Mechanism of the Catalytic Oxidation of Tertiary Alcohols by the Water-Soluble Mn-TMPyP/$KHSO_5$ System: β-Fragmentation versus *O*-Neophyl Rearrangement

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Keywords: Oxidations / Tertiary alcohol / Porphyrins / Neophyl rearrangement / Cleavage reactions / β-Scission

Oxidation of 4-(1-hydroxy-1-phenylethyl)benzoic acid HPEBA with a water-soluble metalloporphyrin as catalyst and $KHSO_5$ as oxygen atom donor gives the major products, acetophenone AC and acetylbenzoic acid ABA, by a C_{aliph}–C_{Ar} bond cleavage, but a minor product, benzoyloxybenzoic acid BOBA, requires the insertion of an oxygen atom to form the ester. This compound becomes the main oxidation product on increasing the amount of acetonitrile in the reaction medium, and its formation is oxygen-dependent. The conversion is drastically lowered by using D_2O instead of H_2O, suggesting that an alkoxyl radical is formed in the rate-determining step. Labeling experiments using $^{18}O_2$ or $H_2{}^{18}O$ under different reaction conditions show that the carbonyl oxygen atoms of AC and ABA originate either from substrate, water or dioxygen. However, the carbonyl oxygen atom in the ester group of BOBA originates from dioxygen while the other oxygen atom of the ester remains unlabeled. These results can be explained by an *O*-neophyl rearrangement of the initial alkoxyl radical to afford a carbon-based radical which then reacts with dioxygen or Mn^{IV}-OH/water. In a competitive reaction pathway, direct β-scission of the alkoxyl radical leads to unlabeled products. The oxidation of other tertiary diaryl alcohols is also discussed.

Introduction

Little is known about the oxidative C–C bond cleavage by biomimetic catalysts, although it is a key step in several reactions catalyzed by cytochrome P-450 in steroidal hormone biosynthesis such as estrogen biosynthesis or the side chain cleavage of cholesterol.[1] In the latter case, the cleavage is achieved by three successive oxidations; two hydroxylation steps at C-20 and C-22 produce a vicinal diol which is then oxidatively cleaved in the third step into two carbonyl compounds. With the aim of simulating this last scission step, the oxidation of aryl-substituted ethane-1,2-diols by chromium(III) tetraphenylporphyrin/4-cyano-*N,N*-dimethylaniline *N*-oxide without[2] and under photocatalysis,[3] or by iron(III) tetraphenylporphyrin/O_2/dihydropyridine[4][5] was shown to induce C–C bond cleavage selectively to give aldehydes and ketones. The photochemical cleavage of 1,2-diphenylethane-1,2-diols has also been observed with water-soluble iron porphyrin complexes to produce benzaldehyde and small amounts of benzoic acid, in which experimental yields and bleaching of the catalyst depend on the presence of O_2.[6][7] Aromatization of a synthetic androgen analogue by a peroxo iron(III) porphyrin complex results in C–C bond cleavage and allows the authors to mimic the third step of aromatase, the enzyme responsible for the conversion of androgens to estrogens in humans, which involves loss of the C-19 aldehyde and aromatization of the A ring of the steroid.[8]

As part of our mechanistic studies on the biomimetic Mn-TMPyP/$KHSO_5$ system – a water-soluble manganese porphyrin complex as catalyst with potassium monopersulfate as oxygen atom donor – we show here how some intermediate tertiary alcohol models can give ketones through cleavage of a C–C bond. As opposed to primary and secondary alcohols, tertiary alcohols are usually resistant to oxidation, and examples of such oxidative conversions are rather unusual and generally related to some structural peculiarity. Chromium(VI) can oxidize allylic- or α-cyclopropyl tertiary alcohols to give rearrangements,[9–11] δ- or γ- unsaturated tertiary alcohols to afford cyclization products,[12][13] and tertiary cycloalkanols to produce fragmentations.[14] Cerium(IV) salts and cobalt(III) complexes can also induce C–C bond cleavage by oxidation of tertiary alcohols, leading mainly to fragmentation reactions.[15][16] Synthetic metalloporphyrins, used as models for cytochrome P-450, are highly efficient catalysts for the oxidation of various substrates but only some rare examples of oxidation of tertiary alcohols are described in the literature. Recently, we have shown that the biomimetic water-soluble Mn-TMPyP/$KHSO_5$ system gives mainly C_{aliph}–C_{aliph} and C_{aliph}–C_{Ar} bond cleavage through a β-fragmentation mechanism in the course of the oxidation of aryl and diaryl tertiary alcohol derivatives.[17][18] We now report a mechanistic study based on a careful examination of the oxidation products of tertiary alcohols, and labeling experiments, which emphasizes, besides the initial observation of β-fragmentation as a possible mechanism to explain the observed product distribution, the role of *O*-neophyl rearrangement. This latter mechanism allows us to understand not only the partial incorporation of oxygen from water and dioxygen in oxidation products but also the formation of an unexpected

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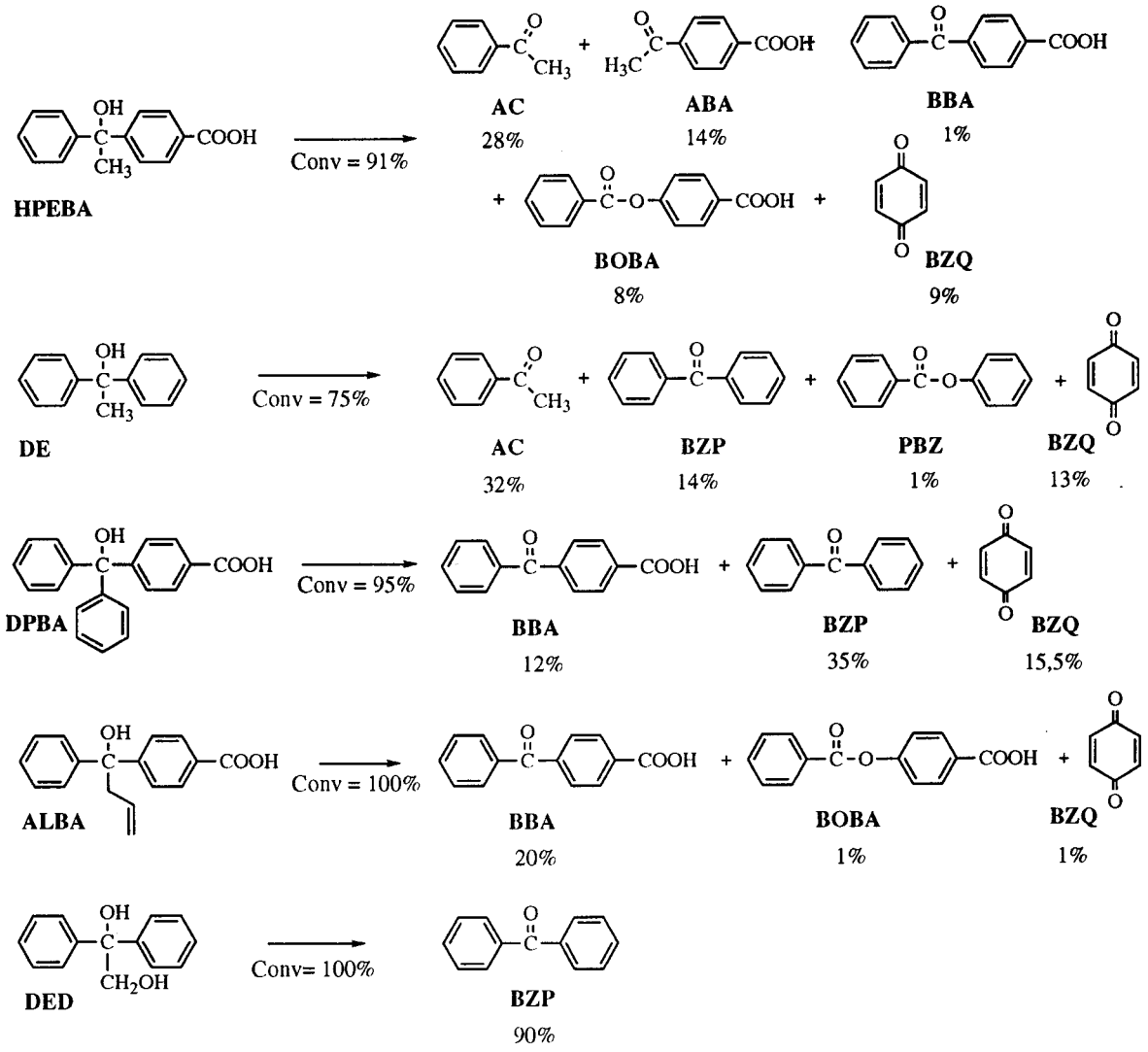


Scheme 1. Identified products and yields from oxidation of HPEBA, DE, DPBA, ALBA and DED with the Mn-TMPyP/$KHSO_5$ system

ester derivative which is characteristic of such a reaction pathway.

Results

Oxidation of HPEBA With Mn-TMPyP/$KHSO_5$

The metalloporphyrin-catalyzed oxidation of 4-(1-hydroxy-1-phenylethyl)benzoic acid HPEBA was performed in air at pH 5 in aqueous phosphate buffer containing 10% acetonitrile, with the manganese(III) *meso*-tetrakis(1-methylpyridinium-4-yl)porphyrin (Mn-TMPyP) as catalyst and $KHSO_5$ as oxidant. Final concentrations of substrate, catalyst and oxidant were 500 μM, 10 μM and 10 mM, respectively. The reaction was monitored by HPLC. After 10 min, the substrate conversion was 90%. Products (Scheme 1) were identified by HPLC co-injection of authentic samples (benzoyloxybenzoic acid, BOBA, which is not commercially available, was synthesized) and by GC-MS analysis of a reaction sample after esterification of the carboxylic groups with diazomethane.

In the case of benzoquinone BZQ, which is not easily detectable by GC-MS, it should be noted that its HPLC peak disappeared after addition of a small amount of sodium dithionite ($Na_2S_2O_4$), which is a specific reductant of benzoquinones. Product yields and selectivities are given in Table 2. The major products, acetophenone AC and *p*-acetylbenzoic acid ABA, are derived from a $C_{aliph}-C_{ar}$ bond cleavage, while a very small amount of *p*-benzoylbenzoic acid BBA resulting from a $C_{aliph}-C_{aliph}$ bond cleavage was obtained. The formation of the unexpected ester BOBA requires the loss of a methyl group and the insertion of an oxygen atom. Surprisingly, the isomeric ester monophenylterephthalate MPTP, corresponding to insertion of the oxygen atom on the phenyl side of the carbonyl ester function, was not detected. This fact was confirmed by preparing an authentic sample of this compound, which proved to have almost the same HPLC elution time as BOBA, but different GC behavior and different NMR and EI-MS spectra. MPTP was not observed, either by GC-MS analysis of the reaction mixture or by NMR spectroscopic analysis of the

collected HPLC peak (the NMR spectrum corresponded to that of BOBA only). When replacing $KHSO_5$ by the same molar amount of H_2O_2, no conversion was observed, and the use of methanol instead of acetonitrile inhibited the oxidation, probably through trapping of the high valent metal-oxo species.[19] We also checked that no reaction occurred in the absence of catalyst and that ABA, BBA, AC and BZQ were stable under the catalytic oxidation conditions. However, in the case of BOBA, 70% conversion was obtained after 10 min, the only identified product being a small amount of benzoquinone. The same behavior was observed with MPTP but, in this case, conversion was 90%. We then decided to study the competitive oxidation of a mixture of substrate and one of the two esters. For a mixture of HPEBA and BOBA, the conversion of HPEBA was almost 100%, while only 10−15% of BOBA was converted. Therefore, the yield of BOBA resulting from the catalytic oxidation is barely affected by further oxidation. The same experiment with MPTP revealed an 85% conversion of the ester. These observations led us to conclude that MPTP was not detected among the reaction products because either: (i) it was further oxidized under the reaction conditions, or (ii) it was not formed during the catalytic reaction. These two possibilities will be discussed later.

Influence of the Acetonitrile/Buffer Ratio

Increasing the acetonitrile content from 10% to 45% in the buffered medium resulted in a decrease in the conversion, from 90% to 35%, and also in a significant change in the product distribution. Figure 1 shows that, with more than 40% acetonitrile, BOBA becomes the main product, while the selectivity in the other four products is slightly lowered. In fact, acetonitrile seems to favor the formation of BOBA. These results highlight the peculiar behaviour of BOBA over that of the other products, and suggest that there are several reaction pathways operating at the same time (at least two), one of them leading only to BOBA.

Influence of Dioxygen

In order to assess the influence of the reaction atmosphere, we carried out the oxidation under different pressures of dioxygen (to avoid leaks, we always added nitrogen to maintain a pressure of 1 atm). For these experiments we used 10% catalyst so that, in each case, the conversion was close to 100%. Figure 2 indicates the evolution of product selectivities as the amount of dioxygen is raised. Once again, the yield of BOBA increases while the yield of the other products is lowered indicating that formation of BOBA is oxygen-dependent. Furthermore, Figure 2 also shows that the yields of BOBA and AC are inversely correlated. In other words, as the yield of BOBA increases, the yield of AC decreases by the same amount, so that the value ([BOBA] + [AC]) remains constant (see also Table 1). This suggests that AC and BOBA have a common intermediate in their formation pathway. This intermediate is able to react with molecular oxygen to give BOBA, or to follow an alternative route leading to AC.

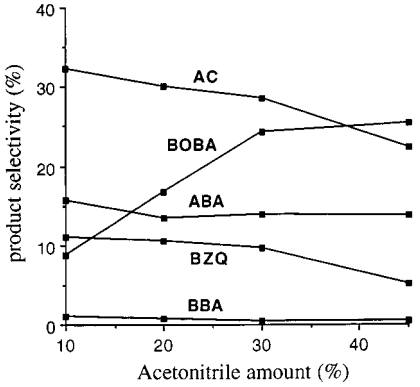


Figure 1. Influence of acetonitrile on selectivity

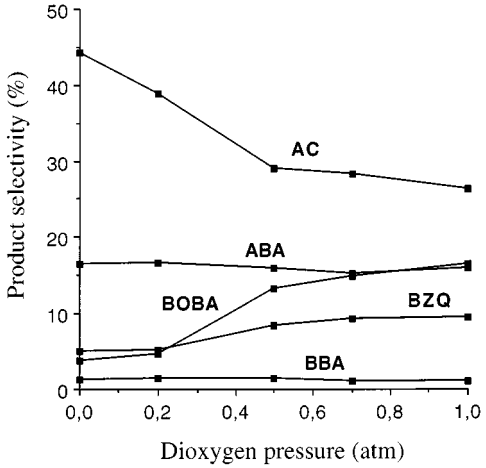


Fig. 2. Influence of dioxygen on selectivity

Table 1. Yields of AC, ABA and BOBA obtained from oxidation of HPEBA under dioxygen or nitrogen atmosphere

Products	Yield (%)	
	under O_2	under N_2
AC	26	44
ABA	16	16
BOBA	16	4

Labeling Experiments

In order to obtain more information about the reaction mechanism, we performed labeling experiments. To this end, we prepared the trideuteriated substrate CD_3-HPEBA, where the CH_3 has been replaced by a CD_3, and subjected it to the Mn-TMPyP/$KHSO_5$ system. Substrate conversion, product yields and selectivities are shown in Table 2. First of all, we observed that the conversion rate is almost the same as the oxidation rate of HPEBA. The absence of an isotope effect allows us to conclude that the rate-determining step of the oxidation does not involve an H-abstraction

Table 2. Yields and selectivities of products obtained from Mn-TMPyP/$KHSO_5$ oxidation of HPEBA in H_2O or D_2O and CD_3-HPEBA in H_2O[a]

Substrate Products	HPEBA in H_2O Yield (%)[b]	Selectivity (%)[b,c]	CD3-HPEBA in H_2O Yield (%)[b]	Selectivity (%)[b,c]	HPEBA in D_2O Yield (%)	Selectivity (%)[c]
AC	28 ± 1	31 ± 1	28 ± 1	34 ± 1	6	19
ABA	14 ± 0.5	15.3 ± 0.4	15.2 ± 0.3	19 ± 0.5	9	21
BBA	0.8 ± 0.1	0.9 ± 0.1	2.6 ± 0.3	3.2 ± 0.4	0.5	1
BOBA	7.7 ± 0.3	8.7 ± 0.3	6.8 ± 0.2	8.0 ± 0.1	2	6
BZQ	9.2 ± 0.4	10.6 ± 0.2	8.0 ± 0.4	9.8 ± 0.3	2	6
Conversion (%)	*91 ± 4*		*83 ± 3*		*37*	

[a] Experiments were performed under the same conditions, with 10% acetonitrile (substrate, $KHSO_5$ and Mn-TMpyP concentrations were respectively 500 μM, 10 mM and 10 μM). – [b] Experimental errors were obtained from three independent experiments. – [c] Selectivity is defined as the ratio of product yield divided by substrate conversion.

from the methyl group. No major changes in product selectivity were observed, except for BBA, whose selectivity, although it remained very low, increased significantly by a factor of 3.5. Thus replacing CH_3 by CD_3 in HPEBA influences only the formation of BBA. The reaction mixture resulting from the oxidation of CD_3-HPEBA was also analyzed by GC-MS. The mass spectra of AC and derivatized ABA showed a unique molecular peak at M + 3 (*m*/*z* 123 and *m*/*z* 181, respectively). These data clearly demonstrate that during the formation of ABA and AC, the methyl group remains unchanged since the three deuterium atoms are still present in the oxidation products.

Another experiment was performed in D_2O instead of H_2O, using HPEBA. An important isotopic effect was detected: the product distribution was not really affected, but the conversion decreased to 37% instead of the 91% observed in H_2O over the same reaction time (Table 2). When the substrate was placed in D_2O, its alcoholic hydrogen was exchanged for a deuterium. The decreased conversion indicates the major role played by the alcoholic hydrogen in the reaction mechanism. Additionally, we checked that with a substrate without exchangeable hydrogen, no such isotopic effect was observed. For example, the epoxidation of carbamazepine with Mn-TMPyP/$KHSO_5$, performed in D_2O, gave 97% conversion, the value obtained in H_2O being 95% in the same reaction conditions.[20] We can therefore conclude that the isotope effect observed with HPEBA is not a solvent isotope effect, but must be related to an isotope effect of the substrate itself.

In order to investigate the origin of the oxygen incorporated in the oxidation products, we performed experiments in the presence of ^{18}O-labeled water or dioxygen. The reactions were carried out with 10% catalyst and 20% acetonitrile for 10 min, so that the conversion was almost complete, and the yield of BOBA was optimized to provide suitable conditions for GC-MS analyses. In control experiments, we checked that HPEBA, AC, BBA and BOBA did not exchange their oxygen with water under these reaction conditions. A small exchange (7%) was found in the case of ABA. Also, $KHSO_5$ itself does not exchange its oxygen with water.[21] The labeling of BZQ was not studied since it was not detected by GC-MS under our conditions. Experiments were performed under air or under 1 atm of nitrogen or dioxygen either labeled or not. The dependence of the amount of labeled oxygen incorporated into each product on the reaction conditions is indicated in Table 3. The percentages were determined by calculating the relative abundances of molecular ions at M, M + 2 and M + 4, corresponding to the incorporation of none, one or two heavy oxygen atoms (the latter case concerns only BOBA). For BOBA, the relative abundances of the peaks at *m*/*z* 105 and 107 ($[Ph-C=O]^+$) provided the separate labeling of the carbonyl oxygen.

These results give us several key data. First, the oxygen incorporated in BOBA comes only from dioxygen, and is selectively introduced at the carbonyl position (no M + 4 peak was detected, and M + 2/M and 107/105 relative abundances were both close to 100% when the reaction was performed under $^{18}O_2$). In other words, 100% of the carbonyl oxygen atom of BOBA originates from dioxygen, while the oxygen atom of the ester remains unlabeled. This is consistent with the fact that BOBA formation is oxygen-dependent (see Figure 2). In contrast, the other three products incorporate labeled-oxygen atoms either from water or dioxygen. With AC and ABA, the labeling depends on the reaction conditions: as the quantity of dioxygen decreases, the amount of oxygen atoms from water increases (runs 2–4, Table 3). Interestingly, when the reaction was performed under 1 atm of dioxygen, AC was found to contain 24% of water-derived oxygen atoms and 65% of dioxygen-derived oxygen atoms. The total contribution of both water and dioxygen is thus 89%, which nearly corresponds to the amount of oxygen atoms incorporated from water when the reaction is performed under nitrogen (*i.e.* 85%). The same observation can be made with ABA. This suggests that there are two competitive pathways leading to AC and ABA, one involving a reaction with water, and the other involving a reaction with dioxygen. As the amount of dioxygen decreases, the preferred pathway become the water-dependent one. In the case of BBA, the labeling does not depend on the reaction conditions, since the amount of oxygen atoms from water remains unchanged whether the reaction is performed under nitrogen or under dioxygen (runs 2 and 4, Table 3).

Oxidation of Other Tertiary Alcohols

For a better understanding of the reactivity of HPEBA we decided to study the catalytic oxidation of some other tertiary alcohols. 1,1-Diphenylethan-1-ol DE (Scheme 1) was chosen to study the influence of the carboxylic group. Under the same experimental conditions as with HPEBA, the conversion was 75% and the oxidation products were the same as those resulting from oxidation of HPEBA, but without the carboxylic group, *i.e.* AC, BZQ, benzophenone BZP and the phenylbenzoate ester PBZ. The small amount of PBZ detected (Scheme 1) may be due to its poor stability in the reaction medium, since a control experiment showed that PBZ is completely oxidized by Mn-TMPyP/$KHSO_5$ in 10 min. The more striking fact is the large amount of BZP formed relative to the very low quantity of BBA obtained from HPEBA. This suggests that removal of the carboxylic group influences the rate of the $C_{aliph}-C_{aliph}$ bond cleavage pathway.

4-(Diphenylhydroxymethyl)benzoic acid DPBA and 4-(1-hydroxy-1-phenylbut-3-en-1-yl)benzoic acid ALBA (Scheme 1), analogous to HPEBA but with a phenyl or an allyl group instead of the methyl susbstituent, were also prepared and oxidized by Mn-TMPyP/$KHSO_5$ under the same conditions as HPEBA. The reactions were followed by HPLC and GC-MS. In both cases, the conversion was almost complete. The identified products and yields are indicated in Scheme 1. In the case of DPBA, the products are formed from the three possible $C_{aliph}-C_{ar}$ bond cleavages. Despite the fact that the loss of the phenyl group is statistically favored, the major product is BZP, resulting from the loss of the *p*-carboxyphenyl group. This is consistent with the selectivity observed for oxidation of HPEBA, where AC, deriving from the loss of the *p*-carboxyphenyl, is formed preferentially over ABA, resulting from the loss of the phenyl group. In contrast, no product deriving from the loss of one of the aromatic rings was detected by GC-MS analysis of the reaction mixture obtained from catalytic oxidation of ALBA. Instead, the major product is formed by loss of the allyl substituent, and we found a small amount of BZQ and BOBA. These observations suggest that the nature of the substituents of the carbinol plays a crucial role in the cleavage selectivity.

The last compound studied was 1,1-diphenylethane-1,2-diol DED (Scheme 1). In the presence of Mn-TMPyP/$KHSO_5$, substrate conversion was complete, and the only identified product was BZP, which was obtained in 90% yield. We also performed the oxidation with labeled water or dioxygen. In both cases, no labeled oxygen was found in the BZP, indicating that the carbonyl oxygen atom of BZP comes from the oxygen of the tertiary alcohol.

Discussion

Formation of Unlabeled Products

In a previous communication,[17] we suggested, based on product distribution from catalytic oxidation of HPEBA, that ABA, BBA, and AC are formed from the β-scission of the alkoxyl radical intermediate **1** by abstraction from the substrate of either H·, or an electron followed by H^+ loss (Scheme 2). Either type of abstraction may be performed by the high-valent $Mn^V=O$ species, generated by $KHSO_5$ with Mn-TMPyP, which is the active species operating in this catalytic system.[20][22] Taking into consideration the present labeling results, we now know that the pathway leading to these products must involve, at least in part, molecular oxygen and water. Since some products remain unlabeled, a β-scission must occur, but it is not the only reaction pathway operating. The experiments performed with CD_3-HPEBA demonstrate that, during the formation of AC and ABA, the methyl group is not modified, allowing us to discard any mechanism involving an oxidative attack on this group. On the other hand, the important role of the alcoholic hydrogen atom is shown by the experiment in D_2O where the conversion is significantly lowered. All these data are consistent with the formation of an alkoxy radical in a rate-determining step, as initially proposed. This radical can undergo β-fragmentation in competition with alternative pathways involving water and/or dioxygen. Thus, we can attribute the formation of the unlabeled fraction of AC, ABA and BBA to the β-scission of the alkoxy radical intermediate **1** (Scheme 2): the three products originate from the three possible cleavages, producing phenyl, *p*-carboxyphenyl and methyl radicals but the loss of the aryl groups is highly preferred, since very small amounts of BBA are formed. Previous studies on the decomposition of the cumyloxyl radical[23][24] and its derivative bearing a *p*-COOH substituent on the phenyl ring[18] revealed a predominent elimination of the methyl group, leading to acetophenone derivatives. Actually, β-scission is a process involving a late tran-

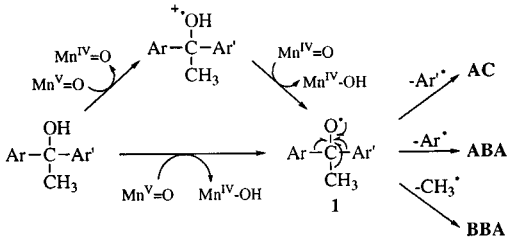
Table 3. ^{18}O-incorporation in AC, ABA, BBA and BOBA during the oxidation of HPEBA by Mn-TMPyP/$KHSO_5$ with $H_2{}^{18}O$ or $^{18}O_2$ (● = ^{18}O-labeled oxygen atom)

Run	Conditions	AC C=●	ABA C=●	BBA C=●	BOBA −C=●	−●−
1	$H_2O/●_2$	65%	23%	15%	95%	0
2	$H_2●/O_2$	24%	14%	22%	0	0
3	$H_2●$/Air	46%	19%	13%[a]	0	0
4	$H_2●/N_2$	85%	38%	22%	0	0

[a] The GC peak corresponding to BBA was too small in this experiment (yield of BBA from oxidation of HPEBA was 1%) to afford an accurate value.

sition state.[25] Consequently, the reaction rate depends on the stability of the generated radical and also of the carbonyl product formed. In our case, and in the case of cumyloxyl radicals, very unstable radicals are released (methyl or aryl radicals), so the orientation of the C−C bond cleavage should be controlled by the stability of the carbonyl products. Thus, the cleavage orientation can be rationalized by the enhanced stability of acetophenone derivatives over benzophenone derivatives (or acetone in the case of loss of a phenyl group from cumyloxyl radicals).[24] Furthermore, other factors such as diminution of the steric strain by expulsion of bulky groups can also influence a β-scission reaction.[24]

In contrast with HPEBA, none of the aryl groups were cleaved during the oxidation of ALBA (see Scheme 1). Instead, the only product detected results from cleavage of the allyl group. Assuming that the β-scission is the only pathway, we propose that, in this case, the much higher stability of the allyl radical[26] over the phenyl and *p*-carboxyphenyl radicals is the driving force for the reaction. Thus, the release of the allyl radical is highly favored, and there is only a minor influence of the stability of the carbonyl products formed concomitantly, or of any other factor.



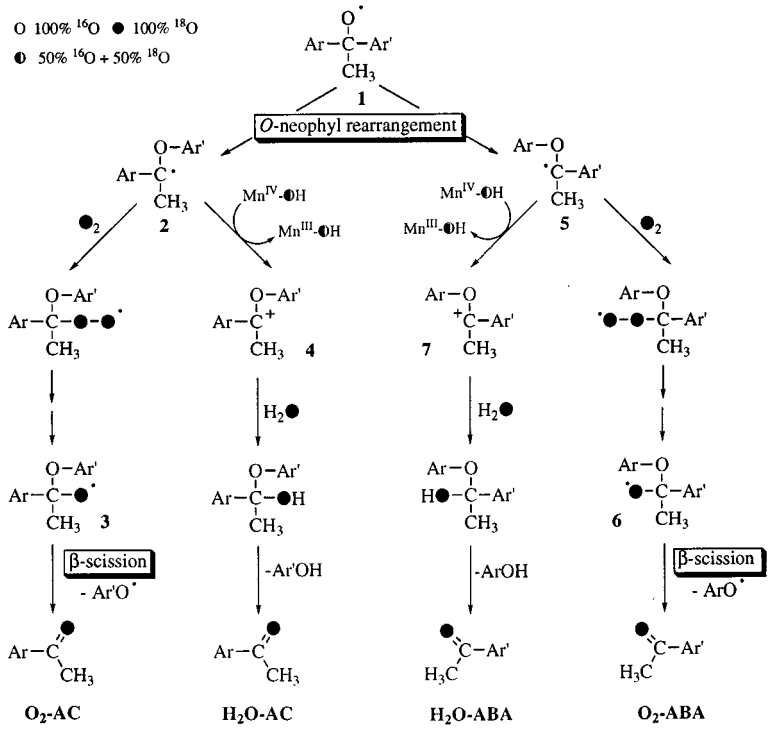
Scheme 2. Formation of unlabeled AC, ABA and BBA through β−scission of the alkoxyl radical **1**; Ar = phenyl and Ar′ = *p*-carboxyphenyl.

Formation of Labeled AC, ABA and BOBA

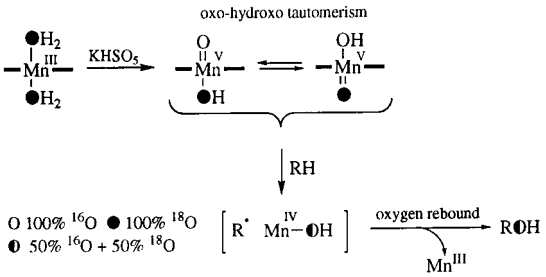
Following the idea that the alkoxy radical is the key intermediate in the oxidation reaction, we decided to investigate how this alkoxy radical can lead to AC, ABA, and BOBA with incorporation of oxygen atoms from water and dioxygen in the carbonyl function (in the case of AC and ABA) or from dioxygen only (in the case of BOBA). Obviously, the observed ^{18}O-incorporation and, more importantly, the formation of the ester BOBA require the involvement of a rearrangement. Aryl-substituted alkoxyl radicals are known to undergo an *O*-neophyl rearrangement, consisting of a 1,2 migration of an aryl group from the carbon to the oxygen, which gives rise to a new, more stable, carbon-centred radical (see for example Scheme 3).[27][28]

Usually, this rearrangement occurs on alkoxy radicals substituted by three α-aryl groups, generating an efficiently stabilized carbon radical, although the 1,1-diphenylethoxyl radical is also known to rearrange in such a way.[29−32] Considering that: (i) the structure of the 1-*p*-carboxyphenyl-1-phenylethoxyl radical **1** is very close to that of 1,1-diphenylethoxyl radical, and (ii) that 1,1-diphenylethanol exhibits a similar reactivity to HPEBA under the present oxidative conditions (see above), we can reasonably suppose that the alkoxyl radical **1** may also undergo an *O*-neophyl rearrangement (Scheme 3). Thus, if either phenyl (Ar) or *p*-carboxyphenyl (Ar′) migrates, two new carbon-centred radicals **2** and **5** are formed, which may escape from the solvent cage and react with dioxygen or Mn^{IV}-OH/water to provide AC and ABA, with a carbonyl oxygen atom from either dioxygen or water. Clearly, if the *p*-carboxyphenyl group migrates to the oxygen, the carbon-centred radical **2** is formed. This radical can react with dioxygen to produce a peroxy radical which can dimerize and provide a new alkoxy radical **3** after a Russell fragmentation. The β-scission of **3** releases a *p*-carboxyphenoxy radical and acetophenone, with a dioxygen-derived carbonyl oxygen atom (O_2-AC). Such a process was shown to occur with the 1,1-diphenylethoxy radical by Ingold *et al.*[29] Alternatively, the *O*-neophyl-rearranged radical can suffer electron abstraction by Mn^{IV}-OH. Reaction of the resulting cation **4** with water produces a hemiacetal, which can subsequently be hydrolysed to form acetophenone containing a water-derived carbonyl oxygen atom (H_2O-AC). Another possible pathway leading to H_2O-AC could be that the radical **2** gives the hemiacetal by a classical oxygen rebound route with Mn^{IV}-OH. However, it has been established that, in water, the active species Mn^{V}=O undergoes an oxo-hydroxo tautomerism,[20][22] leading to a 50% labeled active species Mn^{V}=O if ^{18}O-labeled water is used (Scheme 4).

Thus, after H-abstraction, a 50% labeled Mn^{IV}-OH species is generated. Therefore an oxygen rebound mechanism should lead to a 50% incorporation of labeled oxygen from water in the resulting product. In our case, since there are other pathways operating, there should be less than 50% incorporation of water-derived oxygen atoms in AC, and we should obtain at least the same amount of nonlabeled AC. However, the incorporation of labeled oxygen from water was found to be 85% under a nitrogen atmosphere (run 4, Table 3), and 24% under a dioxygen atmosphere (run 2) but with only 11% of nonlabeled H_2O-AC (runs 1 and 2: 11% = 100% − 65% − 24%). Thus, an oxygen rebound mechanism to explain the incorporation of water-derived oxygen atoms can be ruled out, at least as a main mechanism. A similar pathway, involving an initial migration of the phenyl group instead of the *p*-carboxyphenyl of the alkoxyl radical **1**, leads to O_2-ABA and H_2O-ABA. This mechanism explains why the incorporation of oxygen from water increases as the amount of dioxygen in the reaction atmosphere decreases. Indeed, the carbon-centred radicals **2** and **5** can follow two competitive routes, one involving water and the other involving dioxygen. The importance of each route depends on the amount of dioxygen (or water) available and, when the reaction is performed under nitrogen, the only pathway operating must be the water-dependent one. This is in agreement with the fact that, when the reaction is performed under nitrogen, the number of oxygen atoms from water is equal to the total number of oxygen atoms coming from water + dioxygen when the reaction is performed under dioxygen (run 4 and runs 1, 2, respectively, Table 3).



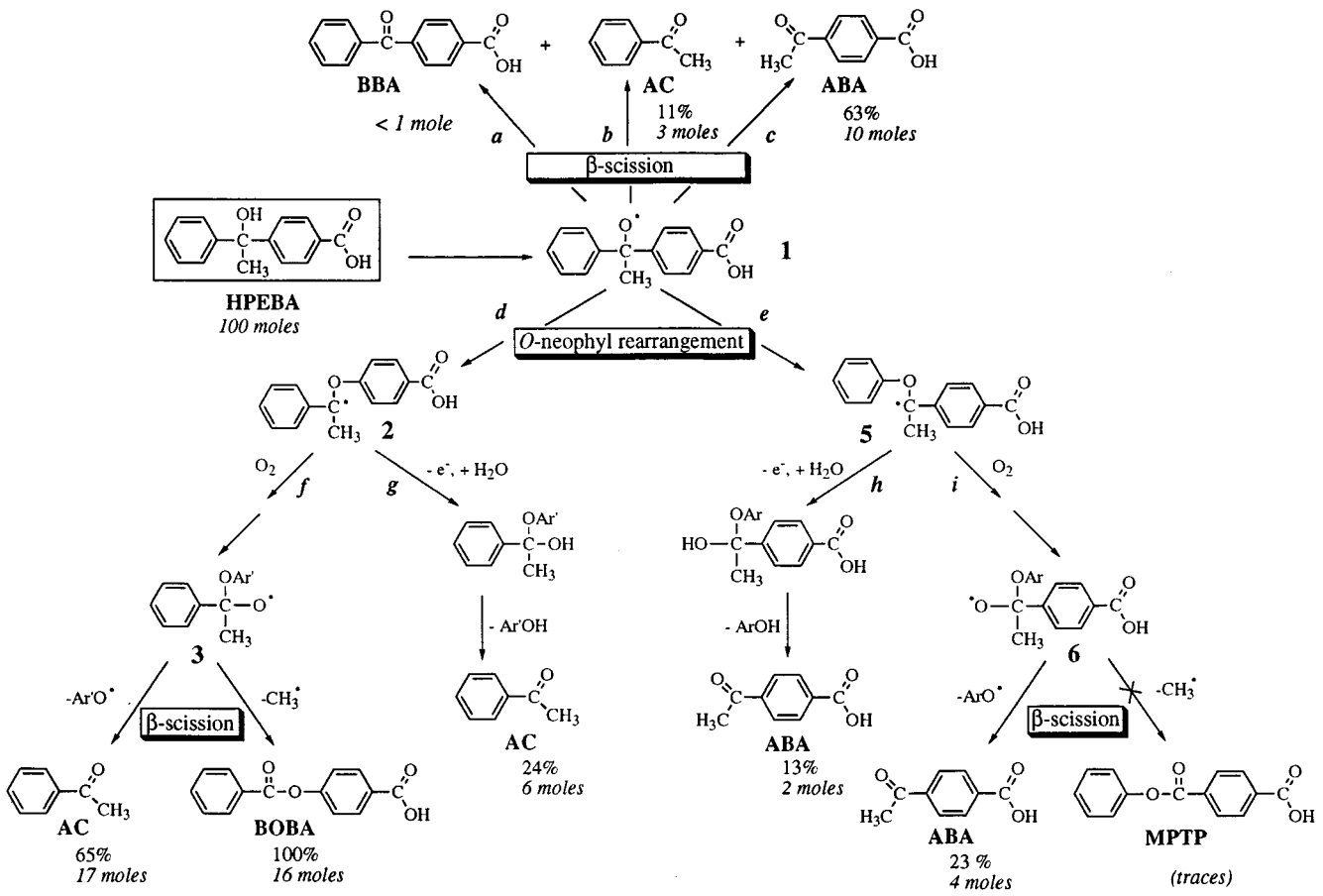
Scheme 3. Formation of ^{18}O-labeled AC and ABA after an *O*-neophyl rearrangement of intermediate **1**, using $H_2{}^{18}O$ or $^{18}O_2$ (direct β-scission from radical **1** generates unlabeled products); Ar = phenyl, Ar′ = *p*-carboxyphenyl



Scheme 4. Oxo-hydroxo tautomerism and oxygen rebound in $KHSO_5$ hydroxylation reaction catalyzed by Mn-TMPyP and performed in $H_2{}^{18}O$

A study of the influence of dioxygen showed that AC and BOBA probably have a common intermediate since, when the amount of dioxygen increases, the quantity of BOBA produced increases as well, but at the expense of AC formation. In addition, BOBA does not derive from a Baeyer-Villiger reaction on BBA because we checked that BBA is stable under the catalytic oxidation conditions. Furthermore, BOBA must incorporate a dioxygen-derived oxygen atom exclusively on the carbonyl position, the other ester oxygen atom being substrate-derived. According to these data, we propose that BOBA is formed through the β-scission of the alkoxy radical **3** (Scheme 5) with loss of a methyl radical. This C-β-scission pathway is in competition with the O-β-scission leading to acetophenone with loss of *p*-carboxyphenoxyl radical. It should be noted that, as far as we are aware, such an alternative between O- and C-β-scission has not previously been reported. A small difference between the bond dissociation energy of a C−C bond or a C−O bond in radical **3** would explain the formation of BOBA and AC from the same radical intermediate. The O_2-dependent pathway to BOBA formed at the expense of AC can now be explained as follows: under anaerobic conditions, the carbon-centred radical **2** (Scheme 3 and 5) follows a water-dependent route leading to AC containing a water-derived carbonyl oxygen atom, but under aerobic conditions, an oxygen-dependent pathway competes with this, leading to AC and BOBA both containing dioxygen-derived carbonyl oxygen atoms.

In a similar manner, the loss of a methyl radical from the oxygen-centred radical **6** (Scheme 5) could lead to MPTP with the same labeling as BOBA. However, MPTP was not detected among the reactions products, but careful analysis of the GC-MS spectra obtained from the labeling experiments showed traces of MPTP with a dioxygen-derived carbonyl oxygen atom. Since it is not stable under the reaction conditions, we wonder whether MPTP is formed and further oxidized, or whether only traces are formed. Our view is that if MPTP is formed, like BOBA, in significant amounts, then the production of ABA should be influenced in the same way as AC by the increase in acetonitrile or dioxygen concentrations. Since ABA proved to be indifferent to these changes of reaction conditions (see Figure 1 and 2), this fact precludes a competitive route leading to MPTP at the expense of ABA formation. Thus, we propose that MPTP is not formed in significant amounts during the reaction. However, we have presently no explanation to rationalize this particular difference in selectivity between C- and O-β-scissions of radicals **3** and **6**.



Scheme 5. Formation pathway of AC, ABA, BOBA and unlabeled BBA; the percentages indicate the part of the product formed through the considered route under a dioxygen atmosphere; the number of mols is the amount of each product formed if the initial amount of HPEBA is 100 mols

Formation of Labeled BBA

The reaction pathways presented in Scheme 5 do not explain the production of partially labeled BBA in the experiments performed in $H_2{}^{18}O$ or under $^{18}O_2$ (Table 3). Although BBA represents only 1% of the products, some additional experimental data were collected to try to understand the role of dioxygen and water in its formation, besides the direct β-fragmentation process. A conceivable pathway which could lead to BBA, after an initial hydroxylation of the methyl group and further oxidation of the resulting 1,1-diarylethane-1,2-diol, can be discarded since: (i) the catalytic oxidation of the related compound 1,1-diphenylethane-1,2-diol DED by Mn-TMPyP/$KHSO_5$ only produces unlabeled products in experiments performed in $H_2{}^{18}O$ or under $^{18}O_2$, and (ii) BBA is more efficiently produced when the methyl group of the substrate is trideuterated (see Table 2), this inverse deuterium isotope effect allows us to eliminate the possibility of an initial hydroxylation of the methyl group. In addition, this isotope effect is different from that observed for the loss of $CD_3^\bullet$ or $CH_3^\bullet$ from $C_6H_6C(CH_3)(CD_3)O^\bullet$ by β-scission (k_H/k_D = 1.15).[25] A carbon-centred radical such as Ar−C·(OH)-Ar′ is a possible intermediate since analogous radicals have been proposed in oxidations catalyzed by cytochrome P-450 or chemical models.[33][34] At present, these results do not allow us to propose a convincing mechanism to explain the available data on this minor reaction product.

Overall Mechanism for HPEBA Oxidation

An overall mechanism, presented in Scheme 5, can now be established with the involvement of two possible evolution pathways for the alkoxy radical **1**: direct β-scission or *O*-neophyl rearrangement. Both AC and ABA can form from **1** through either a direct β-scission (top of Scheme 5) or an *O*-neophyl rearrangement followed (bottom, on the left and on the right) or not (bottom, in the middle) by a β-scission in the ultimate step. BOBA is only produced from **1** through a *O*-neophyl rearrangement followed, after dioxygen addition, by a β-scission in the last step of the reaction (bottom, on the left). BBA is partially produced by direct β-scission of **1** (top) but other pathway(s) remain unidentified at the moment. In Scheme 5, the percentages under the products indicate the part of each product formed through the considered route under 1 atm of dioxygen. Assuming a starting quantity of 100 mols of HPEBA, we obtained for each product the quantities indicated below the percentages. These calculations afford an additional demonstration that

the proposed mechanism is coherent. Indeed, according to this scheme, if the reaction is performed under nitrogen instead of O_2 (according to Table 1, 4 mols of BOBA were still produced under N_2, probably due to the presence of traces of residual dioxygen), routes d + g should lead to 35 mols of AC (17 + 16 + 6 − 4 mols of residual BOBA) containing a water-derived oxygen atom. Adding the 3 mols of AC generated by β-scission gives a total number of 38 mols of AC produced. This quantity is consistent with the 44% yield experimentally observed under nitrogen (see Table 1). In addition, the fact that formation of BOBA was favored by increase in acetonitrile concentration (see Figure 1) can be explained by the decreasing polarity of the medium, which disfavors the β-scission pathway.[35]

Formation of Benzoquinone

Benzoquinone probably derives from the further oxidation of the aryl radicals (phenyl, *p*-carboxyphenyl, phenoxy and *p*-carboxyphenoxy radicals) released in the different β-scission processes. We have checked that phenol, benzoic acid and *p*-hydroxybenzoic acid, three putative evolution products of the aryl radicals (phenol and *p*-hydroxybenzoic acid are also formed through the water-dependent route, see Scheme 5), are quickly oxidized to BZQ by the catalytic system. An additional argument is that the oxidation of ALBA and DED, where almost no aryl radicals are released, gives only 1% of benzoquinone (Scheme 1). In contrast, a significant amount of BZQ is obtained from oxidation of HPEBA, DE and DPBA, for which the oxidation products are derived mainly from a $C_{aliph}-C_{ar}$ bond cleavage with release of aryl radicals (Scheme 1). Consequently, the formation of BZQ can be considered as proof of formation of aryl radicals during the oxidation process.

Conclusions

The catalytic oxidation of several tertiary diaryl alcohols has been achieved with $KHSO_5$ in the presence of Mn-TMPyP. The use of this biomimetic catalytic system represents an alternative and efficient process for oxidative conversion of tertiary alcohols, which are resistant to conventional oxidants. Interestingly, the reaction led to acetophenone and benzophenone derivatives, and also to an unexpected ester. This product distribution, and additional labeling experiments, provide useful insights into the mechanism of the C−C bond cleavage by this cytochrome P-450 model system. The key intermediate in this catalytic oxidation is an alkoxy radical which follows a β-scission route or, alternatively, undergoes an *O*-neophyl rearrangement. This latter route explains the formation of products containing dioxygen- or water-derived oxygen atoms. In addition the unprecedented formation of an ester derivative during the catalytic oxidation of tertiary diaryl alcohols can be considered as a proof of the involvement of an *O*-neophyl rearrangement in the reaction mechanism

Experimental Section

Materials: Potassium monopersulfate (the triple salt $[KHSO_5]_2[KHSO_4][K_2SO_4]$, Curox®) was kindly donated by Peroxid Chemie GmbH. Mn-TMPyP (pentaacetate form) was prepared according to ref.[36] AC, ABA, BBA, BZQ, BZP, PBZ and DE were purchased from Aldrich. $H_2{}^{18}O$ (96.5 atom%) was supplied by Eurisotop (Gif sur Yvette, France) and $^{18}O_2$ (96.8 atom%) was supplied by Leman (Saint Quentin en Yvelines, France).

Instrumentation: HPLC analyses were performed on a Waters Millipore chromatograph equipped with a U6 K injector, a diode array detector (Kontron Instrument) and a 10 μm Nucleosil C18 column (Interchrom). The eluent was a mixture of acetonitrile/triethylammonium acetate buffer 0.1M (pH = 6.5) in proportions 35:65 or 25:75 (v/v) for oxidation of HPEBA, DPBA and ALBA and 45:55 (v/v) for oxidation of DE and DED. The flow rate was 1 mL/min Detection was performed at 240 nm. GC-MS analyses were performed on a Hewlett Packard HP 6890 instrument coupled with a MSD 5973 mass spectrometer, using electron impact ionization at 70 eV. The GC column used was a non polar capillary column [25 m × 0.2 mm HP-5MS, cross-linked diphenyl (5%) and dimethylpolysiloxane (95%)] and the carrier gas was helium. The injector temperature was 250°C, and analyses were performed at 80°C for 2 min, then up to 200°C (10°C/min) where the temperature was maintained for 15 min. MS spectra were obtained on a Nermag R10/10H instrument. ^{1}H NMR spectra were recorded with a Bruker WM 250 spectrometer.

Preparation of HPEBA: The three-step procedure was adapted from ref.[37] and improved in terms of solvent used, purification and yields. *p*-Benzoylbenzoic acid (1 g, 4.4 mmol), (−)-menthol (2.8 g, 18 mmol) and *p*-toluenesulfonic acid (42 mg, 0.2 mmol) were heated for 8 h at 180°C. The crude product was dissolved in 50 mL ether/toluene 1/1 (v/v) and washed three times with a saturated solution of sodium carbonate. After addition of water, the organic layer was steam distilled up to 140°C in order to remove the excess menthol. The aqueous residue was then extracted with toluene, and the extracts were dried with sodium sulfate. After removal of solvent under vacuum, menthyl *p*-benzoylbenzoate was obtained as a brown oil (1.52 g, yield = 94%). − ^{1}H NMR ([D$_6$]DMSO): δ = 0.88 [d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3], 1.02 (m, 7 H, $2CH_3$ + CH), 1.25 (m, 2 H, CH_2), 1.56−1.88 (m, 4 H, 2 CH_2), 2.00 (m, 1 H, CH), 2.13 (m, 1 H, CH), 5.01 (m, 1 H, CH), 7.70 [t, ^3J(H,H) = 7.3 Hz, 2 H, 2 aromatic CH], 7.79−7.92 (m, 3 H, 3 aromatic CH), 7.97 [d, ^3J(H,H) = 8.5 Hz, 2 H, 2 aromatic CH], 8.23 [d, ^3J(H,H) = 8.5 Hz, 2 H, 2 aromatic CH].

Methylmagnesium iodide (3.7 mmol) was added dropwise to a stirred solution of menthyl *p*-benzoylbenzoate (674 mg, 1.8 mmol) in 9 mL anhydrous toluene under nitrogen at room temperature. After hydrolysis with 2 M aqueous hydrochloric acid, the organic layer was washed with water, dried over sodium sulfate and concentrated under vacuum. A brown solid was obtained and identified as menthyl *p*-(1-hydroxy-1-phenylethyl)benzoate (562 mg, yield = 82%). − ^{1}H NMR ([D$_6$]DMSO): δ = 0.84 [d, ^3J(H,H) = 6.9 Hz, 3 H, CH_3], 0.99 (m, 7 H, $2CH_3$ + CH), 1.21 (m, 2 H, CH_2), 1.64 (m, 2 H, CH_2), 1.79 (m, 2 H, CH_2), 1.97 (m, 4 H, CH+CH_3), 2.08 (m, 1 H, CH), 4.93 (m, 1 H, CH), 6.01 (s, 1 H, OH), 7.33−7.48 (m, 3 H, 3 aromatic CH), 7.54 [d, 2 H, ^3J(H,H) = 7.2 Hz, 2 aromatic CH], 7.68 [d, ^3J(H,H) = 8.4 Hz, 2 H, 2 aromatic CH], 7.98 [d, ^3J(H,H) = 8.5 Hz, 2 H, 2 aromatic CH].

Menthyl-*p*-(1-hydroxy-1-phenylethyl)benzoate (474 mg, 1.3 mmol) was dissolved in 30 mL aqueous ethanol containing 2.5 M KOH. The solution was refluxed for 4 hours. After removal of ethanol

under vacuum, menthol was extracted with ether. The aqueous layer was then acidified with hydrochloric acid until a brown oil precipitated, which was extracted with dichloromethane. The organic phase was washed with water saturated in sodium chloride until neutral pH and dried over sodium sulfate. Solvent was removed under vacuum. The resulting product was recrystallized from a dichloromethane/hexane mixture to yield pure HPEBA as a white powder (177 mg, yield = 58%). − ^{1}H NMR ([D$_6$]DMSO): δ = 1.96 (s, 3 H, CH$_3$), 5.97 (s, 1 H, OH), 7.29 [t, ^3J(H,H) = 7.3 Hz, 1 H, aromatic CH], 7.40 [t, ^3J(H,H) = 7.3 Hz, 2 H, 2 aromatic CH], 7.54 [d, ^3J(H,H) = 7.0 Hz, 2 H, 2 aromatic CH], 7.64 [d, ^3J(H,H) = 8.4 Hz, 2 H, 2 aromatic CH], 7.96 [d, ^3J(H,H) = 8.4 Hz, 2 H, 2 aromatic CH], 12.97 (br s, 1 H, COOH). − $C_{15}H_{14}O_3$(242.28): calcd. C 74.36, H 5.82; found C 74.12, H 5.74. − MS (DCI/NH$_3$): *m/z*: 260 [$M^+ + NH_4^+$], 242 [M^+], 225 [$(M - OH)^+$].

Preparation of CD$_3$-HPEBA: The procedure was the same as for HPEBA except that in the second step, methylmagnesium iodide was replaced by trideuterated methylmagnesium iodide (3 mmol). Reaction with menthyl *p*-benzoylbenzoate (727 mg, 2 mmol) followed by saponification gave CD$_3$-HPEBA as a white powder (277 mg, yield = 56% for the two steps). − ^{1}H NMR ([D$_6$]DMSO): δ = 5.97 (s, 1 H, OH), 7.29 [t, ^3J(H,H) = 7.3 Hz, 1 H, aromatic CH], 7.40 [t, ^3J(H,H) = 7.3 Hz, 2 H, aromatic CH], 7.54 [d, ^3J(H,H) = 7.0 Hz, 2 H, 2 aromatic CH], 7.64 [d, ^3J(H,H) = 8.4 Hz, 2 H, 2 aromatic CH], 7.96 [d, ^3J(H,H) = 8.4 Hz, 2 H, 2 aromatic CH], 12.97 (br s, 1 H, COOH); − $C_{15}D_3H_{11}O_3$(245.29): calc. C 73.47, H 5.71; found C 73.24, H 5.55. − MS (DCI/NH$_3$): *m/z*: 263 [$M^+ + NH_4^+$], 245 [M^+], 228 [$(M - OH)^+$].

Preparation of DPBA: The procedure was the same as for HPEBA except that in the second step, methylmagnesium iodide was replaced by phenylmagnesium iodide (3.2 mmol) and hydrolysis was performed with 2M aqueous NH_4Cl instead of 2N HCl. Reaction with menthyl *p*-benzoylbenzoate (787 mg, 2.2 mmol) followed by saponification gave DPBA as a cream-colored solid (330 mg, yield = 48% for the two steps). ^{1}H NMR ([D$_6$]DMSO): δ = 6.74 (s, 1 H, OH), 7.29−7.50 (m, 12 H, aromatic H), 8.00 [d, ^3J(H,H) = 8.4 Hz, 2 H, 2 aromatic CH], 12.96 (br s, 1 H, COOH) − $C_{20}H_{16}O_3 \cdot 0.2\ H_2O$ (307.95): calcd. C 78.00, H 5.37; found C 77.94, H 5.13.

Preparation of ALBA: The procedure was the same as for HPEBA except that in the second step, methylmagnesium iodide was replaced by allylmagnesium bromide (7 mmol) and hydrolysis was performed with 2M aqueous NH_4Cl instead of 2M HCl. Reaction with menthyl *p*-benzoylbenzoate (768 mg, 2.1 mmol) followed by saponification and purification by chromatography on silica gel (eluent used was CH_2Cl_2/MeOH 96/4, v/v) gave ALBA as a yellow oil which solidified under vacuum (79 mg, yield = 14% for the two steps). ^{1}H NMR ([D$_6$]DMSO): δ = 3.19 [d, ^3J(H,H) = 6.7 Hz, 2 H, CH$_2$], 4.95−5.20 (m, 2 H, CH$_2$), 5.78 (m, 1 H, CH), 5.93 (s, 1 H, OH), 7.28 [t, ^3J(H,H) = 7.4 Hz, 1 H, aromatic CH], 7.40 [t, ^3J(H,H) = 7.4 Hz, 2 H, 2 aromatic CH], 7.57 [d, ^3J(H,H) = 8.0 Hz, 2 H, 2 aromatic CH], 7.67 [d, ^3J(H,H) = 8.3 Hz, 2 H, 2 aromatic CH], 7.95 [d, ^3J(H,H) = 8.2 Hz, 2 H, 2 aromatic CH], 12.95 (br s, 1 H, COOH). − MS (DCI/NH$_3$): *m/z*: 303 [$(M^+ + N_2H_7^+$], 286 [$(M^+ + NH_4^+$], 268 [$(M - OH + NH_3)^+$], 251 [$(M - OH)^+$].

Preparation of DED: Phenylmagnesium bromide (3.6 mmol) was added dropwise to a stirred solution of ethyl glycolate (110 mg, 1.06 mmol) in anhydrous toluene (10 mL) under nitrogen at room temperature. After hydrolysis with 2M aqueous NH_4Cl, the organic layer was washed with water, dried over sodium sulfate and concentrated under vacuum. The resulting product was recrystallized from a dichloromethane/hexane mixture to yield pure DED as a white solid (141 mg, yield = 62%). − ^{1}H NMR ($CDCl_3$): δ = 1.8 (br s, 1 H, OH), 3.15 (br s, 1 H, OH), 4.17 (s, 2 H, CH$_2$), 7.25−7.45 (m, 10 H, aromatic H). − $C_{14}H_{14}O_2$ 0.2 H_2O (214.26): calc. C 78.48, H 6.59; found C 78.25, H 6.26.

Preparation of BOBA: Benzoyl chloride (1.3 mL, 10.8 mmol) was added dropwise to a stirred solution of *p*-hydroxybenzoic acid (1 g, 7.2 mmol) and triethylamine (2.6 mL, 18 mmol) in 45 mL of acetonitrile under nitrogen at room temperature. After stirring for 3 h, the mixture was poured into 35 mL diethyl ether and washed with water. The aqueous layer was acidified with hydrochloric acid to precipitate the product, which was extracted with diethyl ether. The organic layer was dried over sodium sulfate and the solvent removed under vacuum. The resulting solid was recrystallized from hot ethanol to give a white powder identified as BOBA (262 mg, yield = 15%). − ^{1}H NMR ([D$_6$]DMSO): δ = 7.55 [d, ^3J(H,H) = 8.6 Hz, 2 H, 2 aromatic CH], 7.74 [t, ^3J(H,H) = 7.7 Hz, 2 H, 2 aromatic CH], 7.89 [t, ^3J(H,H) = 7.4 Hz, 1 H, aromatic CH], 8.16 [d, ^3J(H,H) = 8.5 Hz, 2 H, 2 aromatic CH], 8.27 [d, ^3J(H,H) = 7.2 Hz, 2 H, 2 aromatic CH], 13.1 (br s, 1 H, COOH). − $C_{14}H_{10}O_4 \cdot 0.2H_2O$ (242.23): calc. C 69.42, H 4.16; found C 69.25, H 3.97. − MS (DCI/NH$_3$): *m/z:* 277 [$M^+ + N_2H_7^+$], 260 [$M^+ + NH_4^+$].

Preparation of MPTP: A solution of phenol (100 mg, 1.06 mmol) in 5 mL acetonitrile was added dropwise to a stirred solution of terephthaloyl chloride (1.08 g, 5.3 mmol) and triethylamine (500 μL, 3.6 mmol) in 25 mL of acetonitrile under nitrogen at room temperature. After stirring for 1 h, the mixture was poured into water and extracted with dichloromethane. The organic layer was dried over sodium sulfate and solvent was removed under vacuum. The product was purified by chromatography on silica gel (the eluent was dichloromethane/ethanol 95:5, v/v) as it was found to contain terephthalic acid as a by-product of the reaction. **MPTP** (62 mg, yield = 24%) was obtained as a white powder. ^{1}H NMR ([D$_6$]DMSO): δ = 7.40−7.49 (m, 3 H, 3 aromatic CH), 7.61 [t, ^3J(H,H) = 7.5 Hz, 2 H, 2 aromatic CH], 8.25 [d, ^3J(H,H) = 8.4 Hz, 2 H, 2 aromatic CH], 8.36 [d, ^3J(H,H) = 8.5 Hz, 2 H, 2 aromatic CH], 13.6 (br s, 1 H, COOH).

General Catalytic Oxidation Conditions: Unless otherwise stated, the reaction medium (1 mL of water/acetonitrile 9:1, v/v) contained 66 mM phosphate buffer pH 5, 500 μM substrate (introduced as a 25 mM solution in CH_3CN), 10 mM $KHSO_5$ (introduced as a 250 mM solution in water) and 200 μM *p*-diacetylbenzene (used as internal standard). Mn-TMPyP (10 μM) was introduced as a 1 mM solution in water in five consecutive 2 nmol additions, every two min. The first addition initiated the reaction. Reactions were performed at room temperature and monitored by HPLC. Yields were calculated after 10 min from the initial amount of substrate by comparison with calibration curves. For the oxidation of carbamazepine, a previously reported procedure was used.[19]

Competitive Oxidation of HPEBA with BOBA or MPTP: The reaction was carried out as described above, but with addition of 150 μM of BOBA or MPTP. After 10 min, the products were analyzed by HPLC. The amount of ester coming from the catalytic oxidation was estimated from the substrate conversion, so that the conversion of BOBA or MPTP initially introduced could be calculated.

Experiments Under Different Pressures of Dioxygen: In this case, the mixture contained 20% acetonitrile instead of 10%, and the Mn-TMPyP concentration was 50 μM. The reaction medium was placed in a Schlenk tube connected to a pressure captor and degassed by three consecutive freeze-thaw cycles under vacuum. It was then repressurized with the desired pressure of dioxygen, and nitrogen was added to maintain a final pressure of 1 atm. Mn-

TMPyP (previously degassed) was added in five consecutive additions by gas-tight syringe. HPLC analysis was performed after 10 min.

Experiments with D_2O: Solutions of the required concentrations and volume of buffer plus $KHSO_5$ on the one side, and Mn-TMPyP on the other side, were prepared and lyophilized using a Speed-Vac. Substrate and internal standard in CH_3CN and appropriate volumes of D_2O were added (in this case the total volume was 500 μL). The reaction was then carried out as described above.

Experiments with $H_2{}^{18}O$: In this case, the mixture contained 20% acetonitrile instead of 10%, and the Mn-TMPyP concentration was 50 μM. Solutions of the required concentration and volume of buffer plus $KHSO_5$ on the one side, and Mn-TMPyP on the other side, were prepared and lyophilized using a Speed-Vac. Substrate in CH_3CN and appropriate volumes of $H_2{}^{18}O$ were added (in this case the total volume was 500 μL). In the case of the reaction under dioxygen or nitrogen, the reaction medium was placed in a Schlenk tube connected to a pressure captor and degassed by three consecutive freeze-thaw cycles under vacuum. It was then repressurized with 1 atm of dioxygen or nitrogen. Mn-TMPyP (previously degassed) was added in five consecutive additions by gastight syringe. After 10 min, the mixture was saturated with NaCl and extracted with three 1 mL portions of dichloromethane. The organic phase was concentrated, and a solution of diazomethane in dichloromethane (prepared with an Aldrich MNNG diazomethane generation apparatus) was added to convert the carboxylic functions into methyl esters. After concentration, the sample was analysed by GC-MS (to analyze AC, which does not require prior derivatization, a 30 μL sample was taken after the first extraction and analyzed by GC-MS without further treatment). The percentage of ^{18}O incorporated in each product was determined by the relative abundances of the peaks at: *m/z* 120 and 122 [M^+], and *m/z* 105 and 107 [$(M - CH_3)^+$] for **AC**, *m/z* 178 and 180 [M^+], and *m/z* 163 and 165 [$(M - CH_3)^+$] for ABA methyl ester, *m/z* 240 and 242 [M^+], and *m/z* 209 and 211 [$(M - OCH_3)^+$] for BBA methyl ester, *m/z* 256, 258 and 260 [M^+], and *m/z* 105 and 107 [$(M - OC_6H_4COOCH_3)^+$] for BOBA methyl ester. The values obtained were corrected considering the ^{18}O content of the labeled water. Since BOBA and HPEBA methyl esters had the same mass and almost the same elution time, it was necessary to add 10% catalyst instead of 2% to ensure a complete conversion. In addition, a peak at *m/z* 241 [$(M - CH_3)^+$] corresponding only to HPEBA methyl ester allowed us to check the possible presence of small amounts of nonconverted substrate and to calculate its contribution to the molecular peak. Control experiments to check if the products exchanged their oxygen with $H_2{}^{18}O$ were performed under the same conditions using 200 μM AC, ABA, BBA or BOBA instead of HPEBA.

Experiments with $^{18}O_2$: The reaction conditions were the same as for experiments under different pressures of dioxygen, but in this case the Schlenk tube was repressurized with 1 atm of $^{18}O_2$ and the total volume was 500 μL. After 10 min, the sample was treated and analyzed as described for the $H_2{}^{18}O$ experiments. The values obtained from ^{18}O incorporations were corrected considering the ^{18}O content of the labeled dioxygen.

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