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The Radical Chemistry of *t*-Butyl Hydroperoxide (TBHP) - Part 3 - Further Studies on Hydrocarbon Activation

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Abstract : Further aspects of the chemistry of TBHP in the presence of Fe^{II} and Fe^{III} species have been investigated. Now all the results previously reported with TBHP can be understood in terms of radical chemistry. Oxidation states of iron higher than Fe^{III} are not involved.

In two recent papers[1,2] we have reexamined our interpretation of TBHP chemistry as being based on higher oxidation states of iron. By addition of oxidants to maintain the Fe^{III} state or of reductants to keep the Fe^{II} state, a major simplification of the chemistry results. Thus in the Fe^{III} chemistry, the major role is played by the *t*-butylperoxyl radical and the part played by the *t*-butoxyl radical is minor. In the Fe^{II} based chemistry the roles are reversed. The two earlier papers[1,2] dealt with the chemistry of cyclohexane. In this third paper we are concerned with substrates which are more easily oxidized.

In previous articles[3-6] we have reported the facile oxidation of α- 1 and γ- terpinenes 2 to *p*-cymene 3 using TBHP and Fe^{III}. We have confirmed the efficient conversion of γ-terpinene to *p*-cymene using either Fe^{III}-TBHP or Fe^{II}-TBHP. In a comparison of various atmospheres (Table 1) using Fe^{II} and Fe^{III}, it was clear that the presence of oxygen did not increase the efficiency of the reaction. No oxygenated products from the hydrocarbon were detected under any conditions.

It was of interest to run a competition experiment between α- and γ-terpinenes. γ-Terpinene 2 is a skipped diene and should therefore be more reactive than α-terpinene. However, the difference is small (Table 2).

Table 1 : Influence of the Atmosphere and the Oxidation State of the Iron on the Oxidation of γ-Terpinene

Entry	Conditions	Atmosphere	2	3
1	$FeCl_2$+1VCl_3	Air	4.31	0.81
2	$FeCl_2$+1VCl_3	O_2	4.14	0.97
3	$FeCl_3$	Air	3.72	1.13
4	$FeCl_3$	O_2	3.82	1.11

1 mmol of Fe; 1 mmol of TBHP; 5 mmol of γ-terpinene; 30 mL of pyridine; RT; 24 Hrs.

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Figure 1

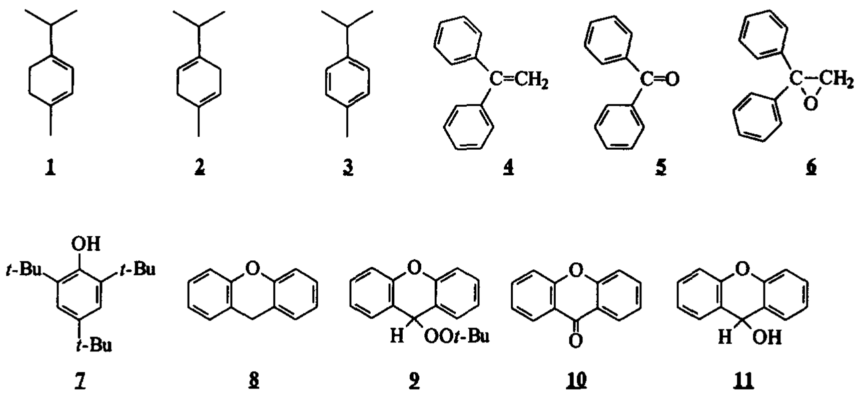


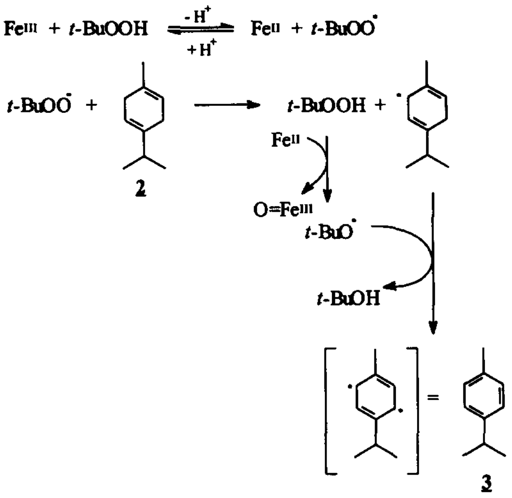
Table 2 : Competition between α- and γ-Terpinene

Entry	Time (hrs)	1	2	3
1	0	5.00	5.00	0
2	0.25	4.91	4.88	0.51
3	0.75	4.88	4.76	0.77
4	1	4.55	4.42	0.75
5	5	4.67	4.53	1.09
6	24	4.61	4.51	1.12

1 mmol of $FeCl_3$; 1 mmol of TBHP; 5 mmol of γ-terpinene; 30 mL of pyridine; RT; Air.

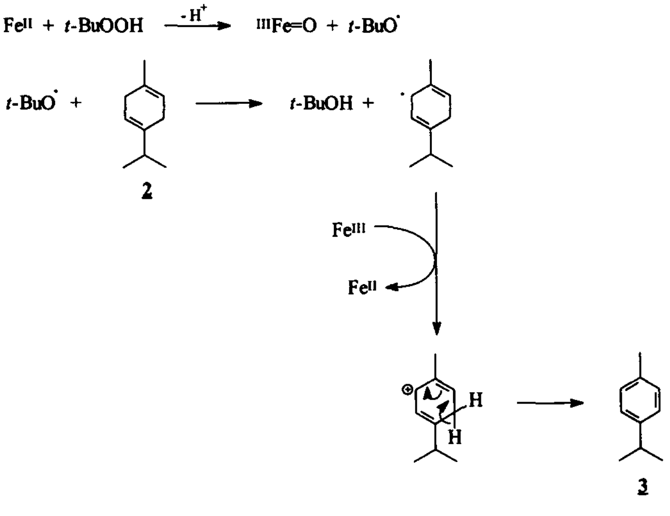
In order to study accurately the mechanism of this aromatization, we have decided to work in stoichiometric amounts of TBHP compared to the iron. Under these specific conditions, 1 mole of TBHP yielded 1 mole of *p*-cymene with the concomitant formation of 1 mole of *t*-butanol. In the case of Fe^{III} catalysis, Fe^{II} was not detected at the end of the reaction, which supports the mechanistic proposal described in Scheme 1a. The duration of the reaction was strongly reduced compared to that of the reaction of functionalization of cyclohexane since the ability of peroxyl radicals to abstract a hydrogen from the substrate is the driving force of the reaction. Therefore, the Fe^{III}-catalyzed functionalization of γ-terpinene is interpreted to result from two consecutive abstractions of hydrogen from the *t*-BuOO$^{\bullet}$ and *t*-BuO$^{\bullet}$ radicals. Fe^{III}, regenerated at the end of the reaction, can enter another catalytic cycle if an additional portion of TBHP is added to the system. This mechanistic interpretation is compatible with the experimental facts since the functionalization of γ-terpinene (or α-terpinene) was quantitative with respect to the amount of TBHP.

Scheme 1a : Fe^{III}-catalyzed Functionalization of γ-Terpinene



In the case of Fe^{II}/TBHP system, we postulate that the reaction was initiated by the abstraction of a hydrogen from *t*-BuO$^{\bullet}$ radicals. The generated carbon radical would then be oxidized to the resulting carbocation with the concomitant reduction of Fe^{III} to Fe^{II}. This mechanistic proposal (Scheme 1b) is supported by the detection of Fe^{II} at the end of the reaction.

Scheme 1b : Fe^{II}-catalyzed Functionalization of γ-Terpinene



Under Fe^{III}-TBHP oxidation, 1,1-diphenylethylene was converted efficiently into benzophenone.[4,5] We examined this reaction again with a control on the valence state of the iron (Table 3). Clearly both oxidation states permit cleavage. As expected,[5] oxygen was shown to be an important source of ketonization (Table 4), although without Fe^{III} and TBHP no reaction was observed. The importance of oxygen was confirmed in Table 5 and it was shown that the TBHP was only needed as a catalyst.[5] The excess of peroxide shown in Table 5 comes from the peroxide formation from the reaction with oxygen (*vide infra*).

Table 3 : Influence of the Oxidation State of the Iron Catalyst

Entry	Conditions	Atmosphere	Time (hrs)	4	5	6
1	$FeCl_2$	Air	16.5	3.71	0.21	0
2	$FeCl_3$	Air	16.5	4.0	0.30	0
3	$Fe(ClO_4)_2$+0.5$SnCl_2$	O_2	8	3.97	0.77	0
4	$Fe(NO_3)_3$	O_2	8	3.00	2.00	0
5	$Fe(NO_3)_3$+5$K_3Fe(CN)_6$	O_2	12.5	2.72	1.58	0
6	$FeCl_3$+5$FeK_3(CN)_6$	O_2	17	2.62	1.96	0.23

1 mmol of Fe; 5 mmol of diphenylethylene; 1 mmol of TBHP; 30 mL of pyridine; RT.

Table 4 : TBHP Profile

Entry	x	Atmosphere	Time (hrs)	4	5	6	$TBHP_{left}$
1	0	O_2	~ 15	~ 5	0	0	0
2	0.5	O_2	12.5	3.13	1.39	0	0.18
3	1	O_2	12.5	3.15	1.92	0	0.24
4	10	O_2	12.5	0.10	3.82	0	0.72

1 mmol of $Fe(NO_3)_3$; 5 mmol of diphenylethylene; x mmol of TBHP; 30 mL of pyridine; RT.

Table 5 : Influence of the Atmosphere on the Fe^{III}-catalyzed Oxidation of 1,1-Diphenylethylene

Entry	Atmosphere	4	5	6	$TBHP_{left}$
1	O_2	3.05	2.14	0.14	1.1-1.3
2	Air	4.61	0.32	0.08	1.3
3	Ar	4.81	0.12	0.10	1.4-1.9

1 mmol of $FeCl_3$; 5 mmol of diphenylethylene; 1 mmol of TBHP; 30 mL of pyridine; RT; 15 hrs.

The effect of picolinic acid (PA), as we have already commented,[1,2] was negligible (Table 6). Since the reactions of TBHP are all radical in character, this is not surprising. In contrast, Gif chemistry is only seen in the presence of the right kind of carboxylic acid. Similarly the Gif solvent pyridine is not essential and the ketonization reaction takes place in acetonitrile and in ethyl acetate (Table 7), but not in tetrahydrofuran (THF) which is a trap for oxygen radicals.[7]

Table 6 : Influence of the Addition of Picolinic Acid (PA)

Entry	PA	Time (hrs)	4	5	6
1	0	0.5	4.57	0.31	0
		2	4.15	0.76	0.09
		17	2.97	2.00	0.23
2	3	0.5	4.63	0.22	0.08
		2	4.44	0.61	0.09
		17	2.31	2.37	0.24

1 mmol of $FeCl_3$; 5 mmol of diphenylethylene; 1 mmol of TBHP; 30 mL of pyridine; RT; Oxygen.

Table 7 : Influence of the Solvent

Entry	Solvent	4	5	6
1	Pyridine	3.42	1.24	0.12
2	CH_3CN	3.42	1.38	0.12
3	EtOAc	4.68	0.94	0.10

1 mmol of $FeCl_3$; 5 mmol of diphenylethylene; 1 mmol of TBHP; 30 mL of solvent; RT; Oxygen; 5 hrs.

If the formation of benzophenone and formaldehyde[8] is due, in the TBHP case, to a radical chain reaction then this should be capable of initiation using AIBN. In agreement (Table 8), a reaction in benzene under oxygen using AIBN and refluxing afforded a better yield of benzophenone than a reaction with 1 TBHP in pyridine at room temperature.

Table 8 : Comparison with a typical Radical Chain Reaction using AIBN as Radical Initiator

Entry	Conditions	Time (hrs)	4	5	6
1	AIBN (benzene) reflux	3	0.13	2.60	1.87
2	TBHP (pyridine) RT	5	3.42	1.24	0.12

5 mmol of diphenylethylene; 2.5 mmol of AIBN (0.5 mmol every 15 minutes) or 1 mmol of TBHP;
30 mL of solvent; Oxygen; 3 hrs.

In our two earlier papers[1,2] we noted that 2,4,6-tri-*t*-butylphenol 7 was an excellent trap for both *t*-butoxyl and *t*-butylperoxyl radicals. This phenol should then inhibit the reaction. Supporting data are given in Table 9.

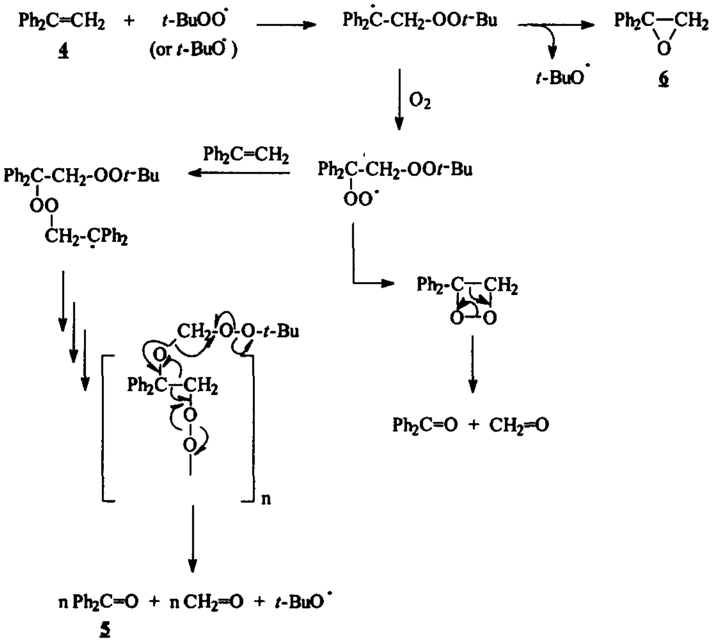
Table 9 : Influence of the Addition of 2,4,6-tri-*t*-Butylphenol 7 on the Oxidation of 1,1-Diphenylethylene

Entry	Conditions	4	5	6
1	5 mmol of 7	4.79	0.36	0
2	0 mmol of 7	3.42	1.24	0.12

1 mmol of $FeCl_3$; 5 mmol of diphenylethylene; 1 mmol of TBHP; 30 mL of pyridine; RT; Oxygen, 5 hrs.

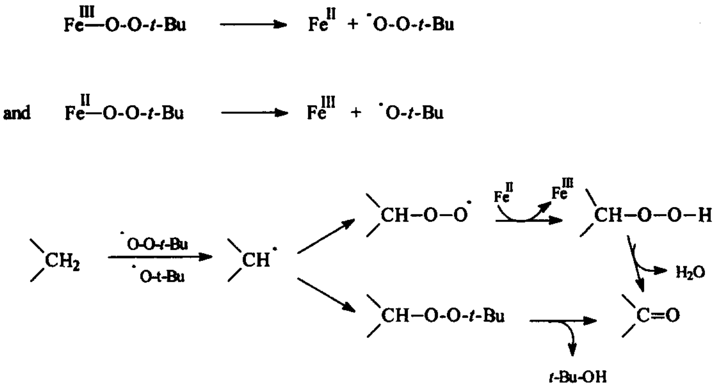
In Scheme 2 we propose a simple mechanism to explain the formation of benzophenone and formaldehyde. Of course, the reaction could also be initiated by a *t*-butoxyl radical or, as already shown (Table 8), by an AIBN derived radical. In our earlier work[5] we noted that the addition of azide ion afforded $Ph_2C(OH)\text{-}CH_2N_3$. We now propose that this is formed by oxidation of the azide ion to the azide radical.

Scheme 2 : Proposed Mechanism for the Functionalization of Diphenylethylene



In our previous studies of TBHP chemistry[3] we showed that fluorene, xanthene and diphenylmethane could also be converted into the appropriate ketones. For fluorenone there was good evidence that it was formed via the hydroperoxide, derived from oxygen, or from the mixed *t*-butylperoxide by fragmentation. These results are in accord with radical chemistry, although the original interpretation[3] was different. We have confirmed that both Fe^{II} and Fe^{III} produce the same chemistry. Thus, we can now propose the revised mechanism shown in Scheme 3. This Scheme can be applied to fluorene, xanthene and diphenylmethane[3].

Scheme 3 : Revised Mechanism for the Oxidation of Fluorene, Xanthene and Diphenylmethane



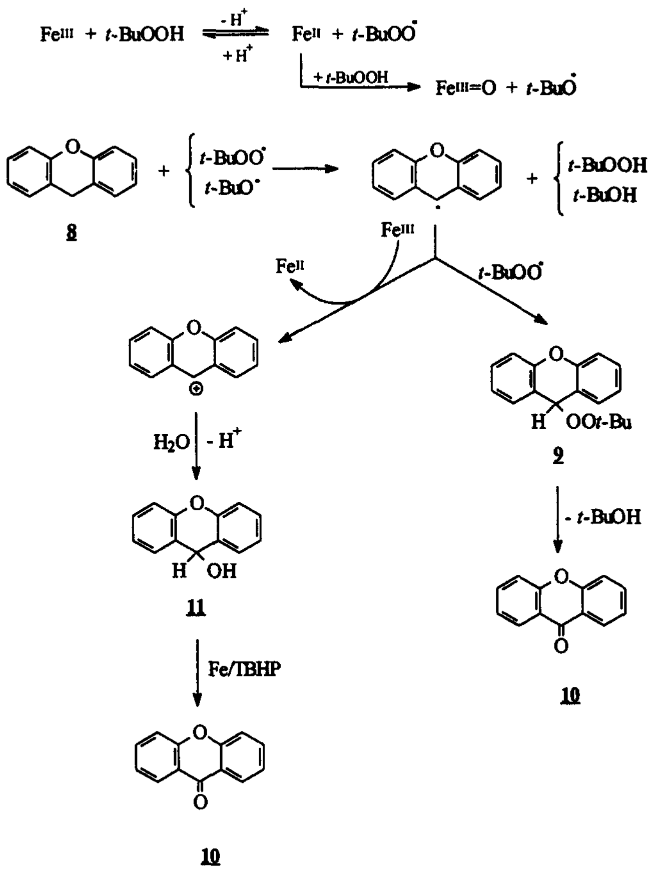
In the previous work,[3] xanthene was shown to be converted to the mixed *t*-butylperoxide and thence to xanthone. Oxygen did not seem to be important in this reaction. We were able to confirm these results as shown in Table 10. The reactions under argon and under oxygen gave the same yield of products. The difference between these results and those for fluorene must be attributed to the greater ease of abstraction of hydrogen from the CH_2 of xanthene by the *t*-BuOO$^•$ radical. Thus, the capture of the derived carbon radical by *t*-BuOO$^•$ is facilitated. The effect must be due to the oxygen bridge. Thus only a simple modification of Scheme 3 would be needed. Under our specific conditions, 9-hydroxyxanthene 11 was formed concomitantly to xanthone 10. We have demonstrated that 11 did not result from the mixed peroxide 9, since the decomposition of the latter under the reaction conditions afforded the xanthone 10 only. On the other hand, the formation of 11 could be explained by the involvement of the resulting carbocation, generated from the oxidation of the xanthyl radical with the concomitant reduction of Fe^{III} to Fe^{II}. This hypothesis is supported by the fact that Fe^{II} was detected at the end of the reaction (Scheme 4).

Table 10 : Fe^{III}-catalyzed Functionalization of Xanthene

Entry	Atmosphere	8	9	10	11
1	Argon bubbling	0	0.42	3.55	0.71
2	Oxygen bubbling	0	0.30	3.52	1.05

0.5 mmol of $Fe(NO_3)_3$; 5 mmol of xanthene; 10 mmol of TBHP; 30 mL of pyridine, 1 hr.

Scheme 4 : Mechanism for the functionalization of Xanthene



In agreement with prior work,[3] the oxidation of triphenylmethane afforded mainly the mixed *t*-butylperoxide. This is in accordance with the coupling of the two long-lived radicals.[9] The formation of triphenylmethylhydroperoxide was seen using an excess of TBHP. This is to be expected from the formation of oxygen, as already explained in Parts 1 and 2.[1,2] The most interesting reaction reported earlier was that the addition of TEMPO stopped completely the generation of the mixed peroxide and gave only the hydroperoxide from oxygenation of the trityl radical. We were able to confirm these results and propose a logical explanation since the reaction of TEMPO with oxygen-centered radicals leads to the formation of a significant amount of oxygen.[10] Therefore, all the results reported here, using Fe/TBHP system, can be understood in terms of radical chemistry.

By dealing with easily oxidable substrates, we have shown that *t*-butyl peroxyl radicals, generated from the reaction of Fe^{III} with TBHP, are able to abstract a hydrogen from the activated methylene groups. These results are additional evidence for the radical character of Fe/TBHP chemistry.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were performed in deuterochloroform with tetramethylsilane (TMS) as an internal reference on a Varian XL 200E spectrophotometer.

Melting points were determined with a Kofler hot stage apparatus.

Gas chromatographic analysis was carried out on a Hewlett-Packard 5890 series II instrument, equipped with a flame ionization detector with N_2 as a carrier gas and a Hewlett Packard 3396 A integrator. The columns used were either a DB-Wax (30 m long, 0.25 μm film thickness, 0.32 mm i.d.) or a DB-5 capillary column (30 m long, 0.32 mm i.d., 25 μm film thickness) from J&W scientific.

Column chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh).

Unless otherwise stated, all solvents and chemicals were purchased from commercial sources and used, after verification, without any further purification. TBHP was used as a 90% aqueous solution, after having checked its purity by iodometric titration.

Preparation of the authentic samples :

- *Preparation of t-butyl fluorenyl peroxide* : The peroxide has been isolated from a usual Fe^{III}/TBHP experiment since several attempts of synthesis from the alcohol in acidic conditions have failed due to the instability of the peroxide (gives spontaneously fluorenone). The procedure was as follows: To a solution of $FeCl_3$, $6H_2O$ (0.27g, 1mmol, 1eq.) and fluorene (5g, 30mmol, 30eq.) in acetonitrile (15mL) was added at room temperature *t*-butyl hydroperoxide (0.11mL, 1mmol, 1eq.). The reaction mixture was stirred at ambient temperature for about 1 hour, quenched with a saturated solution of sodium bicarbonate. The aqueous phase was extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. A purification by column chromatography (hexane/EtOAc : 95/5) gave, in addition to fluorene and fluorenone, *t*-butyl fluorenyl peroxide as a white solid.

White solid : m.p. (°C) : 92-94. ^1H NMR (200 MHz, $CDCl_3$) δ : 1.36 (s, 9H); 5.95 (s, 1H); 7.25-7.43 (m, 4H); 7.62-7.76 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ : 26.6; 80.9; 84.9; 119.9; 126.6; 127.5; 129.3; 141.0; 141.9.

- *Preparation of t-butyl xanthyl peroxide*[11] : A 90% aqueous solution of *t*-butyl hydroperoxide (2.75mL, 5eq.) was added to a solution of 9-hydroxyxanthene (1.0g, 5mmol, 1eq.) in glacial acetic acid

(50mL). After 1 hour at room temperature with stirring, the mixture was poured on crushed ice, stirred vigorously and the precipitated *t*-butyl xanthyl peroxide, which separated, was filtered and recrystallized in ethanol.

Colorless crystals : m.p.(°C) : 72-73. ^{1}H NMR (200MHz, $CDCl_3$) : δ (ppm) : 1.08 (s, 9H, -$C(CH_3)_3$); 5.96 (s, 1H, -<u>H</u>C-*t*-Bu); 7.12-7.25 (m, 4H, Harom.); 7.35-7.44 (m, 2H, Harom.); 7.58-7.63 (m, 2H, Harom.). ^{13}C NMR (60MHz, $CDCl_3$) : δ (ppm) : 26.3; 75.4; 80.3; 116.6; 119.0; 122.8; 130.0; 131.4; 152.6.

- *Preparation of xanthyl hydroperoxide*[12] : 9-hydroxyxanthene (2.0g, 10mmol, 1eq.) in ether (10mL) was stirred for 4 hours with aqueous 30% hydrogen peroxide (30mL, 30eq.). Xanthyl hydroperoxide was precipitated by the addition of light petroleum to the ethereal extract, and recrystallized from petroleum ether.

Colorless crystals : ^{1}H NMR (200MHz, $CDCl_3$) : δ : 5.77 (s, 1H, -C<u>H</u>(OOH)-); 7.06-7.25 (m, 8H, Harom.). ^{13}C NMR (50MHz, $CDCl_3$) : δ : 75.9; 116.6; 118.5; 122.9; 130.1; 131.1; 152.6.

- *Preparation of t-butyl triphenyl peroxide*[12] : *t*-Butyl hydroperoxide, previously dried over MgSO4, (2.75mL, 5eq.) was added to a solution of triphenylmethanol (1.3g, 5mmol, 1 eq.) in glacial acetic acid (100mL) containing concentrated sulfuric acid (0.25mL). After 2 hours at room temperature, the mixture was poured on ice, stirred vigorously, and the *t*-butyl triphenylmethyl peroxide, which separated, was filtered and recrystallized in methanol.

White solid : m.p.(°C) : 70-72. ^{1}H NMR (200MHz, $CDCl_3$) : δ (ppm) : 1.01 (s, 9H, -$C(CH_3)_3$); 7.22-7.44 (m, 15H, Harom). ^{13}C NMR (60MHz, $CDCl_3$) : δ (ppm) : 26.3; 79.7; 127.0; 127.2; 129.2; 143.6.

- *Preparation of triphenyl hydroperoxide*[13] : Triphenylmethanol (1.45g, 5.55mmol, 1eq.), as a saturated ethereal solution (20mL), was stirred for 6 hours with a 30% aqueous solution of hydrogen peroxide (30mL, 50eq.) and concentrated sulfuric acid (0.1mL). The ether extract was washed with a saturated solution of sodium bicarbonate, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

White solid (Purity checked by iodometric titration) : ^{1}H NMR (200MHz, $CDCl_3$) : δ : 7.20-7.45 (m, 15H, Harom.). ^{13}C NMR (50MHz, $CDCl_3$) : δ : 82.0; 127.6; 128.8; 142.3.

Typical experimental procedure for the reactions with fluorene, xanthene and triphenylmethane (NMR Quantification) :

To a solution of the substrate (5mmol) and $FeCl_3,6H_2O$ (1mmol) in pyridine (30mL) was added TBHP (xmmol) with stirring at room temperature. At the end of the reaction (typically 24 hours), an aliquot (5mL) of the reaction mixture was quenched with a 20% aqueous solution of sulfuric acid (25mL) at 0°C and extracted with diethyl ether (3x50mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Quantification was carried out by ^1H NMR using 1,1,2,2-tetrachloroethane or 1,2-dichloroethane (experiments with fluorene and xanthene) as an internal standard and using deuterated chloroform as a solvent.

Typical experimental procedure for the reactions with γ-Terpinene and diphenylethylene (GC Quantification) :

To a solution of $FeCl_3.6H_2O$ (1mmol) and the substrate (5mmol) in pyridine (30mL) was added TBHP (xmmol) with stirring at room temperature. After 24 hours, an aliquot (1mL) of the reaction mixture was added to a saturated solution of aqueous sodium bicarbonate (5mL). The aqueous solution was extracted with diethyl ether (10mL). The organic layer was dried over $MgSO_4$ and filtered. Naphthalene solution (1mL, 0.08M in diethyl ether) was added as an internal standard to the filtrate. The products were analyzed by gas chromatography.

General procedure for quantification :

Unless otherwise stated, all the results are given in mmol.

- *Determination of residual oxidizing power* : An aliquot (1mL) of the reaction mixture was added to a solution of water (5mL) and acetic acid (5mL) containing KI (0.5g). After having stood at room temperature under an argon atmosphere for 30 minutes, the I_2 that had formed was titrated with a $Na_2S_2O_3$ solution (40mM; starch as indicator) until the solution became colorless.

- *General procedure[14] for the titration of Fe^{II} :* An aliquot of the reaction mixture (2mL) was added to a 25% aqueous H_2SO_4 solution (20mL) at room temperature under an argon stream. After 5 minutes, the mixture was diluted to 250mL with distilled water. 5mL of this solution was added to a mixture of $(NH_4)H_2PO_4$ (10mL at 10%) and water (15mL). The pH of the solution was adjusted to 2.0-2.1 with a H_2SO_4 solution (25%). The solution was transferred to a separatory funnel and 4,7-diphenyl-1,10-phenanthroline solution in absolute ethanol (30mL at 0.36mM) was added. After shaking for a few seconds and allowing the solution to stand for several minutes, the solution was extracted with 10mL of $CHCl_3$. The organic phase was transferred to a 25mL volumetric flask and the solution was diluted to volume with absolute ethanol. The absorbance was measured in a 1cm cell at 540nm. The quantity of Fe^{II} was calculated as 1µg of Fe^{II} corresponding to an absorbance of 0.0156.

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