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Iron Porphyrin-Catalyzed Oxidation of 1,2-Dimethoxyarenes: A Discussion of the Different Reactions Involved and the Competition between the Formation of Methoxyquinones or Muconic Dimethyl Esters

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This paper describes the oxidation of an α,β-diarylpropane lignin dimer model and other dimethoxyarenes by several iron porphyrin-based biomimetic systems. From 1-(3,4-dimethoxyphenyl)-2-phenylpropanol (**1**), three types of products are identified: the 3,4-dimethoxybenzaldehyde derived from the C_α–C_β cleavage of the propyl side chain and either quinones or muconic dimethyl esters resulting from oxidations at the level of the dimethoxyaryl group. The selectivity of the reaction is discussed with respect to the nature and reactivity of the high-valent iron–oxo species formed upon reaction of the oxidants, H_2O_2 or magnesium monoperoxyphthalate (MMP), with the iron porphyrins. Fe(TF_5PP)Cl-catalyzed oxidation of **1** by H_2O_2 in an aprotic medium (CH_3CN/CH_2Cl_2), yields a clean "lignin peroxidase-like" reaction with selective formation of the aldehyde. In an aqueous buffered solution, MMP oxidation of *para*-substituted 1,2-dimethoxyarenes catalyzed by an iron tetrakis(pentafluorophenyl)-β-tetrasulfonatoporphyrin, Fe(TF_5PS_4P), clearly depends on the electronic properties of the *para*-substituent. The reaction is selective for *para*-quinone formation in the case of an electron-releasing group and for muconic dimethyl ester formation in the case of an electron-withdrawing group.

Introduction

A number of papers have been published recently on the oxidation of alkenes and alkanes by Fe(III) or Mn(III) porphyrin-based systems that mimic hemoproteins like cytochrome P450.[1] However, much less information is presently available on the oxidation of electron-rich aromatic compounds by these biomimetic systems. There are some papers on the oxidation of anisole,[2] but because of the industrial importance of lignin degradation, most of the papers published recently refer to the oxidation of simple aromatic compounds used as models of lignin moieties. Furthermore, two hemoproteins, lignin peroxidase (LiP)[3] and manganese peroxidase (MnP),[4] involved in lignin degradation by the white rot fungus *Phanerochaete chrysosporium* have been characterized. The main reaction catalyzed by these two enzymes is the C_α–C_β cleavage of the propyl side chain of α,β-diaryl or α-aryl-β-aryloxy moieties of the lignin polymer.[5]

Biomimetic systems using Fe(III) porphyrins[6,7] were found to be efficient both for lignin degradation[7b,9] and for the oxidation of α,β-diaryl propane or α-aryl-β-(aryloxy)propane derivatives used as models of lignin moieties (called hereafter lignin dimer models, e.g., **1**[8] (Figure 1)). However, in all the studies reported on the oxidation of such dimer models by iron porphyrins, the extent of C_α–C_β cleavage was generally relatively low (below 20%), although the substrate was completely consumed. Moreover, very few data are presently available on the nature and ratio of the various products formed upon iron porphyrin biomimetic oxidation of these lignin dimer models or of electron-rich aromatic compounds. Actually, under the conditions reported, the oxidation products derived from those substrates are further oxidized.

This paper describes the oxidation of compound **1** and other dimethoxyarenes by several iron porphyrin-based biomimetic systems and shows that the oxidation of **1** leads to products coming from four main reactions: (i) the C_α–C_β cleavage of the propyl side chain, (ii) the cleavage of a phenyl-C_α bond, (iii) the oxidation of the dimethoxyaryl nucleus with the formation of a quinone, and (iv) the opening of the dimethoxyaryl ring with formation of a muconic acid dimethyl ester. The ratio of these products is controlled by the nature and reactivity of the high-

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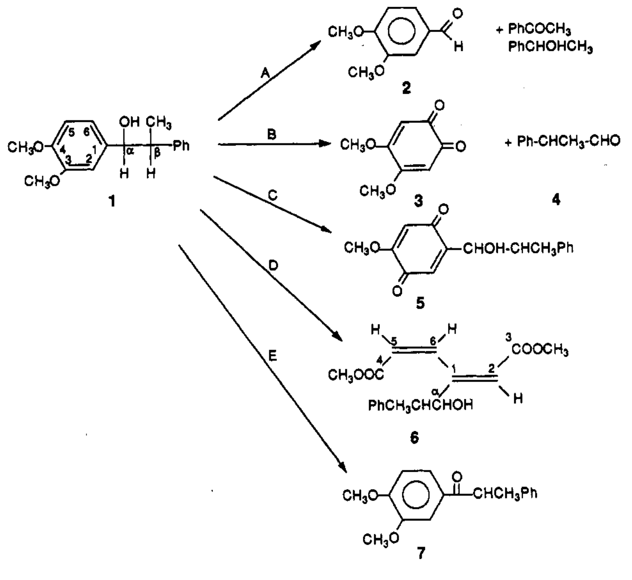
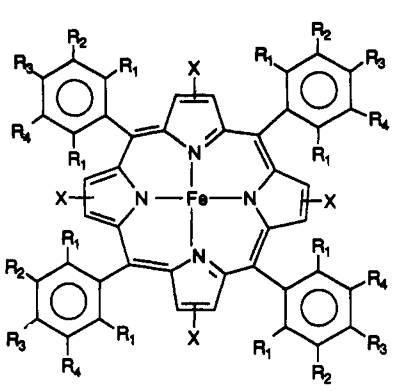


Figure 1. The reactions involved in the oxidation of the lignin dimer model 1.

valent iron–oxo active species formed by reaction of the oxidant with the iron porphyrin catalyst. The paper also shows that, in a more general manner, 1,2-dimethoxyarenes are oxidized either to *para*-quinones or to muconic dimethyl esters depending on the nature of the substituents present on the dimethoxyarene ring

Results

Oxidation of the Lignin Dimer Model 1. For most reactions, robust oxidation-resistant Fe(III) *meso*-tetrakis(pentafluorophenyl)porphyrins were used as catalysts. Two kinds of reaction media were employed: (i) a mixture of organic solvents, either CH_2Cl_2/CH_3CN (1:1) or CH_2Cl_2/CH_3OH (9:1) or (ii) a pH 3 tartrate buffer containing CH_3CN to solubilize the substrate. The first set of reaction conditions have frequently been used for several biomimetic oxidations.[1] In organic solvents, H_2O_2 or C_6F_5IO was the oxygen atom donor and $Fe(TF_5PP)Cl$[10] or Fe(TDCPP)Cl[10] was the catalyst. The second set of conditions have generally been used for reactions catalyzed by lignin peroxidase, the maximum activity being observed around pH 3.[5] Under aqueous conditions, the water-soluble oxidant was H_2O_2 or magnesium monoperoxyphthalate (MMP), and the catalyst was most often the water-soluble iron porphyrin obtained by sulfonation of TF_5PPH_2 by oleum followed by insertion of iron. As previously described,[11] this sulfonated porphyrin, [$Fe(III)(TF_5PS_4P)$, Figure 2] bears one SO_3H substituent on each pyrrole ring and exists as a mixture of four isomers (see the Experimental Section). Its catalytic activity in the presence of MMP was compared with those of the two previously described water-soluble iron porphyrin catalysts, Fe(III)(TSPP)[10] and Fe(III)(TDCSPP),[10] obtained by sulfonation of the *meso*-aryl groups of Fe(TPP) and Fe(TDCPP), respectively (Figure 2).



X=H,H, R_1=Cl, R_2=R_3=R_4=H, Fe(TDCPP).
X=H,H, R_1=R_2=R_3=R_4=F, $Fe(TF_5PP)$.
X=H,H, R_1=R_3=CH_3, R_2=H, Fe(TMP).
X=H,H, R_1=Cl, R_2=R_3=H,R_4=SO_3^-, Fe(TDCSPP).
X=H,H, R_1=R_2=R_4=H, R_3=SO_3^-, Fe(TSPP).
X=H,SO_3^-, R_1=R_2=R_3=R_4=F, $Fe(TF_5PS_4P)$.

Figure 2. The structures of the various iron porphyrins used in this work.

In all the experiments, the starting concentrations of the substrate and the catalyst were 2.5×10^{-2} M and 5×10^{-4} M, respectively (these values correspond to a substrate/catalyst molar ratio of 50). Progressive addition of the oxidant was done until the substrate was completely consumed. The reaction mixtures were studied by ^1H NMR in the presence of an internal standard. ^1H NMR spectra of the oxidation products were compared with those of authentic samples, which were commercially available or prepared either by described methods or by isolation from the oxidation reaction of 1 as indicated in the Experimental Section. The products observed in the oxidation of 1 by the biomimetic systems used in this study were derived from the five reactions depicted in Figure 1: (i) the C_α–C_β cleavage of 1 leading to veratraldehyde **2** and a mixture of acetophenone and 1-phenylethanol, (ii) the C_1–C_α cleavage of 1 leading to *o*-quinone **3** and 2-phenylpropanal **4** (it is noteworthy that **3** and **4** were always formed in almost equimolar amounts (Table I)), (iii) the oxidation of the dimethoxyphenyl group of 1 with formation of *p*-quinone **5**, (iv) the opening of the dimethoxyphenyl group of 1 with formation of muconic dimethyl ester **6**, and (v) the oxidation of the alcohol function of 1 leading to ketone **7**.

As shown in Table I, oxidation of 1 by H_2O_2 catalyzed by $Fe(TF_5PP)Cl$ or Fe(TDCPP)Cl in an aprotic medium afforded the highest yields of C_α–C_β cleavage (50 and 60% from experiments 1 and 2 of Table I). It is noteworthy that C_α–C_β cleavage was the only reaction observed with $Fe(TF_5PP)Cl$. With Fe(TDCPP)Cl, it was also the major reaction, but some oxidation of 1 to ketone **7** also occurred. In fact, formation of **7** was observed only in this case. When tetramesitylporphyrin–iron complex Fe(TMP)Cl[10] was used, compound 1 was not oxidized, and the catalyst was completely bleached. When the reaction was carried out with the same oxidant (H_2O_2) and with $Fe(TF_5PP)Cl$ as the catalyst but in a protic medium (experiment 3), the major reaction became the formation of quinone **5**, and **2** became a minor product. Interestingly, similar product ratios were observed with H_2O_2 in CH_2Cl_2/CH_3OH and

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(10) Abbreviations: iron(III) *meso*-tetrakis(pentafluorophenyl)porphyrin chloride, $Fe(TF_5PP)Cl$; iron(III) *meso*-tetrakis(2,6-dichlorophenyl)porphyrin chloride, Fe(TDCPP)Cl; iron(III) *meso*-tetrakis(4-sulfonatophenyl)porphyrin, $[Fe(TSPP)]^+$; iron(III) *meso*-tetrakis(2,6-dichloro-3-sulfonatophenyl)porphyrin $[Fe(TDCSPP)]^+$; iron(III) *meso*-tetrakis(pentafluorophenyl)-β-tetrasulfonatoporphyrin $[Fe(TF_5PS_4P)]^+$; iron(III) *meso*-tetrakis(2,4,6-trimethylphenyl)porphyrin, Fe(TMP)Cl.

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Table I. Oxidation of 1 Catalyzed by Various Iron(III) Porphyrins

reagents[a] (equiv)	solvent (ratio)	experiment[b]	% yield 2	3	4	5	6	7	1
Fe(TDCPP)Cl/H_2O_2 (10)	CH_2Cl_2/CH_3CN (50/50)	1	50					20	
Fe(TF$_5$PP)Cl/H_2O_2 (3)	CH_2Cl_2/CH_3CN (50/50)	2	60						10
Fe(TF$_5$PP)Cl/H_2O_2 (4)	CH_2Cl_2/CH_3OH (90/10)	3	3	3	3	40	15		6
[Fe(TF$_5$PS$_4$P)]$^+$/H_2O_2 (8)	tartrate/CH_3CN (75/25)	4	30	4	4	25	5		
[Fe(TF$_5$PS$_4$P)]$^+$/MMP (3)	tartrate/CH_3CN (75/25)	5	5[c]			55			
[Fe(TDCSPP)]$^+$/MMP (3)	tartrate/CH_3CN (75/25)	6	25 (20)[d]			20			
[Fe(TSPP)]$^+$/MMP (3)	tartrate/CH_3CN (75/25)	7	20	3	3	22			
Fe(TF$_5$PP)Cl/C_6F_5IO (3)	CH_2Cl_2	8	4	8	8	26	9		

[a] For all reactions, the relative starting concentrations of 1 and catalyst were 2.5×10^{-2} M and 5×10^{-4} M. The relative ratio of oxidant to 1 is indicated in parentheses: Yields were determined by ^{1}H NMR analysis is the presence of 2,6-dichlorobenzaldehyde as an internal standard. [b] Run number of experiment. [c] Five percent of muconic diester 14 derived from 2. [d] Twenty-five percent of 2 and twenty percent of the acid derivative.

Table II. Oxidation of Substituted 1,2-Dimethoxyarenes Catalyzed by Fe(III)(TF$_5$PS$_4$P)

substrate[a]	X	catalyst[b]	oxidant[c]	products (yield, %)	experiment[d]
8	CH_2OH	a	MMP (2)	2 (2), 11 (55)	9
		a	H_2O_2 (8)	2 (8), 11 (50)	10
		b	MMP (3)	2 (5), 11 (55)	11
		c	MMP (3)	2 (9), 11 (50)	12
9	*t*-Bu	a	MMP (3)	12 (85)	13
10	$COCH_3$	a	H_2O_2 (3)	10 (17), 13 (20)	14
		a	MMP (3)	10 (8.5), 13 (35)	15
		a	MMP (3.5)	10 (0), 13 (35)	16
2	CHO	a	H_2O_2 (3)	2 (30), 14 (17)	17
		a	MMP (3)	2 (15), 14 (28)	18
			MMP (3.5)	2 (0), 14 (32)	19
7	$COCHCH_3Ph$	a	H_2O_2 (3)	7 (6), 15 (10)	20
		a	MMP (2)	7 (12), 15 (28)	21
		a	MMP (2.5)	7 (0), 15 (30)	22

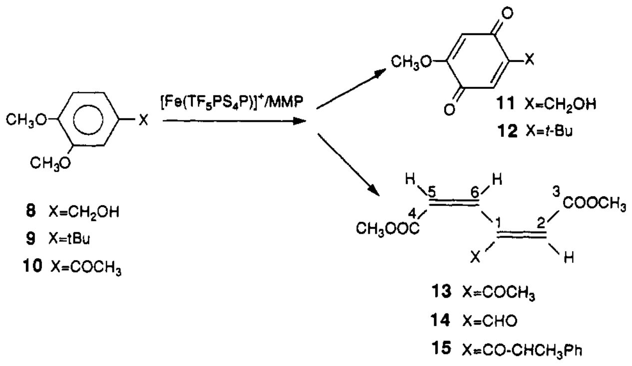
[a] Experimental conditions: 5×10^{-5} mol of substrate, 10^{-6} mol of catalyst in 2 mL of a 75/25 mixture of a pH 3 tartrate buffer and CH_3CN. MMP or H_2O_2 was added as 0.4 N aqueous solution. Yields were determined by ^{1}H NMR in the presence of 2.6-dichlorobenzaldehyde as an internal standard. [b] Catalysts: a refers to [Fe(TF$_5$PS$_4$P)]$^+$, b to [Fe(TDCSPP)]$^+$, and c to [Fe(TSPP)]$^+$. [c] The oxidant to substrate molar ratios are indicated in parentheses. [d] Run number of experiment.

with C_6F_5IO in CH_2Cl_2 (experiments 3 and 8 of Table I); Fe(TF$_5$PP)Cl was used as the catalyst in both conditions.

With MMP as the oxidant in an aqueous medium, different results were obtained with the three water-soluble catalysts used. The highest chemoselectivity was observed in the case of Fe(III)(TF$_5$PS$_4$P) with the almost exclusive formation of quinone 5 (experiment 5 of Table I). The only minor product (5%) observed under these conditions was a muconic diester derived from further oxidation of 2 (see next paragraph). With the two other catalysts, Fe(TSPP) and Fe(TDCSPP), the products deriving from pathway A (Figure 1) were much more important, and these products became the major ones with Fe(TDCSPP) (experiment 6 of Table I).

Oxidation of Dimethoxyarenes Bearing Either an Electron-Releasing or an Electron-Withdrawing Additional Substituent. The good yields of quinone 5 obtained from the chemoselective oxidation of 1 observed with the MMP–Fe(TF$_5$PS$_4$P) system prompted us to study the oxidation of several dimethoxyarenes bearing either an electron-donating or an electron-withdrawing substituent under the same conditions (CH_3CN, tartrate buffer pH 3). For the sake of comparison, similar experiments were performed in the presence of MMP or H_2O_2 with Fe(III)(TSPP) or Fe(III)(TDCSPP) as catalysts. Oxidation of dimethoxyarenes bearing an electron-donating substituent, such as veratryl alcohol (8) and 4-*tert*-butylveratrole (9), by MMP in the presence of Fe(III)(TF$_5$PS$_4$P) was selective and gave almost exclusively *p*-quinones 11 and 12 (55 and 85% yields) (experiments 9 and 13 of Table II) (Scheme I), which were the equivalents of *p*-quinone 5 derived from oxidation of 1. In fact, these reactions were used to isolate and completely characterize quinones 5, 11, and 12 (their spectroscopic properties are described in the Experimental Section). We obtained similar results with 8 by using either Fe(III)(TSPP) or Fe(III)(TDCSPP) instead of Fe(III)(TF$_5$PS$_4$P) or by using H_2O_2 instead of MMP, except that greater amounts of minor product 2 were formed (Table II).

Scheme I



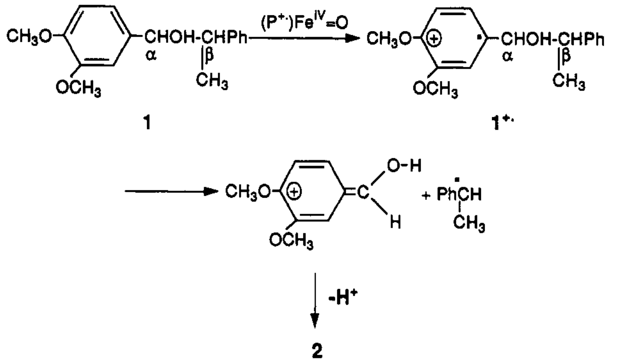
Oxidation of 1,2-dimethoxyarenes bearing an electron-withdrawing group (such as 10 (X = $COCH_3$), 2 (X = CHO), or 7 (X = $COCHCH_3Ph$)) by MMP and Fe(TF$_5$PS$_4$P) led to the corresponding muconic dimethyl esters 13, 14, and 15 (experiments 15, 18, and 21 of Table II) (Scheme I). These compounds were the only products extracted with CH_2Cl_2 from the reaction mixture at the end of the reaction except for small amounts of the starting substrate. After progressive addition of MMP in order to completely consume the starting substrate and extraction of the reaction mixture with CH_2Cl_2, the muconic diesters were

Table III. ^{1}H NMR Data for Muconic Diesters[a] $CH_3OCOCH_ACH_BCXCH_CCOOCH_3$

compound	X	H_A	H_B	H_C	OCH_3	side chain X
14[36]	CHO	6.17 (dd, J_{AB} = 12, J_{AC} = 0.65)	7.04 (dd, J_{BC} = 2.2)	6.55 (dd)	3.78 (3H, s); 3.65 (3H, s)	9.51 (1H, s)
13	$COCH_3$	6.10 (dd, J_{AB} = 11.7, J_{AC} = 1)	7.19 (dd, J_{BC} = 2.2)	6.44 (dd)	3.74 (3H, s), 3.64 (3H, s)	2.40 (3H, s)
15	$COCHCH_3Ph$	6.07 (dd, J_{AB} = 11.6, J_{AC} = 0.8)	7.03 (dd, J_{BC} = 2.2)	6.43 (dd)	3.63 (6H, s)	1.39 (3H, d, J = 6.8), 4.16 (1H, J = 6.8), 7.09, 7.3 (5H, massif)
6	$CHOHCHCH_3Ph$	6.05 (d, J_{AB} = 10)	6.96 (dd, J_{BC} = 2)	6.20 (d)	3.28 (3H, s), 3.35 (3H, s)	1.25 (3H, d, J = 8), 2.89 (1H, q, J = 8), 7.2–7.4 (5H, massif)

[a] ^{1}H NMR analysis in $CDCl_3$: δ in ppm relative to TMS; J in hertz.

Scheme II

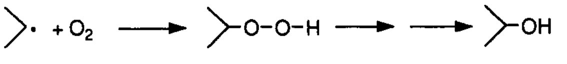


obtained in a pure state in 30–35% yields. They were easily purified and characterized by ^{1}H NMR (Table III), mass spectrometry, and elemental analysis. Using H_2O_2 instead of MMP also afforded the muconic diesters but in lower yields (Table II). It is noteworthy that the formation of muconic diesters was only observed with the Fe(III)(TF_5PS_4P) catalyst. Under identical conditions, Fe(III)(TSPP) was completely bleached upon addition of a few equivalents of MMP. With Fe(III)(TDCSPP) and MMP, veratraldehyde (**2**) was also oxidized into the corresponding acid, as previously reported,[7a] and 3,4-dimethoxyacetophenone (**10**) was partly consumed but without formation of any oxidation product that could be extracted with CH_2Cl_2.

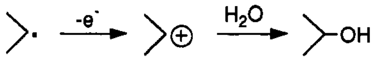
Discussion

Oxidation of the Lignin Dimer Model 1 by LiP. The LiP-catalyzed oxidation of **1** by H_2O_2 is known to lead to products like **2** derived from the C_α–C_β cleavage.[8] The mechanism generally accepted for this reaction involves an electron transfer from **1** either to LiP compound I, described as an iron(IV) porphyrin cation radical ($P^{+\bullet}$)-Fe(IV)=O, or to LiP compound II, which is an iron (IV)–oxo complex (P)Fe(IV)=O.[5] As in all peroxidase reactions, the derived cation radical $1^{+\bullet}$ [12] is formed far away from the Fe=O species and cannot undergo any oxygen atom transfer from it.[13] Therefore, $1^{+\bullet}$ undergoes a β-scission with cleavage of its C_α–C_β bond and formation of the $PhCHCH_3$ radical and a cation that affords veratraldehyde (**2**) after loss of a proton (Scheme II).

Oxidation of 1 by C_6F_5IO Catalyzed by Fe(III) Porphyrins. A high-valent iron–oxo intermediate similar to peroxidase compound I is formed upon reaction of iodosoarenes such as C_6F_5IO with Fe(III) porphyrins.[1a,14] Upon reaction of **1** with such a ($P^{+\bullet}$)Fe(IV)=O species formed from Fe(III)(TF_5PP) and C_6F_5IO (experiments 8 of Table I), $1^{+\bullet}$ should be produced in close proximity to a (TF_5PP)Fe(IV)=O intermediate. Under these conditions, $1^{+\bullet}$ may undergo a C_α–C_β cleavage, as with LiP, but may also be oxidized by the Fe(IV)=O intermediate with a possible transfer of an oxygen atom. Such a direct combination between $1^{+\bullet}$ and Fe(IV)=O is probably the origin of oxidized products **5**, **3**, **4**, and **6** observed in experiment 8 of Table I. However, there are a priori two other ways to introduce an oxygen atom: (i) the reaction of the radical with dioxygen and further decomposition of the hydroperoxide (eq 1) and (ii) a one-electron oxidation



(1)



(2)

of the radical into a cation by the Fe(IV)=O species followed by reaction with water (eq 2). Reaction with O_2 can be ruled out since most reactions leading to quinones or muconic diesters described in this work gave identical results under aerobic and anaerobic conditions. The two-electron transfer from the substrate to the ($P^{+\bullet}$)Fe^{IV}=O species (eq 2) does not seem likely if one considers data coming from LiP, which is unable to directly produce quinones such as **5** or muconic derivatives in the absence of dioxygen.[5] On the basis of these results an oxygen atom transfer from the Fe(IV)=O species to $1^{+\bullet}$ or its analogues seems to be the most feasible explanation for the formation of quinones and muconic diesters by oxidation of dimethoxyarenes.

Formation of *p*-quinone **5** could be due to a combination of the oxygen atom of Fe(IV)=O with the C_6 radical site of the mesomeric form of $1^{+\bullet}$ (**A**, Scheme III) and the addition of H_2O at the cationic site of $1^{+\bullet}$. Elimination of CH_3OH and regeneration of the catalyst from the intermediate A_1 should lead to hydroquinone A_2, which should be further oxidized to quinone **5** by another ($P^{+\bullet}$)-Fe(IV)=O species. Preliminary $H_2{}^{18}O$-labeling experiments confirming the formation of **5** as depicted in Scheme III will be discussed in connection with the oxidation of veratryl alcohol (**8**) by MMP. A possible mechanism for the formation of minor products **3** and **4** (path B of Figure

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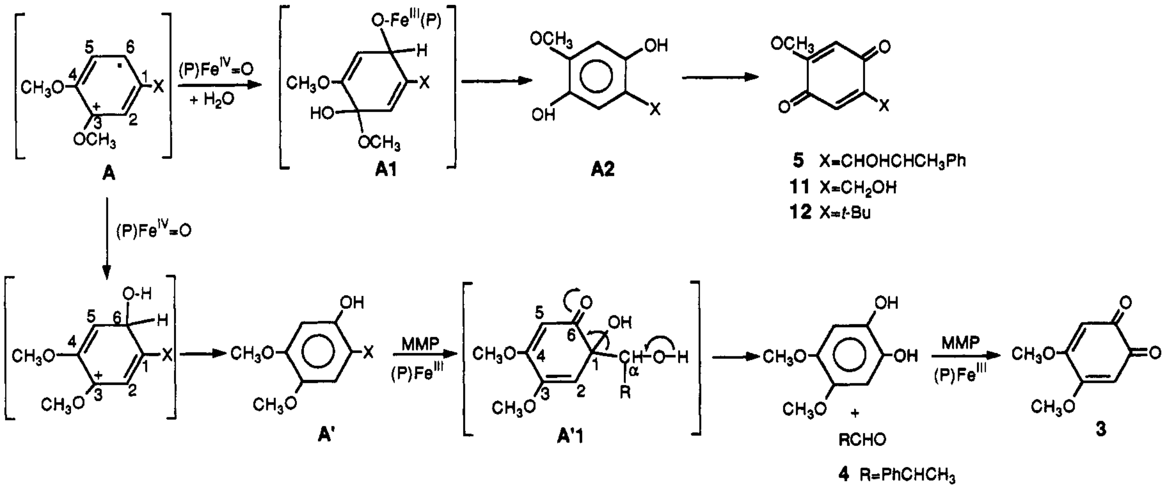
Scheme III



1) could involve an oxygen atom transfer by the Fe=O species at the C_6 radical of **A** followed by loss of a proton to give hydroxyarene **A'**. A further oxidation of **A'** at C_1 by a $(P^{+\bullet})Fe(IV){=}O$ species could lead to intermediate $\mathbf{A'_1}$, which contains a 1,2-diol at C_1 and C_α and readily cleaves its C_1–C_α bond to produce the phenylpropanal **4** and a catechol. This catechol should be further oxidized to *o*-quinone **3** (Scheme III). An intermediate analogous to $\mathbf{A'_1}$, but bearing the ketone function at position C_4 instead of C_6, was proposed to be produced by MnP[15] and to be cleaved by such a mechanism to also give an arylpropanal and a substituted hydroquinone. In agreement with this mechanism for the formation of **3** and **4**, Table I shows that **3** and **4** were always produced in identical yields. The mechanism of formation of muconic diester **6** by oxygen atom transfer to $\mathbf{1}^{+\bullet}$ will be discussed thereafter.

Oxidation of 1 by MMP Catalyzed by Fe(III) Porphyrins. There is now strong evidence in the literature that reactions of carboxylic peracids with Fe(III) porphyrins involve the formation of $(P^{+\bullet})Fe(IV){=}O$ species, equivalent to peroxidase compound I, after a heterolytic cleavage of their O–O bond, both in organic[16,17a] and in aqueous solution[17b,18d] (eq 3).

$$(P)Fe(III) + RCO_3H \rightarrow (P^{+\bullet})Fe(IV){=}O + RCO_2H \qquad (3)$$

Thus, oxidation of **1** by MMP catalyzed by the three water-soluble iron porphyrins used in this study (Table I and Figure 2) should lead to $(P^{+\bullet})Fe(IV){=}O$ active species. Table I shows that these reactions give only **2** and **5** with **2**/**5** ratio depending upon the nature of the porphyrin catalyst. The dependence of the ratio on the catalyst structure could be the result of the degree of efficiency of the control of $\mathbf{1}^{+\bullet}$ by the Fe(IV)=O species in the cage (eq 4). In the case of Fe(III)(TF_5PS_4P), this control with a transfer of oxygen from Fe(IV)=O seems to be very efficient since quinone **5** was almost the only product formed. In contrast with Fe(TSPP) and Fe(TDCSPP), the formation of **2**, which arises from a spontaneous decomposition of $\mathbf{1}^{+\bullet}$, greatly increases. The better control of $\mathbf{1}^{+\bullet}$ by the Fe(IV)=O species in the case of Fe(TF_5PS_4P) is probably due to the greater reactivity of (TF_5PS_4P)Fe(IV)=O, which is made strongly electrophilic by the presence of the four electron-withdrawing SO_3H substituents directly bound to the pyrroles.

$$\begin{tikzcd}
 & & (P)Fe(IV){=}O + \mathbf{1}^{+\bullet} \arrow[d] \\
(P^{+\bullet})Fe(IV){=}O \arrow[r, "\mathbf{1}"] & {[(P)Fe(IV){=}O\ \mathbf{1}^{+\bullet}]} \arrow[ur] \arrow[dr] & \mathbf{2} \\
 & & \mathbf{5}
\end{tikzcd} \qquad (4)$$

Oxidation of 1 by H_2O_2 Catalyzed by Fe(III) Porphyrins. Fe(III) porphyrins rapidly react with H_2O_2 and there are two possible modes of cleavage of the O–O bond: a heterolytic cleavage of this bond with formation of a $(P^{+\bullet})Fe(IV){=}O$ species[19] (eq 5) or a homolytic cleavage leading to (P)Fe(IV)=O and OH• in a cage[18,20] (eq 6). The hydroxyl radical may either diffuse out of the cage into the medium, or, as previously proposed,[18c,d,21] oxidize the iron(IV)–oxo complex to the $(P^{+\bullet})Fe(IV){=}O$ species.

$$(P)Fe(III) + H_2O_2 \longrightarrow (P^{+\bullet})Fe(IV){=}O + OH^- \qquad (5)$$

$$\begin{tikzcd}
(P)Fe(III) + H_2O_2 \arrow[r] & {} & \\
 & & (P)Fe(IV){=}O + OH^\bullet \\
 & {[(P)Fe(IV){=}O\ OH^\bullet]} \arrow[ur] \arrow[dr] & \\
 & & (P^{+\bullet})Fe(IV){=}O + OH^-
\end{tikzcd} \qquad (6)$$

In the Fe(TF_5PP)Cl-catalyzed oxidation of **1** by H_2O_2 in a protic medium (CH_2Cl_2/CH_3OH) (experiment 3 of Table I), the pattern of products observed is very similar to that obtained with the same iron porphyrin catalyst and C_6F_5IO (experiment 8 of Table I); **5** is the major product and **2** and **3** are the minor products. Similar reactivities for H_2O_2 in CH_3OH and for C_6F_5IO in CH_2Cl_2 were previously reported for the iron porphyrin-catalyzed epoxidation of norbornene.[19b] The similarity in the reactivity indicates that the active species involved in both

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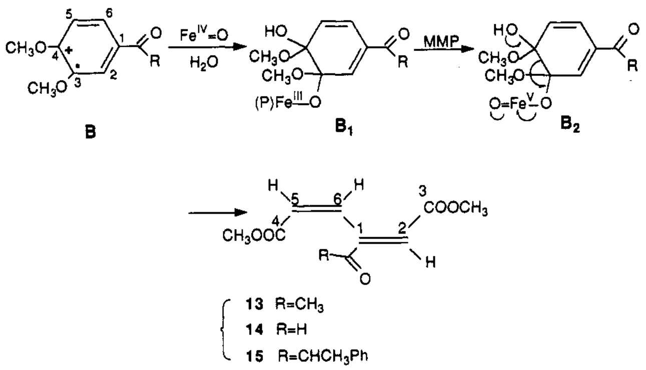
systems is $(P^{+\bullet})Fe(IV){=}O$. In contrast, oxidation of 1 by H_2O_2 with the same catalyst but in an aprotic medium (CH_2Cl_2/CH_3CN) led exclusively to 2 (experiment 2 of Table I). That only 2 was formed strongly suggests that the $(P^{+\bullet})Fe(IV){=}O$ species is not formed under these conditions and that the cleavage of H_2O_2 by (P)Fe(III) is homolytic, with formation of $(P)Fe(IV){=}O$ and $OH\cdot$ (eq 6). Oxidation of 1 by $(P)Fe(IV){=}O$, a species identical to LiP compound II, should lead to $1^{+\bullet}$ and (P)Fe(III), which is unable to induce any oxygen atom transfer. Consequently, $1^{+\bullet}$ undergoes cleavage of its C_α–C_β bond with formation of 2. This homolytic cleavage of the O–O bond of H_2O_2 by $Fe(III)(TF_5PP)$ is in agreement with previous data from the literature.[21] Changing the medium from aprotic (CH_2Cl_2/CH_3CN) to protic (CH_2Cl_2/CH_3OH) seems to favor either a heterolytic cleavage of the O–O bond of H_2O_2[19] or an easier oxidation of $(P)Fe(IV){=}O$ by $OH\cdot$ to $(P^{+\bullet})Fe(IV){=}O$ (eq 4).[18c,d] In the aqueous buffered solution, with $Fe(TF_5PS_4P)$ as the catalyst, the two iron–oxo species are probably present in a 1/1 mixture, as estimated from the ratio of the oxidation products [2/(3 + 5 + 6)] (experiment 4 of Table I).

Chemoselectivity of the Oxidation of Substituted 1,2-Dimethoxyarenes. As shown in Table II, the nature of the main product formed upon $Fe(TF_5PS_4P)$-catalyzed MMP or H_2O_2 oxidation of 1,2-dimethoxyarenes bearing a substituent at the *para* position clearly depends on the electronic properties of this substituent. With a substrate such as 1, 8, or 9, which bears an electron-releasing group X, the main final product is a *p*-quinone (5, 11, or 12, respectively), whereas with a substrate such as 2, 7, or 10, which bears an electron-withdrawing group, the only products observed are muconic dimethyl esters. It is likely that the first step involved in the formation of both kinds of products is the one-electron oxidation of the starting dimethoxyarene by the $(P^{+\bullet})Fe(IV){=}O$ species leading to the cation radical of the substrate. With an electron-releasing substituent X, this cation radical should exist mainly as mesomeric form **A** (Scheme III) with the positive charge at C_3 delocalized on C_1, which bears stabilizing electron-releasing groups. This route leads mainly to a *p*-quinone. Preliminary $H_2{}^{18}O$-labeling experiments performed on the oxidation of veratryl alcohol (8) by MMP in the presence of $Fe(TF_5PS_4P)$ under argon in a $CH_3CN/H_2{}^{18}O$ mixture led to quinone 11 in which only one ^{18}O oxygen atom was incorporated (see Experimental Section for mass spectrometry data). This result is in agreement with the mechanism depicted in Scheme III but not with that in eq 2, which would involve a two-electron transfer from the substrate to the $(P^{+\bullet})Fe(IV){=}O$ species and incorporation of two oxygen atoms from H_2O into the quinone. The second oxygen atom incorporated in quinone 11 can only come from the oxidant since the oxidation of veratryl alcohol (8) was run under anaerobic conditions.

In the presence of an electron-withdrawing group X, **B** rather than **A** should be the main mesomeric form of the cation radical (Scheme IV). In **B**, the positive charge cannot be on both C_3 and C_1 because of the destabilizing effect of the electron-withdrawing group at C_1. Moreover, location of the free radical at C_3 (instead of C_4 as in **A**) should be favored because at C_3 the radical can be considered as captodative,[22] stabilized both by an electron-withdrawing group (X) at C_1 and an electron-releasing group (OMe) at C_3. An oxidation of this free radical by the $Fe(IV){=}O$ species and a reaction of H_2O at the cationic site of the cation radical should lead to intermediate $\mathbf{B}_1$, which is the ferric complex of a 1,2-diol. It has been reported that such 1,2-diols are oxidized by Fe(III) porphyrins and oxygen atom donors with a cleavage of their C–C bonds.[23] Therefore, it is likely that, upon oxygen atom transfer from MMP to the Fe(III) of $\mathbf{B}_1$, an oxidative cleavage of the C_3–C_4 bond of $\mathbf{B}_1$ occurs with formation of a muconic dimethyl ester. Thus, the chemoselectivity of the oxidation of *para*-substituted 1,2-dimethoxyarenes by MMP and $Fe(TF_5PS_4P)$ can be easily explained by the differences in the structures of the main mesomeric forms of the cation radicals formed in the first step.

Scheme IV



Conclusion

The different products formed upon oxidation of an α,β-diarylpropane dimer model of lignin by H_2O_2 or MMP in the presence of an iron porphyrin have been determined. They derive from four main reactions: two different oxidations of the dimethoxyarene group with the formation of either a *p*-quinone or a muconic dimethyl ester, a C_α–C_β bond cleavage of the side chain, and a cleavage of the C_1–C_α bond between the dimethoxyarene nucleus and the α-carbon. The relative importance of these reactions depends on the nature of the porphyrin and of the oxygen atom donor, and a critical factor appears to be the ability of the iron–oxo species to control the intermediate cation radical derived from the substrate. In that respect, it is noteworthy that a clean "LiP-like" side-chain fragmentation was observed when $Fe(TF_5PP)Cl$ and H_2O_2 were used in an aprotic medium.

Actually, 1,2-dimethoxyarenes bearing an X substituent at the *para* position are selectively oxidized by MMP in the presence of $Fe(TF_5PS_4P)$ with the almost exclusive formation of either a *p*-quinone when X is an electron-releasing substituent or a muconic dimethyl ester when X is an electron-withdrawing substituent. To our knowledge, this one-step, selective oxidation of 1,2-dimethoxyarenes bearing an electron-withdrawing group at the *para* position into muconic dimethyl esters has no chemical precedent in the literature. In living organisms, the most efficient enzymatic systems described so far to cleave aromatic compounds are iron-containing dioxygenases,[24] but they are efficient only on catechols and not on 1,2-dimethoxyare-

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nes. LiP[25] and cytochrome P450[26] were reported to catalyze the oxidation of aromatic compounds to muconic acid derivatives in very low yields; however, the substrates used did not contain an electron-withdrawing group.

Experimental Section

Mass spectra were obtained by chemical ionization with NH_3. ^1H NMR spectra were recorded at 20 °C at 250 MHz; chemical shifts are reported in ppm downfield from Me_4Si and coupling constants are in hertz. Elemental analyses were done by the service de microanalyse de l'université Paris VI at Paris.

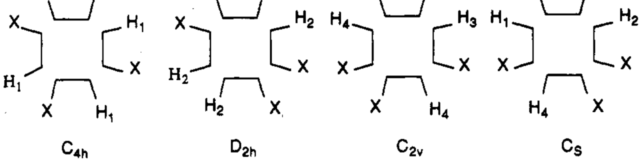
Materials. TF_5PPH_2 and $TDCPPH_2$ were synthesized according to the method described by Lindsey[27] and were metalated by $FeCl_2{\cdot}4H_2O$ in dimethylformamide.[28] Sulfonation of $TDCPPH_2$ was carried out according to the method described by Dolphin et al.[29] Insertion of iron into $TDCSPPH_2$ was accomplished to the method of Zipplies et al.[18a] to give Fe(III)(TDCSPP). Fe(III)(TSPP) was commercially available from Coger. H_2O_2, 35% aqueous solution, and magnesium monoperoxyphthalate hexahydrate (MMP) were purchased from Janssen. Starting products such as veratryl alcohol, veratraldehyde, and 3,4-dimethoxyacetophenone were purchased from Aldrich. C_6F_5IO was prepared as described in the literature.[30]

Synthesis of Fe(TF_5PS_4P). TF_5PPH_2 (500 mg) was dissolved in 20 mL of oleum (15–20% SO_3 in H_2SO_4). After being heated at 170 °C for 10 h and slowly cooling overnight to rt, the mixture was added under stirring to 20 mL of H_2O (0 °C). The green solution was carefully neutralized with aqueous NaOH (10 N). Then an equal volume of ethanol was added to the red solution to precipitate salts. The mixture was filtered and evaporated to dryness. Salts were removed by successive dissolutions of the solid in ethanol, methanol, and acetone followed by filtrations and evaporations. The water-soluble porphyrin $TF_5PS_4PH_2$ was obtained in 80% yield as a purple powder and was completely soluble in ethanol, methanol, acetone, and acetonitrile: UV-vis in 0.1 M phosphate buffer pH 7, λ (ϵ mM^{-1} cm^{-1}) 428 (157), 530 (8.9), 594 (4.4), 672 (1.4) nm; ^1H NMR (CD_3OD, CD_3ONa) δ 8.47, 9.07, 9.18, 9.2 (4 H, pyrrole).

$TF_5PS_4PH_2$ (100 mg) was metalated upon reaction with $FeCl_2{\cdot}4H_2O$ (100 mg) in H_2O (10 mL) under reflux for 24 h. The course of the reaction was followed by UV-vis spectroscopy on the Soret region in acidic solution. At the end of the reaction, the excess iron was precipitated as $Fe(OH)_3$ upon the addition of enough aqueous NaOH (10 N) to bring the mixture to pH 12–13. After neutralization of the filtered solution with aqueous HCl, the solution was evaporated to dryness in the presence of ethanol. The iron complex was first purified by chromatography over a column of chelex (100–200 mesh, Bio-Rad) and then, after evaporation, by dissolution in methanol followed by filtration to remove salts. After evaporation, Fe(III)(TF_5PS_4P) was obtained as a purple powder: UV-vis in 0.1 M tartrate buffer pH 3, λ (ϵ mM^{-1} cm^{-1}) 396 (88.3), 414 (94.2), 501 (8.9), 581 (5.0), 632 (3.6) nm.

The structure of the porphyrin was confirmed by characterization of the sulfochloro derivative $[TF_5P(SO_2Cl)_4P]H_2$. To a mixture of $TF_5PS_4PH_2$ (30 mg) and PCl_5 (120 mg) was added $POCl_3$ (1 mL). The solution was stirred 30 min at 50 °C. The chlorinating agents were evaporated under vacuum, and the residue was dissolved in CH_2Cl_2 and washed with H_2O until the washes were neutral. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The sulfochloro derivative precipitated from CH_2Cl_2 into pentane was then characterized by UV-vis spectroscopy, mass spectrometry, and ^1H NMR: UV-vis (in CH_2Cl_2) λ 439, 538, 567, 611, 699 nm; MS m/z 1369 (M^+, 7), 1305 ($[M - SO_2]^+$ 27), 1272 ($M^+ - SO_2Cl + 1$, 100), 1207 ($[M - SO_2Cl - SO_2]^+$, 22); ^1H NMR ($CDCl_3$) δ 9.63, 9.51, 9.37, 8.81 (4 H, pyrrole), −2.2 (2 H, NH).

The mass spectrum confirmed that the pentafluorophenyl groups remained intact and that sulfonation occurred on the β-pyrrolic positions. This result is also in agreement with the 30 nm red-shifted Soret band relative to TF_5PPH_2 (410 nm). The presence of only singlets for the pyrrole H and the NH was expected in the ^1H NMR spectrum of a mixture of the four possible isomers of $TF_5PS_4PH_2$ obtained by introduction of only one sulfonato group on each pyrrole ring. A priori a total of six pyrrolic proton singlets would be expected for these four isomers. However, only a set of four singlets was observed because of the identical chemical environments of the protons in the isomer with C_s symmetry relative to those of the isomers with C_{4h}, D_{2h}, and C_{2v} symmetry:



Preparation of Starting Materials. 1-(3,4-Dimethoxyphenyl)-2-phenylpropanol (1) was prepared as previously described by Hammel et al.:[8] ^1H NMR ($CDCl_3$) δ 1.07 (d, 3 H, J = 7), 2.98 (quint, 1 H, J = 7), 3.88 (s, 3 H), 3.86 (s, 3 H), 4.61 (d, 1 H, J = 7), 6.87–7.38 (m, 8 H). Anal. Calcd for $C_{18}H_{22}O_4$: C 75; H 7.35. Found: C 74.70; H 7.38.

1-(3,4-Dimethoxyphenyl)-2-phenylpropane (7) was an intermediate in the preparation of 1 and was purified by column chromatography (SiO_2, hexane–EtOAc 70:30): ^1H NMR ($CDCl_3$) δ 1.50 (d, 3 H, J = 7), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.64 (q, 1 H, J = 7), 6.78 (d, 1 H, J = 8), 7.26–7.60 (m, 7 H).

4-*tert*-Butylveratrole (9) was obtained upon alkylation of 4-*tert*-butylcatechol with CH_3I/K_2CO_3 in DMF at 60 °C and was characterized by its ^1H NMR spectrum.[31]

Typical Procedure for Oxidations. The oxidant (H_2O_2 or a 0.4 N aqueous solution of MMP) was added with stirring at rt in 25-μL aliquots every 3 min to a solution of the iron porphyrin catalyst (1 μmol) in 2 mL of either CH_2Cl_2/CH_3OH (90:10 v/v) or 0.1 M tartrate buffer pH 3/CH_3CN (75:25 v/v) containing 50 μmol of substrate. Thirty minutes after the last addition, the products were carefully extracted with CH_2Cl_2, in the presence of a saturated aqueous NaCl solution. The organic layer was dried over $MgSO_4$ and was evaporated under vacuum without heating. H_2O_2 (35%) was added in aliquots of 5 μL for experiments 1 and 2, and the reaction mixture was kept stirring overnight.

The residue was dissolved in 0.5 mL of $CDCl_3$ in the presence of 2,6-dichlorobenzaldehyde (25 μmol, 0.5 equiv) as an internal standard for ^1H NMR analysis, under the following conditions: sweep width 6000 Hz, 30 °C pulse of 2 μs, relaxation delay of 5 s, FID acquired with 16 or 32 scans. For experiments run with compound 1, yields were determined on the basis of the ratio of the integral for the aldehydic proton of the internal standard (10.5 ppm) and the integral of the following specific signals of the different oxidation products: 9.83 (s, 1 H) for 2, 5.74 (s, 2 H) for 3, 9.6 (d, 1 H) for 4, 5.89 (s, 1 H) for 5, 6.07 (d, 1 H) for 6, 4.64 (q, 1 H), and 1.50 (d, 3 H) for 7, 4.61 (d, 1 H) and 1.07 (d, 3 H) for 1. The presence of benzoic acid and oxidation products 2, 3, and 4 was confirmed by GC on a capillary column (DB 1701 0.25 μm, 30 × 0.252 mm, Interchim) by comparison of their retention times with those of authentic samples.

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Labeling Experiments. $H_2{}^{18}O$-labeled quinone (**11**) (1 mg) was prepared by catalytic oxidation of **8** (2.1 mg) by MMP (0.4 N in $H_2{}^{18}O$ enriched to 99.8%) in the presence of Fe(TF_5PS_4P) (1 mg) under argon in a mixture of 250 μL $H_2{}^{18}O$ and 200 μL of CH_3CN. A blank experiment was performed under the same conditions with $H_2{}^{16}O$. Unlabeled **11**: MS *m/z* 168 (M^+, 12.06), 169 ($[M + 1]^+$, 100), 170 ($[M + 2]^+$, 12.57). ^{18}O-labeled **11**: MS *m/z* 168 (M^+, 3.24), 169 ($[M + 1]^+$, 25.11), 170 ($[M + 2]^+$, 12.85), 171 ($[M + 3]^+$, 100), 172 ($[M + 4]^+$, 9.75), 173 ($[M + 5]^+$, 3.24). Comparison of the mass spectra of the samples of **11** obtained from oxidation of **8** in $H_2{}^{18}O$ and $H_2{}^{16}O$ indicated that the labeled product had incorporated 0.8 atom of ^{18}O. The 0.2 atom of ^{16}O was probably due to the presence of $H_2{}^{16}O$ in the commercially available magnesium perphthalate, which exists as a hexahydrate salt.

Preparation and Characterization of Quinones. 4,5-Dimethoxy-1,2-benzoquinone (**3**) was prepared by oxidation of 1,2-dihydroxybenzene with PbO_2 in methanol[32] and was characterized by its ^1H NMR spectrum.[33] Quinones **11** and **12** were isolated from experiments 9 and 13 (Table II), respectively, and were identified by their ^1H NMR spectra (ref 34 for **11** and ref 35 and **12**). Quinone **5** was prepared from 500 μmol of **1** and 10 μmol of Fe(TF_5PS_4P) as described in experiment 5 (Table I). Crystallization in ethanol (mp 70 °C): ^1H NMR ($CDCl_3$) δ 1.31 (d, 3 H, $J = 6.5$), 3.07 (quint, 1 H, $J = 6.5$), 3.83 (s, 3 H), 4.81 (dd, 1 H, $J = 6$, $J = 1.3$), 5.89 (s, 1 H), 6.4 (d, 1 H, $J = 1.3$), 7.14–7.31 (m, 5 H). Anal. Calcd for $C_{16}H_{16}O_4$: C 70.58; H 5.88. Found: C 70.06; H 5.85.

Preparation and Characterization of Muconic Diesters. Oxidation of 2.50 mmol of **10**, **2**, or **7** catalyzed by 10 μmol of Fe(TF_5PS_4P) in the presence of the number of equivalents of MMP described in experiments 16, 19, or 22 (Table II), respectively, afforded the corresponding muconic diester **13**, **14**, or **15**, on a preparative scale. After purification by a single column chromatography (SiO_2, hexane/EtOAc 50/50 for **13** and 70/30 for **14** and **15**), the products were characterized by elemental analysis (except for **13**, which was obtained as an oil), mass spectrometry, and ^1H NMR spectroscopy (Table III). **13**: MS *m/z* 230 ($[M + NH_4]^+$, 50), 213 ($[M + 1]^+$, 100). **14**: mp 60 °C (crystallization solvent: CH_2Cl_2/hexane); MS *m/z* 216 ($[M + NH_4]^+$, 95), 199 ($[M + 1]^+$, 100). Anal. Calcd for $C_9H_{10}O_5$: C 54.54; H 5.05. Found: C 54.46; H 5.04. **15**: mp 150 °C (crystallization solvent: CH_2Cl_2/hexane); MS *m/z* 320 ($[M + NH_4]^+$, 100), 303 ($[M + 1]^+$, 80). Anal. Calcd for elemental analysis for $C_{17}H_{18}O_5$: C 67.5; H 5.96. Found: C 66.93, H 5.88. Muconic diester **6** was isolated from experiment 6 (Table I), in which 500 μmol of **1** and 10 μmol of Fe(TF_5PP)Cl were used. After separation from the other oxidation products by TLC (SiO_2-60F_{254} Merck, 1 mm, $CHCl_3$/AcOEt 90:10, R_f 0.2), its ^1H NMR spectrum was completely consistent with its muconic structure (Table III), but, because of its relative instability and the low amounts recovered, it could not be further characterized.

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