Synthesis of coenzyme Q₀ through divanadium-catalyzed oxidation of 3,4,5-trimethoxytoluene with hydrogen peroxide†

Olga V. Zalomaeva, a, b Vasilii Yu. Evtushok, a, b Gennadii M. Maksimov, a Raisa I. Maksimovskaya id a and Oxana A. Kholdeeva *a, b

The selective oxidation of methoxy/methyl-substituted arenes to the corresponding benzoquinones has been first realized using aqueous hydrogen peroxide as a green oxidant, acid tetrabutylammonium salts of the γ-Keggin divanadium-substituted phosphotungstate [γ-PW₁₀O₃₈V₂(µ-O)₂]⁵⁻ (I) as a catalyst, and MeCN as a solvent. The presence of the dioxovanadium core in the catalyst is crucial for the catalytic performance. The reaction requires an acid co-catalyst or, alternatively, a highly protonated form of I can be prepared and employed. The industrially relevant oxidation of 3,4,5-trimethoxytoluene gives 2,3-dimethoxy-5-methyl-1,4-benzoquinone (ubiquinone 0 or coenzyme Q₀, the key intermediate for coenzyme Q₁₀ and other essential biologically active compounds) with 73% selectivity at 76% arene conversion. The catalyst retains its structure under turnover conditions and can be easily recycled and reused without significant loss of activity and selectivity.

Introduction

The selective aromatic oxidation of arenes bearing methoxy and methyl substituents offers an efficient access to a range of benzoquinones, which play an important role in biological systems and are useful intermediates in the synthesis of fine chemicals, nutraceuticals and pharmaceuticals. Ubiquinones (also called coenzymes Qₙ, among which Q₁₀ is the most known coenzyme) act as biochemical oxidizing agents that mediate electron-transfer processes involved in energy production. Their synthetic analogue, idebenone, has been developed as a drug for the treatment of Alzheimer’s disease and other cognitive defects. 2,3-Dimethoxy-5-methyl-1,4-benzoquinone, known as ubiquinone 0 or coenzyme Q₀ (CoQ₀), can serve as a key intermediate in the synthesis of coenzyme Q₁₀ and other ubiquinones (Scheme 1).

The selective oxidation of methoxytoluene to the corresponding p-benzoquinones can be accomplished using dimethyldioxirane as an oxidant, mineral acid as a catalyst and acetone as a solvent. Several synthetic methods were reported for the production of CoQ₀ through the oxidation of commercially available 3,4,5-trimethoxytoluene (TMT) with the green oxidant – hydrogen peroxide. Among catalysts applied were potassium hexacyanoferrate(III), methyltrioxorhenium(VII) (MTORe), mineral acids (H₂SO₄, HNO₃), and heteropolyacids of the general formula HₙXM₁₂O₄₀ (where X = P or Si, n = 3 (P) or 4 (Si), and M = Mo or W). So far, the best yields of CoQ₀ have been claimed for systems that employed formic acid as a solvent and phosphomolybdic heteropolyacid as a catalyst or a mixture of acetic and formic acids without any catalysts. However, the use of hydrogen peroxide in combination with carboxylic acids imposes practical problems related to reactor corrosion and safety risks associated with the in situ formation of explosive peroxy acids. Growing environmental concerns stimulated the development of more safe and sustainable catalytic methods for the production of methoxy-substituted p-benzoquinones.
Scheme 2 Oxidation of TMT in the presence of TBA$_{5-n}$H$_n$-I.

In 2012, Mizuno and co-workers discovered an efficient system for hydroxylation of arenes that involved the divanadium-substituted γ-Keggin phosphotungstate (Bu$_4$N)$_4$[γ-PW$_{10}$O$_{38}$V$_2$][μ-O][μ-OH]) [hereinafter, TBA$_4$H-I] as a catalyst, mineral acid as a co-catalyst, H$_2$O$_2$ as an oxidant, and MeCN/t-BuOH (1:1) as a solvent. At a substrate to oxidant ratio of 50, mono- and dialkyl(alkoxy)arenes afforded the corresponding phenols with excellent chemoselectivity and unusual regioselectivity. More recently, we investigated the catalytic performance of TBA$_4$H-I in some industrially important reactions, such as oxidation of 2,3,6-trimethylphenol (TMP) and pseudocumene to 2,3,5-trimethyl-γ-benzoquinone (TMBQ, Vitamin E precursor) using H$_2$O$_2$, and found that TMP can be converted to TMBQ with a nearly quantitative yield and 80–90% oxidant utilization efficiency. In contrast to the oxidation of alkylarenes, this reaction did not require an acid co-catalyst.

In the present work, we explored further the catalytic properties of TBA$_{5-n}$H$_n$-I ($n = 1–2$) in H$_2$O$_2$-based aromatic oxidation and first employed this catalyst system to accomplish the challenging oxidative transformation of TMT into co-dation and first employed this catalyst system to accomplish the challenging oxidative transformation of TMT into co-dation and first employed this catalyst system to accomplish such as acetic or formic acid.

Results

In most procedures reported in the literature for TMT oxidation with H$_2$O$_2$, the reaction proceeds in acidic medium, such as acetic or formic acid. Some of them require addition of mineral acid in catalytic amounts to accelerate the formation of peroxy acid, which is the real oxidizing species in these systems. In view of our interest in the development of a more safe and environmentally friendly approach to the synthesis of CoQ$_0$, we have checked whether a mineral acid can play a role of the sole catalyst in a less corrosive and harmful solvent, for example, MeCN. While TMT conversion was negligible without any catalyst (Table 1, entry 1), in the presence of HClO$_4$, it attained 22% after 40 min at 60 °C. However, selectivity toward the target product was low (Table 1, entry 2) and the yield of CoQ$_0$ did not exceed 4%.

Previously, the group of Mizuno demonstrated that efficient hydroxylation of arenes can be realized in the presence of the divanadium-substituted polyoxometalate (POM) TBA$_4$H-I and 1 equiv. of HClO$_4$ as the co-catalyst. They rationalized the effect of the co-catalyst in terms of the in situ generation of a catalytically active diprotonated form of I, TBA$_3$[γ-PW$_{10}$O$_{38}$V$_2$][μ-OH]$_2$] (TBA$_3$H$_2$-I). To minimize the use of the acid co-catalyst, we attempted to develop a simple and affordable procedure for the preparation of a TBA salt of polyanion I that would contain an increased amount of protons as counter cations. Some modifications of the previously reported synthetic procedure, viz. additional acidification of the reaction mixture (pH 0.8 versus pH 2.0 used for the preparation of TBA$_4$H-I) before final precipitation with TBAOH (see Experimental for details), allowed us to obtain POM with an increased amount of protons (1.5–1.7 H$^+$ per POM molecule).

Table 1 TMT oxidation with H$_2$O$_2$ in the presence of HClO$_4$ and I$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>TBA$<em>{3.5}$H$</em>{1.5}$-I</th>
<th>HClO$_4$ (mM)</th>
<th>Time (min)</th>
<th>TMT conv. (%)</th>
<th>CoQ$_0$ select.$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>60</td>
<td>3</td>
<td>—</td>
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<tr>
<td>2</td>
<td>—</td>
<td>2.5</td>
<td>40</td>
<td>22</td>
<td>17</td>
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<tr>
<td>3</td>
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<td>—</td>
<td>30</td>
<td>36</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
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<td>0.6</td>
<td>30</td>
<td>65</td>
<td>66</td>
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<tr>
<td>5</td>
<td>2.5</td>
<td>1.25</td>
<td>30</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>2.5</td>
<td>30</td>
<td>69</td>
<td>53</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: TMT (0.1 M), H$_2$O$_2$ (0.2 M), MeCN 1 mL, 60 °C. $^b$ Yield based on converted TMT.

Fig. 1 $^{31}$P NMR spectrum of TBA$_{3.5}$H$_{1.5}$-I (0.0015 M) in dry CH$_3$CN.
is to generate TBA3H2- above mentioned hypothesis that the role of an acid co-catalyst its catalytic performance. Both TMT conversion and CoQ0 yield increase with increasing amounts of protons in the catalyst. In the presence of TBA3H2-, 73% selectivity could be attained at 68% TMT conversion. Importantly, a similar result was acquired using either TBA3H1.5-1 and 0.5 equiv. of HClO4 or TBA3H1.7-I and 0.3 equiv. of HClO4 indicating that it does not matter what is the source of protons, POM or mineral acid. Given that the synthesis of TBA3H1.5-I is more simple and reproducible than the synthesis of TBA3H2-I (see Experimental for details), we performed further studies and optimization of the catalytic system using TBA3H1.5-I.

Fig. 2 demonstrates how the protonation state of I affects its catalytic performance. Both TMT conversion and CoQ0 yield increase with increasing amounts of protons in the catalyst. In the presence of TBA3H2-I, 73% selectivity could be attained at 68% TMT conversion. Importantly, a similar result was acquired using either TBA3H1.5-I and 0.5 equiv. of HClO4 or TBA3H1.7-I and 0.3 equiv. of HClO4 indicating that it does not matter what is the source of protons, POM or mineral acid. Given that the synthesis of TBA3H1.5-I is more simple and reproducible than the synthesis of TBA3H2-I (see Experimental for details), we performed further studies and optimization of the catalytic system using TBA3H1.5-I.

To verify the uniqueness of polyanion I in the oxidation of TMT, we compared the catalytic performance of TBA3.5H1.5-I with some other representative POMs, including a Si-containing analog, TBA3H12[T-SiW10V2O40]8 and conventional α-Keggin heteropoly acids, such as vanadium-free H3PW12O40 and di-vanadium-substituted H3P2Mo10V2O40 (the latter has two vanadium atoms statistically distributed over 12 positions of the α-Keggin structure). A comparison of their catalytic properties is shown in Fig. 3. One can see that both the Si-analogue of I and the heteropoly acids are poor catalysts for the production of CoQ0. Although 35–60% conversion of TMT was attained after 1 h, selectivity towards ubiquinone 0 did not exceed 27%. On the other hand, 73% selectivity at 70% TMT conversion was reached after 0.5 h in the presence of 2.5 mol% of TBA3H1.5-I combined with 0.5 equiv. of mineral acid. These results indicate that the presence of both the dimeric vanadium core and the P central atom in the specific γ-Keggin structure are imperative for efficient catalysis of the title reaction. A simple vanadium complex, VO(acac)2, revealed 42% TMT conversion in 5 min, but the yield of CoQ0 was below 2%.

To figure out optimal reaction conditions, we studied the influence of all reaction parameters on TMT conversion and CoQ0 selectivity. The results are presented in Table 2. Previously, it was shown that 1-based oxidation of alkylarenes gave better yields of oxygenated products in a solvent mixture of MeCN and t-BuOH (1:1, v/v). However, in the case of TMT, the addition of t-BuOH resulted in worsening of both aren conversion and quinone selectivity relative to the reaction in MeCN (Table 2, compare entries 1 and 2).

![Fig. 2 TMT oxidation in the presence of TBA3Hn-I. Reaction conditions: TMT (0.1 M), H2O2 (0.2 M), I (2.5 mM), MeCN 1 mL, 60 °C, 30 min.](image)

![Fig. 3 TMT oxidation in the presence of different POMs. Reaction conditions: TMT (0.1 M), H2O2 (0.2 M), POM (2.5 mM), MeCN 1 mL, 60 °C.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat : TMT : H2O2</th>
<th>TMT (M)</th>
<th>Time (min)</th>
<th>TMT conv. (%)</th>
<th>CoQ0 select (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.025 : 1 : 2</td>
<td>0.1</td>
<td>30</td>
<td>70</td>
<td>73 (67)</td>
</tr>
<tr>
<td>2</td>
<td>0.025 : 1 : 2</td>
<td>0.1</td>
<td>15</td>
<td>43</td>
<td>56</td>
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<tr>
<td>3</td>
<td>0.025 : 1 : 2</td>
<td>0.1</td>
<td>240</td>
<td>39</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
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<td>71</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>0.013 : 1 : 2</td>
<td>0.1</td>
<td>30</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>0.05 : 1 : 2</td>
<td>0.1</td>
<td>5</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>0.025 : 1 : 2</td>
<td>0.05</td>
<td>45</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>0.025 : 1 : 2</td>
<td>0.2</td>
<td>15</td>
<td>51</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>0.025 : 1 : 3</td>
<td>0.1</td>
<td>15</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>10</td>
<td>0.025 : 1 : 3</td>
<td>0.1</td>
<td>45</td>
<td>85</td>
<td>64</td>
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<tr>
<td>11</td>
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<td>0.1</td>
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<tr>
<td>12</td>
<td>0.025 : 1 : 2</td>
<td>0.1</td>
<td>30</td>
<td>64</td>
<td>65</td>
</tr>
</tbody>
</table>

**Table 2** TMT oxidation in the presence of TBA3.5H1.5-I

*a* Reaction conditions: HClO4 (1.25 mM), MeCN 1 mL, 60 °C. *GC yield based on converted TMT.* † Isolated yield. ‡ MeCN/t-BuOH (1:1, v/v) instead of MeCN. § 30 °C. ‡H2O2 added in three portions. h H2O2 added in two portions. † † 0.1 M of MeOH was added.
The oxidation rate was reduced significantly by decreasing the reaction temperature: after 4 h at 30 °C, TMT conversion reached only 39%. However, some enhancement in the CoQ0 selectivity was observed (Table 2, compare entries 1 and 3). At 80 °C, the attainable level of conversion was the same as at 60 °C, but selectivity to CoQ0 decreased to 66% (Table 2, entry 4).

A 2-fold reduction of the catalyst concentration with simultaneous alteration of the co-catalyst amount did not strongly affect the catalytic performance (Table 2, compare entries 1 and 5). On the other hand, a 2-fold augmentation of the catalyst concentration led to some decrease of TMT conversion and CoQ0 selectivity (Table 2, entry 6). A proportional diminution of concentrations of all the reactants relative to the standard conditions resulted in some increase of TMT conversion but led to a reduction in CoQ0 selectivity (Table 2, entry 7). Oppositely, only 51% substrate conversion was reached in a more concentrated reaction mixture, showing a similar level of selectivity (Table 2, compare entries 1 and 8).

According to the reaction stoichiometry (see Scheme 2), two equivalents of \( \text{H}_2\text{O}_2 \) are required to convert TMT to CoQ0. However, under the standard reaction conditions of entry 1 (Table 2), the reaction stopped after 30 min, reaching a substrate conversion of 70%. Semiquantitative evaluation with Quantofix peroxide test sticks revealed that practically no oxidant was present in the final reaction mixture. Therefore, incomplete TMT conversion with 2 equiv. of \( \text{H}_2\text{O}_2 \) may be an indication of some unproductive decomposition of the oxidant. When the concentration of \( \text{H}_2\text{O}_2 \) was reduced twice relative to the required stoichiometric amount, the oxidant utilization efficiency was improved considerably (70% versus 52%) along with selectivity to the target quinone (82% versus 73%). Fig. 4 shows that \( \text{H}_2\text{O}_2 \) efficiency tends to decrease with increasing \( \text{H}_2\text{O}_2 \) concentration. The reaction selectivity follows a similar trend. A stepwise addition of the oxidant to the reaction mixture allowed higher TMT conversions to be achieved, keeping quinone selectivity at the same level (Table 2, compare entries 9 and 10, 1 and 11).

During the reaction course, we revealed the formation of a product that reached a maximum yield of ca. 15% at the initial stage and then disappeared (Fig. 5). In the final reaction mixture, only 1–2% of this compound was detected. GC-MS analysis identified it as 2,3,4-trimethoxy-6-methylphenol (TMMP). The bell-shaped accumulation curve depicted in Fig. 5 suggests that TMMP is, most likely, an intermediate product formed during the conversion of TMT to CoQ0. GC-MS also detected trace amounts of a compound that could be assigned to 3,4-dimethoxy-6-methylpyrocatechol or 2,3-dimethoxy-6-methyl-hydroquinone. These facts strongly support a mechanism that involves electrophilic hydroxylation of TMT to form TMMP at the first step of the oxidation process (Scheme 3).

At high conversions, CoQ0 was the only product detected by GC, GC-MS, and \(^1\text{H} \) NMR. However, CoQ0 yields determined by means of GC or \(^1\text{H} \) NMR using the internal standard suggested the presence of some by-products, most likely, tars.

To examine reusability of TBA\(_{3.5}\)H\(_{1.5}\)-I in the oxidation of TMT, we performed 3-fold scaled experiments, in which the catalyst was separated from the reaction mixture by precipitation with diethyl ether and used repeatedly under the conditions of entry 1, Table 2. The recycling performance is shown in Fig. 6. Only minor reduction of arene conversion and product selectivity was observed during at least four recycles. Importantly, the reaction time did not increase, indicating stable catalytic activity. The FTIR spectrum of the recovered catalyst confirmed the retention of the POM structure (see Fig. S1†).

Some decrease of TMT conversion and product yield might be caused by a partial transformation of the POM catalyst to a methoxy derivative, (Bu\(_4\)N)\(_2\)[\( \gamma \)-PW\(_{10}\)O\(_{36}\)V\(_2\)(\( \mu \)-OH)(\( \mu \)-OMe)], that could be formed during the reaction course upon interaction of polyanion I with methanol, which is one of the reaction pro-

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**Fig. 4** The effect of \( \text{H}_2\text{O}_2 \) concentration on TMT oxidation in the presence of TBA\(_{3.5}\)H\(_{1.5}\)-I. Reaction conditions: TMT (0.1 M), I (2.5 mM), HClO\(_4\) (1.25 mM), MeCN 1 mL, 60 °C.

**Scheme 3** Plausible route of TMT oxidative transformation to CoQ0.
ducts (see Scheme 2). Earlier, Nakagawa et al. studied the interaction of methanol and other alcohols with the Si-containing analogue of I and proved the formation of such methoxy derivatives.23 Indeed, $^{51}$V NMR detected the appearance of a signal at $-562$ ppm during the reaction progress, which could be assigned to the methoxy derivative of I (Fig. 7b). To verify this hypothesis, we performed an experiment where 1 equiv. of MeOH was added to a solution of TBA$_{3.5}$H$_{1.5}$-I in MeCN. Indeed, the appearance of the $^{51}$V NMR signal at $-562$ ppm was detected (Fig. 7c). The addition of methanol to the initial reaction mixture produced a rate-retarding effect (Fig. 8) and decreased TMT conversion and selectivity to CoQ$_0$ (Table 2, entry 12). It should be noted, however, that most of the methoxy derivative was hydrolyzed back to I upon the recycling workup since the recovered POM was present in its initial state ($\delta =-579$ ppm). Therefore, $^{31}$P and $^{51}$V NMR along with FTIR spectroscopic technique confirmed the retention of the $\gamma$-Keggin structure of I after the catalysis.

To estimate the scope of the TBA$_{3.5}$H$_{1.5}$/H$_2$O$_2$ catalytic system, we studied the oxidation of some other representative methoxyarenes (Scheme 4). The results are summarized in Table 3. For all substrates, the formation of the corresponding quinones occurred with moderate to good yields (22–70%) at conversions $\geq 74\%$. It is noteworthy that the oxidation of 1,2,3-trimethoxybenzene (Scheme 4, d) gave only 2,3-dimethoxy-1,4-benzoquinone while, for K$_3[\text{Fe(CN)}_6]$-catalyzed8 and non-catalytic9 oxidations, the formation of two isomeric quinones, 2,3- and 2,6-dimethoxy-1,4-benzoquinone, was observed. This fact implies that steric factors, most likely, control the oxidation process in the case of the bulky divanadium-POM catalyst.
For the sake of comparison, we also performed TMT oxidation following two protocols reported in the literature\cite{14,16} but in a lower scale (1 mL). The comparison is shown in Fig. 9. In a mixture of formic and acetic acids, CoQ0 yield achieved 58\%, which is a bit higher than the yield obtained in the presence of TBA3.5H1.5-I (52\%). On the contrary, the quinone yield was significantly lower (ca. 30\%) in the presence of phosphomolybdic acid in AcOH. An evident advantage of the TBA3.5H1.5-I-based catalyst system is greater oxidant utilization efficiency (see Fig. 9), which allows one to attain a good product yield using just the stoichiometric amount of the oxidant. In addition, we avoid the use of carboxylic acids as solvents and, therefore, preclude corrosion and formation of explosive peroxy acids upon interaction with H2O2.

Conclusions

In summary, we have developed a new method for the synthesis of the important fine chemical coenzyme Q0 via oxidation of commercially available 3,4,5-trimethoxytoluene with 30\% H2O2 in MeCN employing acid tetrabutylammonium salts of the divanadium-substituted polyoxometalate [γ-PW10V2O40] as a catalyst. Coenzyme Q0 was obtained with selectivity as high as 73\% at 76\% arene conversion. The catalytic performance, a simple procedure for the preparation of a highly protonated derivative TBA3.5H1.5-I has been developed. The use of this derivative enables significant reduction of the amount of acid co-catalyst without deterioration of the catalytic performance. The catalyst could be easily separated from the reaction mixture and recycled without appreciable loss of activity and selectivity.

Experimental

Materials and instrumentation

3,4,5-Trimethoxyltoluene (97\%) and 2,3-dimethoxy-5-methyl-1,4-benzoquinone (99\%) were obtained from Aldrich, 2,3-dimethoxytoluene (98\%) and 2,4,6-trimethoxytoluene (97\%) were purchased from Alfa, 3,5-dimethoxytoluene (99\%), 1,2,3-trimethoxybenzene (98\%) and 1,3,5-trimethoxybenzene (99\%) were obtained from Acros. Acetonitrile (Panreac, HPLC grade) was dried and stored over activated 4 Å molecular sieves. All the other compounds were the best available reagent grade and used without further purification. The concentration of H2O2 (ca. 35 wt% aqueous solution) was determined iodo-metrically prior to use. GC analyses were performed using a gas chromatograph Chromos GC-1000 equipped with a flame ionization detector and a quartz capillary column BPX5 (30 m × 0.25 mm). GC-MS analyses were carried out using an Agilent 7000B system with a triple-quadrupole mass-selective detector Agilent 7000 (HP-5 ms quartz capillary column 30 m × 0.25 mm). 1H, 31P and 51V NMR spectra were recorded on a Bruker AVANCE-400 spectrometer at 400.130, 161.67 and 105.24 MHz, respectively. Chemical shifts for P and V, δ, were determined relative to 85\% H3PO4 and VOCI3, respectively. Infrared spectra were recorded with KBr pellets on an Agilent 660 FTIR spectrometer.

General catalyst preparation

γ-Cs7PW10O46\cdot5H2O. The synthesis of the cesium salt of the dilacunary phosphotungstic acid was carried out either following the protocol reported in the literature that employs expensive and caustic CsOH,\cite{22} or using a modified procedure described below. 14.6 g of WO3 were mixed with 20 g of anhydrous Cs2CO3 in a nickel melting pot. A small amount of Cs2CO3 was added to cover WO3. The mixture was calcined at 620 °C for 6 h. Then the residue was stored in air overnight. Upon storing, the mixture adsorsbs water from air that leads to its swelling and makes it easier to be removed from the melting pot. The solid was mixed with 50 ml of water. The white precipitate was removed by filtration. Firstly, 2 ml of 3.25 M H3PO4 (W : P = 5 mol/mol), and then 3 M HNO3 were added to the mother liquor until pH reached 7. During the adjustment of the pH a white precipitate was formed. The mixture was heated to boiling and then filtered. The white solid was separated, washed with hot water and dried. Then another portion of 3 M HNO3 was added to the filtrate until pH reached 7, and a new portion of the white solid was treated as described above. Total yield of γ-Cs7PW10O46\cdot5H2O was ca. 80\% (17.5 g). The IR spectrum of the obtained solid corresponded to that of γ-Cs7PW10O46\cdot5H2O prepared by the conventional procedure.\cite{24} IR (KBr, cm\(^{-1}\)) : 1080, 1050, 1025, 937, 892, 820, 755.

TBA4H-I. The monoprotonated derivative TBA4H-[γ-PV2W10O40] was prepared according to the procedure reported by Kamata et al.\cite{22} with some modifications reported elsewhere.\cite{20} 51V NMR (MeCN): –581 ppm, 31P NMR (MeCN): –14.1 ppm.
**TBA\textsubscript{3.5}H\textsubscript{1.5}I.** POM with the increased amount of H\textsuperscript{+}, that is the mixture of mono- and diprotonated forms, TBA\textsubscript{3}H-I and TBA\textsubscript{3}H\textsubscript{2}I, having an averaged composition of TBA\textsubscript{3.5}H\textsubscript{1.5}I, was prepared according to the following procedure. NaVO\textsubscript{2}·2H\textsubscript{2}O (145 mg) was dissolved in 12 mL of H\textsubscript{2}O and the pH of the solution was adjusted to 0.8 with 3 M HCl. Then Cs\textsubscript{2}·6PV\textsubscript{2}W\textsubscript{10}O\textsubscript{40}·5H\textsubscript{2}O (1.3 g) was added to the solution, and a yellow precipitate was formed. The mixture was diluted with 20 mL of H\textsubscript{2}O and the pH of the solution was again adjusted to 0.8 with 3 M HCl. After separation of an insoluble residue by filtration, TBABr (474 mg) was added to the liquor. A yellow precipitate was separated, washed with water and dried in air. Potentiometric titration with TBAOH (0.39 M in H\textsubscript{2}O) revealed the presence of ca. 1.5 acid protons per anion I. CHN analysis calef (% for TBA\textsubscript{3.5}H\textsubscript{1.5}PV\textsubscript{2}W\textsubscript{10}O\textsubscript{40}: C 19.4, H 3.7, N 1.4; found: C 19.1, H 3.45, N 1.4. \textsuperscript{51}V NMR (MeCN, 0.005 M): δ = 1623, 1481, 1380, 1097, 1061, 1039, 964, 911, 876, 805, 700, 535.

**TBA\textsubscript{3}H\textsubscript{2}I.** The diprotonated derivative TBA\textsubscript{3}PV\textsubscript{2}W\textsubscript{10}O\textsubscript{40} was prepared according to the reported procedure:22 TBA\textsubscript{3}HPV\textsubscript{2}W\textsubscript{10}O\textsubscript{40} (150 mg) was dissolved in 2 mL of MeCN and 1 equiv. of HClO\textsubscript{4} was added to the solution. The mixture was diluted with 20 mL of ethyl ether. After precipitation of an yellow oil, the mother liquor was separated. The oil was dried under vacuum to obtain yellow crystals of TBA\textsubscript{3}H\textsubscript{2}I. \textsuperscript{31}P NMR (MeCN): δ = 579 ppm; \textsuperscript{13}C NMR (MeCN): 1623, 1481, 1380, 1097, 1061, 1039, 964, 911, 876, 805, 700, 535. It should be noted, however, that scaling up of this synthesis protocol to obtain a sufficient amount of crystalline TBA\textsubscript{3}H\textsubscript{2}I was not successful.

**Other POMs.** TBA\textsubscript{4}SiW\textsubscript{12}O\textsubscript{40}V\textsubscript{2}H\textsubscript{2}O was synthesized following the protocol described by Nakagawa et al.\textsuperscript{25} Heteropolyacid H\textsubscript{5}PMo\textsubscript{12}V\textsubscript{2}O\textsubscript{40} was prepared according to the literature.\textsuperscript{26}

**General methods for catalytic oxidation and product analysis**

**TMT oxidation.** Catalytic oxidations of TMT with H\textsubscript{2}O\textsubscript{2} in the presence of TBA\textsubscript{3.5}H\textsubscript{1.5}I or TBA\textsubscript{3}H\textsubscript{2}I were carried out in temperature-controlled glass vessels at 60 °C under vigorous stirring (500 rpm). Concentrations of the reactants were in the range of [TMT] = 0.05–0.2, [I] = 0.0013–0.05, [HClO\textsubscript{4}] = 0–0.025, and [H\textsubscript{2}O\textsubscript{2}] = 0.1–0.45 M. Typically, the reactions were initiated by the addition of H\textsubscript{2}O\textsubscript{2} either in one portion or step-wise to a mixture containing an aromatic substrate, I, HClO\textsubscript{4}, and an internal standard in 1 mL of a solvent (MeCN or its mixture with t-BuOH). Samples were taken during the reaction course by using a syringe and analyzed. The oxidation products were identified by GC, GC-MS and \textsuperscript{1}H NMR using authentic samples. The substrate conversions and product yields were quantified by GC using chlorobenzene as the internal standard. Each experiment was reproduced at least two times. The experimental error in the determination of substrate conversions and product yields by GC normally did not exceed 2%. Semiquantitative Quantofix peroxide test sticks were used for estimating the amount of H\textsubscript{2}O\textsubscript{2} at the end of catalytic reactions. The catalyst reusability was examined in 3-fold scaled experiments (the total reaction volume 3 mL). The catalyst was separated from the reaction mixture by precipitation with diethyl ether, dried in air and used repeatedly with the next portion of the reagents.

**Oxidation of methoxyarenes.** Catalytic oxidations of various methoxyarenes with H\textsubscript{2}O\textsubscript{2} in the presence of TBA\textsubscript{3.5}H\textsubscript{1.5}I were carried out in temperature-controlled glass vessels at 60 °C under vigorous stirring (500 rpm). Concentrations of the reactants were as follows: [substrate] = 0.1, [TBA\textsubscript{3.5}H\textsubscript{1.5}I] = 0.0025, [HClO\textsubscript{4}] = 0.00125, and [H\textsubscript{2}O\textsubscript{2}] = 0.2 M. The reactions were initiated by the addition of H\textsubscript{2}O\textsubscript{2} to a mixture containing an aromatic substrate, the TBA\textsubscript{3}H\textsubscript{2}I catalyst and HClO\textsubscript{4} in 1 mL of MeCN. The oxidation products were identified by GC-MS and \textsuperscript{1}H NMR spectra in accordance with the reported data.\textsuperscript{7,8} The substrate conversions and product yields were quantified by \textsuperscript{1}H NMR and/or GC using chlorobenzene as the internal standard. Each experiment was reproduced at least two times.

**Product characterization**

**2,3-Dimethoxy-5-methyl-1,4-benzoquinone.** \textsuperscript{1}H NMR (400 MHz; CD\textsubscript{3}CN, 25 °C): δ = 6.41 (q, J = 1.9 Hz, 1H); 3.91 (s, 3H); 3.89 (s, 3H); 3.07 (s, 3H). GC-MS (EI): m/z 182 (M\textsuperscript{+}, 25%), 167 (13), 154 (7), 137 (66), 126 (23), 111 (28), 96 (17), 83 (100), 69 (70), 68 (60).

**2,3-Trimethoxy-6-methylphenol.** GC-MS (EI): m/z 198 (M\textsuperscript{+}, 100%), 183 (95), 168 (10), 155 (16), 140 (61), 137 (23), 122 (15), 69 (75).

**2,3-Dimethoxy-6-methylproocatehol (or 2,3-dimethoxy-6-methyl-hydroquinone).** GC-MS (EI): m/z 184 (M\textsuperscript{+}, 96%), 169 (100), 154 (15), 141 (19), 137 (13), 126 (60), 123 (27), 69 (85).

**2-Methoxy-5-methyl-1,4-benzoquinone.** \textsuperscript{1}H NMR (400 MHz; CD\textsubscript{3}CN, 25 °C): δ = 6.52 (q, J = 1.6 Hz, 1H); 5.94 (s, 1H); 3.75 (s, 3H); 2.07 (s, 3H). GC-MS (EI): m/z 152 (M\textsuperscript{+}, 14%), 137 (4), 122 (10), 109 (6), 69 (100).

**2-Methoxy-6-methyl-1,4-benzoquinone.** \textsuperscript{1}H NMR (400 MHz; CD\textsubscript{3}CN, 25 °C): δ = 6.49 (m, 1H); 5.89 (d, J = 2.3 Hz, 1H); 3.75 (s, 3H); 2.07 (s, 3H). GC-MS (EI): m/z 152 (M\textsuperscript{+}, 15%), 137 (4), 122 (17), 122 (13), 109 (11), 69 (100).

**2,6-Dimethoxy-3-methyl-1,4-benzoquinone.** \textsuperscript{1}H NMR (400 MHz; CD\textsubscript{3}CN, 25 °C): δ = 5.85 (s, 1H); 3.97 (s, 3H); 3.80 (s, 3H); 1.97 (s, 3H). GC-MS (EI): m/z 152 (M\textsuperscript{+}, 47%), 167 (6), 149 (6), 139 (40), 111 (21), 83 (83), 69 (100).

**2,3-Dimethoxy-1,4-benzoquinone.** \textsuperscript{1}H NMR (400 MHz; CH\textsubscript{3}CN, 25 °C): δ = 6.53 (s, 2H); 3.86 (s, 6H). GC-MS (EI): m/z 168 (M\textsuperscript{+}, 12%), 153 (11), 123 (28), 82 (20), 69 (100).
2,6-Dimethoxy-1,4-benzoquinone. $^1$H NMR (400 MHz; CDCl$_3$, 25 °C): δ 5.84 [s, 2H]; 3.81 [s, 6H]. GC-MS (EI): m/z 168 (M$^+$ 24%), 138 (22), 125 (55), 97 (14), 80 (16), 69 (100).

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