

Insight into the Chemoselective Aromatic vs Side-chain Hydroxylation of Alkylaromatics with H₂O₂ Catalyzed by a Non-Heme Imine Based Iron Complex

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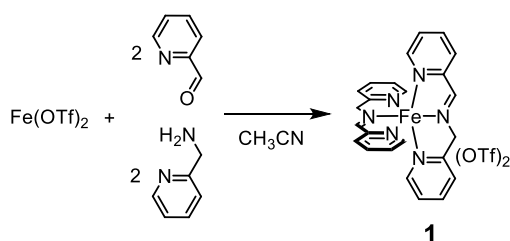
Abstract: The oxidation of a series of alkylaromatic compounds with H₂O₂ catalyzed by an imine non-heme-iron complex prepared in situ by reaction of 2-picolylaldehyde, 2-picolylamine, and Fe(OTf)₂ in a 2:2:1 ratio leads to a marked chemoselectivity for aromatic ring hydroxylation over side-chain oxidation. This selectivity is herein investigated in detail. Side-chain/ring oxygenated products ratio was found to increase upon decreasing the bond dissociation energy (BDE) of the benzylic C-H bond in line with expectation. Evidence for competitive reactions leading either to aromatic hydroxylation via electrophilic aromatic substitution or side-chain oxidation via benzylic hydrogen atom abstraction, promoted by a metal-based oxidant, has been provided by kinetic isotope effect analysis.

Introduction

The conversion of aromatic compounds to phenolic products by hydroxylation of aryl rings represents one of the most challenging transformation in synthetic organic chemistry. The relevance of phenolic moieties in a variety of natural products, pharmaceutical compounds and fine chemicals obtained in industrial processes^[1,2] calls for the development of simple synthetic protocols for the direct insertion of hydroxyl functions in aromatic rings. Notwithstanding, only few oxidizing systems are available for the catalytic conversion of aromatic substrates to phenols.^[3-10]

Among these catalytic systems a special attention has been devoted to those involving the environmentally friendly and sustainable oxidant H₂O₂ and catalysts based on abundant and low toxic metals, such as iron and manganese. Along this line good results have been obtained in the aromatic oxidation catalyzed by heme and non-heme metal complexes which are biomimetic models of natural oxygenases, although most of them are stoichiometric transformations.^[11-31]

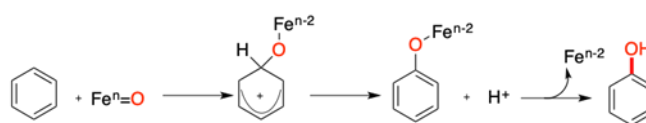
We have recently reported that the iminopyridine complex **1**, easily obtained by in situ self-assembly of 2-picolylamine, 2-picolylaldehyde and iron(II) triflate in a 2:2:1 ratio in acetonitrile (Scheme 1)^[32-36] efficiently catalyzes the hydroxylation of aromatic rings with H₂O₂ under mild conditions.^[37]



Scheme 1. Self-assembled imine-based non-heme iron(II) complex **1**.

Kinetic isotope effect (KIE) studies, use of radical scavengers, substituent effects on inter- and intramolecular selectivity and rearrangement experiments converged to the operation of a

metal-based electrophilic aromatic substitution (S_EAr) pathway with no involvement of free radical species (Scheme 2).^[35,37] Concerning the nature of the active species (metal based oxidant) we were not able to isolate the intermediate, formed upon addition of H₂O₂ to **1**, which is competent for the oxidation.^[35] Generally activation of H₂O₂ by non-heme iron complexes is due to the formation of Fe^{III}-OOH intermediates which undergo either an heterolytic O-O bond cleavage to produce a highly reactive Fe^V=O complex or an homolytic cleavage of the same bond leading to a Fe^{IV}=O complex and HO•.^[35,38-45] Both intermediates mediate aromatic hydroxylation, albeit with different rates, selectivities and KIEs.^[11-24,45,46] With **1** and H₂O₂, we observed a KIE and a selectivity consistent with those reported in (stoichiometric) aromatic hydroxylation mediated by putative Fe^V=O species.^[37] On these basis we proposed the formation of a similar high-valent iron-oxo complex after initial oxidation of the Fe(II) complex **1** to Fe(III) followed by detachment of a pyridine arm, coordination and activation by H₂O₂.^[34,37]



Scheme 2. Proposed mechanism for aromatic hydroxylation of C-H bonds promoted by imine-based non-heme iron(II) complex/H₂O₂.

One of the major challenges in aromatic hydroxylation of substrates bearing benzylic C-H bonds is the competition of side-chain oxidation. Most of the oxidation processes and in particular those involving free radical species such as HO• and HOO•, are characterized by a poor selectivity^[9,13,14,16,47-51] with a certain preference for the aromatic side-chain in view of the relatively low bond dissociation energies (BDEs) of the benzylic C-H bonds especially when secondary or tertiary benzylic C-H bonds are present.^[13,14,47-49,52,53]

When applied to the oxidation of alkylaromatics (toluene, ethylbenzene, cumene), the **1**/H₂O₂ system showed a marked preference (chemoselectivity) for aromatic ring hydroxylation

over aliphatic side-chain oxidation. Phenolic compounds were obtained in satisfactory yields accompanied by small amounts of side-chain oxygenated products.^[37,54] Remarkably, the chemoselectivity for aromatic hydroxylation was significantly higher than that displayed by other iron catalysts,^[20,47,55-57] allowing the inclusion of **1**/H₂O₂ system in the restricted family of the most selective catalytic systems.^[4,8-10,24]

In this context it is interesting to note that the **1**/H₂O₂ system allowed the direct conversion of phenylalanine to tyrosine isomers without overoxidation or side-chain functionalization.^[36]

In order to gain more insight into this high chemoselectivity and define its potential, in this work we focused our attention on the oxidation chemoselectivity of polycyclic alkylaromatic substrates containing more reactive benzylic C-H bonds characterized by relatively low BDE values (75-82 kcal/mol, Chart 1).^[59]

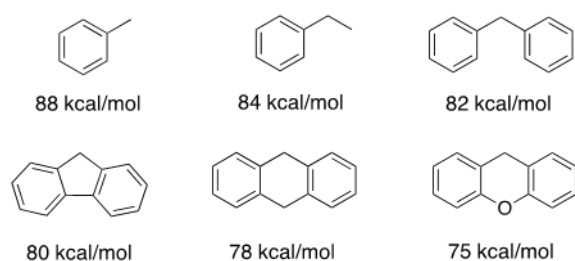


Chart 1. Benzylic C-H BDE values for some alkylaromatic substrates.

In particular, the variation of ring/side-chain oxidation products ratio has been analyzed in terms of substrate benzylic C-H BDE values. Deuteration of the benzylic hydrogens provided additional insights into the mechanism of aliphatic side-chain oxidation.

Results and discussion

Oxidation reactions were carried out by mixing Fe(OTf)₂(CH₃CN)₂ (2.5 μmol, OTf⁻ = CF₃SO₃⁻), 2-picolylaldehyde and 2-picolylamine (5.0 μmol each) followed by the substrate (250 μmol) in CH₃CN at 25°C. A solution of H₂O₂ (50 μmol, diluted from a 35% w/w H₂O₂ solution) was then added by a syringe pump in 30 minutes and the reaction was left under vigorous stirring for 90 minutes. After addition of the internal standard the reaction mixture was filtered over a short pad of SiO₂ eluting with AcOEt, and analyzed by GC and ¹H NMR (see Electronic Supplementary Information). Reactions have been carried out in defect of the oxidant (0.2 eq with respect to the substrate) in order to minimize the formation of overoxidation products which may alter the aromatic vs side-chain selectivity values.^[60] Control experiments were performed in the presence of H₂O₂ and Fe(OTf)₂(CH₃CN)₂ only, with no ligand added, to compare the differences in terms of reactivity and selectivity between the metal-based mechanism catalyzed by complex **1** and the Fenton-type reactions promoted by Fe(OTf)₂/H₂O₂.^[61,62] Products and yields, referred to the amount of

oxidant, are reported in Table 1. With all substrates the mass balance was satisfactory (> 90%).








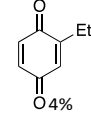


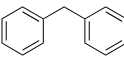
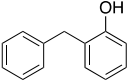
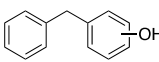
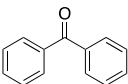
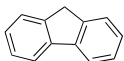
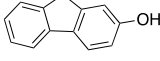
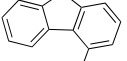
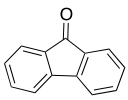
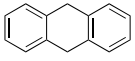
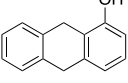
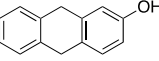
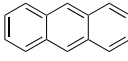
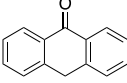
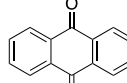
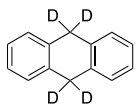
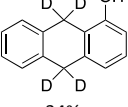
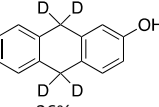
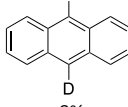
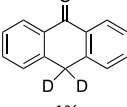
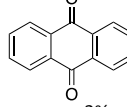
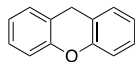
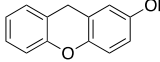
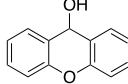
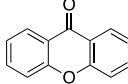
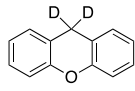
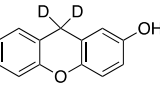
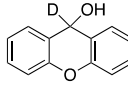
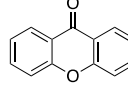
Oxidation of toluene led to the formation of *o*-cresol (6%), a mixture of *m*- and *p*-cresols (5%) as the main reaction products. Remarkably only a small amount (< 1%) of benzaldehyde (Table 1, entry 1) deriving from benzylic hydrogen atom abstraction was detected, indicating a high selectivity of the **1**/H₂O₂ system for the aromatic hydroxylation. Control experiments in the absence of the imine ligand showed that no phenolic products are formed with the substrate quantitatively recovered.

Ethylbenzene was found to be more reactive than toluene and the oxidation reaction gave a mixture of *o*-, *m*- and *p*-ethylphenol (37% of *ortho* and 45% of *meta* + *para*), accompanied by the overoxidation product 2-ethyl-*p*-benzoquinone (4%) (entry 2). Small amounts of side-chain oxidation products, 1-phenylethanol (2%) and acetophenone (3%), were also observed. Thus, even in the oxidation of ethylbenzene, which bears weaker secondary benzylic C-H bonds, **1**/H₂O₂ system is highly selective for aromatic over aliphatic oxidation with a 94:6 ring/side-chain chemoselectivity (ring-oxygenated products/side-chain-oxygenated products). Control experiments, carried out in the absence of imine ligand (Fenton conditions), showed the exclusive formation of side-chain oxidation products, with 1-phenylethanol and acetophenone formed in 8% and 4% yields, respectively. This result supports the operation of a metal-based oxidant in the reaction of ethylbenzene with **1**/H₂O₂ system and excludes any involvement of HO• radical.^[49,58,62]

In the oxidation of diphenylmethane (entry 3) almost exclusive formation of aromatic oxidation products, *o*-, *m*- and *p*-benzylphenol (27% of *ortho* and 42% of *meta* + *para*) was again observed accompanied by only small amount (1%) of the benzylic oxidation product benzophenone. Also with this substrate a high ring/side-chain chemoselectivity is observed (> 98). The higher chemoselectivity for aromatic hydroxylation compared to that observed for ethylbenzene is likely a consequence of the higher steric hindrance of the benzylic C-H bonds of diphenylmethane. As a matter of fact, the oxidizing species formed upon treatment of **1** with H₂O₂ has been found to be rather sensitive to steric effects.^[33,34] Blank experiments with the Fe(OTf)₂/H₂O₂ system showed the exclusive formation of benzophenone (8%).

In a control experiment the reaction product *p*-benzylphenol was used as substrate in the oxidation with **1**/H₂O₂ system. No products have been detected and the substrate was recovered quantitatively. This result is somewhat surprising in view of the activation of phenolic compounds towards electrophilic aromatic substitutions by the electron-releasing hydroxyl group and may be due to the binding of the phenolic products on the imine iron catalyst which prevents further oxidation as previously reported for related systems.^[11,12,17] The oxidation of fluorene led to the formation of 2-hydroxyfluorene (13%) and 4-hydroxyfluorene (14%) due to aromatic oxidation and 9-fluorenone (14%) due to benzylic oxidation (entry 4). Again, aromatic hydroxylation prevails over benzylic oxidation, but the ring/side-chain chemoselectivity drops to 66:34.

Table 1. Products and yields of the oxidation of a series of alkylaromatics with H₂O₂ in CH₃CN at room temperature catalyzed by complex 1.^a

Entry	Substrate	Recovered Substrate ^b	Products ^c	TN ^d
1		95	 <i>o</i> - 6%  <i>m</i> -, <i>p</i> - 5%  < 1%	2.6
2		80	 <i>o</i> - 37%  <i>m</i> -, <i>p</i> - 45%  4%  2%  3%	20
3		82	 <i>o</i> - 27%  <i>m</i> -, <i>p</i> - 42%  1%	14
4		89	 13%  14% HO  14%	11
5		90	 16%  8%  13%  1%  2%	9
6		85	 34%  26%  8%  1%  2%	13
7		88	 4%  5%  29%	13
8		95	 5%  4%  9%	5.4

^aReaction conditions: 20 mol% H₂O₂, 1 mol% catalyst 1, CH₃CN at 25 °C, reaction time 90 minutes, oxidant added by a syringe pump (30 min). The reported results are the average of at least two runs. Recovered substrates and product yields (%), determined by GC and/or ¹H NMR analysis. Error ±5%. ^bReferred to the initial amount of substrate. ^cYields are referred to the amount of oxidant. ^dTN defined as moles of oxidation products/mole of Fe. Ketones and aldehydes were considered as double ox products and quinones as triple ox products.

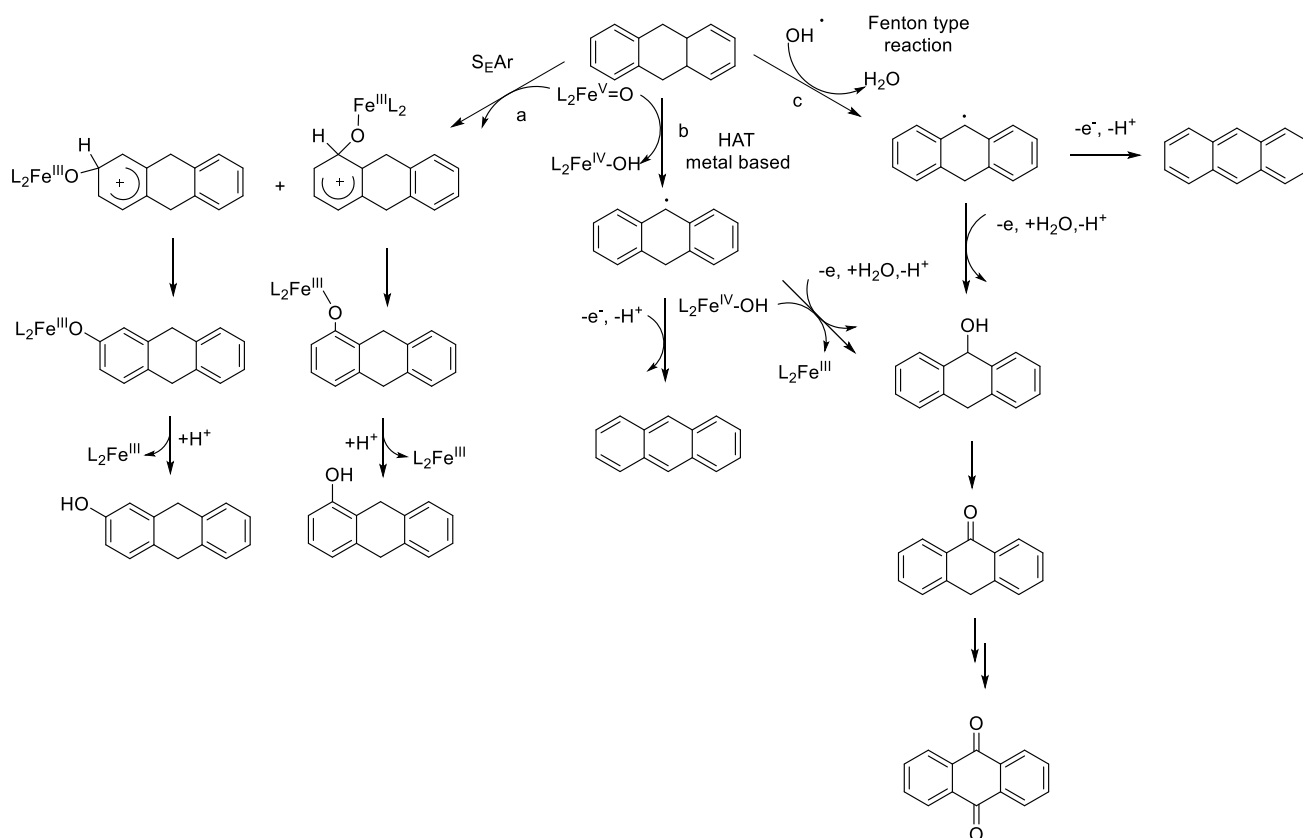
The decrease of selectivity for the aromatic oxidation observed with this substrate can be rationalized on the basis of a higher HAT reactivity of benzylic C-H bonds of fluorene (benzylic BDE_{C-H} = 80 kcal/mol). As a matter of fact, 9-fluorenone is the exclusive oxidation product observed when the reaction is carried out in the absence of the imine ligand in control experiments as well as in previous reports with iron catalysts^[14,58,63] or well-defined Fe^{IV}-oxo complexes.^[38,39,41,64] Product analysis of the oxidation of 9,10-dihydroanthracene (DHA) showed formation of the aromatic oxidation products 1-hydroxydihydroanthracene (16%) and 2-hydroxydihydroanthracene (8%) (entry 5). As observed with fluorene, benzylic

oxidation competes with the aromatic one leading to the formation of anthracene (13%), anthrone (1%) and anthraquinone (2%). Remarkably, product yields and selectivity for hydroxylation under argon were almost the same as those under air, showing that the possibility of participation by molecular oxygen in air can be excluded. Again, aromatic hydroxylation prevails over the benzylic oxidation, but a lower ring/side-chain chemoselectivity is observed (60:40). Control experiments showed that no oxidation of 9,10-dihydroanthracene occurs when the reaction is performed either in the absence of the oxidant or of the catalyst, while using Fe(OTf)₂ and H₂O₂ in the absence of the imine ligand, side-

chain oxidation products are exclusively formed in relatively high yields: anthracene (43%), anthrone (30%) and anthraquinone (9%). The increase of HAT reactivity of the benzylic positions in the Fenton type reaction can be again rationalized on the basis of the relatively low benzylic BDE_{C-H} value of DHA (78 kcal/mol). Indeed, HAT from 9,10-dihydroanthracene to $Fe^{IV}=O$ complexes is usually facile and fast to eventually provide anthracene or anthrone.^[38,39,41,64]

In the case of 9,10-dihydroanthracene, the competition between aromatic and side-chain oxidation and the mechanism of the hydrogen atom transfer from the benzylic C-H bonds have

been investigated in more detail. Formation of oxidation products of DHA with $1/H_2O_2$ system may be described according to the mechanism reported in Scheme 3. In the metal based electrophilic aromatic substitution (path a) the first step involves the electrophilic attack of the putative iron(V)-oxo active species to the aromatic ring to give the Wheland complex. In the next step the aromaticity is restored by deprotonation, leading to the formation of 1- and 2-hydroxydihydroanthracene and the iron(III) catalyst.



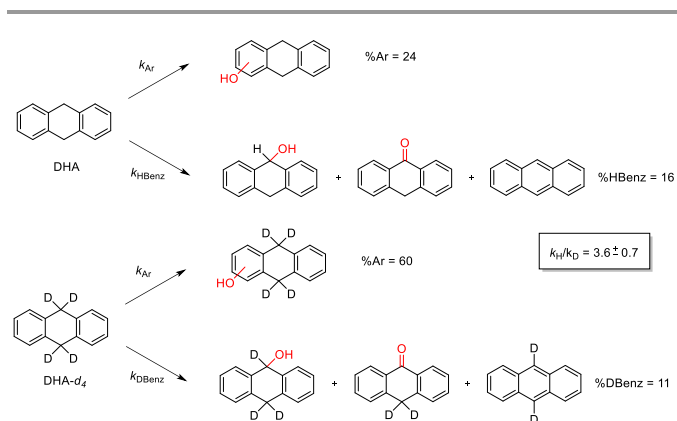
Scheme 3. Proposed mechanism for DHA oxidation by $1/H_2O_2$ system.

Concerning the side-chain oxidation process, in principle, two possible mechanistic pathways are feasible: a metal based HAT process promoted by a high-valent iron-oxo species (path b) or a HAT process promoted by oxygen-centered radicals ($OH\cdot$) formed through Fenton-type reactions of the iron complex with H_2O_2 (path c).^[65]

In the HAT metal-based process an initial hydrogen atom abstraction from the substrate to the iron(V)-oxo complex leads to the formation of an Fe(IV)-OH complex and a benzylic radical which, in turn, can produce i) anthracene by a desaturation process or ii) 9-hydroxy-9,10-dihydroanthracene by reaction with Fe(IV)-OH complex (oxygen rebound) or by oxidation and reaction with a water molecule in a nonrebound process.^[66,67] 9-Hydroxy-9,10-dihydroanthracene can be further oxidized to anthrone and anthraquinone. Alternatively, a Fenton-type reaction promoted by the highly reactive and rather unselective

$HO\cdot$ (or $HOO\cdot$) can occur.^[51,62,68-70] This species can abstract a hydrogen atom from the benzylic C-H bond of the substrate leading to the formation of a benzylic radical, which can be easily oxidized to cation. The latter can react with H_2O leading to 9-hydroxy-9,10-dihydroanthracene which then follows the pathways described above.

In order to gain more insight into this reaction mechanism a product isotope effect study has been carried out. Product analysis of the oxidation of DHA and its deuterated counterpart DHA-*d4* by $1/H_2O_2$ system have been compared. While aromatic oxidation occurs with the same rate constants k_{Ar} , benzylic oxidation is characterized by a rate constant k_{HBenz} or k_{DBenz} for DHA or DHA-*d4*, respectively, as shown in Scheme 4.



Scheme 4. Aromatic and benzylic products distribution in the oxidation of DHA and DHA-*d*4 by the **1**/H₂O₂ system.

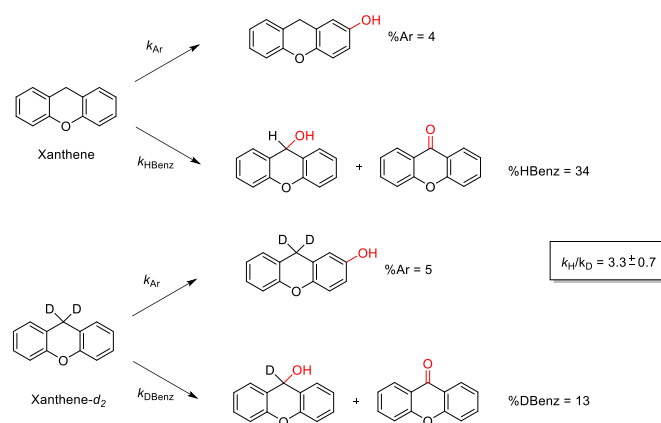
According to Scheme 4, the ratio of the overall yields of benzylic (%Benz) and aromatic (%Ar) oxidation products, (%Benz)/(%Ar), can be considered equal to the ratio of the corresponding rate constants, $k_{\text{HBenz}}/k_{\text{Ar}}$ and $k_{\text{DBenz}}/k_{\text{Ar}}$ for DHA and DHA-*d*4, respectively. Under the reasonable assumption that the k_{Ar} values are the same for both DHA and DHA-*d*4, from the ratios (%HBenz)/(%HAr) and (%DBenz)/(%DAR) it is possible to determine the $k_{\text{H}}/k_{\text{D}}$ for the benzylic HAT process. From product yields of the oxidation of DHA and DHA-*d*4 reported in Table 1, entries 5 and 6, respectively a KIE ($k_{\text{H}}/k_{\text{D}}$) value of 3.6 ± 0.7 is obtained.

This result rules out a Fenton type HAT process but supports the involvement of a selective metal based oxidant that is able to discriminate between C–H and C–D bonds. This KIE value is also in accordance with that previously observed in cyclohexane hydroxylation catalyzed by complex **1** (KIE = 3.3).^[33] In fact, reactions initiated by highly reactive oxygen-centered radicals, such as hydroxyl radicals are generally characterized by $k_{\text{H}}/k_{\text{D}}$ values between 1 and 2.^[35,61,71-73] A value of 3.6 for $k_{\text{H}}/k_{\text{D}}$ is instead in line with those obtained with other non-heme amine-based iron complexes reported in the literature (KIE values in the range 3–4) for which the involvement of a Fe^V=O has been proposed,^[40,44,45] but lower than that reported for characterized Fe^{IV}=O species.^[38,39,41,64] Furthermore, when the oxidation of DHA was performed under argon, no significant variation of the reaction selectivity was observed. The poor sensitivity to the presence/absence of O₂ also does not support the operation of a free radical-based oxidation since the presence of O₂ is known to affect both the efficiency and the selectivity of oxidative processes with Fenton-type systems.^[35,58,72,74] Thus the results obtained with the non-heme imine iron complex clearly indicate that both aromatic and aliphatic side-chain oxidations are performed by the same high valent iron-oxo species, similar to that observed in non-heme PDP iron complexes.^[30,45]

Eventually, xanthene oxidation was considered. This substrate has the lowest benzylic BDE_{C-H} value (75 kcal/mol) in the series of Table 1. The oxidation of xanthene led to the formation of 2-hydroxyxanthene (5%) as the only phenolic product, accompanied by larger amounts of 9-hydroxyxanthene (4%) and

xanthone (29%), which are products of benzylic oxidation (entry 7). The ring/side-chain chemoselectivity observed for this substrate (33:64) is in accordance with the most reactive benzylic C–H bond. Blank experiments in the absence of the imine ligand show the exclusive formation of benzylic oxidation products, 9-hydroxyxanthene (1%) and 9-xanthone (65%).

In order to confirm that the HAT from benzylic C–H bonds occurs by metal based process also with this substrate, a KIE study has been carried out (see Scheme 5). Products and yields of the oxidation of xanthene and xanthene-*d*2 are reported in Table 1, entries 7 and 8, respectively. From product yields, a KIE value of 3.3 ± 0.7 is obtained confirming that benzylic HAT process from xanthene is promoted by a metal-based oxidant.



Scheme 5. Aromatic and benzylic products distribution in the oxidation of xanthene and xanthene-*d*2 by the **1**/H₂O₂ system.

Table 2 summarizes the aromatic vs side-chain chemoselectivity together with the benzylic BDE_{C-H} values of alkylaromatic substrates. The data reported clearly indicate that a high selectivity for aromatic hydroxylation is observed for most alkylaromatic substrates with benzylic BDE_{C-H} higher than 82 kcal/mol. This implies that the oxidation will selectively occur on the aromatic ring for most benzylic substrates. A fair correlation between the selectivity data and the strength of benzylic C–H bonds is outlined by the ring/side-chain chemoselectivity, which regularly decreases on decreasing the benzylic BDE_{C-H} values (Figure 1). With xanthene the low benzylic BDE_{C-H} value (75 kcal/mol) determines an inversion of selectivity with benzylic oxidation prevailing over the aromatic one.

Table 2. Correlation between benzylic BDE_{C-H} of alkylaromatics and aromatic vs side-chain chemoselectivity in the oxidation promoted by the **1**/H₂O₂ system.Cl

Substrate	BDE (kcal/mol)	Ring/side-chain chemoselectivity
Toluene	88	> 98:2
Ethylbenzene	84	94:6
Diphenylmethane	82	98:2
Fluorene	80	66:34
9,10-Dihydroanthracene	78	60:40
Xanthene	75	33:67

This result is in qualitative accordance with the general correlation between the amount of side-chain oxygenated products and the strength of aliphatic C-H bonds reported in several iron-catalyzed alkylbenzene oxidations.^[11-24,39,64] However, the **1**/H₂O₂ system shows a remarkably high chemoselectivity for aromatic hydroxylation, higher than that found with most of the catalytic systems reported in related studies.^[20,47,55-57]

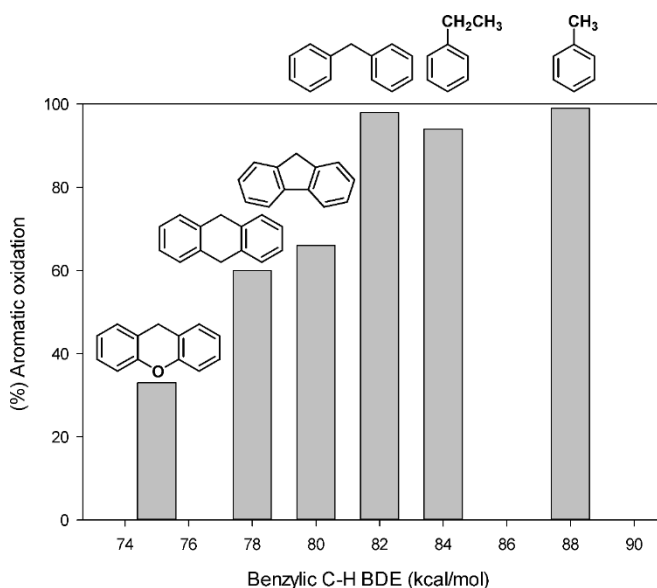


Figure 1 Percentage of aromatic oxidation as a function of the benzylic BDE_{C-H} of alkylaromatics in the oxidation promoted by the **1**/H₂O₂ system.

Conclusions

Imine-based iron complex **1** prepared in situ by reaction of 2-picolylaldehyde, 2-picolylamine, and Fe(OTf)₂ efficiently catalyzes the oxidation of alkylaromatic compounds with H₂O₂ as oxidant under mild conditions. A remarkable chemoselectivity for the aromatic oxidation is observed with monocyclic aromatic systems. With more activated polycyclic substrates the side-chain/ring oxygenated products ratio

regularly increases on decreasing the bond dissociation energy (BDE) of the benzylic C-H bond in line with expectation. An inversion of chemoselectivity is found with xanthene where benzylic oxidation products are more abundant than phenolic ones. A clear evidence for metal based competitive reactions leading either to aromatic hydroxylation (electrophilic aromatic substitution) or side-chain oxidation (benzylic hydrogen atom abstraction) has been provided by the analysis of deuterium kinetic isotope effects and the poor sensitivity of the product yields to the presence/absence of O₂.

Experimental

Oxidation procedure

Oxidations were carried out by mixing Fe(CF₃SO₃)₂(CH₃CN)₂ (1.09 mg, 2.50 μmol), 2-picolylamine (50 μL of a solution 0.1 M in CH₃CN, 5.0 μmol) and 2-picolylaldehyde (50 μL of a solution 0.1 M in CH₃CN, 5.0 μmol) in a vial at 25 °C. Substrate (250 μmol) and CH₃CN were then added up to a total volume of 1 mL. A solution of H₂O₂ in CH₃CN (1.74 M diluted from a 35% w/w H₂O₂) was added over 30 minutes by syringe pump under vigorous stirring and left reacting for additional 1 hour. At the end an internal standard was added and the reaction mixture was filtered over a short pad of SiO₂ with 10 mL of AcOEt and analyzed by GC, GC-MS and ¹H NMR. Oxidation products were identified by comparison with authentic specimens (*o*-cresol, *m*-cresol, *p*-cresol, benzaldehyde, 2-ethylphenol, 3-ethylphenol, 4-ethylphenol, 1-phenylethanol, acetophenone, 2-benzylphenol, 3-benzylphenol, 4-benzylphenol, benzophenone, 2-hydroxyfluorene, 9-fluorenone, anthracene, anthrone, anthraquinone, 9-xanthone) or by comparison of their spectral data with those reported in the literature (2-ethyl-*p*-benzoquinone,^[75] 4-hydroxyfluorene,^[76] 2-xanthanol, 9-hydroxyxanthene^[77]).

1-Hydroxydihydroanthracene, 2-hydroxydihydroanthracene, were isolated from the crude reaction mixture of an oxidation reaction carried out on a semipreparative scale by column chromatography (see ESI).

Conflicts of interest

There are no conflicts to declare.

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