Very Important Publication

Aromatic C–H Hydroxylation Reactions with Hydrogen Peroxide Catalyzed by Bulky Manganese Complexes

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Abstract: The oxidation of aromatic substrates to phenols with H2O2 as a benign oxidant remains an ongoing challenge in synthetic chemistry. Herein, we successfully achieved to catalyze aromatic C–H bond oxidations using a series of biologically inspired manganese catalysts in fluorinated alcohol solvents. While introduction of bulky substituents into the ligand structure of the catalyst favors aromatic C–H oxidations in alkylbenzenes, oxidation occurs at the benzylic position with ligands bearing electron-rich substituents. Therefore, the nature of the ligand is key in controlling the chemoselectivity of these Mn-catalyzed C–H oxidations. We show that introduction of bulky groups into the ligand prevents catalyst inhibition through phenolate-binding, consequently providing higher catalytic turnover numbers for phenol formation. Furthermore, employing halogenated carboxylic acids in the presence of bulky catalysts provides enhanced catalytic activities, which can be attributed to their low pKₐ values that reduces catalyst inhibition by phenolate protonation as well as to their electron-withdrawing character that makes the manganese oxo species a more electrophilic oxidant. Moreover, to the best of our knowledge, the new system can accomplish the oxidation of alkylbenzenes with the highest yields so far reported for homogeneous arene hydroxylation catalysts. Overall our data provide a proof-of-concept of how Mn(II)/H2O2/RCO2H oxidation systems are easily tunable by means of the solvent, carboxylic acid additive, and steric demand of the ligand. The chemo- and site-selectivity patterns of the current system, a negligible KIE, the observation of an NIH-shift, and the effectiveness of using tBuOOH as oxidant overall suggest that hydroxylation of aromatic C–H bonds proceeds through a metal-based mechanism, with no significant involvement of hydroxyl radicals, and via an arene oxide intermediate.

Keywords: Aromatic C–H oxidation; Bioinspired oxidation; Fluorinated alcohol solvents; Halogenated carboxylic acids; Manganese catalysts; Phenols

Introduction

Oxidations of organic compounds are essential reactions widely studied in academia as well as in the chemical industry. The interest mainly arises from the fact that the oxygenated organic molecules can be further used to produce different classes of valuable chemicals, such as pharmaceuticals. Despite many
research efforts, the selective oxidation of organic substrates still represents a critical challenge in synthetic chemistry. For instance, the direct one-step hydroxylation of aromatic molecules to the corresponding phenols could provide easy access to relevant building blocks for more complex molecules, thereby representing a highly desired reaction.

To date, several bioinspired iron and manganese complexes have been shown to perform aliphatic C–H oxidations\(^\text{[1]}\) as well as olefin oxidation reactions,\(^\text{[2]}\) whereas hydroxylation of aromatic compounds has remained an ongoing issue since recent years.\(^\text{[3]}\) In earlier studies, an iron complex supported by the tpa ligand (tpa = tris(2-pyridylmethyl)amine) was found to be capable of stoichiometrically oxidizing ligated perbenzoic acids through the self-hydroxylation of the aromatic ring, forming iron(III)-salicylate complexes.\(^\text{[4]}\) Also, an iron complex based on the bpmen ligand (bpmen = N,N'-dimethyl-N,N'-bis(2-picolyl)ethylenediamine) showed activity for the hydroxylation of aromatic compounds using H\(_2\)O\(_2\), although strong coordination of phenolates to the iron(III) center prevented efficient catalysis.\(^\text{[5b,d]}\) An iron complex supported by a N-heterocyclic carbene ligand has been shown to be capable of hydroxylating benzene and alkylbenzenes with H\(_2\)O\(_2\) as well, albeit at low conversions and yields for phenol products, and with the formation of benzylic oxidized products from alkylbenzene substrates.\(^\text{[5e,g]}\) Recent research progress indicates that iron complexes supported by bpbp-type ligands (bpbp = N,N'-bis(2-pyridylmethyl)-2,2'-bipyridolidine) can hydroxylate aromatic substrates with H\(_2\)O\(_2\).\(^\text{[5h]}\) However, overoxidation products and modest selectivities for oxidation of the aromatic ring were observed, resulting in mixtures of products in which oxidation has taken place on aromatic as well as aliphatic positions. A manganese complex supported by the Bn-TPEN ligand (Bn-TPEN = N-benzyl-N,N'-tris(2-pyridylmethyl)-1,2-diaminoethane) has been found to oxidize naphthalene, among other substrates, with iodosylbenzene as oxidant.\(^\text{[5j]}\) However, efficient catalytic turnover numbers (TON) were not achieved. Later, a manganese tpa complex incorporated into mesoporous silica-alumina was described to be active in the selective hydroxylation of benzene derivatives with H\(_2\)O\(_2\).\(^\text{[5k]}\) Interestingly, incorporation of the complex into the mesoporous support was necessary to get useful catalytic activities. Very recently, intramolecular aromatic hydroxylation, as well as intermolecular hydroxylation of benzene to phenol, has been demonstrated with an iron complex based on the Bn-TPEN ligand through O–O bond heterolysis of an Fe(III)–OOH species to form an Fe(V)=O oxidant.\(^\text{[6]}\)

Other transition-metal complexes have also been developed as homogeneous catalysts for aromatic C–H oxidations with H\(_2\)O\(_2\) as the oxidant.\(^\text{[3]}\) Itoh \textit{et al.} demonstrated the catalytic ability of a nickel complex supported by a tripod tetratentate aminopyridine ligand in the direct hydroxylation of aromatics using a significant excess of oxidant (Figure 1).\(^\text{[4a]}\) High TONs were only achieved using extremely low concentrations of catalyst under long reaction times; yet, absolute yields of phenol products did not exceed 7.5%. Remarkably though, when the complex was used at 10 mol% loading with respect to the substrate, 21% phenol yield was formed (2 turnovers per nickel).\(^\text{[4e]}\) Later, Kodera \textit{et al.} described a dinuclear copper complex as catalyst for the hydroxylation of aromatics, showing good selectivities for phenol products (Figure 1).\(^\text{[3a,3b]}\) Again, an elevated TON (12,550) was obtained at a low catalyst concentration, with phenol yields up to 21% for benzene oxidation. Di Stefano \textit{et al.} reported an iminopyridine iron complex capable of oxidizing aromatic substrates, as well as aromatic amino acids, under mild reaction conditions (Figure 1).\(^\text{[4q–r]}\) However, for all these examples, aromatic oxidation of alkylbenzenes is effectively accompanied by benzylic hydroxylation. In addition, recently reported nickel, copper and cobalt complexes supported by aminopyridine ligands accomplished the oxidation of benzene to phenol in improved yields (29–41%) (Figure 1).\(^\text{[4e–s]}\)

Previously, we have shown that bulky iron complexes with tips moieties (tips = tris-(isopropyl)silyl) catalyze the site-selective oxidation of alkyl C–H bonds with H\(_2\)O\(_2\), affording high product yields and enhanced preferential oxidation of secondary over tertiary C–H bonds.\(^\text{[11]}\) Likewise, manganese complexes supported by aminopyridine ligands catalyze chemo- and enantioselective aliphatic C–H oxidations with H\(_2\)O\(_2\).\(^\text{[11e,k–o,11l]}\) Recently, White \textit{et al.} reported that a

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure1.png}
\caption{Examples of metal complexes previously employed in aromatic C–H hydroxylation reactions with H\(_2\)O\(_2\).}
\end{figure}
bulky manganese complex with pendant o-CF₃-substituted aryl rings can oxidize methylene groups in the presence of aromatic functionalities.[10] The authors also report non-productive aromatic substrate oxidation as a side-reaction. Finally, fluorinated alcohols have recently been shown to be suitable solvents for oxidation chemistry, preserving the first-formed alcohol products and, thus, reducing overoxidation reactions.[10,7a,8] Herein, we focus on the use of bioinspired manganese complexes for the oxidation of aromatic substrates. We demonstrate that the application of bulky Mn catalysts in the presence of fluorinated alcohol solvents favors oxidation at the aromatic ring over the oxidation of benzylic positions, providing an improved route to produce phenols. On the basis of previous literature examples which propose that product inhibition through metal-phenolate binding prevents catalytic turnover in aromatic oxidation reactions, we rationalized that the presence of bulky tips groups in position 5 of the pyridine rings may help in preventing product inhibition. Our study also shows that the yields of the aromatic reactions are further improved by using halogenated carboxylic acids as additives, which in part can be attributed to their lower pKₐ values which reduces product inhibition through a favorable acid-base equilibrium between the carboxylic acid and the (substituted) phenol products. Overall, our study has resulted in the development of a selective manganese-based catalyst system that performs arene hydroxylation reactions with H₂O₂ as a benign oxidant with improved yields of (substituted) phenol products with respect to the previously described homogeneous catalysts.

Results and Discussion

Aliphatic vs Aromatic C–H Oxidation

For our study we have investigated complexes of the type [M(OTf)₂(L)] based on the bpmcn, bpbp, bpsi and bpmen ligand families (Scheme 1) (bpmcn = N,N'-dimethyl-N,N'-bis(2-picoly)-cyclohexane-trans-1,2-di-amine, bpsi = N,N'-bis(2-picoly)-2,2'-bis-isoidoline). We have included manganese complexes containing electron-rich, as well as bulky pyridines.

Initially, we focused our attention on the hydroxylation of propylbenzene as substrate using 1 mol% of Mn⁶⁶(bpmcn), Mn⁶⁶⁵⁶(bpmcn), or Mn⁶⁶⁶⁶(bpmcn) as catalyst (Table 1). Catalytic oxidation reactions were carried out by mixing the Mn(II) catalyst and AcOH (2 equiv.) into a solution of propylbenzene (1 equiv.) in TFE (TFE = 2,2,2-trifluoroethanol) at 0 °C. A sub-stoichiometric amount of aqueous H₂O₂ (0.5 equiv., 35% w/w solution) was added dropwise through a syringe pump over a period of 30 min. Interestingly, chemoselectivity was found to be largely dependent on the catalyst used. The bulky manganese complex Mn⁶⁶⁶⁶(bpmcn) favors the oxidation at the aromatic ring, providing the para-phenol as the major product, together with ortho-phenol and propyl-p-benzoquinone as minor products. Some 1-phenyl-1-propanol was also detected as minor product in this case, showing a ratio of aromatic:aliphatic oxidation of 7.3:1. In contrast, when the electron-rich catalyst Mn⁶⁶⁶⁶(bpmcn) was used the chemoselectivity changed completely, and preference for the oxidation at the benzylic position was observed with a ratio of aromatic:aliphatic oxidation products of 1:13.5. This observation is in agreement with previous reports on the use of electron-
Table 1. Oxidation of propylbenzene in TFE with different manganese catalysts.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Mn(nbpmpcn)</td>
<td>68</td>
<td>9 (18)</td>
<td>1 (3)</td>
<td>2 (8)</td>
<td>2 (4)</td>
<td>n.d.</td>
<td>88</td>
<td>7.3:1</td>
</tr>
<tr>
<td>Mn(bmpcn)</td>
<td>65</td>
<td>1 (2)</td>
<td>n.d.</td>
<td>n.d.</td>
<td>12 (23)</td>
<td>1 (4)</td>
<td>85</td>
<td>1:13.5</td>
</tr>
<tr>
<td>Mn(bpm)</td>
<td>72</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>3 (11)</td>
<td>4 (9)</td>
<td>n.d.</td>
<td>89</td>
<td>2.1:1</td>
</tr>
</tbody>
</table>

[a] Remaining starting material (r.s.m) in %.
[b] Yields in % with respect to substrate determined by GC against an internal standard. In parenthesis yields in % with respect to H₂O₂. Yields are calculated considering that 2 equiv. of H₂O₂ are necessary for the formation of the ketone and quinone products.
[c] Mass balance (MB) was calculated considering remaining starting material and all products formed, plus a percentage of substrate loss calculated with blank experiments (an average of 6% of substrate is lost): MB = (r.s.m %) + (Product Yields %) + (Substrate loss).
[d] Ratio (aromatic:aliphatic) = [n(p-phenol) + n(o-phenol) + n(quinone)]/[n(alcohol) + n(ketone)]. n.d. = non-detected.

rich manganese complexes for asymmetric benzylic oxidations, where no aromatic oxidation products were detected.[6,7a,8b] With the parent Mn(bpm) complex, we observed both oxidation at the aromatic ring as well as at the benzylic position in a ratio of 2.1:1, respectively, showing a slight preference for aromatic oxidation.

Worthy of note are the blue colors that progressively form in the reaction mixtures after starting the addition of H₂O₂ to the reaction mixture containing the substrate and the catalyst (Mn(nbpmpcn) or Mn(bmpcn)). We hypothesize that these colors are due to charge transfer bands arising from phenolate binding to the Mn center, which in turn inhibits the catalyst and prevents further catalytic turnover.[9] Consistent with this hypothesis, ESI-MS analysis of a mixture of Mn(tipsbpm) (1 mol%), tert-butylbenzene (1 equiv.), AcOH (2 equiv.) and H₂O₂ (1 equiv.) at 0 °C in TFE showed a main peak at m/z = 493.8060, which corresponds to the formation of a complex ion composed of a Mn(tipsbpm) fragment and a coupled bis(phenolate) fragment ([Mn(tipsbpm)(C₆H₄OC-(CH₃)₂)]²⁺, calcd m/z 493.8064) (SI, Section 5.7, Figure S11). Importantly, the blue color was observed immediately after the start of H₂O₂ addition in the case of Mn(bpm), whereas for the reaction with Mn(nbpmpcn) the blue color appears later in the course of the reaction. These observations lead us to believe that the bulky tips groups help in preventing phenolate binding, and thus allow for higher catalytic turnover numbers. A control experiment without an aromatic substrate did not show the appearance of the blue colors described above.

Comparing our result on arene hydroxylation catalyzed by Mn(nbpmpcn) with previous literature examples, such as the systems described by Itoh[4b] and Kodera,[4b] we can conclude that the current system performs the hydroxylation of an alkylbenzene with yields commensurate to state-of-the-art homogeneous catalysts, at a relatively low catalyst loading. Furthermore, the nature of the ligand in the current system seems key for diverting the chemoselectivity of the catalyst from oxidation of the more activated benzylic position to the hydroxylation of the aromatic ring, showing a catalyst dependent selectivity. Yet, overall the reactions shown in Table 1 suffer from moderate conversions and yields, but do show reasonable mass balances. Noteworthy is that blank experiments without catalyst showed that a certain amount of substrate is lost during the reaction and analysis protocol (~6%). This loss was taken into account to calculate the mass balances in Table 1.

Screening of Catalysts

Based on these results, we selected bulk manganese complexes with different amine backbones for further screening for the oxidation of aromatic C–H bonds (Scheme 1). A bulky iron complex, Fe(2mmpcn), was also included in our study. The parent complexes without any substituents on the pyridines were considered as well. For all cases, the metal center adopts a C₂-symmetric cis-α topology, with the two pyridines trans to each other. A new manganese complex supported by a bulky tripodal tetradeptate ligand based on the tpa motif (tpa) was also included.

Tert-butylbenzene was used as a model substrate since it lacks benzylic C–H bonds to selectively screen for activity in aromatic oxidation. Using stoichiometric amounts of H₂O₂, crude mixtures were analyzed by GC, detecting mainly 4-tert-butylphenol as the oxidized product, next to unreacted substrate. Interest-
ingly, no ortho-hydroxylation product was observed, which is in contrast to, e.g., the oxidation of tert-butylbenzene catalyzed by an iminopyridine Fe(II) complex. In general, poor mass balances were observed for these reactions. We believe that a side reaction might happen, leading to overoxidized by-products, which we have not been able to identify yet. However, interest was focused here on the formation of the phenol product. First, a screening of different solvents was done (Scheme 2). Next to TFE, HFIP (HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol) was found to be an appropriate solvent as well, allowing similar phenol formation as TFE. Interestingly, acetonitrile is not a suitable solvent, showing no formation of the desired phenol product. The positive effect of using fluorinated alcohol solvents may be attributed to their strong hydrogen donor ability, which decreases the nucleophilicity of the phenol, thereby allowing higher catalytic turnover numbers by hampering product inhibition. These findings inspired us to use manganese complexes in the presence of fluorinated alcohol solvents in further investigations.

Next, we proceeded to screen the different complexes shown in Scheme 1 using TFE as the solvent (SI, Table S1). Overall, complexes bearing bulky, tip appended ligands exhibited a better catalytic activity, showing higher conversion and phenol production compared to their parent complexes. Maximum yields for the 4-tert-butylphenol product were obtained using Mn\(^{\text{tips-bpmcn}}\), Mn\(^{\text{ctips-bpbi}}\), and Mn\(^{\text{ctips-bpmcn}}\) (SI, Table S1, entry 2, 7 and 9), whereas the other complexes show good conversions but lower yields. The current findings suggest the relevance of steric effects in aromatic hydroxylation reactions, whereas electronic effects may play a less important role. We believe that product inhibition in complexes with bulky ligands occurs to a lower extent in comparison to complexes with non-bulky ligands. Besides, iron complex Fe\(^{\text{tips-bpmcn}}\), supported by a bulky bpmcn ligand, provided a poor yield (SI, Table S1, entry 3). Iron complexes with N4 ligands have been reported as catalysts for aromatic oxidation by Bryliakov and co-workers. Yet, we believe that product inhibition in these catalysts through phenolate-iron coordination is more prominent than with our manganese complexes, which translates in a much lower catalytic efficiency for the iron catalysts. Accordingly, we focused our study exclusively on the use of manganese complexes as catalysts. Complex Mn\(^{\text{ctips-tpa}}\), which bears a stericly encumbered tripodal tetradentate aminopyridine ligand based on the tpa scaffold, also provided a poor 4-tert-butylphenol yield (SI, Table S1, entry 11), indicating that the use of linear tetradentate aminopyridine ligands with a cis-α topology seems preferred over the use of tripodal ligands. Manganese triflate was also tested as catalyst, showing no reaction.

Catalyst Mn\(^{\text{ctips-bpmcn}}\) was then chosen for further reaction optimization (SI, Table S2) since it showed the better selectivity for phenol production. However, at this point yields for phenol product were still modest (up to 15% yield).

## Carboxylic Acid Additives

Carboxylic acids have been investigated in detail as additives in \(\text{H}_2\text{O}_2\)-mediated oxidation catalysis. We found that very low phenol product formation was observed when the oxidation of tert-butylbenzene was run without the addition of any carboxylic acid, showing that this additive is crucial for reactivity (Table 2, entry 1). As previously discussed in the literature, catalysis might proceed through a “carboxylic acid-assisted” pathway, in which the acid helps in the heterolytic cleavage of the O–O bond of a Mn(III) hydroperoxo intermediate to form a Mn(V) oxo complex.

**Table 2. Oxidation of tert-butylbenzene using different carboxylic acids.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carboxylic acid (2 equiv.)</th>
<th>4-tert-butylphenol yield (%)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Acetic acid</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>Propionic acid</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Butyric acid</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Isobutyric acid</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Pivalic acid</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>2-ethylhexanoic acid</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>Chloroacetic acid</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>Dichloroacetic acid</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>Trichloroacetic acid</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>Fluorooacetic acid</td>
<td>26</td>
</tr>
<tr>
<td>12</td>
<td>Difluoroacetic acid</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>Trifluoroacetic acid</td>
<td>n.d.</td>
</tr>
<tr>
<td>14</td>
<td>Iodoacetic acid</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>(\text{N,N\text{-dime}}\text{thylglycine})</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>2-nitrobenzoic acid</td>
<td>23</td>
</tr>
<tr>
<td>17</td>
<td>3-nitrobenzoic acid</td>
<td>25</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Reaction conditions: Mn\(^{\text{ctips-bpmcn}}\):\(\text{H}_2\text{O}_2\):substrate: RCO,H = 1:100:100:200, in HFIP at 0°C.

\(^{[b]}\) Conversion and yields determined from crude reaction mixtures by GC. n.d. = non-detected.
species, responsible for the oxidation of the aromatic substrate.\(^{[1m,10]}\) Alternatively, the acid could also help in C–H bond activation, as in acetate-assisted C–H activation with palladium.\(^{[11]}\) Since the introduction of bulky substituents in the ligand has been found to be a key feature in order to obtain catalytic turnover, several bulkier carboxylic acids were tested. Carboxylic acids with longer alkyl chains, \textit{i.e.} propionic acid and butyric acid, showed lower phenol formation compared to acetic acid (Table 2, entries 5, 6 and 7). Therefore, our findings show that the desired oxidized product also decreased (Table 2, entries 3 and 4). When bulkier carboxylic acids such as isobutyric acid, pivalic acid, and 2-ethylhexanoic acid were tested, yields for the desired oxidized product also decreased (Table 2, entries 5, 6 and 7). Therefore, our findings show that the introduction of bulk into the carboxylic acid additive decreases product formation. Similar trends were observed when either HFIP or TFE were used as solvent (SI, Table S3-S6 and Figure S3-S6).

Next, we considered the use of halogenated carboxylic acids, which have been used previously in oxidation reactions.\(^{[1u,74,12]}\) Interestingly, we have found that chloroacetic acid, dichloroacetic acid, fluoroacetic acid, and difluorooacetic acid afford a significant increase in yield for the desired phenol product, with up to 29% 4-tert-butylphenol yield (Table 2, entry 9). The reason of this improvement could be related to the pK\(_a\) of the carboxylic acids, which varies significantly within the series of tested aliphatic carboxylic acids. The role of the lower pK\(_a\) of these carboxylic acids in arene hydroxylation reactions could be twofold. First, it keeps the phenol products protonated, which hampers catalyst deactivation by phenolate binding. Second, the electron-withdrawing character of these acids makes the proposed Mn(V) oxo species more electrophilic, which may result in a more reactive oxidant towards arenes. The use of nitrobenzoic acids also lead to increased phenol formation compared to the use of acetic acid. However, in these cases side-product formation through arene hydroxylation of the nitrobenzoic acid was observed. In the presence of halogenated carboxylic acids higher catalytic activities were achieved in HFIP compared to TFE (SI, Table S3 and S6).

Increasing the acidity has a positive effect, going from acetic acid (pK\(_a\)=4.76) to 3-nitrobenzoic acid (pK\(_a\)=3.46), chloroacetic acid (pK\(_a\)=2.87), fluoroacetic acid (pK\(_a\)=2.59), 2-nitrobenzoic acid (pK\(_a\)=2.17) and dichloroacetic acid (pK\(_a\)=1.35) (Figure 2).\(^{[23]}\) However, the use of trichloroacetic acid (pK\(_a\)=0.66) or trifluoroacetic acid (pK\(_a\)=0.52) lead to a dramatic decrease in catalytic activity, which might be due to protonation of the amine moieties of the ligand. Iodoacetic acid (pK\(_a\)=3.18) provided good conversion but a poor phenol yield, which could be explained by the weaker C-halogen bond that may lead to side reactions (Table 2, entry 14). N,N-dimethylglycine was also not a suitable additive, showing poor yield for the desired phenol product, as well as low substrate conversion (Table 2, entry 15). Thus, we can conclude that steric bulk on the carboxylic acid additive is detrimental for the arene hydroxylation reaction, and that there is an optimum pK\(_a\) of the acid additive.

While it may be initially regarded as a modest value, the 29% yield obtained for 4-tert-butylphenol in a completely site selective manner is remarkable when compared with literature precedents; a recently reported iminopyridine Fe(II) catalyst has been shown to be capable of oxidizing tert-butylbenzene to 4-tert-butylphenol in 23% yield, together with the ortho-phenol and benzoquinone as minor products, which at that time were the highest numbers reported for tert-butylbenzene oxidation.\(^{[9e]}\) Further investigations on the effect of halogenated carboxylic acids showed that the conversion and yield do not drastically change between 0.5 to 8 equiv. of acid when Mn(rippbpmcn) is used as catalyst (SI, Table S5 and Figure S5). This allows catalysis to be performed at a much lower carboxylic acid loading.

Next, bulky manganese complexes with different amine backbones in the ligand structure were tested in the aromatic hydroxylation of tert-butylbenzene using optimized chloro- and dichloroacetic acid loadings (Figure 3). The use of chloroacetic acid afforded similar efficiencies for the four catalysts tested, Mn(rippbpmcn) being the one that showed better conversion and yield. For dichloroacetic acid, we observed that Mn(rippbpmcn) and Mn(rippbph) performed best, with Mn(rippbpmcn) showing significantly higher conversion and yield. In contrast, Mn(rippbpbi) and Mn(rippbpmcn) showed very poor results when using dichloroacetic acid. A similar reactivity trend was observed when TFE was used as solvent (SI, Table S7).
and Figure S9). Therefore, we can conclude that the amine backbone in the ligand structure of the manganese complexes has a considerable impact on catalytic activity. Besides, we believe that the simpler ethylene diamine backbone is less stable under acidic conditions, since with dichloroacetic acid as additive a poor 4-tert-butylphenol yield is afforded. Consistent with this hypothesis, this complex is more efficient under low carboxylic acid loadings; hydroxylation of tert-butylbenzene with Mn(II)bpmcn leads to only 6% 4-tert-butylphenol yield when 2 equivalents of chloroacetic acid are used, whereas 15% yield is obtained with 0.5 equiv. of the acid.

Finally, we have further investigated the role of the halogenated carboxylic acid additives by examining the use of dichloroacetic acid with different manganese complexes for the hydroxylation of propylbenzene, this time at a low H$_2$O$_2$ loading (SI, Table S11). Our earlier findings showed that for Mn(II)bpmcn the use of dichloroacetic acid provides an enhanced catalytic activity compared to the use of AcOH (compare Tables 1 and S11). On the other hand, for the electron-rich complex Mn(IMdbpmcn) a complete change in chemoselectivity from aliphatic to aromatic hydroxylation was observed when switching to dichloroacetic acid, albeit at low yields (compare Tables 1 and S11). For the parent complex Mn(bpmcn) an increased activity for aromatic hydroxylation was observed when dichloroacetic acid was employed instead of AcOH. Remarkably, traces of 1-phenyl-1-propanol were detected for all these catalysts when dichloroacetic acid was employed, revealing that the use of a halogenated carboxylic acid increases the selectivity towards the oxidation of aromatic C–H bonds for these complexes in a general sense, avoiding the generation of products originating from oxidation at a more activated benzylic position.

**Substrate Scope**

Aromatic C–H hydroxylation of different substrates has been explored under the optimized experimental conditions using the manganese complex Mn(II)bpmcn (Table 3). For comparison purposes, some of the best results described so far in the literature with transition-metal complexes are collected in Tables S9 and S10. In general, our current Mn(II)H$_2$O$_2$/Cl$_2$CHCOOH catalytic system affords higher yields and substantially improved selectivities for aromatic over aliphatic C–H oxidation.

At first, we considered benzene as substrate, which leads to phenol in a remarkable yield of 32%, along with para-benzoquinone in 7% yield (Table 3, entry 1). Interestingly, when phenol was used as the substrate, 13% yield of para-benzoquinone was observed, showing that the primary oxidation product in benzene hydroxylation can indeed engage in a second oxidation step (Table 3, entry 2). Next, we extended our study to the oxidation of alkylbenzenes. Oxidized products were obtained in remarkable total product yields ranging from 29 to 37%, with the para-phenol as the main product in all cases, which is reminiscent to reactions proceeding via an electrophilic aromatic substitution type of mechanism. Toluene was oxidized to para-cresol in 22% yield, together with ortho-cresol and methyl-para-benzoquinone in 8 and 1% yield, respectively (Table 3, entry 3). Recent studies on aromatic oxidations have shown other complexes to be capable of oxidizing the aromatic ring of toluene as well, showing however significant amounts of aliphatic oxidation towards benzyl alcohol or benzaldehyde products.$^{[3g,4a,b,c,f]}$ Remarkably, Mn(II)bpmcn shows an excellent selectivity for oxidation of the aromatic ring over the aliphatic site chain. Oxidation of other alkylbenzene derivatives with more reactive benzylic C–H bonds was also explored. Ethylbenzene provided 4-ethylphenol as the major product in 26% yield, along with 2-ethylphenol and ethyl-para-benzoquinone in 8 and 2% yield, respectively (Table 3, entry 4). For the oxidation of propylbenzene, we observed 4-propylphenol, 2-propylphenol and propyl-para-benzoquinone in 24, 8, and 2% yield, respectively (Table 3, entry 5).

Cumene was also considered, which bears a more encumbered isopropyl substituent with a weak 3° benzylic C–H bond. 4-Isopropylphenol and 2-isopropylphenol were obtained in 30 and 5% yield, respectively. Minor amounts of isopropyl-para-benzoquinone were detected in 2% yield (Table 3, entry 6). To the best of our knowledge, hydroxylation of this group of alkylbenzene substrates catalyzed by the current system provides the highest yields reported to date with homogeneous catalysts. Remarkably, only traces of benzylic oxidation products were detected in these reactions, suggesting that the current catalytic system is selective for aromatic hydroxylation reac-
Table 3. Product analysis in the oxidation of benzene and its derivatives catalyzed by Mn\(^{\text{([bpmcn])}}\)[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (r.s.m. %)[b]</th>
<th>(p)-Phenol (%)[c]</th>
<th>(o)-Phenol (%)[c]</th>
<th>Quinone (%)[c]</th>
<th>Benzylic oxidation (%)[d]</th>
<th>Mass balance (%)[e]</th>
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[a] Reaction conditions: Mn\(^{\text{([bpmcn])}}\):H\(_2\)O\(_2\):substrate:Cl\(_2\)CHCOOH = 1:100:100:50, in HFIP at 0 °C for 30 min.
[b] Remaining starting material (r.s.m.) determined from crude reaction mixtures by GC.
[c] Product yields determined from crude reaction mixtures by GC.
[d] Benzaldehyde or ketone products were not detected.
[e] Mass balance was calculated considering remaining starting material and all products formed, plus a percentage of substrate loss calculated from blank experiments: MB = (r.s.m %) + (Product Yields %) + (Substrate loss %).
[f] Percentage of substrate loss was not calculated.
tions. A cautious note must be introduced at this point because some of these compounds show the lowest mass balance of all substrates tested in this study, which raises the possibility that benzylic oxidation products are also formed but overoxidized to non-detected products. Important to note is that no formation of ketone products was observed, i.e. secondary oxidation of initial benzylic alcohol products does not seem to take place. Blank experiments without catalyst were done to calculate the amount of substrate loss during the reactions, and were used to calculate the mass balances in Table 3.

We observed a correlation between the bulk of the lateral alkyl chain in the aromatic substrate and the product profile. Our results clearly show that increasing the bulk of the substituents on the substrate translates into a decreased formation of ortho-phenol product, which is likely due to steric effects of both the catalyst and the substrate. The amounts of ortho-phenol were similar for toluene, ethylbenzene, and propylbenzene. However, when a bulkier substrate, such as cumene, was used, the yield for the ortho-phenol decreased. More remarkable is the oxidation of tert-butylbenzene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, was used, the yield for the ortho-phenol decreased. Important to note is that no tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7). The current data contrast with the oxidation of cumene, where no ortho-phenol product was detected at all, i.e. 4-tert-butylphenol was detected as the only product in 29% yield (Table 3, entry 7).

Using bromobenzene as substrate, 2-bromophenol and 4-bromophenol were obtained in 14 and 8% yield, respectively. 2-Bromo-1,4-benzoquinone was also detected in 5% yield (Table 3, entry 8). The formation of ortho and para phenols is in agreement with classical aromatic substitution reactions, halogen and alkyl substituents being ortho and para directing groups. However, of importance is the different selectivity observed for bromobenzene compared to the alkylbenzene substrates; where the ortho-phenol was obtained as the main oxidized product in the former case, the para-phenol was the major product in the latter case.

An electron-donating substituent was expected to enhance the reactivity of the arene substrate in our system. Nonetheless, anisole showed a poor reactivity, with 4-methoxyphenol and 2-methoxyphenol being produced in only 6 and 4% yield, respectively (Table 3, entry 9). No benzoquinone was detected in this case. For benzonitrile, bearing an electron-withdrawing cyano group, no oxidized products were detected (Table 3, entry 10). While the cyano group could deactivate the aromatic ring towards electrophiles, the coordinating ability of the methoxy and cyano groups in anisole and benzonitrile might also interfere with catalysis. We believe that the poor catalytic activity for anisole may be due to strong binding of the first formed hydroxylated product to the metal center (indicated by a strong color change to purple). Indeed, competitive experiments using equimolar amounts of anisole and tert-butylbenzene show only 2% 4-tert-butylphenol yield, demonstrating catalyst deactivation in the presence of anisole.

Amino acid substrates are particularly interesting because of their biological significance and their molecular complexity, containing different types of C–H bonds. We therefore examined the catalytic hydroxylation of phenylalanine. Our idea was to extrapolate the reactivity that we have observed using simple aromatic substrates to the oxidation of more complex molecules. Interestingly, we found that oxidation at the para-position of the aromatic ring of a protected phenylalanine yields the corresponding tyrosine as the main product in 7% yield, which represents 7 catalytic turn-overs per Mn (Scheme 3). The hydroxylation of phenylalanine might be further optimized by variation of reaction conditions and protecting groups.

Mechanistic Considerations

Finally, our efforts have been devoted to the understanding of the mechanism of the aromatic hydroxylation reaction. Generally, activation of H2O2 by manganese or iron complexes supported by aminopyridine ligands leads to electrophilic oxidants.

The involvement of such radicals in anisole and benzonitrile might also interfere with catalysis. We believe that the poor catalytic activity for anisole may be due to strong binding of the first formed hydroxylated product to the metal center (indicated by a strong color change to purple). Indeed, competitive experiments using equimolar amounts of anisole and tert-butylbenzene show only 2% 4-tert-butylphenol yield, demonstrating catalyst deactivation in the presence of anisole.
give a specific distribution of ortho-, meta- and para-
phenol isomers. Several of our observations speak
against the involvement of hydroxyl radicals in our
aromatic hydroxylation reaction, and point towards a
metal-based oxidation mechanism.

Our catalysis experiments show that oxidation of
electron-rich benzene derivatives leads to the forma-
tion of para and ortho phenol products, with no
formation of the meta isomer. This clearly contrasts
with other catalysts capable of performing aren
hydroxylation, such as the systems reported by Itoh, Bryliakov and Di Stefano
where mixtures of ortho-, meta- and para-phenols were observed (SI, Table S10); and thus, suggests that the current reaction
dergoes through a more selective species. In con-
text, when switching to electron-poor substrates, no
aromatic hydroxylation reaction takes place with the
current system. These observations agree with the
proposal of an electrophilic manganese-o xo species,
with a reactivity sensitive to the electronic nature of
the substrate.

Previous studies have shown that the oxidation of
toluene with hydroxyl radicals affords cresols with
a distribution of 71:9:20 for ortho:meta:para isomers. The
current work has shown that the bulky Mn-
(\textit{bpmcn}) catalyst is capable of oxidizing toluene
with high selectivity, affording a ratio of 27:0:73 for
the ortho-, meta- and para-cresols, respectively. There-
fore, our data clearly show a distinct distribution of
isomers compared with the reaction involving hydroxyl
radicals, and consequently point towards the involve-
ment of a metal-based mechanism.

To get further insight in the mechanism, we
considered performing the hydroxylation reaction with
another oxidant than \textit{H}_2\textit{O}. Remarkably, we found that
catalytic hydroxylation of \textit{t}-butylbenzene by Mn-
(\textit{bpmcn}) in fluorinated alcohol solvents can also be
accomplished employing \textit{t}-BuOOH as oxidant, generat-
ing 4-\textit{t}-butylphenol as the oxidized product in 9%
yield. It is known that oxidations with \textit{t}-BuOOH can
proceed through a Fenton-type process, generating
free-diffusing \textit{t}-butoxy and \textit{t}-butylperoxy radicals
that can engage in hydrogen abstraction reactions with
aliphatic C–H bonds. However, \textit{t}-BuOOH activation
does not produce hydroxyl radicals, and \textit{t}-butoxy
radicals, unlike hydroxyl radicals, do not add to
aromatic rings. Another evidence against the in-
volvement of hydroxyl radicals is that the aromatic
hydroxylation reactions catalyzed by Mn(\textit{bpmcn})
are not affected by the presence, or absence, of air.
Independent experiments carried out under air and
under a nitrogen atmosphere showed similar efficien-
cies for the generation of 4-\textit{t}-butylphenol (SI, Table S12). In contrast, a significant impact of air on
product yields is observed when oxidations are
mediated by oxygen-centered radicals.

Next, we carried out a kinetic isotope effect (KIE)
experiment using a 1:1 mixture of benzene and
perdeuterated benzene as substrate and Mn(\textit{bpmcn})
as catalyst. From the ratio of phenol to phenol-\textit{d}, a
KIE value of 0.97 ± 0.06 was determined for this
reaction. This value rules out Fenton-type processes,
for which a KIE of 1.7 has been reported. Overall,
our combined data suggest that aromatic hydroxylation
reactions catalyzed by Mn(\textit{bpmcn}) occur through a
metal-based mechanism with no significant involve-
ment of hydroxyl radicals. Besides, the high bond
dissociation energy of aromatic C–H’s discards a HAT
initiated process. Instead, the data is consistent with an
aromatic hydroxylation mechanism via electrophilic
attack of the high valent metal oxo on the aromatic
ring. As a first option, the KIE value found in this
study is compatible with the formation of a Wheland
type of intermediate found in an electrophilic aromatic
substitution mechanism. Alternatively, an initial aren
epoxidation reaction conducted by the high valent
manganese-o xo species, followed by an acid catalyzed
re-aromatization to form the corresponding phenol
could be a plausible mechanism. Both proposed
processes show a negligible KIE, which is consistent
with a change in hybridization from \textit{sp}^3 to \textit{sp}^2 of
the aromatic carbon where the oxidation takes place.

To get further insight into the aren hydroxylation
mechanism, we performed a catalytic experiment using
1-\textit{t}-butyl-4-deutero benzene to probe the occurrence
of an NIH shift (Scheme 5). This characteristic feature of
aren hydroxylation reactions based on the migra-

\textbf{Scheme 4.} Proposed mechanistic cycle based on the carboxylic acid assisted O–O cleavage of non-heme Fe and Mn complexes.\cite{10,23,16}
GC-MS analysis of the reaction with 1-
complexes in combination with H
to the corresponding phenol products using manganese
direct one-step hydroxylation of aromatic C
philic, which also reduces catalyst inhibition by
indicating that an NIH-shift takes place during the
para
deuterobenzene indeed showed the exclusive formation
para
ment of an arene oxide as a reaction intermediate.[24]
Based on our previous experiments, we know that
hydroxylation of tert-butylbenzene only occurs at the
para-position of the benzene ring. Combined GC and
GC-MS analysis of the reaction with 1-tert-butyl-4-deuterobenzene indeed showed the exclusive formation of
para-phenol products (26%), with a 4-tert-butyl-2-deuterophenol and 4-tert-butylphenol ratio of 47/53,
indicating that an NIH-shift takes place during the
reaction. On basis of this observation, we suggest that
the aromatic hydroxylation reaction most likely occurs
through an arene epoxidation mechanism, involving
the generation of a cyclohexadienone intermediate
after arene oxide formation.

We propose that the use of an electron-deficient
acid can make the metal oxo species more electrophilic, which also reduces catalyst inhibition by
phenolate protonation. These effects, together with a
sterically demanding aminopyridine ligand, translate
into an oxidizing agent which is reactive towards the
para-position of the aromatic ring instead of the
(benzylic) aliphatic C–H bonds. Overall, we believe
that there is a synergy between the carboxylic acid
and the manganese complex, as was recently also shown
for methylene and tertiary C–H oxidation catalyzed by
other manganese complexes with chloroacetic acid as
additive.[19,20,22] Further investigations into the exact
role of halogenated carboxylic acids are required to
understand how chemoselectivity is governed in these
aromatic hydroxylation reactions.

Conclusion

We have presented a new catalytic procedure for the
direct one-step hydroxylation of aromatic C–H bonds
to the corresponding phenol products using manganese
complexes in combination with H₂O₂. Pivotal to our
findings is the use of sterically encumbered tetradenate
aminopyridine ligands in combination with a
halogenated carboxylic acid additive and a fluorinated
alcohol solvent. We have shown that complexes with
bulky ligands perform better in arene oxidations by
preventing coordination of the phenolate products to
the manganese center. Remarkably, the use of bulky
manganese complexes favors aromaticate oxidation over
(benzylic) aliphatic C–H bond oxidation, whereas
electron-rich manganese complexes selectively oxidize
the weaker benzylic C–H bonds, demonstrating a
dependency of the chemoselectivity on the catalyst. A
synthetically relevant property of the current Mn
system is that oxidation of a broad range of aromatic
substrates can be accomplished. Notable is the oxidation of monoalkylbenzenes using Mn/player
as the catalyst, which to our knowledge provide the
highest phenol product yields reported to date for
homogeneous catalysts. The overall product profiles
of this system, in combination with a negligible KIE
effect and the effectiveness of using BuOOH as
oxidant, overall point towards a metal-based mech-
nism with no significant involvement of oxygen-
centered radicals. Besides, the observation of a NIH
shift indicates that aromatic oxidation with the current
system is likely to occur via an arene epoxidation
pathway.

Future efforts will be focused on the understanding
of the factors that govern product selectivity, as well as
of possible catalyst deactivation pathways that lead to
the still moderate product yields observed in this study.
Additional investigations of the current catalytic
system will also focus on a further insight in the
overall modest mass balances obtained. Overall, our
current findings represent a next step in the design of
molecular catalysts for the selective oxidation of
aromatic substrates, and provide a stepping stone for
the further development of selective oxidation catalysts
based on manganese.

Experimental Section

General Procedure for Catalytic Hydroxylation
Reaction

A 3 mL or 20 mL vial was charged with: substrate (1 equiv.)
and the indicated loading of catalyst and corresponding solvent
(0.5 mL or 2 mL). The carboxylic acid was added with
indicated loading. The vial was cooled on an ice bath or
acetoniirile/dry ice bath, depending on the desired temperature,
with stirring. Subsequently, a solution of H₂O₂ in the
indicated solvent (indicated loading, diluted from 35%
H₂O, aqueous solution) was delivered by syringe pump over
30 min. After the oxidant addition, the resulting mixture was
brought to room temperature, and at this point, a 0.8 M biphenyl
solution in CH₂CN (0.5 equiv.) was added as internal standard.
The solution was filtered through a Celite©, silica and alumina
plug, which was subsequently rinsed with 2×1 mL EtOAc.
Then the sample was submitted to GC analysis to determine the
mass balance, the conversion, and relative ratio of products by
comparison with authentic samples. Yields forethyl-p-benzo-
quinone, propyl-p-benzoquinone and isopropyl-p-benzoquinone

Scheme 5. Deuterium labeling study.
were calculated with the response factor of methyl-p-benzoquinone.

Detailed experimental procedures and characterization data for all new compounds are described in the supporting information. CCDC-1994176 contains the supplementary crystallographic data for (S,S)-Mn(II)bpbi. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supporting information: E.M. and R.K.G. wrote the manuscript. All authors analyzed the data. M.B. analyzed data. M.L. performed X-ray analysis. E.M. and R.K.G. provided comments on the experiments and manuscript during its preparation.

Competing interests: The authors declare no competing financial interest.

Author contributions: R.K.G and M.C. devised the project and designed experiments. E.M. performed the experiments and analyzed the data. M.B. analyzed data. M.L. performed X-ray analysis. E.M. and R.K.G. wrote the manuscript. All authors provided comments on the experiments and manuscript during its preparation.

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Aromatic C–H Hydroxylation Reactions with Hydrogen Peroxide Catalyzed by Bulky Manganese Complexes


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