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Oxidation of 1,2,4-trimethylbenzene (TMB), 2,3,6-trimethylphenol (TMP) and 2-methylnaphthalene to 2,3,5-trimethylbenzoquinone (TMBQ) and menadione (vitamin K_3)

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ABSTRACT

The synthesis of industrially important quinones as intermediates for vitamin syntheses is reviewed with special emphasis on recent developments in our own group.

The synthesis of quinones as intermediates for the preparation of vitamins is of general interest in organic chemistry [1]. In this regard, the selective oxidation of suitable arenes to the desired quinone represents the key synthetic step in the preparation of menadione (vitamin K_3) and 2,3,5-trimethylbenzoquinone (TMBQ), a crucial intermediate in synthesis of vitamin E (Fig. 1), which are important food additives. Notably, both vitamins are produced on a several thousand ton scale per year. In addition, oxidations of arenes to quinones constitute important biological processes [2], which are involved in photosynthesis and respiratory chain.

More specifically, menadione shows antihaemorrhagic effects and is applied as an animal feed additive [3]. In addition, it is used as a precursor of vitamins K_1 and K_2. Among the industrially relevant quinones, 2,3,5-trimethylbenzoquinone **2** represents one of the intermediates for the synthesis of vitamin E (α-tocopherol) [4], which is used extensively as antioxidant in food, medical treatments, and cosmetics [5]. While in nature, quinones are produced by oxidation of aromatic amines, polyhydric phenols, and polynuclear hydrocarbons or enzymatic oxidation of polyphenols [6], the key step in the synthesis of vitamin E is the conversion of 2,3,6-trimethylphenol **1** (TMP) to **2** (Scheme 1).

To date several protocols have been established for the direct oxidation of TMP to TMBQ [7], however only few of them are of industrial relevance. The industrial manufacture of menadione **4** is similarly based on the selective oxidation of an arene. Here, 2-methylnaphthalene **3** is selectively oxidized to **4** (Scheme 2).

Unfortunately, still the latter oxidation is performed by using stoichiometric amounts of chromium trioxide in sulfuric acid. Depending on the reaction conditions product yields between 38 and 60% have been reported [8]. Due to the large amount of chromium-containing waste, e.g. 18 kg of waste per kg of product [8], significant research efforts have been made to replace this process by more environmentally benign routes.

In the technical process of TMP a $CuCl_2$-mediated oxidation with oxygen is used in the presence of lithium chloride. Applying a biphasic solvent of water and an aliphatic alcohol yields of up to 98% can be achieved [9]. Unfortunately, stoichiometric amounts of copper are applied under these conditions. This results in large amounts of copper waste and product contamination. Thus, the development of more environmentally friendly procedures for the oxidation of TMBQ is also of actual interest.

In order to develop improved oxidation processes for quinones, which reduce or eliminate the use and generation of waste, it is clear that the choice of the respective oxidant determines to a large extent the practicability and efficiency of the overall reaction. Clearly, air is an ideal oxidant and several catalytic routes for the oxidation of 2-methylnaphthalene **3** and TMP **1** to the corresponding quinones (**2** and **4**) have been developed [7d,9,18,23,24]. In addition to molecular oxygen, hydrogen peroxide, H_2O_2, is the most "green", and waste-avoiding oxidant. It can oxidize organic compounds with an atom efficiency of 47% and generates only water as co-product. Due to its properties H_2O_2 is particularly useful for liquid-phase oxidations for the synthesis of fine

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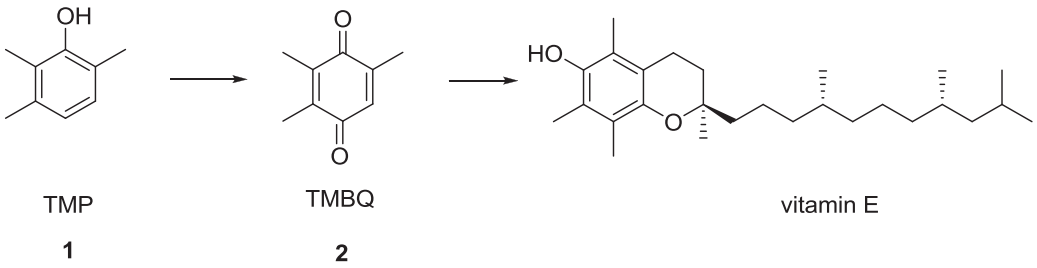
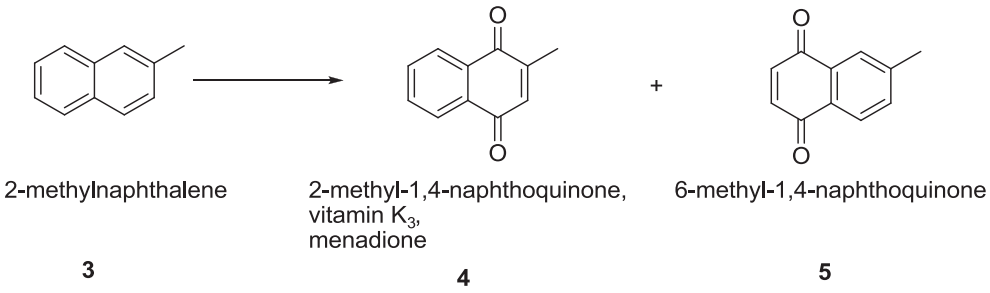
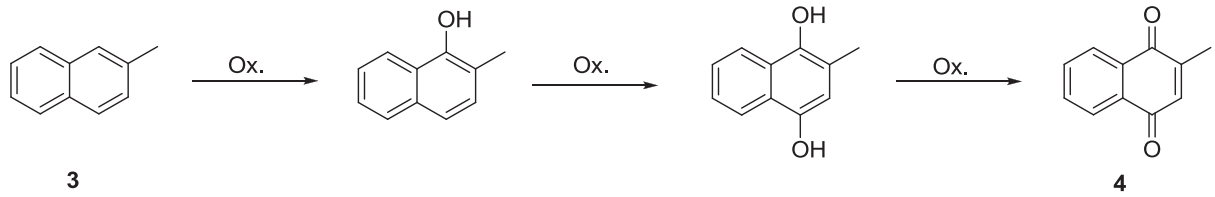


Scheme 1. Schematic synthesis of vitamin E.



Scheme 2. Oxidation of 2-methylnaphthalene to the corresponding quinones.



Scheme 3. Proposed pathway for the Pd-catalyzed oxidation of 2-methylnaphthalene.

chemicals, pharmaceuticals, and electronic materials [10]. As early as 1940 Arnold et al. reported the synthesis of vitamin K_3 in about 30% yield by using hydrogen peroxide (30%) in acetic acid at 80 °C [11]. 30 years later the Mitsubishi Gas Chemical Co. patented an improved method for vitamin K_3 synthesis using 12 equiv. HCl and 4 equiv. H_2O_2 (60%) in MeOH [12]. In 1985, Yamaguchi et al. reported the first metal-catalyzed synthesis [13]. Here, the oxidation of 2-methylnaphthalene was carried out in acetic acid with aq. 60% H_2O_2 in the presence of Pd(II)-polystyrene sulfonic acid resin. At 50 °C after 8 h the conversion was 93% and 2-methyl-1,4-naphthoquinone was obtained in yields between 50 and 60%. The catalyst recovered by filtration was reusable. However, the

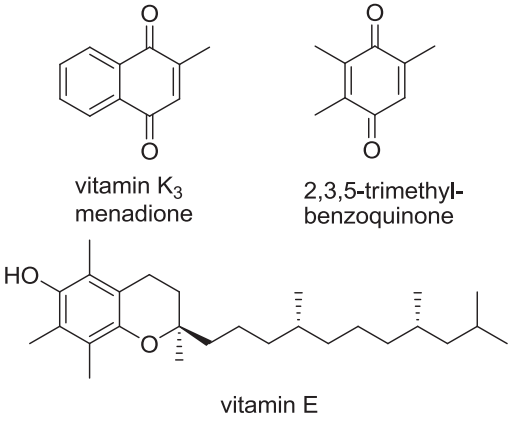
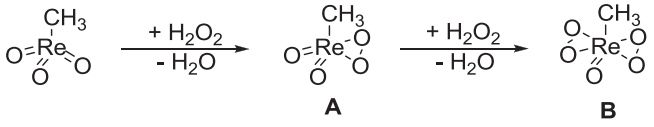


Fig. 1. Vitamins K_3 and E, and vitamin E precursor.

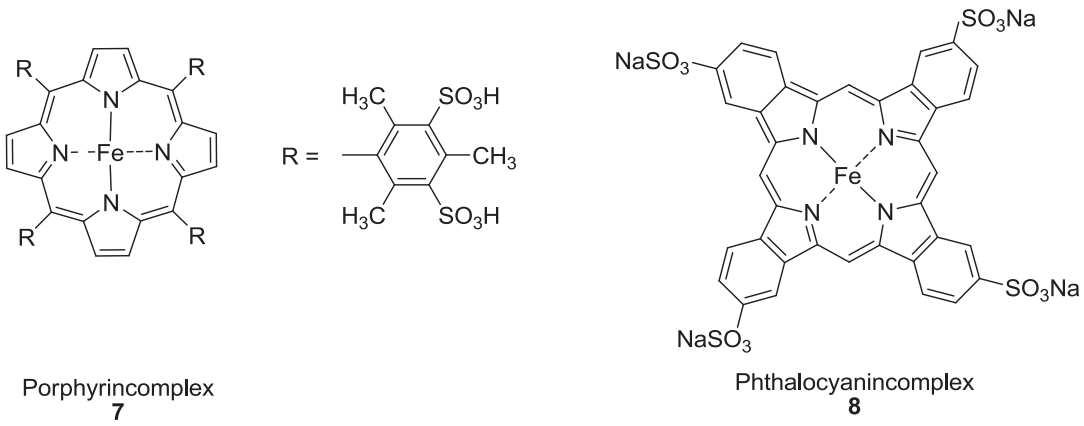


Scheme 4. Formation of the active catalyst species from MTO.

regioselectivity of the process was not discussed in this study. Mechanistic investigations by the Yamaguchi group suggested a hydroxylated naphthalene intermediate before the quinone is formed [1]. As shown in Scheme 3, 2-methylnaphthalene is oxidized to 2-methylnaphth-1-ol, before 2-methylnaphth-1,4-diol is formed and finally the oxidation to the corresponding 2-methyl-1,4-naphthoquinone takes place.

An interesting catalytic oxidation of 2-methylnaphthalene using hydrogen peroxide was described by Herrmann et al. in the beginning of the 1990s [14]. This reaction is catalyzed by methyltrioxorhenium (MTO), which is also active for several other transformations such as olefine metathesis or aldehyde olefination [15].

Applying acetic acid/acetic anhydride as solvent in the presence of catalytic amounts of CH_3ReO_3 (1 mol%), **3** is preferentially oxidized by hydrogen peroxide (85% in water) to the 1,4-quinone **4**. At 40 °C and after 4 h the conversion amounts to 89% (quinone yield 52%). The high regioselectivity is particularly remarkable, favouring the isomeric 2-methylnaphthoquinones **4** and **5**, which are formed in a 7:1 ratio (46% yield of **4**). From a mechanistic point of view MTO reacts with hydrogen peroxide to form two η^2-peroxorhenium complexes, the mono-peroxorhenium and the di-peroxorhenium species (A and B in Scheme 4) [16]. Complex B represents the most



Porphyrincomplex
7

Phthalocyanincomplex
8

Fig. 2. Iron-porphyrin- and phthalocyanin complexes for arene oxidations.

active catalyst for the oxidation of the substrate. To prevent MTO deactivation by water hydrolysis, a mixture of acetic acid and acetic anhydride with H_2O_2 (85% in water) is employed minimizing the amount of water [17].

In 1994, Takai et al. published the first catalytic system with molecular oxygen as oxidant [18]. By using an oxovanadium(IV)-1,3-diketone complex as a catalyst in the presence of molecular oxygen and crotonaldehyde, 2-methylnaphthalene was smoothly oxidized to the corresponding 1,4-naphthoquinone (Scheme 5). Under similar conditions menadione was obtained in a yield of 55%. The disadvantage of this system is the necessity of an auxiliary reducing agent and two equivalents of oxygen are used per oxidation taking place. Unfortunately, more than stoichiometric amounts of toxic crotonaldehyde have to be added successively.

The current state-of-art oxidation system for arenes to quinones was developed by Thiel and co-workers in 2006. Here, yields up to 71% of menadione are obtained [19]. Their reported method utilized 50% hydrogen peroxide (aq.) in a mixture of glacial acetic acid and acetic anhydride without any metal catalyst! Instead a strong Brønsted acid is used to catalyze the reaction. Different acids such as perchloric acid, phosphorus acid or sulfuric acid have been applied as catalysts. The observed ratio of regioisomers is approximately 8:1. From a mechanistic perspective two possible reaction paths were considered (Scheme 6). On the one hand, initial epoxidation and subsequent rearrangement leads to the target molecules (A). On the other hand, protonation and acylation of the arene gives the mono-hydroxylated derivative (B). Notably, the hydroxylated intermediate was detected by gas chromatography.

Due to their interesting redox chemistry and easy availability also iron-based catalysts have been applied for the synthesis of quinones from arenes. The first example was published in 1997 by Meunier and co-workers, who described an iron-porphyrin catalyzed oxidation of **3**. The reported system makes use of a sulfonated porphyrin, allowing the catalyst to be water-soluble (Fig. 2) [20]. Unfortunately, potassium peroxomonosulfate had to be used as oxidant and vitamin K_3 is obtained only in moderate 44% yield due to the low regioselectivity of the oxidation. A different iron catalyst system

Salcomin
9

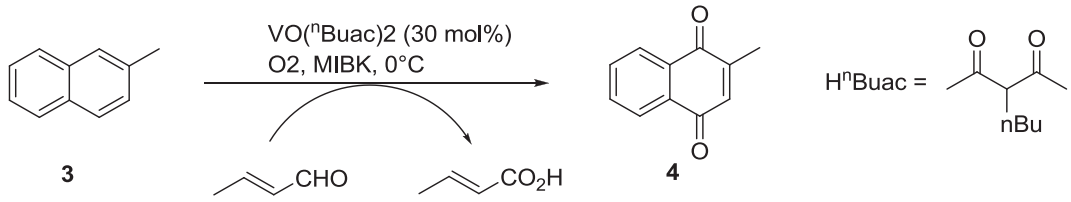
Fig. 3. Salcomin catalyst for oxidation of TMP **1** to TMBQ **2**.

utilized tetrasulfonic phthalocyanine (FePcS) immobilized on silica (Fig. 2) [21]. Sorokin et al. reported that the FePcSs are bound together to form an active dimer. The reaction was run in acetonitrile using 4 mol% of the catalyst and *t*-BuOOH as oxidant providing quinones and vitamin K_3 in yields of 65% and 45%, respectively. This dimeric ironphthalocyanin complex was also used for the oxidation of TMP **1** to TMBQ **2** in yields up to 87%.

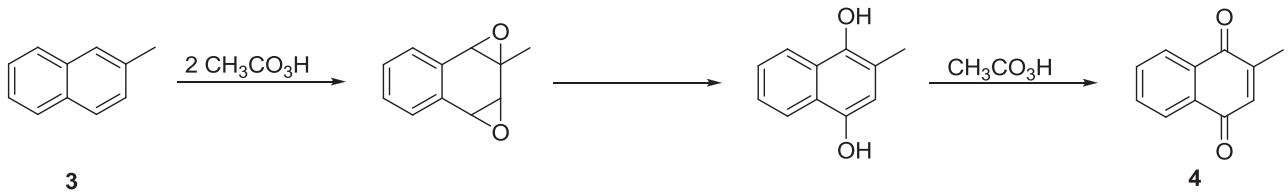
Most recently, we described an efficient oxidation of **3** using easily available iron complexes [22]. Applying an acetonitrile/water mixture the desired quinone is obtained in 89% yield, making this procedure one of the best methods up to date for the preparation of **4**.

Regarding the direct oxidation of 2,3,6-trimethylphenol (TMP) **1** to TMBQ **2** the work of Schuster et al. is noteworthy. They reported that Salcomin (a salencobalt(II) complex) catalyzed this oxidation under oxygen atmosphere to the corresponding quinone in 80–95% yield at 45 °C within 1 h [23] (Fig. 3).

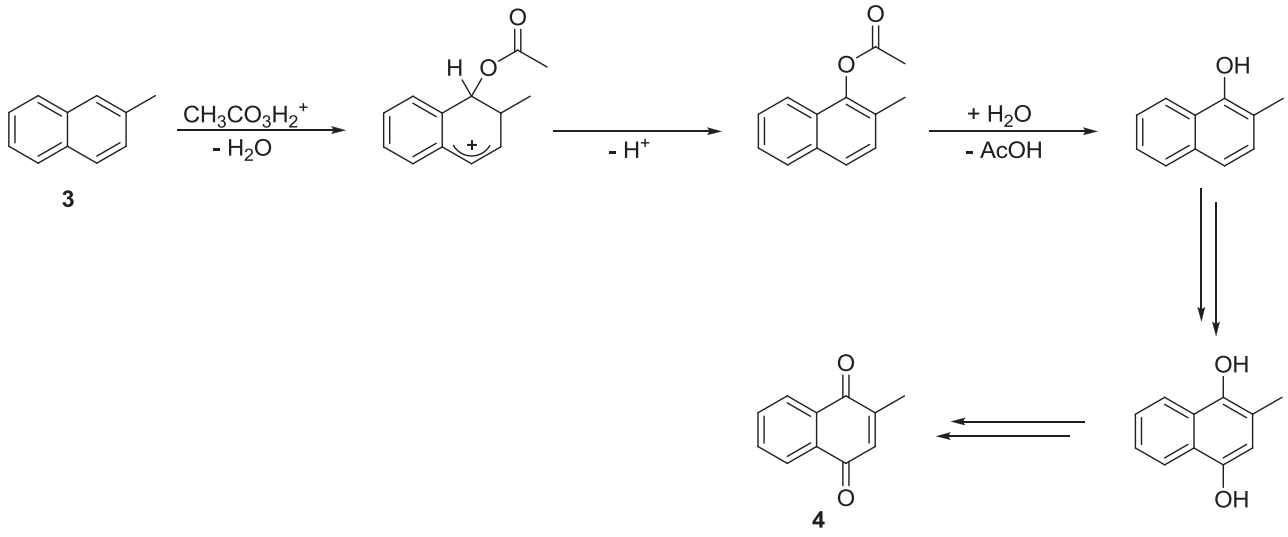
An industrial process developed by Shimizu et al. for this oxidation is performed in the presence of heteropolyacids. Apparently, the process is run in a two-phase solvent system of acetic acid and a non-polar solvent such as dichloromethane. As oxidizing agents both oxygen and hydrogen peroxide have been used. The yields for **2** achieved are in between 70% and 85% [24]. Another industrially applied method for the synthesis of TMBQ **2** is based on the use of copper (II)-chloride. Attempts to reduce the stoichiometric amounts of copper salts, led to a catalyst system consisting of $CuCl_2$ (1.5 wt%) and hydroxylamine hydrochloride (2.8 wt%) as an



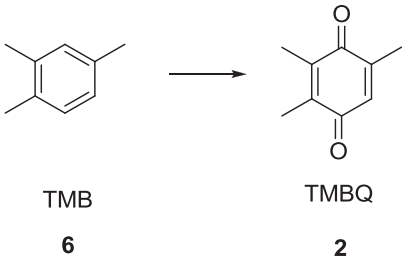
Scheme 5. Oxidation of **3** with O_2 and oxovanadium catalyst.



B: Electrophilic aromatic substitution pathway



Scheme 6. Possible reaction pathways towards vitamin K_3 according to Thiel and co-workers.



Scheme 7. Oxidation of TMB **6** to TMBQ **2**.

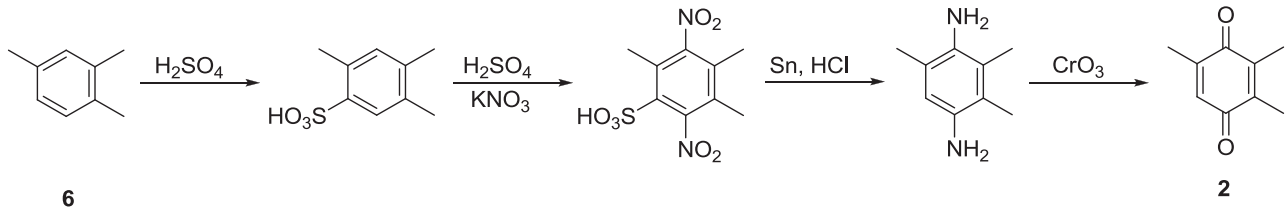
additive. Reactions of TMP performed in acetic acid resulted in a yield of 80% of **2**. However, the disadvantage of this system is the use of *tert*-BuOOH as a terminal oxidant. Conversion and yield of TMBQ using oxygen are low [7d]. Already in 1983, the Ito group developed a Ru-catalyzed reaction of TMP in acetic acid as solvent [7b]. In the presence of 1 mol% $RuCl_3$ and two equivalents H_2O_2 yields up to 90% of the desired quinine were achieved. Until to date this is still among the most effective catalytic processes; however there is no application in industry due to the high price of the catalyst. During the last years also a novel heterogeneous Ti (IV)/SiO_2-catalyst was developed by Kholdeeva et al. [7e]. Here, the oxidation of TMP with H_2O_2 in acetonitrile at 80 °C proceeded in yields up to 96% [7f].

An economically interesting alternative synthesis of **2** is based on the potential oxidation of 1,3,4-trimethylbenzene (TMB) to give TMBQ (Scheme 7).

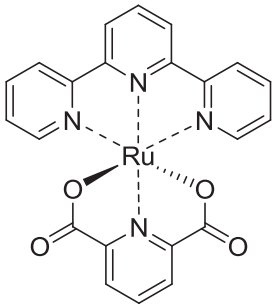
So far, this straightforward oxidation has been scarcely reported in the open literature. Although in Scheme 8 a process for the conversion of **6** to **2** is shown that has been used even on industrial scale. Unfortunately, it needed several steps before the final quinone is generated (Scheme 8).

Initially, TMB is sulfonated in the 5-position blocking it from the following nitration of the remaining aromatic positions. Subsequent reduction of the nitro groups and cleavage of the sulfonic acid are realized using stoichiometric amounts of tin in hydrochloric acid. Finally, oxidation by chromium (VI)-oxide gives the target compound resulting in an overall yield of 30% [25]. The disadvantages of this method is the four step linear synthesis as well as large amounts of waste including the highly toxic tin-and chromium compounds.

Obviously, the challenge for this substrate is the direct oxidation with benign oxidants. However, such processes have been described in literature only with moderate success, e.g. the



Scheme 8. Multistep synthesis of TMBQ **2** from TMB **6**.



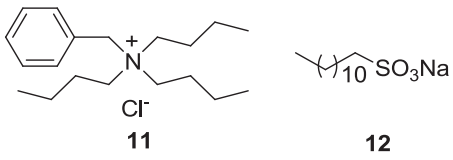
10

Fig. 4. Ru(tpy)(pydic)-catalyst employed for vitamin-K_3 synthesis.

oxidation of TMB by organic peracids in dichloromethane resulted in yields of up to 15% [7a]. By-products in this reaction are 2,3,6-trimethylphenol and 2,4,5-trimethylphenol. Oxidation with H_2O_2 in formic acid was reported by Takehira et al. in 1989 and is more environmentally friendly; however the achieved yield is also low with 16% [7c]. In general, these single-step procedures showed either low conversions and/or low selectivities to the desired product. Analogous to their MTO-catalyzed oxidation of 2-methylnaphthalene, Jacob et al. reported the reaction of TMB to TMBQ, too [26]. The reaction was run with 8 mol% MTO and a 20-fold excess of 30% H_2O_2. After 75% conversion a yield of 50% of TMBQ was obtained. In addition, the corresponding hydroquinone was generated with up to 25%.

A drawback of most arene oxidations to quinones is the use of acidic solvents, *i.e.* acetic acid, or the necessity to add inorganic acid catalysts causing environmental pollution and carrying corrosion issues with it, especially on larger scale. In general, high concentrations of hydrogen peroxide (50–83%) are needed in order to achieve acceptable yields of menadione or TMBQ from its aromatic precursors [27]. Due to the explosive nature of highly concentrated hydrogen peroxide, especially in combination with metal salts, this may cause severe safety problems [19]. Thus, the development of selective arene oxidations under neutral conditions with commercially available 30% hydrogen peroxide aqueous solutions is still an important and challenging goal.

We have a long standing interest in developing novel methods for the synthesis of quinones. Around 2006, we started to explore the catalytic oxidation of arenes to give quinones [28]. Based on our experience in the synthesis of ruthenium(II) complexes with tridentate nitrogen ligands and their application in oxidation catalysis [29], we investigated the utility of such complexes in arene oxidations. In exploratory experiments, the reaction of 2-methylnaphthalene with 30% hydrogen peroxide (2.3 equiv.) in the presence of different Ru catalysts was examined (Scheme 2). To our delight 0.2 mol% of specific ruthenium complexes catalyzed the reaction at r.t. to 40 °C within 1 h in the absence of any organic solvent. Owing to solubility problems the reactions were performed with or without a catalytic amount of phase transfer agents. Among the various Ru complexes, Ru(II)(terpyridine)(2,6-pyridinedicarboxylate) **10** showed significant activity (Fig. 4).



11 12

Fig. 5. Phase transfer catalysts used for the synthesis of menadione **4**.

Apart from the desired menadione **4** also the regioisomeric product **5** is formed in minor amount (Table 1, entry 1). At a conversion of 67% the ratio of quinones **4** and **5** was 2.8:1 leading to isolated yields of 51%. In addition, benzoic acids are formed as side-products in minor amount. Next, the easily accessible catalyst **10** was investigated in more detail. Applying only a slight excess of hydrogen peroxide (1.2 equiv.) excellent chemoselectivity (86%) was observed (Table 1, entry 2). It is noteworthy that the starting material can be recovered and re-used for this oxidation protocol. Increasing the catalyst concentration resulted in an increase of the unproductive decomposition of hydrogen peroxide. Hence, an excess of hydrogen peroxide has to be used in order to get comparable yields (Table 1, entries 8–9). The addition of 1–2.5 mol% of phase transfer catalysts **11** and **12** (Fig. 5) resulted in a significant improvement of the catalyst activity (Table 1, entries 3, 5, 7, 10). For example 2-methylnaphthalene was completely consumed in 20 min in the presence of only 0.2 mol% Ru catalyst **10** and 1 mol% of sodium dodecyl sulfate to give naphthoquinones **4** and **5** in 56% isolated yield (TOF = 840 h^{-1}). Interestingly, both cationic and anionic phase transfer catalysts showed a similar rate increase. To demonstrate the usefulness of this protocol the most effective catalyst systems, 0.2 mol% **10** + 2.5 mol% **11** (catalyst system **A**), and 0.2 mol% **10** + 1 mol% **12** (catalyst system **B**) were further employed in the oxidation of electron-rich and electron-poor naphthalenes.

In, 2010 we described an improved Ru-catalyzed oxidation of 2-methylnaphthalene with increased yields and (regio)selectivities as well as the extension of this procedure towards other arenes and phenols [30]. Here, the oxidation of **3** using 0.5 mol% of catalyst **10** and 3.5 equiv. of hydrogen peroxide (<30 wt%) was explored in more detail (Scheme 2). First, the reaction was performed in different polar solvents, especially alcohols, to optimize the solubility of complex **10** (Table 2) [31]. Hence, we propose the formation of a solvent coordinated active catalyst species. Among the different protic solvents the selectivity towards **4** is increasing with growing

Table 1
Selective oxidation of 2-methylnaphthalene with different Ru catalysts.[a]

Entry	Cat. (mol%)	PTC (mol%)	T (°C)	**1**/H_2O_2	Conv. (%)[b]	Yield (%)[c]	Sel. (%)	**4**:**5**[d]
1	**10** (0.2)	–	40	1:7	67	51	77	2.8:1
2	**10** (0.2)	–	40	1:3.6	58	50	86	2.9:1
3	**10** (0.2)	**11** (2.5)	40	1:3.6	70	54	77	3.2:1
4	**10** (0.2)	–	40	1:7	67	51	77	3.1:1
5	**10** (0.2)	**11** (2.5)	40	1:7	88	64	73	3.0:1
6	**10** (0.2)	–	40	1:10	65	49	75	2.9:1
7	**10** (0.2)	**11** (2.5)	40	1:10	97	52	54	3.0:1
8	**10** (0.5)	–	40	1:7	73	56	77	2.9:1
9	**10** (1.0)	–	40	1:10	58	41	71	2.9:1
10	**10** (0.2)	**12** (1)	r.t.	1:3.6	99	56	56	2.8:1

[a] 1 mmol starting material, 0.5 mL H_2O.
[b] Conversion was determined by GC.
[c] Isolated yield of quinones **4** and **5**.
[d] The ratio between products **4** and **5** was determined by GC and ^{1}H NMR.

Table 2
Oxidation of 2-methylnaphthalene: influence of different polar solvents on yield and selectivity.[a]

Entry	Solvent	Conversion (%)[b]	Yield **4** + **5** (%)[b]	Selectivity **4** (%)[b]	Ratio **4:5**[b]
1	Methanol	92	35	35	10:1
2	Ethanol	99	36	34	15:1
3	*n*-Propanol	100	27	25	11:1
4	*n*-Butanol	100	27	23	05:1
5	*t*-Amyl alcohol	81	14	15	08:1

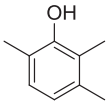
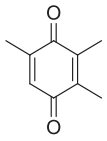
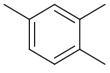
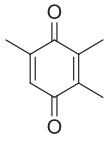
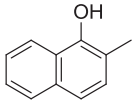
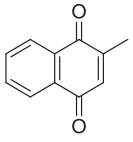
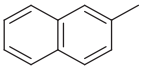
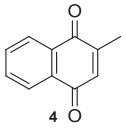
[a] Reaction conditions: 0.5 mmol **3**, 0.5 mol% **A**, 3.5 equiv. H_2O_2 (30 wt%), addition time 1 h, 20 °C.
[b] Determined by GC using dodecane as internal standard.

Table 3
Oxidation of 2-methylnaphthalene: testing of different parameters and optimizing the reaction conditions.[a]

Entry	Cat. (mol%)	*T* (°C)	H_2O_2/**3**	*t* (h)	Conv. (%)[b]	Yield **4** + **5** (%)[b]	Select. **4** (%)[b]	Ratio of **4**:**5**[b]
1	0.5	20	3.5	1	92	36	35	10:1
2	0.5	20	4.4	1	100	40	36	9:1
3	0.5	20	7.7	1	100	42	38	8:1
4	0.5	20	11	1	100	39	34	8:1
5	0.5	0	3.5	1	90	31	31	10:1
6	0.5	40	3.5	1	83	35	39	10:1
7	0.1	20	3.5	1	15	2	13	–
8	1	20	3.5	1	100	49	44	9:1
9	2	20	3.5	1	100	49	44	9:1
10	0.5	20	3.5	0	97	39	36	10:1
11	0.5	20	3.5	24	100	34	32	14:1
12[c]	0.5	20	3.5	1	93	34	33	11:1
13[c]	0.5	20	3.5	24	99	47	42	9:1
14[c]	1	20	4.4	24	100	67	58	6:1
15[c]	**1**	**40**	**4.4**	**7**	**100**	**74 (70)**[d]	**60 (58)**[d]	**5:1**[e]
16[c]	1	40	4.4	3	100	71	57	4:1

[a] Reaction conditions: 0.5 mmol **3**, MeOH (9 mL).
[b] Determined by GC using dodecane as internal standard.
[c] The substrate was solved in MeOH (1 mL) and added to the solution by a syringe pump.
[d] Isolated yield.
[e] Determined by ^{1}H NMR.

Table 4
Iron-catalyzed selective oxidation of arenes to the corresponding quinones under optimized conditions.

Entry[a]	Substrate	Major product	Cat.	Conv. (%)[a]	Select. (%)[a,b]
1			**C**	>99	79 (77)[c]
2			**C**	69	38
3			**C**	>99	55
4			**D**[e]	>99	55[d]

[a] Conversion and yield were determined by GC analysis after 1.5 h, using dodecane (0.44 mmol) as internal standard.
[b] Selectivity refers to the chemoselectivity of quinone from arene.
[c] Isolated yield.
[d] 2-Methyl-1,4-naphtho-quinone **4**: 44% yield, 6-methyl-1,4-naphtho-quinone **5**: 11% yield.
[e] Catalytic system **C**: select.: 36%, **4**:**5** ~ 3:1.

polarity. In methanol and ethanol up to 35% chemoselectivity was obtained (Table 2, entries 1 and 2).

The ratio of quinones **4** and **5** increased up to 15:1 (Table 2, entry 2) and is significantly higher compared to our previous work [28]! For the further experiments methanol was selected as the solvent of choice. Next, we investigated the influence of the concentration of hydrogen peroxide (Table 3, entries 1–4) and catalyst (Table 3, entries 7–9) as well as the temperature (Table 3, entries 5 and 6) on the reaction system. After that, we found out that changing the time for addition of the hydrogen peroxide did not affect the reaction significantly (Table 3, entries 10 and 11). To our delight, continuous addition of the substrate by a separate syringe pump parallel to the hydrogen peroxide resulted in a significant increase in the selectivity (Table 3, entry 13). Hence, oxidation of 2-methylnaphthalene in the presence of 1 mol% catalyst **10** and 4.4 equiv. hydrogen peroxide at room temperature proceeded smoothly to yield 58% of **4** (Table 3, entry 14). To increase the selectivity further on and to shorten the reaction time, the temperature was raised to 40 °C, producing a maximum yield of 74% of the corresponding quinones, respectively (Table 3, entry 15)!

An additional cutback of the reaction time appears to be possible without loss of selectivity (Table 3, entry 16). To explore a possible reuse of the catalyst, the reaction mixture was separated by column chromatography and a second run was performed with the catalyst, but showed no reactivity at all. After having optimized the oxidation of 2-methylnaphthalene, we were interested in the synthesis of other arenes and monohydroxylated arenes especially of TMPQ **2**. To our delight, yields up to 83% were achieved for the oxidation of TMP **1** to **2**. More specifically, 2-methyl-1-naphthol, a possible intermediate in the oxidation of **3** towards **4** [19], is oxidized in a yield of 78%.

Based on our work in ruthenium-catalyzed oxidation of arenes to the corresponding quinones, we asked ourselves whether iron complexes might be also suitable for this task. Evidently, iron is an ideal candidate for catalysis, because of its abundant availability and its relative low toxicity compared to precious metals [32–34]. In addition, iron is involved in manifold biological systems as fundamental key element. Based on the development of iron-catalyzed epoxidations [35], we applied a three component catalyst system consisting of $FeCl_3 \cdot 6H_2O$, pyridine-2,6-dicarboxylic acid (H_2Pydic), and different benzylamines for the oxidation of TMP with hydrogen peroxide [22].

In preliminary tests we discovered that TMP is indeed smoothly oxidized in the presence of different iron catalysts. Best results are obtained in *t*-amyl alcohol as solvent with 7.5 mol% catalyst ($FeCl_3 \cdot 6H_2O$/H_2Pydic/amine = 1/1/2.2) and 4 equiv. of H_2O_2 (30%) at 0 °C. Notably, the co-ligand (amine) controlled the chemoselectivity to a major extent. However, the combination of $FeCl_3 \cdot 6H_2O$/H_2Pydic/*n*-butylbenzylamine (catalyst system **C**) provided the best chemoselectivity (79%) (Table 4, entry 1).

Next, we tested the optimized catalyst system **C** in the oxidation of more challenging non-activated arenes. Here, as an industrially important benchmark system the reaction of 2-methylnaphthalene to vitamin K_3 was also investigated. Under the previous conditions (see above) only moderate selectivity was obtained for 2-methylnaphthalene (36%). Thus, to improve the selective oxidation for this substrate, we re-optimized the catalytic system. To our delight, it was possible to reduce the catalyst loading to 2.5 mol% Fe and the amount of oxidant to 3.5 equiv. and still smooth oxidation was observed when working at room temperature instead of 0 °C. Best results were obtained in the presence of $FeCl_3 \cdot 6H_2O$/H_2Pydic/benzylamine = 1/1/2.2 (catalyst system **D**), when a second loading of the catalyst and H_2O_2 was added after 30 min (1.25 mol% and 1.8 equiv., respectively). It is evident that the chemoselectivity for the oxidation of 2,3,6-trimethylbenzol (TMB) to TMBQ (Table 3, entry 2) is lower compared to the oxidation of TMP, which is an intermediate in the former reaction. 2-Methyl-1-naphthol (Table 3, entry 3) and 2-methylnaphthalene (Table 3, entry 4) gave the desired quinones, both in 55% yield. However, in the latter oxidation two regioisomers **4** and **5** in a 4:1 ratio are formed, which is similar to other metal-catalyzed oxidations [8,13b,18–21,36].

In summary, various interesting methods for the oxidation of arenes to quinones have been established in the past decades. Several catalytic routes were developed using molecular oxygen, percarboxylic acids or hydrogen peroxide as more benign oxidants to replace stoichiometric amounts of chromium [36b], cerium [36c], or manganese [36a] salts. With respect to the catalyst a range of metal complexes based on palladium [1,13], rhenium [14], vanadium [18], chromium [36], cerium [37], ruthenium [28,30] and iron [22] have been applied in such oxidations. Moreover, phthalocyanine [21], and porphyrin [20] complexes as well as zeolites [36d] were used in the catalytic oxidation of 2-methylnaphthalene to menadione. In addition, copper [7d,9], cobalt [23], ruthenium [7b,28,30], titanium [7f], rhenium [26], chromium [25] and iron [20–22] complexes were used in the catalytic oxidation of TMB or TMP to TMBQ. Nevertheless all these catalytic developments still improvements are needed in order to realize future industrial applications in this area. Despite the significant disadvantages of existing industrial processes, until now no catalytic procedure has been developed to replace these processes. Although sometimes high yields are obtained, catalysts are to expensive or low turnover numbers are achieved. Furthermore, the oxidant might not be save enough for large-scale synthesis. In this respect, further research is encouraged in order to provide "real" sustainable processes for this important class of quinones.

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