Selective Oxidation of Benzylic and Allylic Alcohols Using Mn(OAc)₃/Catalytic 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
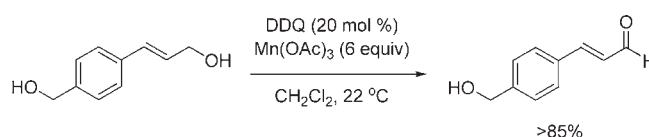
Casey C. Cosner, Pablo J. Cabrera, Katherine M. Byrd, Asia M. Adams Thomas, and Paul Helquist*

Department of Chemistry and Biochemistry, 251 Nieuwland Science Hall, University of Notre Dame, Notre Dame, Indiana 46556, United States

phelquis@nd.edu

ABSTRACT

A practical, chemoselective oxidation of alcohols employing catalytic quantities of DDQ as the oxidant and Mn(OAc)₃ as the co-oxidant is described. Electron-rich benzylic alcohols are oxidized efficiently to their corresponding carbonyls, but less electron-rich benzylic alcohols remain unchanged. Allylic alcohols are rapidly oxidized to their corresponding aldehyde or ketone counterparts in high yields. This protocol is operationally simple, employs an inexpensive source of Mn(OAc)₃, has short reaction times, and exhibits a significant chemoselectivity favoring allylic alcohols over benzylic alcohols. This procedure also avoids the use of very large excesses of reagents and sometimes poor reproducibility that characterize previously developed reagents such as MnO₂.

Over the years, a plethora of reagents and conditions have been developed for the mild oxidation of alcohols to carbonyl compounds.[1] Some of the many available reagents are chemoselective for specific classes of alcohols. A classic example is MnO₂, which has long served as a reagent for the oxidation of benzylic or allylic alcohols.[2] Although in very common use, MnO₂ requires proper activation to obtain acceptable yields reproducibly; the reactions are often very slow, and they typically employ 10-fold or larger excesses of the reagent.

We recently became interested in seeking alternative conditions when we had a need to effect the transformation exemplified in eq 1. Traditional methods
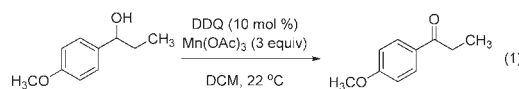
(i.e., Swern oxidation,[3] Dess-Martin periodinane,[4] IBX,[5] or MnO₂) either provided inadequate yields of the desired

product or failed completely. DDQ,[6] however, provided the desired product in 95% yield in less than 10 min. While we were initially encouraged by this result, the high cost of DDQ discourages its use in large-scale operations. We therefore sought a protocol that would allow the

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catalytic use of DDQ in the presence of a less expensive stoichiometric co-oxidant. Recently, Floreancig reported the use of catalytic amounts of DDQ in the presence of excess MnO_2 for other types of oxidative transformations, including cyclizations of ether-containing enol esters to form pyranones, aromatizations, and *O*-PMB deprotections.[7] $Mn(OAc)_3$, which functions as a mild single electron acceptor,[8] has also been used for regeneration of DDQ in the removal of PMB protecting groups.[9] While this previous work did not include the oxidation of alcohols, we wished to determine whether this or a similar protocol would be amenable to our needs. As a result of investigating this question, we are now pleased to report a new, modified catalytic oxidation procedure that is simple to perform, provides short reaction times, utilizes a readily prepared co-oxidant, and is not only selective for allylic and benzylic alcohols but which also exhibits selectivity for allylic alcohols in the presence of benzylic alcohols.

Based upon the preceding background, we chose to employ $Mn(OAc)_3$ as the co-oxidant along with catalytic DDQ. While the cost of commercially available $Mn(OAc)_3$ is rather high, we routinely prepare batches of greater than 40 g from inexpensive $Mn(OAc)_2$.[10] The reagent is air- and moisture-stable and can be stored in ordinary glassware exposed to air for months at a time.

Our studies began with the aforementioned oxidation of 1-(4-methoxyphenyl)ethanol, an electron-rich benzylic alcohol, with 1.1 mol equiv of DDQ by itself as a benchmark (Table 1, entry 1). We then examined systematically the effect of $Mn(OAc)_3$, beginning with the use of 3 mol equiv of this co-oxidant. As expected, decreasing the amount of DDQ resulted in a drastic decrease of product yield (entries 2−6). Even DDQ loadings as high as 50 mol % did not lead to significant product formation. We therefore examined the effect of doubling the amount of $Mn(OAc)_3$ to 6 mol equiv. Under these conditions, we could lower the amount of DDQ necessary for the reaction to 20 mol % (entry 7). Lower catalyst loadings of DDQ resulted in lower yields. To demonstrate which species is the active oxidant, we conducted the same reaction without DDQ (entry 8). No oxidation product was observed, even after extended reaction times, indicating that DDQ is the active oxidant in the reaction mixture and that the $Mn(OAc)_3$ does indeed serve to regenerate the benzoquinone. It is noteworthy that the loadings of DDQ (20 mol %) and co-oxidant (6 mol equiv) are equal to those reported by Floreancig for quite different transformations.[7] Under these conditions, we obtained consistently reproducible results when $Mn(OAc)_3$ was used free from excess acetic acid remaining from the preparation of the reagent.[10]

Having optimized this initial example of the catalytic DDQ oxidation, we next tested the scope and limitations of these conditions for benzylic and allylic alcohols. As can be seen in Table 2, a distinct pattern of reactivity emerges for benzylic alcohols. Activated

Table 1. Optimization of DDQ Oxidation

entry	DDQ (mol %)	$Mn(OAc)_3$ (equiv)	time (h)	yield[a] (%)
1	110	0	0.2	95[b]
2	50	3	12	55
3	20	3	12	45
4	15	3	12	37
5	10	3	12	20
6	5	3	12	<10
7	20	6	3	100 (79)[b]
8	0	6	12	0

[a] Yield based on ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated, purified yield.

systems, i.e., those bearing electron-donating groups, underwent faster conversions and gave higher overall yields than unactivated systems (compare entries 1 and 2). Very activated systems, such as *p*-dimethylamino-phenylpropanol (entry 3), gave superior results; high yields were obtained in reaction times of typically 6 h or less. A biphenyl substrate (entry 4) underwent smooth oxidation to provide the ketone product in good yield, and 9-hydroxyfluorene (entry 5) gave a very high yield of product after 6 h. The reaction failed in the presence of chlorine and nitro substituents and for the heterocyclic systems that were tested (entries 6−9). Allylic alcohols serve as especially good substrates for this oxidation procedure (entries 10−13).[6] We were pleased to observe the clean, complete conversion of cinnamyl alcohol to cinnamaldehyde (entry 10). 2-Cyclohexenol underwent clean oxidation in approximately 90% yield (entry 11). An acyclic secondary allylic alcohol proved to be a very good substrate (entry 13).

Having observed that allylic alcohols in general and some benzylic alcohols are good substrates for the DDQ/Mn(OAc)_3 oxidation, we next conducted competition studies to determine chemoselectivity patterns for different classes of alcohols. Use of a mixture of 2-cyclohexenol and cyclohexanol (eq 2) demonstrates that an aliphatic alcohol remains unchanged while the allylic alcohol is oxidized to the enone in excellent yield. Furthermore, an electron-rich benzylic alcohol is selectively oxidized in the presence of a nonactivated benzylic alcohol (eq 3). Finally, we conducted intermolecular and intramolecular competition studies between benzylic and allylic alcohols (eqs 4 and 5). Due to its sensitivity, the enal product formed in eq 5 was characterized as the corresponding methyl ester (see Supporting Information).[11] A very clear chemoselectivity is seen for the oxidation of allylic alcohols.

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Table 2. Substrate Scope of the Mn(OAc)$_3$/Catalytic DDQ Oxidation

entry	substrate	product	time (h)	yield[a]
1			3	79%
2			12	7%
3[b]			1	91%
4			4	78%
5			6	82%
6			12	0%
7			12	0%
8			12	0%
9			12	0%
10			2	>95%[c]
11			2	90%[c]
12			1	>95%[c]
13			2	83%

[a] Yields refer to isolated, purified products. [b] 2 equiv of Mn(OAc)$_3$ were used. [c] Calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

In conclusion, we have developed an alcohol oxidation protocol that utilizes catalytic quantities of DDQ with Mn(OAc)$_3$ as the co-oxidant. The method employs mild conditions and is highly chemoselective. While the process oxidizes certain activated benzylic alcohols selectively, the
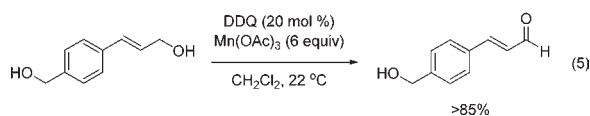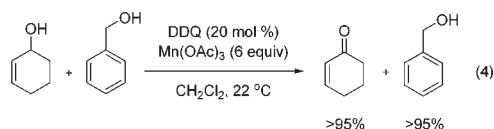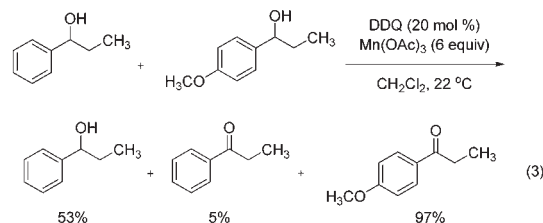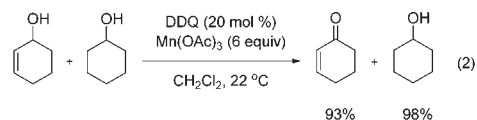
reaction is most selective for allylic alcohols, which are efficiently converted to the corresponding unsaturated carbonyl compounds. The reaction times are relatively short, ranging from 1 to 6 h for the preferred substrates. Given the highly selective nature of this oxidation, the fast reaction times, and ease with which the reaction can be conducted, we believe that this method will serve as a useful protocol for selective oxidations in multistep syntheses.

Supporting Information Available. General experimental details, spectral data, and copies of selected ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. References 6h–j were added to the version reposted March 23, 2011.