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Published in:
Chemsuschem

DOI:
10.1002/cssc.201300378

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2013

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 09-01-2019
Manganese-Catalyzed Selective Oxidation of Aliphatic C–H groups and Secondary Alcohols to Ketones with Hydrogen Peroxide


An efficient and simple method for selective oxidation of secondary alcohols and oxidation of alkanes to ketones is reported. An in situ prepared catalyst is employed based on manganese(II) salts, pyridine-2-carboxylic acid, and butanedione, which provides good-to-excellent conversions and yields with high turnover numbers (up to 10000) with H₂O₂ as oxidant at ambient temperatures. In substrates bearing multiple alcohol groups, secondary alcohols are converted to ketones selectively and, in general, benzyl C–H oxidation proceeds in preference to aliphatic C–H oxidation.

Introduction

Selective oxidation of alcohols to ketones together with direct conversion of C–H bonds to alcohols and ketones are crucial, yet also highly challenging, processes in synthetic organic chemistry, pharmaceuticals, and fine and bulk chemical synthesis (Scheme 1).[1] Traditional methods for achieving such transformations, although highly effective in general, are becoming increasingly undesirable because of rising demands to reduce environmental impact and increase the mass and energy efficiency of processes. Hence the drive to develop benign methods compels us to explore the use of methods using 1st row transition-metals and clean (mass-efficient) oxidants.[2] Hydrogen peroxide is a highly favorable oxidant in this regard, second only to oxygen,[3] with water as the sole by-product.[4] Several highly effective catalytic methods for the oxidation of alcohols with H₂O₂ have been reported, not least the system of Noyori and co-workers, based on tungsten oxide/PTC (where PTC is phase transfer catalyst),[5] and the systems of Beller and co-workers, employing iron catalysts[6] and catalysts based on rhenium, molybdenum, and tungsten oxides.[7] However, the use of high temperatures and/or catalyst loadings and potentially toxic PTCs drives the search for alternative methods. Manganese-based catalysts are attractive in C–H and alcohol oxidations because of their generally low toxicity and the often high reaction rates and turnover numbers that can be achieved even at room temperature. Manganese catalysts, based on salen ligands[8] have been employed in the oxidation of alcohols with iodosobenzene as oxidant[8a] and catalyzed enantioselective kinetic resolution of secondary alcohols.[8b] Manganese catalysts based on polypyridyl and triazacyclonane-based ligands,[9–11] as well as porphyrins,[12] have also been used.[13]

Recently, our group reported an efficient method for the epoxidation and cis-dihydroxylation of alkenes catalyzed by an in situ prepared manganese(II) catalyst and which is near-stoichiometric in H₂O₂.[14–16] This catalytic system consists of a Mn²⁺ salt, pyridine-2-carboxylic acid, and sub-stoichiometric amounts of ketone, and showed good-to-excellent selectivity, high turnover numbers (up to 300 000) and high turnover frequencies (up to 30 s⁻¹) at room temperature, with a wide solvent scope.[16]

Here, we report the application of this catalytic system to the oxidation of alcohols and alkanes under ambient conditions and low catalyst loadings (Scheme 2). For substrates that do not bear alkene moieties, we show that high yields and selectivity can be achieved in the oxidation of secondary alcohols with good-to-excellent selectivity of secondary over primary alcohol oxidation. Furthermore, at higher catalyst loadings...
Results and Discussion

In the present study, the oxidation of alcohols was initially investigated using conditions optimized earlier for alkene oxidation (Scheme 2),[16] that is, using substrate (0.5 M), manganese perchlorate (0.01 mol%), pyridine-2-carboxylic acid as catalyst (0.5 mol%), and butanedione (0.5 equiv. in acetonitrile) with \( \text{H}_2\text{O}_2 \) (1.5 equiv.). Under these conditions, cyclohexanol was oxidized to cyclohexanone in 73% yield, albeit with incomplete conversion (Table 1, entry 1). With 3.0 equiv of \( \text{H}_2\text{O}_2 \), full conversion and 91% yield of cyclohexanone was obtained. Importantly, the reactions proceeded without formation of significant amounts of side products (e.g., Baeyer–Villiger oxidation products and double oxidation).

These conditions were applied to a series of secondary alcohols (Table 1). Cyclic and acyclic aliphatic alcohols were converted cleanly to their corresponding ketone products (Table 1, entries 2 and 3). For 5-nonanol, the conversion achieved was, however, lower, which was ascribed to its lower solubility in acetonitrile compared with the other alcohols examined. The relatively wide solvent scope of the present catalyst system, which was previously demonstrated,[16] allows for the low solubility of 5-nonanol to be overcome by using acetone in place of acetonitrile and provided 5-nonanone in high yield (Table 1, entry 4).

The oxidation of sterically encumbered alcohols was also investigated. 2,4-dimethyl-pentan-3-ol was converted (71%) with 68% yield to 2,4-dimethyl-pentan-3-one (Table 1, entry 5). Similarly the natural product isoborneol was converted to camphor in excellent yield (Table 1, entry 6). The reactions in general were found to be scalable, without significant difference in conversion or yield (see the Supporting Information for details). Notably, at larger scale, complete conversion was achieved by extraction of the product and unreacted starting material from the reaction mixture and subjecting the mixture to the same reaction conditions a second time. In the case of isoborneol at a 4 g scale, full conversion and an isolated yield of 87% was achieved.

A series of secondary benzylic alcohols were oxidized to their corresponding ketones under these reaction conditions, in good yields (Table 1). Even bromo-phenyl or oxidatively sensitive methoxy-phenyl-bearing substrates proceeded in moderate-to-good conversion. In general, lower conversion can be overcome by decreasing the initial concentration of the substrate as with,[16] for example, 1-(4'-methoxyphenyl)ethanol (Table 1, entry 11).

The oxidation of hemiacetals was explored through tetrahydro-2H-pyran-2-ol, which can be viewed as a cyclic alcohol with an ether functional group. Full conversion and moderate yield (44%) of valerolactone was achieved. The moderate yield of the desired product was primarily a result of the ring opening to generate the corresponding carboxylic acid in situ (Scheme 3).

The selective oxidation of secondary aliphatic and aromatic alcohols in the presence of primary alcohols was explored through competition experiments (Schemes 4 and 5). Oxidation of an equimolar mixture of 1- and 2-phenyl-ethanol provided 75% conversion of 1-phenyl-ethanol to acetoephone with only trace conversion of 2-phenyl-ethanol. For substrates

![Scheme 2. Oxidation of cyclohexanol to cyclohexanone.](image)

![Scheme 3. Oxidation of tetrahydro-2H-pyran-2-ol to valerolactone (yield determined by \(^1\)H NMR spectroscopy).](image)

Table 1. Oxidation of secondary alcohols.[a,4]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conv.[b] (%)</th>
<th>Product</th>
<th>Isolated Yield [%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>full</td>
<td>91[b]</td>
<td>(73%)</td>
<td>(73[b])</td>
</tr>
<tr>
<td>2</td>
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<td>78</td>
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<tr>
<td>3</td>
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<td>4</td>
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<td>72</td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>68[b]</td>
<td></td>
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<tr>
<td>6</td>
<td>full</td>
<td>95</td>
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<tr>
<td>7</td>
<td>97</td>
<td>90</td>
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<td>8</td>
<td>92</td>
<td>77</td>
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<td>90</td>
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<tr>
<td>10</td>
<td>88</td>
<td>75</td>
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<tr>
<td>11</td>
<td>70</td>
<td>64</td>
<td></td>
<td></td>
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<tr>
<td>12</td>
<td>78</td>
<td>76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.5 M substrate (1 mmol), 50 μM Mn(ClO₄)₂·6H₂O, 2.5 mm pyridine-2-carboxylic acid, 5.0 mm NaOAc, 0.25 m butanedione, and 1.5 m H₂O₂ in acetonitrile. [b] Conversion and yield, based on substrate, determined by \(^1\)H NMR spectroscopy. [c] Isolated yield, unless stated otherwise. [d] 0.75 m H₂O₂ (1.5 equiv. with regard to substrate) was used. [e] 0.4 μm substrate (0.8 mmol). [f] In acetone. [g] 0.25 m substrate (0.5 mmol).
bearing both secondary and primary aliphatic alcohol moieties, oxidation of the secondary alcohol also proceeded preferentially (Scheme 5).

In addition to the oxidation of secondary alcohols to ketones, the direct oxidation of methylene units to ketones with the present catalytic system was explored.

The direct oxidation of aliphatic compounds such as cyclohexane and cyclooctane proceeded with good conversion and selectivity to the corresponding mono-ketone product. (Table 2, entries 1 and 2). In contrast to alcohol oxidation, however, higher catalyst loadings (0.1 mol %) and up to 4.0 equiv. of H₂O₂ were required (Scheme 6). In addition to the ketone product, the corresponding alcohol, together with a mixture of diketones, was observed in amounts that were dependent on the exact reaction conditions. At catalyst loadings of 0.1 mol %, the oxidation at the benzylic positions for a wide range of alkylated aromatics could be achieved at room temperature (Table 2, entries 3–12). For both ethylbenzene and propylbenzene, the corresponding aromatic ketone product was obtained with good selectivity (Table 2, entries 3 and 4). In contrast, oxidation of toluene proceeded with lower conversion (35–40 %) and low yield of a mixture of benzyl alcohol (8–10 %), benzaldehyde (8–10 %) and benzoic acid and with a low mass balance as a result of the formation of an insoluble polymeric material.

1-Ethyl-4-methyl-benzene was found to undergo good conversion (70 %) with moderate yield of 4-methyl-acetophenone as the main product, albeit with significant amounts of a white polymeric by-product (Scheme 7). In general, for cyclic systems, full conversion was achieved with moderate-to-excellent isolated yields of the corresponding ketone (Table 2, entries 5–9). Surprisingly, in many cases, substantial amounts of the intermediate alcohol product were obtained, which would suggest that the rate of C–H oxidation, although slower, is nevertheless comparable with the rate of alcohol oxidation. The doubly oxidized product, anthracene-9,10-dione, was obtained from 9,10-dihydroanthracene in excellent yield, (Table 2, entry 7). In contrast, the mono-oxidized alcohol and ketone products were obtained as the primary product in the oxidation of 9,10-dihydrophenanthrene (Table 2, entry 9).

The selective oxidation of 1,2,3,4-tetrahydro-1-naphthol to the corresponding ketone, without further oxidation at the other benzylic position, confirms that benzylic positions are marginally less susceptible to oxidation than secondary aryl alcohols (Table 1, entry 10). Nevertheless, if there is sufficient oxidant available, further oxidation to the diketone products is observed.

p-Methoxy- and o-nitro-phenylethanes could be converted to the corresponding aryl-methyl-ketones as well (Table 2, entry 10 and 11). The lower yield of 1-(4-methoxy)phenylethane reflects the lower conversion also observed for the corresponding alcohol 1-(4-methoxyphenyl)ethanol (Table 1, entry 11). Similarly, lower conversion was observed for o-nitrophenylethane (Table 2, entry 11).

Surprisingly, oxidation of 2-benzyl-pyridine to phenyl(pyridin-2-yl)methanone proceeded with good conversion and selectivity without formation of the N-oxide product (Table 2, entry 12).
The selectivity towards methylene over methyl C–H groups was investigated using 1-methylpyrrolidin-2-one. Good conversion (83%) to and moderate isolated yield (34%) of 1-methylpyrrolidin-2,5-dione was achieved (Table 2, entry 13); however, the selectivity was poor with several side products also observed.

With regard to the mechanism for conversion of aliphatic C–H groups to alcohols and subsequently to ketones, it is likely that an active species similar to that previously reported serves.

The oxidation of alkenes [15, 16] is responsible. The involvement of active oxygen species such as oxygen and hydroxyl radicals should also be considered, however. The direct involvement of atmospheric oxygen can be excluded based on mass balance; at the conversions observed, it would not be possible to obtain the oxygen required from the dissolved oxygen present. The disproportionation of the \( \text{H}_2\text{O}_2 \) present could provide considerable more oxygen; however, this can also be discounted because of the relatively low level of catalase type activity observed. Hence, the presence of both alcohol and ketone products can be ascribed to sequential oxidation rather than, for example, a Russell’s mechanism[17] between alkyl radicals and oxygen.

### Conclusions

Herein, we demonstrate that selective oxidation of secondary alcohols can be achieved at room temperature with an in situ prepared manganese catalyst with high turnover numbers (up to 10000) and with near stoichiometric amounts of \( \text{H}_2\text{O}_2 \). The reaction is scalable from 100 mg to 4 g and, in many examples, highly selective. Although we have demonstrated previously that this catalyst system is tolerant of several common protecting groups,[16] the selectivity of the catalyst towards secondary alcohols over primary alcohols is also demonstrated, which reduces the need for the introduction prior to oxidation and subsequent removal of protecting groups and is complimentary to catalytic methods for selective primary alcohol oxidation based on copper and TEMPO-based (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl) catalysts.[3c, 6a] For benzylic alcohol oxidation and in particular for cyclic systems, selective oxidation to the monoketone product can be achieved under mild conditions and with good efficiency in terms of the oxidant \( \text{H}_2\text{O}_2 \).

### Experimental Section

Caution: The drying or concentration of solutions that potentially contain \( \text{H}_2\text{O}_2 \) should be avoided. Prior to drying or concentrating, it is necessary to test for the presence of \( \text{H}_2\text{O}_2 \) by using peroxide test strips followed by neutralization on solid \( \text{NaHSO}_3 \) or another suitable reducing agent. When working with \( \text{H}_2\text{O}_2 \), suitable protective safeguards should be in place at all times.

Caution: Exposure to butanedione vapors has been linked with lung disease. It should be handled in a properly ventilated fumehood and exposure to vapors should be avoided.

### General procedure for oxidation of secondary alcohols

The alcohol (1 mmol) was added to a stock solution containing \( \text{Mn(ClO}_4)\text{)_2} \cdot \text{6H}_2\text{O} \) (0.01 mol%, 0.0361 mg) and pyridine-2-carboxylic acid (0.5 mol%, 0.123 mg) in acetonitrile to generate a final substrate concentration of 0.5 mM. \( \text{NaOAc} \) (aq. 0.6 M, 1 mol%, 16.7 \( \mu \)L) and butanedione (0.5 equiv., 43.5 \( \mu \)L) were added to generate a final volume of 2 mL. The solution was stirred with cooling in an ice/water bath before addition of \( \text{H}_2\text{O}_2 \) (50 wt%, 3.0 equiv., 170 \( \mu \)L). After 12–16 h stirring at room temperature, brine (10 mL) was added and the reaction was extracted with dichloromethane. The combined organic layers were reduced in vacuo. The products were isolated by flash column chromatography on silica gel of

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conv. [%]</th>
<th>Product/s (isolated yield [%])</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>63</td>
<td>(34)</td>
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<tr>
<td>2</td>
<td></td>
<td>60</td>
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<td>80</td>
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<tr>
<td>4</td>
<td></td>
<td>50</td>
<td>(3)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>full</td>
<td>(60) (12) (4)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>full</td>
<td>(66) (9) (25)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>full</td>
<td>(99)</td>
</tr>
<tr>
<td>8[a]</td>
<td></td>
<td>full</td>
<td>(76)</td>
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<tr>
<td>9</td>
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<td>90</td>
<td>(37) (50)</td>
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<td>75</td>
<td>(28) (17)</td>
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<td>(73)</td>
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<td>13</td>
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<td>83</td>
<td>(34)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.5 mM substrate (1 mmol), 5 mM pyridine-2-carboxylic acid, 0.5 mM Mn(ClO\(_4\))\(_2\)-6H\(_2\)O, 10 mM NaOAc, 0.75 mM butanedione, and 2.0 mM H\(_2\)O\(_2\) in acetonitrile. [b] Isolated yield, based on substrate, unless stated otherwise. [c] 'H NMR yield, based on substrate, see the Supporting Information for details. [d] 0.25 mM substrate (0.5 mmol).
230–400 mesh particle size. Products were characterized by NMR spectroscopy (see the Supporting Information).

**General procedure for oxidation at alkyl and benzylic moieties C–H**

The alkane (1 mmol) was added to a stock solution of Mn(ClO₄)₂·6H₂O (0.1 mol %, 0.361 mg) and pyridine-2-carboxylic acid (1.0 mol %, 0.246 mg) in acetonitrile to generate a final substrate concentration of 0.5 M. NaOAc (aq, 0.6 M, 2 mol %, 33.4 μL) and butanedione (1.5 equiv., 130.5 mL) were added to generate a final volume of 2 mL. The solution was stirred with cooling in an ice/water bath before addition of H₂O₂ (50 wt %, 4.0 equiv., 227 L). After 12–16 h, brine (10 mL) was added and the reaction was extracted with dichloromethane (thrice 10 mL). The combined organic layers were reduced in vacuo. The products were isolated by flash column chromatography on silica gel of mesh particle size 230–400. Products were characterized by NMR spectroscopy (see the Supporting Information). In certain cases a solid material was also obtained, which, on the basis of FTIR, Raman, and NMR analysis, appeared to be a polymer.

**Acknowledgements**

This research has been performed with the framework of the CatchBio program. The authors thank the European Research Council (Starting Investigator Grant 279549, FM, DU, WRB), the University of Groningen (Ubbio Emmius studentship, PS), the Foundation for Technology and Science (STW Grant No. 11059, CatchBio program). The authors thank the European Research Fund for Technology and Science, the Education, Culture and Science, and butanedione (1.5 equiv., 130.5 mL) were added to generate a final substrate concentration of 0.5 M. The solution was stirred with cooling in an ice/water bath before addition of H₂O₂ (50 wt %, 4.0 equiv., 227 L). After 12–16 h, brine (10 mL) was added and the reaction was extracted with dichloromethane (thrice 10 mL). The combined organic layers were reduced in vacuo. The products were isolated by flash column chromatography on silica gel of mesh particle size 230–400. Products were characterized by NMR spectroscopy (see the Supporting Information). In certain cases a solid material was also obtained, which, on the basis of FTIR, Raman, and NMR analysis, appeared to be a polymer.

**Keywords:** alcohol oxidation · alkane oxidation · catalysis · manganese


Received: April 22, 2013
Revised: June 23, 2013

Part of a Special Issue on “CatchBio”. To view the complete issue, visit: