) afforded slightly higher conversions of 79 and 77%, respectively, under sunlight. 4-Chlorobenzyl alcohol (entry 4) was found to give a 90% conversion in natural light, compared with a lower 64% conversion under artificial illumination. The highly electron-deficient 4-trifluoromethyl benzyl alcohol and 4-nitrobenzyl alcohol (entries 6 and 7) were found to give conversions of 62 and 40%, respectively. These conditions allow a fast and highly efficient synthesis, even in relatively poor sunlight (March, latitude 52°56′ N, 32 m above sea level). Although routinely carried out on 1 mmol scale, no reduction in conversion is observed on 10 mmol scale (entries 4 and 7; 90 and 47% conversion in sunlight after 5.5 h, respectively).

Table 2. Photochemical Alcohol Oxidations in Natural Light (Reactions Carried out on 1 mmol Scale in Pyrex Vessels)



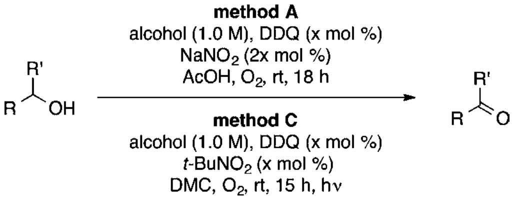
entry	alcohol	method	conversion in sunlight /%	conversion in artificial light /%
1		B	79	62
2		B	77	64
3		B	43[a]	42[a]
4		B	90 (90)[b]	64
5		C	57	50
6		C	62[c]	38[c]
7		C	40[a] (47)[b]	21[a]

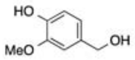
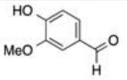
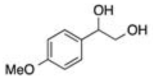
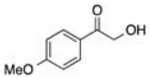
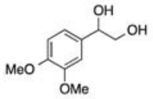
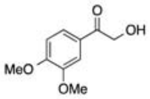
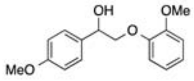
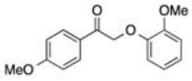
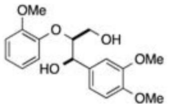
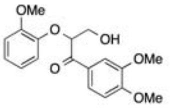
[a] 20 mol % of DDQ and nitrite used. [b] 10 mmol scale, 5.5 h. [c] 10 mol % of DDQ and nitrite used.

We also investigated the relative rates of reaction of allylic alcohols versus benzylic alcohols (see Supporting Information for details). In these competition experiments, using perillyl alcohol and 3,5,5-trimethylcyclohex-2-en-1-ol combined with either benzyl alcohol or 4-chlorobenzyl alcohol, the allylic alcohols are oxidized faster.

Finally, we sought to apply the procedure to several β-O-4 lignin models (Table 3) to determine its applicability and selectivity. A number of lignin models have been employed ranging from simple benzylic alcohols to complex oligomers,[37] and various oxidative methods for lignin degradation have been developed recently. These include vanadium oxo catalysts,[12] cobalt complexes,[9] TEMPO-based oxidants,[8,10] and biotransformations.[11] Under our conditions, vanillyl alcohol (Table 3, entry 1) oxidized cleanly to the aldehyde to give vanillin in 78% yield. Reactions with simple diols (entries 2 and 3) showed complete selectively to give the benzylic ketones in high yields of 89–93%. In addition, some alternative β-O-4 lignin models were investigated (entries 4 and 5), both of which afforded excellent yields. In particular, one lignin model (entry 5) required only 1.5 mol % of the DDQ catalyst, with no irradiation, to afford an excellent 92% yield of the ketone, comparable to other methods.[8,10]

Table 3. Lignin Model Oxidations with Catalytic Amounts of DDQ



	substrate	product	DDQ mol %	yield /%
1			5	78[a]
2			5	93[a]
3			5	89[b]
4			10	94[a] (47)[b]
5			1.5	92[b]

[a] Synthesized using method C. [b] synthesized using method A.

In summary, we have developed a highly efficient oxidation of benzylic and allylic alcohols under visible light irradiation using catalytic amounts of DDQ and sodium nitrite or *tert*-butyl nitrite. The procedure can be performed effectively even in relatively poor sunlight or alternatively using a visible light source; substrates which are usually unreactive with DDQ, such as 4-nitrobenzyl alcohol, afford high yields upon irradiation with visible light. The method can also be applied to β-O-4 lignin models, potential precursors to high-value aromatic compounds, selectively oxidizing the secondary benzylic alcohol in high yield.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): C.J.M. and H.F.S. are are stockholders in GlaxoSmithKline.

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