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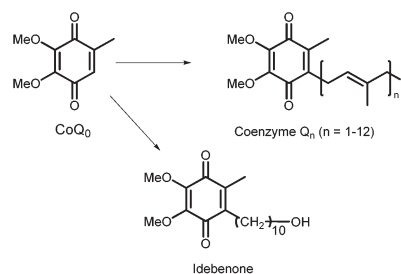
rsc.li/daltonSynthesis of coenzyme Q₀ through divanadium-catalyzed oxidation of 3,4,5-trimethoxytoluene with hydrogen peroxide†Olga V. Zalomaeva,^a Vasilii Yu. Evtushok,^{a,b} Gennadii M. Maksimov,^a Raisa I. Maksimovskaya^a and Oxana A. Kholdeeva^{*a,b}

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.¹ Ubiquinones (also called coenzymes Q_n, among which Q₁₀ is the most known coenzyme) act as biochemical oxidizing agents that mediate electron-transfer processes involved in energy production.^{2,3} Their synthetic analogue, idebenone, has been developed as a drug for the treatment of Alzheimer's disease and other cognitive defects.⁴ 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).^{5,6}

The selective oxidation of methoxytoluenes to the corresponding *p*-benzoquinones can be accomplished using dimethyldioxirane as an oxidant, mineral acid as a catalyst and acetone as a solvent.⁷ Several synthetic methods were reported for the production of CoQ₀ through the oxidation of commercially available 3,4,5-trimethoxytoluene (TMT) with the green

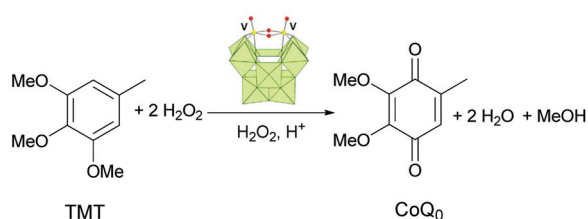
Scheme 1 Bioactive compounds derived from CoQ₀.

oxidant – hydrogen peroxide.^{8–16} Among catalysts applied were potassium hexacyanoferrate(III),⁸ methyltrioxorhenium(VII) (MTORe),^{11,12} mineral acids (H₂SO₄^{10,16} or HNO₃¹⁵), and heteropolyacids of the general formula H_nXM₁₂O₄₀ (where X = P or Si, *n* = 3 (P) or 4 (Si), and M = Mo or W).^{13,14} So far, the best yields of CoQ₀ have been claimed for systems that employed formic acid as a solvent and phosphomolybdic heteropolyacid as a catalyst¹⁴ or a mixture of acetic and formic acids without any catalysts.¹⁶ 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.^{1d,17,18}

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Scheme 2 Oxidation of TMT in the presence of $\text{TBA}_{5-n}\text{H}_n\text{-I}$.

In 2012, Mizuno and co-workers discovered an efficient system for hydroxylation of arenes that involved the divanadium-substituted γ -Keggin phosphotungstate (Bu_4N) $_4$ [$\gamma\text{-PW}_{10}\text{O}_{38}\text{V}_2(\mu\text{-O})(\mu\text{-OH})$] (hereinafter, $\text{TBA}_4\text{H-I}$) as a catalyst, mineral acid as a co-catalyst, H_2O_2 as an oxidant, and $\text{MeCN}/t\text{-BuOH}$ (1 : 1) as a solvent.¹⁹ 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 $\text{TBA}_4\text{H-I}$ in some industrially important reactions, such as oxidation of 2,3,6-trimethylphenol (TMP)²⁰ and pseudocumene²¹ to 2,3,5-trimethyl-*p*-benzoquinone (TMBQ, Vitamin E precursor) using H_2O_2 , and found that TMP can be converted to TMBQ with a nearly quantitative yield and 80–90% oxidant utilization efficiency.²⁰ 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 $\text{TBA}_{5-n}\text{H}_n\text{-I}$ ($n = 1\text{--}2$) in H_2O_2 -based aromatic oxidation and first employed this catalyst system to accomplish the challenging oxidative transformation of TMT into co-enzyme Q_0 (Scheme 2). The extension of this method toward other methoxyarenes is also reported. We carefully investigated the role of the acid co-catalyst and a possibility to replace it by using a highly protonated form of **I**. The catalyst stability and recyclability issues have also been addressed.

Results

In most procedures reported in the literature for TMT oxidation with H_2O_2 , the reaction proceeds in acidic medium, such as acetic or formic acid.^{9–11,13,15,16} 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.^{10,15,16} 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

Table 1 TMT oxidation with H_2O_2 in the presence of HClO_4 and **I**^a

Entry	$\text{TBA}_{3.5}\text{H}_{1.5}\text{-I}$ (mM)	HClO_4 (mM)	Time (min)	TMT conv. (%)	CoQ_0 select. ^b (%)
1	—	—	60	3	—
2	—	2.5	40	22	17
3	2.5	—	30	36	83
4	2.5	0.6	30	65	66
5	2.5	1.25	30	70	73
6	2.5	2.5	30	69	53

^a Reaction conditions: TMT (0.1 M), H_2O_2 (0.2 M), MeCN 1 mL, 60 °C.

^b Yield based on converted TMT.

divanadium-substituted polyoxometalate (POM) $\text{TBA}_4\text{H-I}$ and 1 equiv. of HClO_4 as the co-catalyst.^{19,21} They rationalized the effect of the co-catalyst in terms of the *in situ* generation of a catalytically active diprotonated form of **I**, $\text{TBA}_3[\gamma\text{-PW}_{10}\text{O}_{38}\text{V}_2(\mu\text{-OH})_2]$ ($\text{TBA}_3\text{H}_2\text{-I}$).¹⁹ 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,²² *viz.* additional acidification of the reaction mixture (pH 0.8 *versus* pH 2.0 used for the preparation of $\text{TBA}_4\text{H-I}$) before final precipitation with TBABr (see Experimental for details), allowed us to obtain POM with an increased amount of protons (1.5–1.7 H^+ per POM molecule). IR spectroscopy corroborated the retention of the polyanion structure (Fig. S1†). In dry dilute MeCN solution, such POM revealed two separate ^{31}P NMR signals at -13.7 and -14.1 ppm, which according to the literature,²² can be assigned to di- and monoprotinated forms, $\text{TBA}_3\text{H}_2\text{-I}$ and $\text{TBA}_4\text{H-I}$, respectively. Fig. 1 shows a typical ^{31}P NMR spectrum where the ratio of the two signals is *ca.* 2 : 1, which implies the formulation of $\text{TBA}_{3.3}\text{H}_{1.7}\text{-I}$. The corresponding ^{51}V NMR spectrum revealed two poorly resolved signals at -579 ($\text{TBA}_3\text{H}_2\text{-I}$) and -581 ($\text{TBA}_4\text{H-I}$) ppm (Fig. S2 in ESI†). In more concentrated or wet solutions only one averaged NMR signal is observed at -13.9 (^{31}P) and -579 (^{51}V) due to fast exchange on the NMR time scale. Potentiometric titration with aqueous TBAOH confirmed the presence of two types of acid protons in the POM and made possible accurate determination of the

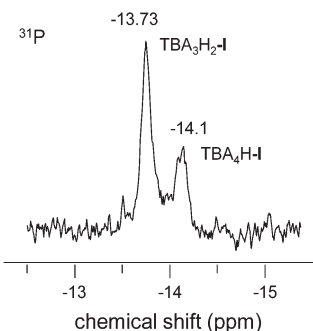


Fig. 1 ^{31}P NMR spectrum of $\text{TBA}_{3.3}\text{H}_{1.7}\text{-I}$ (0.0015 M) in dry CH_3CN .



ratio between the two forms of **I**. Fig. S3† depicts a representative potentiometric titration curve for the sample of TBA_{3.5}H_{1.5}-**I**. The results of the potentiometric titration are in good agreement with CNH analysis (see Experimental).

It is noteworthy that TBA_{3.5}H_{1.5}-**I** itself is able to convert TMT to CoQ₀ with selectivity as high as 83% (Table 1, entry 3). However, arene conversion was only 36% and could not be increased by increasing the reaction time. The addition of HClO₄ led to improvement in both substrate conversion and CoQ₀ yield. The optimal amount of acid turned out to be close to 0.5 equiv. (Table 1, compare entries 4–6), corroborating the above mentioned hypothesis that the role of an acid co-catalyst is to generate TBA₃H₂-**I** in the diprotonated form.

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 TBA_{3.5}H_{1.5}-**I** and 0.5 equiv. of HClO₄ or TBA_{3.3}H_{1.7}-**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 TBA_{3.5}H_{1.5}-**I** is more simple and reproducible than the synthesis of TBA₃H₂-**I** (see Experimental for details), we performed further studies and optimization of the catalyst system using TBA_{3.5}H_{1.5}-**I**.

To verify the uniqueness of polyanion **I** in the oxidation of TMT, we compared the catalytic performance of TBA_{3.5}H_{1.5}-**I** with some other representative POMs, including a Si-containing analog, TBA₄H₂[γ-SiW₁₀V₂O₄₀], and conventional α-Keggin heteropoly acids, such as vanadium-free H₃PW₁₂O₄₀ and di-vanadium-substituted H₅PMo₁₀V₂O₄₀ (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

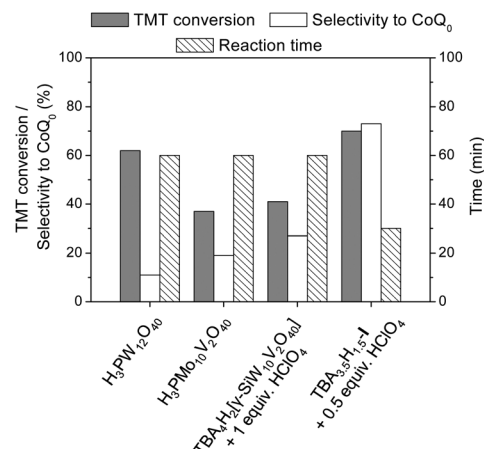


Fig. 3 TMT oxidation in the presence of different POMs. Reaction conditions: TMT (0.1 M), H₂O₂ (0.2 M), POM (2.5 mM), MeCN 1 mL, 60 °C.

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 TBA_{3.5}H_{1.5}-**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 **I**-based oxidation of alkylarenes gave better yields of oxygenated products in a solvent mixture of MeCN and *t*-BuOH (1 : 1, v/v).^{19,21} However, in the case of TMT, the addition of *t*-BuOH resulted in worsening of both arene conversion and quinone selectivity relative to the reaction in MeCN (Table 2, compare entries 1 and 2).

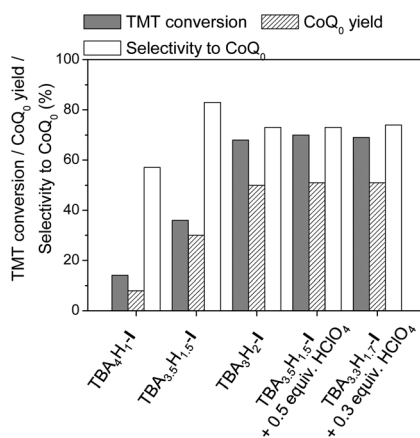


Fig. 2 TMT oxidation in the presence of TBA_{3.5}H_{1.5}-**I**. Reaction conditions: TMT (0.1 M), H₂O₂ (0.2 M), **I** (2.5 mM), MeCN 1 mL, 60 °C, 30 min.

Table 2 TMT oxidation in the presence of TBA_{3.5}H_{1.5}-**I**^a

Entry	Cat : TMT : H ₂ O ₂	TMT (M)	Time (min)	TMT conv. (%)	CoQ ₀ select. (%)
1	0.025 : 1 : 2	0.1	30	70	73 (67) ^c
2 ^d	0.025 : 1 : 2	0.1	15	43	56
3 ^e	0.025 : 1 : 2	0.1	240	39	77
4 ^f	0.025 : 1 : 2	0.1	5	71	66
5	0.013 : 1 : 2	0.1	30	69	70
6	0.05 : 1 : 2	0.1	5	66	64
7	0.025 : 1 : 2	0.05	45	75	67
8	0.025 : 1 : 2	0.2	15	51	75
9	0.025 : 1 : 3	0.1	15	65	63
10 ^g	0.025 : 1 : 3	0.1	45	85	64
11 ^h	0.025 : 1 : 2	0.1	30	76	73
12 ⁱ	0.025 : 1 : 2	0.1	30	64	65

^a Reaction conditions: HClO₄ (1.25 mM), MeCN 1 mL, 60 °C. ^b GC yield based on converted TMT. ^c Isolated yield. ^d MeCN/*t*-BuOH (1 : 1, v/v) instead of MeCN. ^e 30 °C. ^f 80 °C. ^g H₂O₂ added in three portions. ^h H₂O₂ added in two portions. ⁱ 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 H₂O₂ 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 H₂O₂ may be an indication of some unproductive decomposition of the oxidant. When the concentration of H₂O₂ 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 H₂O₂ efficiency tends to decrease with increasing H₂O₂ 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

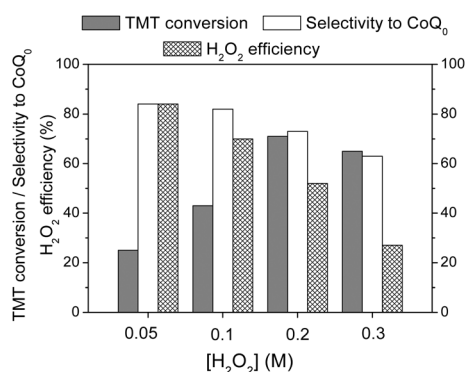


Fig. 4 The effect of H₂O₂ concentration on TMT oxidation in the presence of TBA_{3.5}H_{1.5}-I. Reaction conditions: TMT (0.1 M), I (2.5 mM), HClO₄ (1.25 mM), MeCN 1 mL, 60 °C.

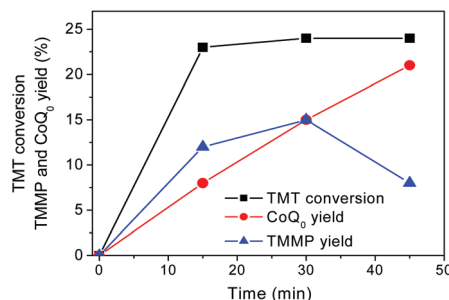


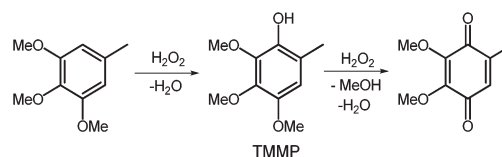
Fig. 5 TMT consumption and product formation *versus* time. Reaction conditions: TMT (0.1 M), H₂O₂ (0.05 M), TBA_{3.5}H_{1.5}-I (2.5 mM), HClO₄ (1.25 mM), MeCN 1 mL, 40 °C.

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 ¹H NMR. However, CoQ₀ yields determined by means of GC or ¹H 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, (Bu₄N)₃[γ-PW₁₀O₃₈V₂(μ-OH)(μ-OMe)], that could be formed during the reaction course upon interaction of polyanion I with methanol, which is one of the reaction pro-



Scheme 3 Plausible route of TMT oxidative transformation to CoQ₀.



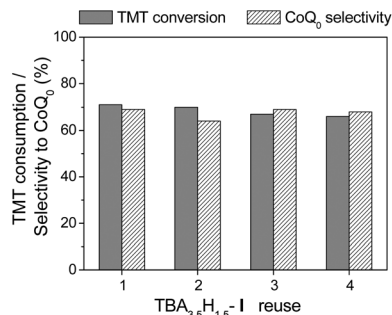


Fig. 6 Reuse of TBA_{3.5}H_{1.5}-I in TMT oxidation. Reaction conditions: TMT (0.1 M), H₂O₂ (0.2 M), TBA_{3.5}H_{1.5}-I (2.5 mM), HClO₄ (1.25 mM), MeCN (3 mL), 60 °C, 15 min.

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, ⁵¹V 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 ⁵¹V 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 CoQ₀ (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

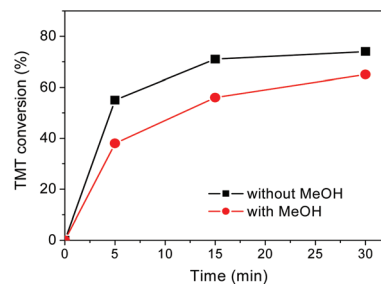


Fig. 8 The effect of MeOH on TMT conversion. Reaction conditions: TMT (0.1 M), H₂O₂ (0.2 M), TBA_{3.5}H_{1.5}-I (2.5 mM), HClO₄ (1.25 mM), [MeOH] 0.1 M, MeCN 1 mL, 60 °C.

was present in its initial state (δ −579 ppm). Therefore, ³¹P and ⁵¹V NMR along with FTIR spectroscopic technique confirmed the retention of the γ -Keggin structure of **I** after the catalysis.

To estimate the scope of the TBA_{3.5}H_{1.5}-I/H₂O₂ 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 K₃[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.

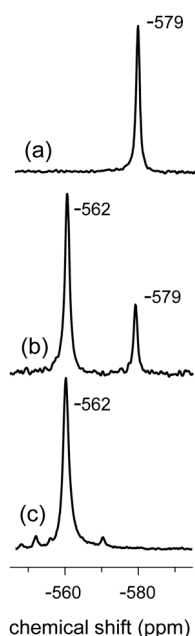
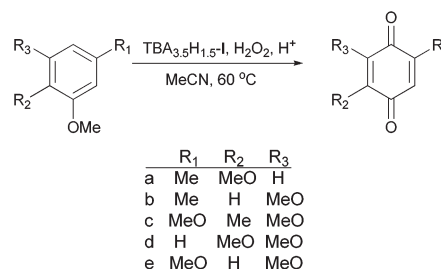


Fig. 7 ⁵¹V NMR spectra in CH₃CN: (a) initial TBA_{3.5}H_{1.5}-I (0.0025 M), (b) reaction mixture after 10 min, and (c) TBA_{3.5}H_{1.5}-I (0.0025 M) + 1 equiv. of MeOH.



Scheme 4 Oxidation of methoxyarenes in the presence of TBA_{3.5}H_{1.5}-I.

Table 3 Oxidation of methoxyarenes catalyzed by TBA_{3.5}H_{1.5}-I^a

Entry	Substrate	Conversion [%]	Selectivity to quinone ^b [%]
1	a	92	76
2	b	81	59
3	c	74	39
4	d	82	27
5	e	77	56

^a Reaction conditions: Arene (0.1 M), H₂O₂ (0.2 M), TBA_{3.5}H_{1.5}-I (2.5 mM), HClO₄ (1.25 mM), MeCN 1 mL, 60 °C, 5–30 min. ^b Based on the converted substrate.



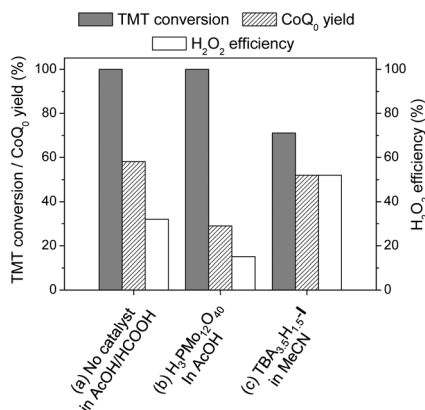


Fig. 9 Comparison of I-catalyzed TMT oxidation with reported systems. Reaction conditions: (a) TMT (1.4 M), H₂O₂ (5.5 M) added dropwise for 10 min, HCOOH 0.35 mL, AcOH 0.18 mL, 35 °C; (b) TMT (2.2 M), 50% H₂O₂ (7 M), H₃PMo₁₂O₄₀ (0.7 M), HCOOH 0.5 mL, 25 °C; and (c) as in Table 2, entry 1.

For the sake of comparison, we also performed TMT oxidation following two protocols reported in the literature^{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 TBA_{3.5}H_{1.5}-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 TBA_{3.5}H_{1.5}-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]⁵⁻ as a catalyst. Coenzyme Q₀ was obtained with selectivity as high as 73% at 76% arene conversion. The procedure is affordable, safe and sustainable. The catalyst system is applicable to oxidation of a variety of di- and trimethoxyarenes, producing the corresponding benzoquinones in moderate to good yields. Since the presence of an acid is crucial for the catalytic performance, a simple procedure for the preparation of a highly protonated derivative TBA_{3.5}H_{1.5}-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-Trimethoxytoluene (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 iodometrically 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 VOCl₃, respectively. Infrared spectra were recorded with KBr pellets on an Agilent 660 FTIR spectrometer.

General catalyst preparation

γ-Cs₇PW₁₀O₃₆·5H₂O. The synthesis of the cesium salt of the dilacunary phosphotungstate was carried out either following the protocol reported in the literature that employs expensive and caustic CsOH,²⁴ 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 adsorbs 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-Cs₇PW₁₀O₃₆·5H₂O was *ca.* 80% (17.5 g). The IR spectrum of the obtained solid corresponded to that of γ-Cs₇PW₁₀O₃₆·5H₂O prepared by the conventional procedure.²⁴ IR (KBr, cm⁻¹): 1080, 1050, 1025, 937, 892, 829, 755.

TBA₄H-I. The monoprotonated derivative TBA₄H [γ-PV₂W₁₀O₄₀] was prepared according to the procedure reported by Kamata *et al.*²² with some modifications reported elsewhere.²⁰ ⁵¹V NMR (MeCN): −581 ppm, ³¹P NMR (MeCN): −14.1 ppm.



TBA_{3.5}H_{1.5}-I. POM with the increased amount of H⁺, that is the mixture of mono- and diprotonated forms, TBA₄H-I and TBA₃H₂-I, having an averaged composition of TBA_{3.5}H_{1.5}-I, was prepared according to the following procedure. NaVO₃·2H₂O (145 mg) was dissolved in 12 mL of H₂O and the pH of the solution was adjusted to 0.8 with 3 M HCl. Then Cs₇[γ-PW₁₀O₃₆]·5H₂O (1.3 g) was added to the solution, and a yellow precipitate was formed. The mixture was diluted with 20 mL of H₂O 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 H₂O) revealed the presence of *ca.* 1.5 acid protons per anion I. CHN analysis calcd (%) for TBA_{3.5}H_{1.5}[PV₂W₁₀O₄₀]: C 19.4, H 3.7, N 1.4; found: C 19.1, H 3.45, N 1.4. ⁵¹V NMR (MeCN, 0.005 M): −579 ppm; ³¹P NMR (MeCN): −13.9 ppm. IR (KBr, cm^{−1}): 1623, 1481, 1380, 1097, 1061, 1039, 964, 911, 876, 805, 700, 535.

TBA₃H₂-I. The diprotonated derivative TBA₃[γ-H₂PV₂W₁₀O₄₀] was prepared according to the reported procedure:²² TBA₄[γ-HPV₂W₁₀O₄₀] (150 mg) was dissolved in 2 mL of MeCN and 1 equiv. of HClO₄ was added to the solution. The mixture was diluted with 20 mL of diethyl ether. After precipitation of a yellow oil, the mother liquor was separated. The oil was dried under vacuum to obtain yellow crystals of TBA₃H₂-I. ⁵¹V NMR (MeCN): −579 ppm, ³¹P NMR (MeCN): −13.7 ppm. IR (KBr, cm^{−1}): 1630, 1480, 1380, 1090, 1062, 1042, 1015, 967, 876, 805, 700, 536. It should be noted, however, that scaling up of this synthesis protocol to obtain a sufficient quantity of crystalline TBA₃H₂-I was not successful.

Other POMs. TBA₄[γ-SiW₁₀O₃₈V₂(μ-OH)₂] was synthesized following the protocol described by Nakagawa *et al.*²⁵ Heteropolyacid H₅PMo₁₀V₂O₄₀ was prepared according to the literature.²⁶

General methods for catalytic oxidation and product analysis

TMT oxidation. Catalytic oxidations of TMT with H₂O₂ in the presence of TBA₄H-I or TBA_{3.5}H_{1.5}-I were carried out in temperature-controlled glass vessels at 30–80 °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, [HClO₄] = 0–0.025, and [H₂O₂] = 0.1–0.45 M. Typically, the reactions were initiated by the addition of H₂O₂ either in one portion or stepwise to a mixture containing an aromatic substrate, I, HClO₄, 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 ¹H 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 H₂O₂ at the end of catalytic reac-

tions. The catalyst reusability was examined in 3-fold scaled experiments (the total reaction mixture 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. To isolate the ubiquinone product, the reaction mixture was diluted with water followed by extraction with CH₂Cl₂. After concentration under vacuum at room temperature, pure CoQ₀ was isolated by preparative column chromatography on silica gel using gradient elution with hexane and hexane/ethyl acetate. The ¹H NMR spectrum of the isolated product (Fig. S4 in ESI†) was identical to that of the authentic sample. The vanadium content in the isolated product was below the detection limit of ICP-AES analysis.

Oxidation of methoxyarenes. Catalytic oxidations of various methoxyarenes with H₂O₂ in the presence of TBA_{3.5}H_{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_{3.5}H_{1.5}-I] = 0.0025, [HClO₄] = 0.00125, and [H₂O₂] = 0.2 M. The reactions were initiated by the addition of H₂O₂ to a mixture containing an aromatic substrate, the TBA_{3.5}H_{1.5}-I catalyst and HClO₄ in 1 mL of MeCN. The oxidation products were identified by GC-MS and ¹H NMR (Fig. S5–S9†). All GC-MS and ¹H NMR spectra are in accordance with the reported data.^{7,8} The substrate conversions and product yields were quantified by ¹H 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. ¹H NMR (400 MHz; CDCl₃, 25 °C): δ 6.41 (q, *J* = 1.9 Hz, 1H); 3.91 (s, 3H); 3.89 (s, 3H); 2.07 (s, 3H). GC-MS (EI): *m/z* 182 (M⁺, 25%), 167 (13), 154 (7), 137 (66), 126 (23), 111 (28), 96 (17), 83 (100), 69 (70), 68 (60).

2,3,4-Trimethoxy-6-methylphenol. GC-MS (EI): *m/z* 198 (M⁺, 100%), 183 (95), 168 (10), 155 (16), 140 (61), 137 (23), 122 (15), 69 (75).

3,4-Dimethoxy-6-methylpyrocatechol (or 2,3-dimethoxy-6-methyl-hydroquinone). GC-MS (EI): *m/z* 184 (M⁺, 96%), 169 (100), 154 (15), 141 (19), 137 (13), 126 (60), 123 (27), 69 (85).

2-Methoxy-5-methyl-1,4-benzoquinone. ¹H NMR (400 MHz; CD₃CN, 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⁺, 14%), 137 (4), 122 (10), 109 (6), 69 (100).

2-Methoxy-6-methyl-1,4-benzoquinone. ¹H NMR (400 MHz; CD₃CN, 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⁺, 15%), 137 (4), 124 (17), 122 (13), 109 (11), 69 (100).

2,6-Dimethoxy-3-methyl-1,4-benzoquinone. ¹H NMR (400 MHz; CDCl₃, 25 °C): δ 5.85 (s, 1H); 3.97 (s, 3H); 3.80 (s, 3H); 1.97 (s, 3H). GC-MS (EI): *m/z* 182 (M⁺, 47%), 167 (6), 149 (6), 139 (40), 111 (21), 83 (83), 69 (100).

2,3-Dimethoxy-1,4-benzoquinone. ¹H NMR (400 MHz; CH₃CN, 25 °C): δ 6.53 (s, 2H); 3.86 (s, 6H). GC-MS (EI): *m/z* 168 (M⁺, 12%), 153 (11), 123 (28), 82 (20), 69 (100).



2,6-Dimethoxy-1,4-benzoquinone. ^1H 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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