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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 a 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 H_2O_2 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

Insight into the chemoselective aromatic vs. sidechain hydroxylation of alkylaromatics with H_2O_2 catalyzed by a non-heme imine-based iron complex[†]

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The oxidation of a series of alkylaromatic compounds with H_2O_2 catalyzed by an imine-based 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 product 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.

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 iminopyridine complex 1, easily obtained by an *in situ* self-assembly of 2-picolylamine, 2-picolylaldehyde and iron(π) 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

Kinetic isotope effect (KIE) studies, the 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 H_2O_2 to 1, which is competent for the oxidation.³⁵ Generally, activation of H_2O_2 by nonheme iron complexes is due to the formation of Fe^{III} –OOH intermediates which undergo either heterolytic O–O bond



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



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cleavage to produce a highly reactive Fe^{V} =O complex or 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 this basis, we proposed the formation of a similar high-valent iron-oxo complex after the initial oxidation of Fe(II) complex **1** to Fe(III) followed by detachment of a pyridine arm, and coordination and activation by H₂O₂.^{34,37}

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 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, and cumene), the $1/H_2O_2$ 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 $1/H_2O_2$ system in the restricted family of the most selective catalytic systems.^{4,8-10,24}

In this context, it is notable that the $1/\rm{H_2O_2}$ 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⁻¹, Chart 1).⁵⁹





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

Results and discussion

Oxidation reactions were carried out by mixing Fe(OTf)₂(CH₃-CN₂ (2.5 µmol, TfO⁻ = $CF_3SO_3^-$), 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 using 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 ESI[†]). Reactions have been carried out under oxidant-deficient conditions (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, referring to the amount of oxidant, are reported in Table 1. With all the 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 $1/H_2O_2$ 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 the 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, the 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 sidechain oxidation products, with 1-phenylethanol and acetophenone forming in 8% and 4% yields, respectively. This result supports the operation of a metal-based oxidant in the reaction of ethylbenzene with the 1/H₂O₂ system and excludes any involvement of HO' radicals.49,58,62

Table 1 Products and yields of the oxidation of a series of alkylaromatics with H_2O_2 in CH_3CN at room temperature catalyzed by complex 1^a



^{*a*} Reaction conditions: 20 mol% H_2O_2 , 1 mol% catalyst 1, CH_3CN at 25 °C, reaction time: 90 minutes, oxidant added using 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%. ^{*b*} Refers to the initial amount of substrate. ^{*c*} Yields refer to the amount of oxidant. ^{*d*} TN defined as the moles of oxidation products/mole of Fe. Ketones and aldehydes were considered as the double oxidation products and quinones as the triple oxidation products.

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 a 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 H_2O_2 has been found to be rather sensitive to steric effects.^{33,34} Blank

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experiments with the $Fe(OTf)_2/H_2O_2$ system showed the exclusive formation of benzophenone (8%).

In a control experiment, the reaction product p-benzylphenol was used as a 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 electronreleasing hydroxyl group and may be due to the binding of the phenolic products on the imine-based 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 benzylic oxidation, over but the ring/side-chain chemoselectivity drops to 66:34.

The decrease of selectivity for the aromatic oxidation observed with this substrate can be rationalized on the basis of a higher HAT reactivity of the benzylic C-H bonds of fluorene (benzylic BDE_{C-H} = 80 kcal mol⁻¹). 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 the 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, the 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 H_2O_2 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⁻¹). 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 the oxidation products of DHA with $1/H_2O_2$ system may be described according to the mechanism reported in Scheme 3.



Scheme 3 Proposed mechanism for DHA oxidation by the 1/H₂O₂ system.

In the metal-based electrophilic aromatic substitution (path a), the first step involves the electrophilic attack of the putative iron(v)-oxo active species on 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(m) catalyst.

Concerning the side-chain oxidation process, in principle, two possible mechanistic pathways are feasible: a metalbased HAT process promoted by a high-valent iron–oxo species (path b) or a HAT process promoted by oxygen-centered radicals (HO') formed through Fenton-type reactions of the iron complex with H_2O_2 (path c).⁶⁵

In the HAT metal-based process, 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 the 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 anthraguinone. Alternatively, a Fenton-type reaction promoted by the highly reactive and rather unselective HO' (or HOO') 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 a cation. The latter can react with H₂O 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- d_4 by $1/H_2O_2$ system has been compared. While the 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- d_4 , respectively, as shown in Scheme 4.

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



u/kn = 3.6 ± 0.7

%DBenz = 11

DHA and DHA- d_4 , respectively. Under the reasonable assumption that the $k_{\rm Ar}$ 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 $k_{\rm H}/k_{\rm D}$ value for the benzylic HAT process. From the product yields of the oxidation of DHA and DHA- d_4 reported in Table 1, entries 5 and 6, respectively, a KIE ($k_{\rm H}/k_{\rm D}$) 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 the 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 $k_{\rm H}/k_{\rm D}$ values between 1 and 2.^{35,61,71–73} A value of 3.6 for $k_{\rm H}/k_{\rm D}$ is instead in line with those obtained with other non-heme amine-based iron complexes reported in the literature (KIE values in the range of 3-4) for which the involvement of a Fe^V=O species 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-based 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⁻¹) in the series of Table 1. The oxidation of xanthene led to the formation of 2-hydroxyxanthene (4%) as the only phenolic product, accompanied by larger amounts of 9-hydroxyxanthene (5%) and xanthone (29%), which are the 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 the benzylic C–H bonds occurs *via* the 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 the product yields, a KIE value of 3.3 ± 0.7 is obtained confirming that the benzylic HAT process from xanthene is promoted by a metal-based oxidant.

Table 2 summarizes the aromatic *vs.* side-chain chemoselectivity together with the benzylic BDE_{C-H} values of the alkylaromatic substrates. The data reported clearly indicate that a high selectivity for aromatic hydroxylation is



Scheme 5 Aromatic and benzylic product distribution in the oxidation of xanthene and xanthene- d_2 by the $1/H_2O_2$ system.

Table 2 Correlation between benzylic BDE_{C-H} of alkylaromatics and aromatic vs. side-chain chemoselectivity in the oxidation promoted by the 1/ H_2O_2 system

Substrate	BDE (kcal mol ⁻¹)	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

observed for most alkylaromatic substrates with benzylic BDE_{C-H} higher than 82 kcal mol⁻¹. 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 the benzylic C–H bonds is outlined by the ring/side-chain chemoselectivity, which regularly decreases on decreasing benzylic BDE_{C-H} values (Fig. 1). With xanthene, the low benzylic BDE_{C-H} value (75 kcal mol⁻¹) determines an inversion of selectivity with benzylic oxidation prevailing over the aromatic one.

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 $1/H_2O_2$ 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}

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 H_2O_2 as oxidant under mild conditions. A remarkable chemoselectivity for the aromatic oxidation is observed with monocyclic aromatic systems. With more activated polycyclic



Fig. 1 Percentage of aromatic oxidation as a function of benzylic BDE_{C-H} of alkylaromatics in the oxidation promoted by the $1/\rm{H}_2O_2$ system.

substrates, the side-chain/ring oxygenated product ratio regularly increases on decreasing 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. 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 O_2 .

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 0.1 M solution in CH₃CN, 5.0 µmol) and 2-picolylaldehyde (50 µL of a 0.1 M solution in CH₃CN, 5.0 µmol) in a vial at 25 °C. Substrate (250 μ mol) 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 solution) was added over 30 minutes using a syringe pump under vigorous stirring and left reacting for additional 1 hour. Finally, 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 comparing with authentic specimens (o-cresol, m-cresol, p-cresol, benzaldehyde, 2-ethylphenol, 3-ethylphenol, 4-ethylphenol, acetophenone, 1-phenylethanol, 2-benzylphenol, 3-benzylphenol, 4-benzylphenol, benzophenone, 2-hydroxyfluorene, 9-fluorenone, anthracene, anthrone, anthraquinone, and 9-xanthone) or by comparing of their spectral data with

those reported in the literature (2-ethyl-*p*-benzoquinone,⁷⁵ 4-hydroxyfluorene,⁷⁶ 2-xanthenol,⁹ 9-hydroxyxanthene⁷⁷).

1-Hydroxydihydroanthracene and 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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