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Institute Feature

Transition Metal Catalysts Bearing Multidentate Ligands for Efficient and Environmental Benign Oxidations by H_2O_2

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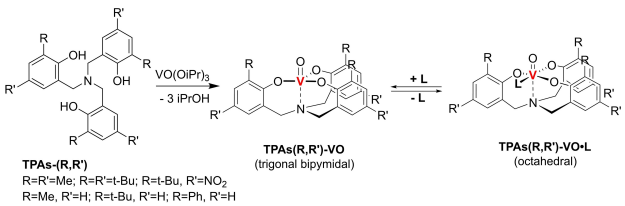
In this perspective, two different classes of multidentate ligands (aminotriphenolate and dipyridinimine) and the corresponding metal (Ti, V, Mo, W, Fe) complexes are described. These catalysts can activate efficiently the environmental benign H_2O_2 oxidant, promoting a wide variety of oxidative processes (sulfoxidations, *N*-oxidations, epoxidations, haloperoxidation, alcohol oxidation, hydroxylation).

1. Introduction

Hydrogen peroxide is an environmental and powerful oxidant with a low molecular weight and releasing water as by-product. However, it is quite inert and to react selectively with organic compounds the peroxide functionality requires to be activated via the formation of a peroxo intermediate that then can further react.[1] One of the main strategies for H_2O_2 activation consists in the use of transition metal catalysts, which form the corresponding peroxo-metallo species that are able to carry out the oxidation reaction more easily and with much higher selectivities. Peroxometal complexes reactivity is strongly influenced by the metal ion and the nature of its coordination sphere, both defining the chemo and stereoselectivity in the presence of chiral ligands. Another important characteristic that homogeneous molecular catalysts for H_2O_2 activation require is to be very robust, in order to maintain the catalyst integrity under turn-over conditions and allowing the occurrence of many catalytic cycles. This is a particularly difficult task because reactions are usually performed also in the presence of large excess of oxidant and, in some cases, at very acidic or basic pH values. One of the main successful strategies is the use of multidentate ligands.[2] Furthermore, if they are highly symmetric the number of possible stereoisomeric active species in solution is reduced, facilitating the characterization of the active species and precursors in solution and the study of the reaction mechanism. In this perspective article we will describe two different classes of multidentate ligands and the corresponding metal complexes (Ti, V, Mo, W, Fe) developed in two of the Interuniversity Consortium Chemical Reactivity and Catalysis (CIRCC) laboratories, Padua and Rome, capable to activate H_2O_2 efficiently in rather diverse classes of oxidations (sulfoxidations, *N*-oxidations, epoxidations, haloperoxidations, alcohol oxidations, hydroxylations).

2. Aminotriphenolate Metal Complexes

One of the main research topics of the Padua unit of CIRCC during the last years is related to the H_2O_2 activation with early transition metal complexes bearing multidentate, highly symmetric ligands, i.e. triphenolamines **TPAs** (Scheme 1). Such ligands can be easily prepared via two main synthetic routes: a Mannich type reaction starting from *o,p*-disubstituted phenols and hexamethylenetetramine (HMTA)[3] or a more recent methodology, developed in Licini's laboratories, based on a three-fold reductive amination using ammonium acetate as nitrogen source and $NaBH(OAc)_3$ as reducing agent on 3-substituted salicylic aldehyde protected at the phenol OH as benzylic ethers. The methodology allows the obtainment of crystalline TPAs with bulky substituents like *t*-Bu in α position to the phenol groups and the OBn protective group can be



Scheme 1. Synthesis of vanadium oxo-aminotriphenolate complexes with trigonal bipyramidal geometry (TPAs-VO) and octahedral (TPAS-VO•L) geometries.[8]

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easily removed by Pd/C catalyzed hydrogenolysis, allowing the recovering TPAs as white solids.[4]

TPAs easily coordinate to transition metal ions (d^0,d^1)[5] but examples of complexes of the main group (d^8) or late transition metals are also present.[6] The aminotriphenolate metal complexes are generally mononuclear, with a 1:1 ligand metal ratio, and they adopt mainly trigonal bipyramidal (TBP, penta-coordinate) or octahedral (OCT, hexa-coordinate) geometries. In Scheme 1 an example of the synthesis of TPA-V(V) complexes exhibiting TBP or OCT geometries is reported.[7,8]

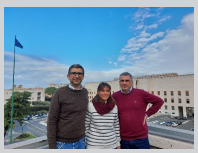
Aminotriphenolate metal complexes are stable for months at the solid state and have a good solubility in most organic solvents, including alcohols. In solution they are stable also under turn over conditions (strongly acidic conditions, in the presence of water/alcohols or large excess of oxidants (H_2O_2, ROOH) and air).[7,9,10] Their robustness is due to the tetradentate nature of the ligand and to the presence of bulky substituents in ortho position to the phenol groups, which protect the upper part of the metal complexes. Licini, Zonta and coworkers prepared a series of Ti(IV),[10,11] V(V),[7,8] Mo(VI)[12] and W(VI)[13] complexes, fully characterized by NMR, ESI-MS and X-ray crystallography, and they were studied as powerful catalysts in oxygen transfer reactions (sulfoxidation, *N*-oxidation, epoxidation and haloperoxidation). The activation of H_2O_2 occurs via generation of hydroperoxo-metal species which are able to perform an oxygen transfer to different nucleophiles (olefines, sulfides, amines, halides).

2.1. Sulfoxidations

The first studies on H_2O_2 activation for oxygen-transfer sulfoxidations were performed with Ti(IV) complexes. TPAs-Ti(IV) complexes can be easily obtained by reaction of **TPAs** with $Ti(OiPr)_4$ in CH_2Cl_2 or MeOH and they were used directly in the presence of H_2O_2[9] or cumyl hydroperoxide (CHP)[10] for sulfoxidation reactions (Figure 1).[11]

The tetradentate nature of the ligands allows to obtain robust complexes capable to perform sulfoxidations in methanol using aqueous solution of hydrogen peroxide as oxidant without any hydrolysis or ligand exchange of the Ti(V) catalysts. The best catalytic performances were obtained using **TPA(t-Bu,H)-Ti** reaching TOFs up to 1700 h^{-1} and 8000 TONS (0.01% catalyst loading) (Figure 1).[9,10] The catalytic system is effective with dialkyl and aryl alkyl sulfides affording with high selectivity the corresponding sulfoxide with complete H_2O_2/CHP consumption and without any oxidant decomposition. Furthermore, ^{1}H NMR and ESI-MS experiments allowed the detection and characterization of the Ti(IV) peroxo-derivative (Scheme 2).

More detailed kinetic and computational studies on the catalytic system highlighted the role of the coordination of a



Stefano Di Stefano received his PhD in Chemical Sciences in 2000 at the University of Rome La Sapienza. After a period in Merck Sharp & Dohme working in the field of clinical research, he came back to La Sapienza where he is now a Full Professor of Organic Chemistry. His research interests concern supramolecular chemistry and catalysis, dynamic covalent chemistry, chemically driven molecular machines and dissipative systems. He has been involved in many national and international scientific collaborations.

Carla Sappino received her PhD in Chemical Sciences in 2017 at the University of Rome "La Sapienza" in the group of Dr. Giuliana Righi, working on the application in asymmetric catalysis of magnetic nanoparticles functionalized with chiral ligands. After a postdoctoral fellow in the Pericas group at the ICIQ, Tarragona (Spain), in 2020 she joined the group of Prof. Stefano Di Stefano (supramolecular catalysis for C H oxidation) and then the group of Prof. Ilaria Fratoddi (functionalization of metal nanoparticles).

Osvaldo Lanzalunga received his PhD degree from the University of Rome "La Sapienza" in 1994. After postdoctoral experience at the Max Planck Institut für Strahlenchemie, Mülheim (Germany) he became Researcher and is currently Full Professor in Organic Chemistry at the Dipartimento di Chimica of the University "La Sapienza". His scientific research is mainly focused on the chemistry of radicals and radical ions, on the role of structural and medium effects on hydrogen atom transfer and electron-transfer (ET) reactions involving oxygen-centered radicals and on the role of ET processes in organic and bioorganic reactions.

Giulia Licini obtained her PhD at the University of Padua under the supervision of Giorgio Modena in 1988. After a post-doc at the Colorado State University (CSU) in Albert I. Meyer group, she came back to the University of Padua where she is now Full Professor in Organic Chemistry. Her research interest is mainly related to catalytic small molecule activation (H_2O_2, CO_2, O_2), metalloenzymes mimesis, reaction mechanism studies and, more recently, aerobic oxidative catalytic biomass valorization.

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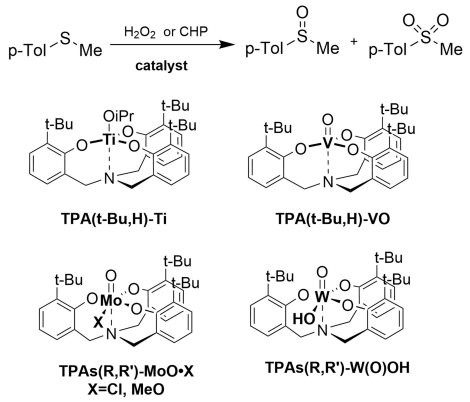
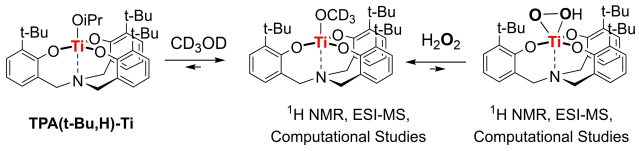


Figure 1. Sulfoxidation of methyl-p-tolyl sulfide with H_2O_2/CHP catalyzed by TPA-Ti(IV), V(V), Mo(VI) and W(VI) complexes. Reaction conditions: **TPA(t-Bu,H)-Ti**: $[Sulfide]_0 = [H_2O_2]_0 = 0.5$ M, cat ≥ 0.01 %; MeOH, 28 °C. **TPA(t-Bu,H)-VO**: $[Sulfide]_0 = [H_2O_2]_0 = 0.5$ M, cat ≥ 0.1 %; 28 °C, MeOH. **TPA(t-Bu,H)-Mo(O)X (X=OMe, Cl)**: $[sulfide]_0 = [H_2O_2]_0 = 0.1$ M, cat = 1 %,MeOH, 60 °C. **TPA(t-Bu,H)-W(O)OH**: $[sulfide]_0 = [H_2O_2]_0 = 0.1$ M, cat = 1 %, CH_3CN, 25 °C.



Scheme 2. Reaction of **TPA(t-Bu,H)-Ti** with H_2O_2 in methanol: generation of the peroxo-titanium complex.[10]

solvent molecule (MeOH) to the **TPA(t-Bu,H)-Ti** peroxo-complex behaving as an on-off switch for the oxygen transfer to sulfides.[11] More recent theoretical studies, supported by experiments, further elucidates the reaction mechanism of the oxygen transfer reaction.[12] The reactivity of three different **TPAs-Ti** complexes with increasing bulkiness (H,H; Me,H and t-Bu,H) on the substituents on the upper part of the complexes in the oxidation of dimethyl and methyl-p-tolyl sulfides using H_2O_2 or CHP as oxidants has been investigated and compared. The study highlights the occurrence of a blended situation where 'in' and 'out' of sphere reaction pathways are possible and that steric issues play a major role in the formation of the different intermediates in the oxygen transfer process. The Ti(IV) catalyzed oxygen transfer moves from a pre-coordination of the sulfide to the metal center ("in" transition states) for the less hindered systems to "out" pathways with no preliminar coordination of the substrate to the metal center for the more sterically hindered substrates and peroxocomplexes.

Chiral enantiopure TPA ligands and the corresponding Ti(IV) complexes, bearing a stereocenter at one of the benzylic functions, were also prepared. **(*R*)-TPA-(R=R'=t-Bu)-Ti** was prepared and studied by Bull, Davidson and collaborators for the stereoselective sulfoxidation of benzyl phenyl sulfide with ee up to 47 %.[13] On the other side other unsymmetrical enantiopure complexes (Figure 2) were prepared by Licini and Zonta and the **(*S*)-TPA-(R=R'=Ph)-Ti** used as ^{1}H NMR chiral solvating agent for sulfoxides.[14]

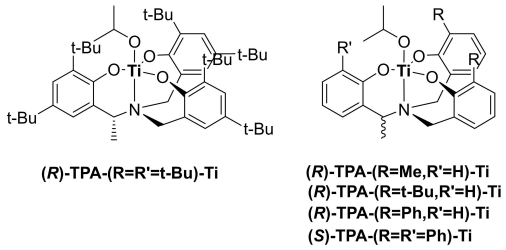


Figure 2. Chiral, enantiopure TPAs-Ti(IV) complexes.[13,14]

Sulfoxidation could be carried out also using **TPA(t-Bu,H)-VO** as catalyst. **TPA(t-Bu,H)-VO** efficiently catalyzed the sulfoxidation of methyl-*p*-tolyl sulfide in MeOH at room temperature with TOFs up to 8000 h^{-1}, 9900 TONs (down to 0.01 % catalyst loading) and working at rather high substrate concentrations (1.0 M) (Figure 1, M=V).[7] The catalytic system (0,1 %) is effective with dialkyl and aryl alkyl sulfides affording, with complete selectivity and quantitative yields, the corresponding sulfoxide without H_2O_2 decomposition.

The reactivity of the corresponding molybdenum derivative (**TPA(t-Bu,H)-Mo(O)Cl**) was explored as well. Complete conversion of the methyl-*p*-tolyl sulfide into the corresponding sulfoxides was obtained, however 1 % catalyst loading, and higher temperatures (60 °C) were necessary to perform the reactions.[15] **TPA(t-Bu,H)-W(O)OH** is also able to catalyzed sulfoxidation reactions using H_2O_2 as oxidant with catalyst loadings down to 1 % in MeOH affording quantitative yields and a very high sulfoxide/sulfone ratio for a series of aryl/alkyl sulfides.[16] The reaction is also effective with diphenyl sulfides. High conversions but with lower sulfoxide/sulfone ratios can be obtained with cyclic aliphatic sulfides like thiomorpholine ($SO:SO_2 = 90:10$) and 1,4-oxathiane ($SO:SO_2 = 75:25$).

2.2. Secondary amines oxidation to nitrones

TPA(t-Bu,H)-Ti complex was also employed as effective catalyst of the selective oxidation of secondary amines to the corresponding nitrones (Figure 3).[17] The reactions could be

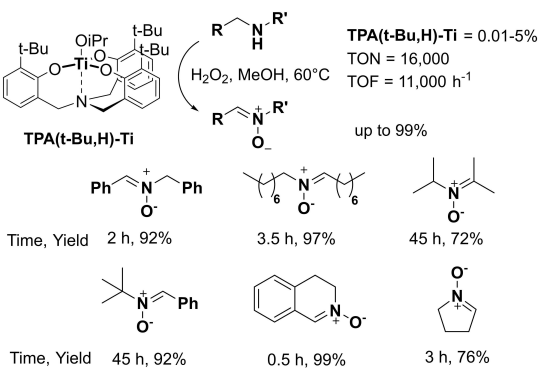


Figure 3. TPA(t-Bu,H)-Ti catalyzed secondary amine oxidation to nitrones. Scope of the reaction.[17]

carried out with catalyst loading down to 0.01% obtaining TONs up to 16,000 and TOF up to 11,000 h^{-1}. Kinetic experiments allow to verify that the reaction occurs via formation of the corresponding *N*-hydroxylamine followed by further *N*-oxidation and elimination of a water molecule to yield the nitrone. The system allowed the obtainment of a series of synthetically useful nitrones with different substrates (Figure 3)

2.3. Epoxidations

TPA(t-Bu,H)-Mo(O)Cl and **TPA(t-Bu,H)-W(O)OH** are also effective catalysts for the stereospecific epoxidation of simple olefines. Preliminary experiments showed that **TPA(t-Bu,H)-Mo(O)Cl** is able to activate *tert*-butyl hydroperoxide (TBHP) and CHP.[15]

In the oxidation of cyclooctene using TBHP as oxidant (2 equiv) in chloroform the catalyst loading could be decreased down to 0.001%, obtaining TONs up to 88,000 and TOFs = 7,500 h^{-1} (Figure 4). On the contrary with H_2O_2 no oxidation occurs.[16]

The catalytic system is active with a large series of substrates affording conversions and selectivities up to 99%.

TPA(t-Bu,H)-W(O)OH catalytic activity (5% catalyst loading) was tested with cyclooctene using both TBHP (in $CHCl_3$) and H_2O_2 (in CH_3CN). In this case both oxidants were active but only with H_2O_2 (2 equiv) complete conversions and high yields (94%) of the epoxide could be obtained. Furthermore, a significant catalyst decomposition was observed at the end of the reaction: therefore, the scope of the substrate was not further investigated.[16]

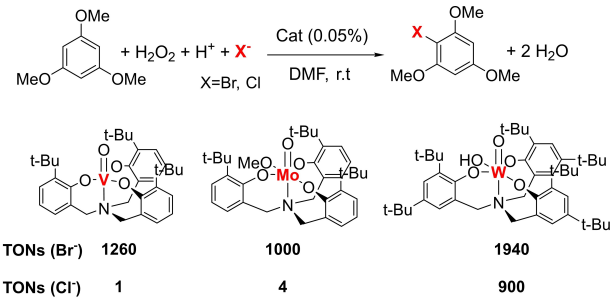
2.4. Haloperoxidation

Metal-catalyzed haloperoxidations allow the oxidation of halides (iodide, bromides, chlorides) by H_2O_2/ROOH generating the corresponding 'X^+' species capable to react with organic compounds to form halogenated derivatives.[18] Such reactivity is a bio-mimesis of important enzymes, the haloperoxidases, which in natural systems catalyze the halogenation of organic compounds via oxidation of halides with H_2O_2 as well as oxygen transfer reactions (sulfoxidations and epoxidations).[19] Haloperoxidases can contain metal cofactor like eme groups or vanadium centers. We found that **TPA(t-Bu,H)-VO**, **TPA(t-Bu,H)-Mo(O)Cl** and **TPA(t-Bu,t-Bu)-W(O)OH** can act as biomimetic metal-dependent haloperoxidases and efficiently catalyze the bromide and, to minor extent, the chloride peroxidation to obtain bromo and chloro-organic compounds.

Initially the reactivity of the thee complexes (**TPA(t-Bu,H)-VO**, **TPA(t-Bu,H)-Mo(O)Cl** and **TPA(t-Bu,t-Bu)-W(O)OH**) were explored in the 1,3,5-trimethoxybenzene bromination in DMF using tetrabutylammonium bromide in the presence of $HClO_4$ as stoichiometric proton source.[7,20] In all cases catalyst loading could be decreased down to 0,05% and all catalysts allowed the formation of bromo-trimethoxybenzene with TONs up to 1260 (V), 1000 (Mo) and 1940 (W) respectively (Scheme 3).[20]

Under the same conditions in the presence of tetrabutylammonium chloride only **TPA(t-Bu,t-Bu)-W(O)OH** gave significant conversions to 2-chloro-1,3,5-trimethoxybenzene with yields up to 60% and TONs of 900.

The scope of the reaction for the haloperoxidation of a series of organic compounds (activated aromatics, alkenes, alkynes) was then explored. A comparison of the catalytic performances among the different TPAs-based catalysts (5% catalyst loading) on haloperoxidation of 1-octene to the corresponding 1,2-dihalide derivative (Figure 5) using inorganic salts as halogen sources (KBr and LiCl) and carrying out reactions in a mixture of acetic acid:dichloromethane (1:1). shows that TPAs-V and TPAs-W are the best catalysts for bromoperoxidation while TPAs-W is the only effective catalyst



Scheme 3. 1,3,5-trimethoxybenzene bromination or chlorination catalyzed by TPA(*t*-Bu,H)-VO, TPA(*t*-Bu,H)-Mo(O)OMe and TPA(*t*-Bu,*t*-Bu)-W(O)OH (0.05%): turn-over numbers. Reaction conditions: $[TMB]_0 = [HClO_4]_0 = 20$ mM, $[H_2O_2]_0 = 20–40$ mM, $[TBAX]_0$ (X=Br, Cl) = 0.1 M, cat ≥ 0.05%; 28 °C, DMF.

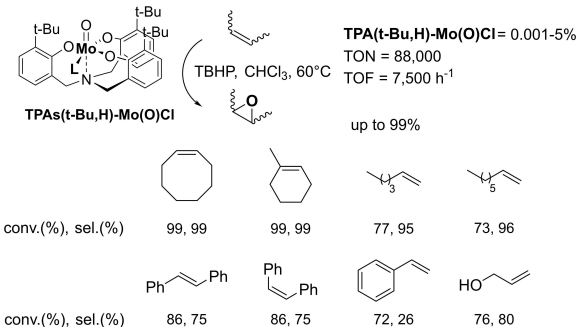
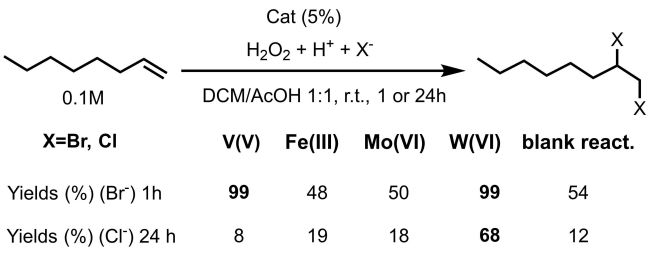


Figure 4. TPA(t-Bu,H)-Mo(O)Cl catalyzed epoxidation. Scope of the reaction.



X=Br, Cl	V(V)	Fe(III)	Mo(VI)	W(VI)	blank react.
Yields (%) (Br^-) 1h	**99**	48	50	**99**	54
Yields (%) (Cl^-) 24 h	8	19	18	**68**	12

Figure 5. 1-octene haloperoxidation (X=Br, Cl) in AcOH:CH_2Cl_2 = 1:1 [octene]$_0$ = 0.1; $[X^-]_0$ = 0.4 M; H_2O_2 = 0.2 M; cat = 5%: effect of the catalyst.

for chloroperoxidation. Due to the presence of AcOH as solvent, a not negligible blank reaction is also present.

The substrate scope was explored using **TPA(t-Bu,t-Bu)-W(O)OH** as catalyst (Figure 6).[20]

3. Dipyridinimines Iron Complexes

A significant contribution by the CIRCC Rome Unit to the field of oxidative processes using hydrogen peroxide as environmentally friendly oxidant was focused on reactions catalyzed by nonheme metal complexes using the imine based ligands.

Although imines chemistry had been largely employed in the design of ligands for metal complexes, their use in the field of iron-based catalysis for C–H oxidations was very limited and scattered[21] before the work by Di Stefano and coworkers published in 2014.[22] Here, iron imine-based complex **[DPI(H)]$_2$Fe** was simply obtained by mixing 2 molar equivs of 2-aminomethylpyridine, pyridine-2-carbaldehyde and 1 molar equiv. of Fe(OTf)$_2$ in acetonitrile at 25 °C. Remarkably 2-aminomethylpyridine, pyridine-2-carbaldehyde and Fe(OTf)$_2$ are all cheap and commercially available materials. Interestingly, formation of ligand **DPI(H)** turned out to be strongly accelerated by the *template* effect of the iron(II) salt (Figure 7). The one pot assembled iron complex **[DPI(H)]$_2$Fe** was then employed as a catalyst in the H_2O_2 oxidation of hydrocarbon substrates reaching catalytic efficiencies in line with the other non-heme iron complexes. However, the benefit of this approach lies in the straightforward one-pot in situ preparation of the catalyst.

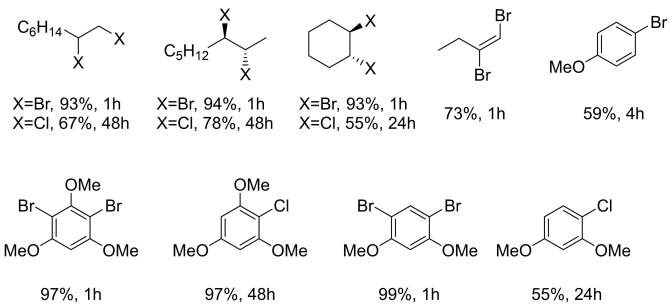


Figure 6. Products (yields, time) obtained by haloperoxidation (X=Br, Cl) catalyzed by **TPA(t-Bu,t-Bu)-W(O)OH** (5 %) in AcOH:CH_2Cl_2 = 1:1 of alkenes, alkynes and activated benzenes (0.1 M) by H_2O_2 (0.2 M) in the presence of NaBr (0.2 M) or LiCl (0.2 M).

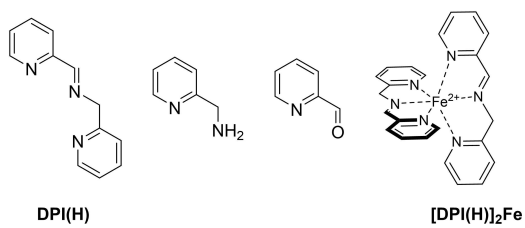


Figure 7. From left to right: the imine ligand **DPI(H)**, 2-aminomethylpyridine, pyridine-2-carbaldehyde and the imine-based complex **[DPI(H)]$_2$Fe**.

Shortly after the first report, Di Stefano and Costas and coworkers reported a full characterization and a detailed study on the operation of the imine based iron complex **[DPI(H)]$_2$Fe**.[23] The ligand/metal ratio in the complex is 2 to 1 and the two ligands chelate the iron in a meridional fashion filling the first Fe coordination sphere (hexadentate) in a octahedral geometry and keeping the two counterions in the second sphere. The complex exhibits a low spin, diamagnetic nature. ESI-MS and UV-vis investigations showed that complex **[DPI(H)]$_2$Fe** has a high stability in acetonitrile solution under the employed oxidative reaction conditions: although it undergoes a slow degradation, it remains the main iron species in solution most of the reaction time.

Several experiments have been carried out to investigate the nature of the active oxidant in the **[DPI(H)]$_2$Fe** /H_2O_2 system. As a general scheme the Fe^{II} complex is initially oxidized by H_2O_2 to the metal hydroperoxo complex Fe^{III}–OOH, which then undergoes the O–O bond cleavage leading either to an Fe^{IV}=O or a formal Fe^{V}=O species. The former, together with a hydroxyl radical (HO$^{\bullet}$) derives from an homolytic cleavage; this pathway is typical with pentadentate ligands and usually produces a radical chain oxidation mechanism. The latter, instead, comes from a heterolytic O–O cleavage, assisted by a water molecule (or a carboxylic acid molecule if present). Two *cis* labile coordination sites on the Fe sphere, generally found in tetradentate nonheme complexes, are necessary for this mechanism to take place generating selective metal based oxidants.

Mechanistic evidence supporting a metal-based pathway for the C–H oxidation catalyzed by **[DPI(H)]$_2$Fe** and thus excluding the involvement of free radicals were provided. Turning to specifics, to distinguish between metal-based and free-radical oxidation mechanisms, the following experiments, that are among the main tools used for this purpose,[24] were carried out:

- Cyclohexane (cHex) oxidation with a large excess of the substrate under air. In the presence of such an excess of cyclohexane the metal-based oxidation will occur preferentially at the expense of the substrate with respect to the newly formed cyclohexanol, giving a high A/K (alcohol/ketone) ratio. On the contrary in a free radical process a A/K ≈1 is observed because of the Russel type termination.
- Competitive *c*Hex vs *c*Hex-d_{12} oxidation to assess the KIE. A selective, metal based mechanism is able to clearly discriminate between C–H and C–D bond giving KIE values >2. Free radicals oxidations have a KIE value between 1 and 2.
- 3°/2° selectivity test in the oxidation of adamantane. The higher this ratio, the more selective (hence metal based) the catalysis. The ratio for known metal-based catalysts goes from 15 to 30; radical oxidation produces products in a 3°/2° functionalization around 2.
- Evaluation of the stereoretention in the 1,2-*cis*-dimethylcyclohexane oxidation. Due to the fast racemization of the radical intermediate, in a radical oxidation a very low degree of stereoretention is expected.

The results of these experiments are summarized in Table 1 and the comparison with a radical based oxidation promoted

Table 1. Comparison among oxidations of hydrocarbon probe substrates catalyzed by **[DPI(H)]2Fe**[a] and hydroxyl radical (HO•).

Catalyst	Cyclohexane A/K (A + K)[b] KIE[c]	Adamantane 3°/2°[d]	DMCH RC [%][e]
[DPI(H)]$_2$Fe	11.5 (4.2) 3.3	13	97
HO•	~1 ~1	~2	~10

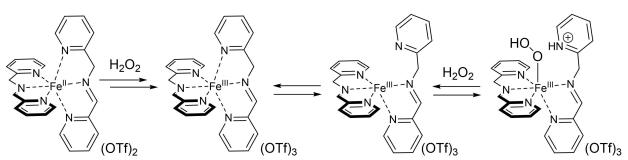
[a] Reaction conditions: cat:H_2O_2:AcOH:substrate = 1:10:50:1000. Catalyst (10 μmol) prepared in situ, 0.40 mL CH_3CN, 40 C, 80 min. GC yields. [b] A = cyclohexanol, K = cyclohexanone. 1000 mol equiv. of cyclohexane. [c] KIE measured in the competitive oxidation of a 1:3 mixture of cyclohexane/cyclohexane-d_{12}. Total 1 mmol of substrates. [d] DMCH = 1,2-cis-dimethylcyclohexane, 3°/2° = 3x(1-adamantanol)/(2-adamantanol + 2-adamantanone). 100 μmol of adamantane, 180 min. [e] RC = 100 x (*cis*-OH − *trans*-OH)/(*cis*-OH + *trans*-OH).

by the hydroxyl radical is shown. All data collected firmly point toward a metal based mechanism.

Then, going deeper to catch details about the nature of the active oxidant species, labeling experiments with $H_2{}^{18}O$ and $H_2{}^{18}O_2$ aimed to unravel the origin of the oxygen incorporation, were performed revealing some peculiar aspects. The labeling experiments excluded O atom incorporation from water molecule, and it proved that almost all the oxygen came from H_2O_2 with a minor amount from atmospheric oxygen due to a secondary radical path.

From these observations it was inferred that complex **[DPI(H)]$_2$Fe** cannot coordinate hydrogen peroxide and water simultaneously, as the tetradentate ligands with two cis labile coordination sites typically do,[25] hence a water assisted O–O lysis can be excluded (as well as the analogous acid assisted mechanism). Therefore, complex **[DPI(H)]$_2$Fe** must activate the hydrogen peroxide exploiting only one coordination site. The hypothesis advanced to enclose all the clues collected involves a first oxidation of the hexadentate **DPI(H)Fe(II)** to an intermediate **DPI(H)Fe(III)** from which one pyridine arm rapidly detaches. As a consequence, the metal becomes pentadentate letting the iron bind and activate H_2O_2 (Scheme 4). Probably an assistance from the detached protonated pyridine occurs, playing a role and supporting the fact that complex **[DPI(H)]$_2$Fe** has a catalytic activity considerably higher than that previously reported with pentadentate ligands. However, the nature of the oxidant species still remains uncertain.

Complex **[DPI(H)]$_2$Fe** was then employed in the catalysis of the H_2O_2 oxidation of several classes of organic compounds.



Scheme 4. Proposed mechanism for the formation of the hydroperoxo complex intermediate in the C–H oxidation mediated by **[DPI(H)]$_2$Fe**.

3.1. Alcohols Oxidation

First, the alcoholic function was considered,[26] and the oxidation of cyclohexanol to cyclohexanone was explored as model reaction, using different reaction conditions. Main findings of the screening were the following: i) the reaction afforded the ketone as a clean product with quite high yields (74%), ii) the slow infusion of H_2O_2 appeared crucial to the positive outcome of the reaction, iii) the system responds negatively when conditions are moved from 25 °C and acetonitrile as solvent, which were identified as optimal conditions, iv) increasing the steric hindrance on the substrate leads to a marked decrease in the catalytic activity, supporting the steric origin of the selectivity. When complex **[DPI(H)]$_2$Fe** was used in the oxidation of benzylic alcohols, again an unusual behavior emerged. In spite of the higher reactivity expected in a HAT process due to the lower BDE of the benzylic C–H(OH) bond, the aromatic ketones were obtained in much lower yields than the previously studied compounds. Instead, some phenolic by-products were detected. The hypothesis here is that the highly electrophilic oxidizing species formed in the reaction between complex **[DPI(H)]$_2$Fe** and H_2O_2, would preferentially hydroxylate the aromatic ring affording phenolic products. This result was confirmed performing some competitive experiments. For example, the competitive oxidation of cyclohexanol and 1-phenylethanol gave preferentially cyclohexanone with respect to acetophenone (16% vs 8%). The same experiment in the presence of a tetradentate complex [(TPA)Fe(CF_3SO_3)$_2$] led to an opposite selectivity (10% vs 17%).

3.2. Hydroxylation

Moving from these findings, the possibility to optimize the hydroxylation of aromatic compounds was then investigated.[27] Phenols, in fact, are widely present in pharmaceuticals and fine chemicals, nevertheless the chemical synthesis affords products in rather low yield (5% over a three steps process).[28] Hydroxylation of aromatic compounds must deal with the high stability coming from the aromaticity and the high BDE of aromatic C–H bonds so that they require strong oxidative power and, at the same time, overoxidation must be avoided (being the products more reactive of the substrates) as well as overfunctionalization since different oxidation sites are present. Hence a highly selective oxidant must be considered. Some bioinspired iron complexes, competent for selective C–H oxidations are also known to hydroxylate aromatic compounds, but except very few cases,[28] the irreversible phenol binding to the iron center soon deactivates these complexes, inhibiting the catalysis. Based on the phenolic by-products previously observed[25] and on the fact that all the just cited exceptions involve some modification in the architecture of the ligand, the authors wonder if the unique encumbered pentacoordinated active species of complex **[DPI(H)]$_2$Fe** previously postulated could bypass the described phenol inhibition.

First complex **[DPI(H)]$_2$Fe** was tested in the hydroxylation of benzene with hydrogen peroxide as the terminal oxidant and

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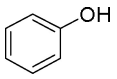
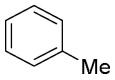
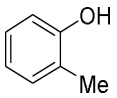
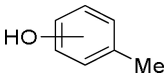
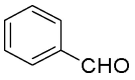
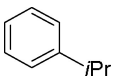
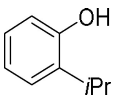
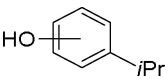
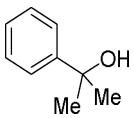
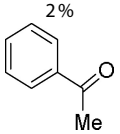
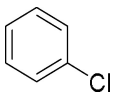
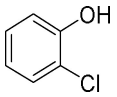
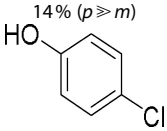
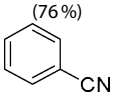
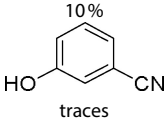
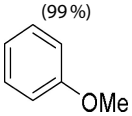
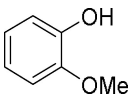
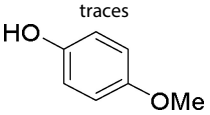
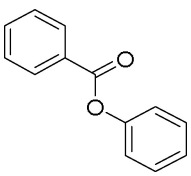
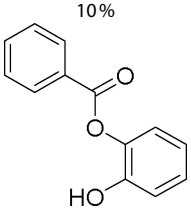
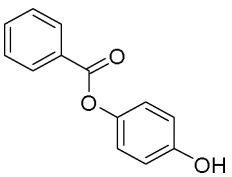
Table 2. Oxidation of 0.36 M aromatic compounds by H_2O_2 in CH_3CN at room temperature catalyzed by complex **[DPI(H)]$_2$Fe**.[a]

Substrate (unreacted)	Product 1 (*o* phenol)	Product 2 (*p* + *m* phenol)	Product 3(Chain ox.)	Product 4 (Chain ox.)	Selectivity for aromatic oxidation
 (55%)		–	–	–	–
 (47%)		 10% (*p*:*m* = 3:1)	–	 2%	92
 (65%)	 7%	 14% (*p* ≫ *m*)	 6%	 traces	80
 (76%)	 7%	 10%	–	–	–
 (99%)	–	 traces	–	–	–
 (58%)	 10%	 8%	–	–	–
 (48%)	 20%	 24%	–	–	–

[a] All data are reported in percentage with respect to the initial amount of the substrate. Reaction conditions: 250 mol% H_2O_2, 1 mol% catalyst 1, CH_3CN at 25 °C, reaction time 90 min, oxidant added in one shot at time 0.

remarkably it afforded phenol as main product in 23% yield. When the hydroxylation was carried on substituted benzenes, the regioselectivity and the conversion resulted mainly dictated by the electronic effects of substituents. As an electrophilic aromatic substitution, the reaction was enhanced by electron-releasing groups and the products were mainly ortho/para substituted. On the other hand, electron-withdrawing groups completely shut down the reaction. The same clear selectivity was shown in an intramolecular competitive hydroxylation of phenyl benzoate, bearing an electron-rich and an electron-poor ring. In this case, no hydroxylation occurred on the benzoate-type ring (Table 2).

Noteworthy, oxidation of alkylbenzenes brought to an outright preference for aromatic over aliphatic hydroxylation despite the presence of the reactive benzylic position. The same trend was experienced in an intermolecular competitive oxidation of a 1:1 mixture of cyclohexane and benzene. Interestingly, modulating the electronic properties of the ring, aromatic oxidation could be furtherly favored (in the presence of electron-releasing groups) or completely suppressed (with electron-withdrawing groups), (Table 2 and 3).

The marked selectivity and the sensitivity to electronic effects point to a metal-based mechanism mediated by an electrophilic species. Other mechanistic-relevant observations aimed to exclude free radicals involvement were collected. In particular the reaction resulted insensitive to atmospheric oxygen and to the presence of radical traps, and the KIE value of 0.98 measured in the competitive oxidation of benzene and perdeuterated benzene was consistent with an $sp^2 \rightarrow sp^3$

Table 3. Competitive oxidation between cyclohexane and a substituted benzene.[a]

Substituted benzene	Combined yield of ArX oxidation	Combined yield of CyH oxidation	ArX:CyH ratio
Ar–NO_2	Traces	9%	< 0.01
Ar–H	10%	2%	5
Ar–OMe	11%	< 1%	12.5

[a] Conditions: **[DPI(H)]$_2$Fe**:ArX: CyH:H_2O_2 1:50:50:100, CH_3CN, rt, 90 min.

change. This is involved in a metal-based S_EAr or an arene epoxidation mechanism, even if the former appears the most likely hypothesis. The nature of the active oxidizing species remained uncertain, but the ability to oxidize arenes and the selectivity observed closely resemble the results obtained with known non-heme Fe^V=O species derived from tetracoordinated iron complexes. In contrast, while the latter tetracoordinated complexes are not able to mediate the reaction catalytically as they undergo phenol inhibition, complex **[DPI(H)]$_2$Fe** delivers phenolic products in satisfying yields. The mechanism previously hypothesized (Scheme 4) is consistent with all data collected.

Expanding the scope of application in oxidative processes of the **[DPI(H)]$_2$Fe**/H_2O_2 catalytic system, Lanzalunga and co-workers investigated its performance in the oxidation of a series of aliphatic and aromatic *N*-acetyl amino acid methyl esters.[29]

When aliphatic amino acids underwent the reaction, the preference for side-chain or α-C–H oxidation appeared dictated by substrate structure. Oxidation of alanine derivative afforded methyl pyruvate as the only product (Table 4, entry 1). When the side chain contains more reactive secondary and tertiary CH bonds, as for Val and Leu derivatives, a mixture of products were obtained (entry 2). On the contrary, a selective side chain oxidation was obtained when a δ-C–H bond is present (proline derivative, entry 3). The regioselectivity pattern observed in the tested substrates recalls a hydrogen atom transfer (HAT) mechanism from substrates to the oxidizing species.[30] A separate discussion deserves the oxidation of aromatic amino acids. In confirmation of what previously described for aromatic compounds, when Phe derivative is oxidized with the **[DPI(H)]$_2$Fe**/H_2O_2 system, only the three isomeric *o*, *m*, *p* phenolic derivatives are collected, while no overoxidation to quinone and no traces of C–H oxidation were observed (entry 4).

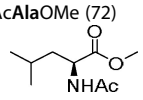
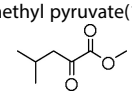
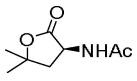
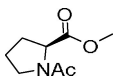
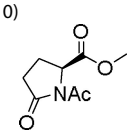
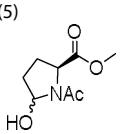
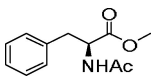
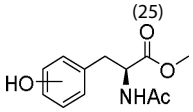
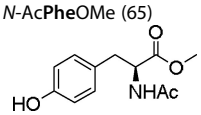
On the same line, no reaction occurred when Tyr was used as substrate, despite the fact that phenols are particularly reactive with HAT reagents (entry 5). Such evidence points to exclude a HAT pathway for aromatic substrates while is in accordance with the metal based S_EAr mechanism already proposed. The strong preference of complex **[DPI(H)]$_2$Fe** for aromatic over aliphatic oxidation was proved also in competitive experiments with Phe derivative and aliphatic Leu and Val, where the only products detected were the phenols derived from Phe. When a more reactive competitor was used, as Pro derivative, also the C-5 HAT oxidation product of Pro was formed but the yield of phenols remained unchanged.

Later on, a detailed study was conducted on the oxidations, promoted by the **[DPI(H)]$_2$Fe**/H_2O_2 system, of a series of alkylarenes characterized by different benzylic C–H bond dissociation energies (BDEs).[31]

As reported in Table 5, the imine-based complex **[DPI(H)]$_2$Fe** shows a clear selectivity for the aromatic hydroxylation for those substrates having a benzylic BDE higher than 82 kcal mol^{-1}. Upon decreasing the BDE, the side-chain oxidation starts to compete up to the point where the ring/side-chain product ratio is reversed with xanthene.

Evidence for a metal-based mechanism were again provided both for the aromatic hydroxylation (via S_EAr) and for the side-chain oxidation (benzylic HAT). In particular a high KIE of 3.6 was measured in the 9,10-dihydroanthracene benzylic oxidation. This value is in accordance with selective metal-based oxidants for which a Fe^V=O species has been proposed, and clearly excludes a Fenton-type process (having KIE between 1 and 2). The results obtained suggest that both the aromatic and the aliphatic oxidations are promoted by the same high valent iron-oxo species, whose activation could be described by the mechanism proposed in Scheme 3. Besides the peculiar oxidative properties, the great advantage of the imine based complex **[DPI(H)]$_2$Fe**, as already stressed, lies in its extreme ease of preparation: a one pot in situ self-assembly from commercially available compounds. The same strategy and almost the same straightforward synthesis was exploited to obtain an iron complex with a much more sophisticated architecture bearing two supramolecular crown-ether receptors.[32] To obtain complex **[DPI(Ar')]$_2$Fe**, first an efficient two-step synthesis of the parent aldehyde was developed (Figure 8). A Miyaura borylation

Table 4. Oxidation of amino acids by H_2O_2 in CH_3CN at room temperature catalyzed by complex **[DPI(H)]$_2$Fe**.[a]

Entry	Substrate [unreacted %]	Products [yields %]	
1	 *N*-Ac**Ala**OMe (72)	 methyl pyruvate(13)	
2	 *N*-Ac**Leu**OMe (73)	 (10)	 (5)
3	 *N*-Ac**Pro**OMe (64)	 (10)	 (25)
4	 *N*-Ac**Phe**OMe (65)	 (*o*:*m*:*p* 11:3:13)	
5	 *N*-Ac**Tyr**OMe (98)	–	

[a] Reaction conditions: 250 mol% H_2O_2, 1 mol% catalyst 1, CH_3CN at 25 °C, reaction time 30–90 min, oxidant added by syringe pump (30 min).

Table 5. Correlation between benzylic BDEC–H of alkylaromatics and aromatic vs. side-chain chemoselectivity in the oxidation promoted by the **[DPI(H)]$_2$Fe**/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

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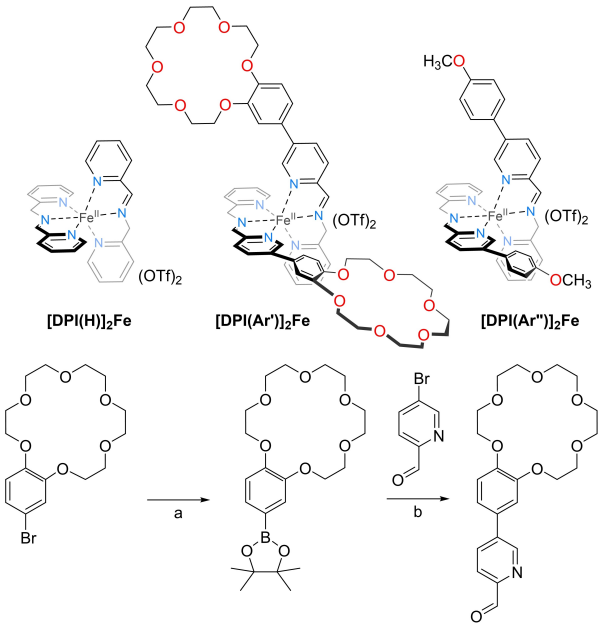
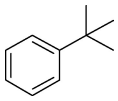
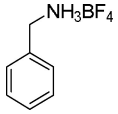
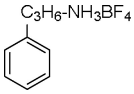


Figure 8. Top: Imine-based complexes synthesized. From left to right: complexes **[DPI(H)]$_2$Fe**, **[DPI(Ar')]$_2$Fe**, **[DPI(Ar")]$_2$Fe**. Bottom: Synthesis of the aldehyde precursor of **[DPI(Ar')]$_2$Fe**: a) 1.5 mol equiv. B_2Pin_2, 1.3 mol equiv. $BaCO_3$, 1.3 mol equiv. KOAc, 3% $Pd_2(dba)_3$, 9% SPhos, in toluene at 100 °C for 15 h, 99%. b) 1.0 mol equiv. 5-bromopyridine-2-carboxaldehyde, 6% $Pd(OAc)_2$, 18% SPhos, 2.7 mol equiv. Li_2CO_3, 1.8 mol equiv. LiCl, in THF/H_2O, 1:1 for 72 h at 60 °C + 2 h at 80 °C, 79%.

on the commercially available 4′-bromobenzo-18-crown-6 afforded the boronic ester derivative. In this case, the classic procedure was modified to counterbalance the electron releasing effect of the crown ether. A Ba^{2+} salt that strongly binds the crown ether was added to the mixture to induce an umpolung of the electronic properties of the ring. This way, the electron vacancy of the aryl-halide necessary for the back-bonding from Pd(0) that trigger the Miyaura was restored. A following Suzuki–Miyaura cross-coupling delivered the desired aldehyde in high yield.

As for complex **[DPI(H)]$_2$Fe**, the formation of complex **[DPI(Ar')]$_2$Fe** proceeded one pot combining a solution of $Fe(CH_3CN)_2(OTf)_2$, the synthesized aldehyde and 2-picolylamine (Figure 8) in a 1:2:2 ratio, although in this case, the in situ formation of the complex required 60 h. Under the same conditions complex **[DPI(Ar")]$_2$Fe** is assembled in 20 min. The new complexes were tested in the hydroxylation of *tert*-butylbenzene. Although slightly less efficient, complex **[DPI(Ar')]$_2$Fe** and **[DPI(Ar")]$_2$Fe** were active catalysts of the aromatic hydroxylation with the H_2O_2 oxidant. To test the potential ability of the crown ether receptors to orientate the substrates[33] and hence modify the natural regioselectivity of the reaction, a series of aromatic compounds bearing primary ammonium groups as anchoring sites were subjected to oxidation. Related results, which are summarized in Table 6, suggest a general preference of both complexes **[DPI(Ar')]$_2$Fe** and **[DPI(Ar")]$_2$Fe** for *meta* and *para* functionalization with respect to complex **[DPI(H)]$_2$Fe**, while no clear effect due to

Table 6. Oxidation of *tert*-butylbenzene and primary ω-phenylalkylamine BF_4^- salts (0.320 M) with H_2O_2 catalyzed by complexes **[DPI(H)]$_2$Fe**, **[DPI(Ar')]$_2$Fe** or **[DPI(Ar")]$_2$Fe**.[a]

[Substrate]	Catalyst	Conv.	*Products (o:m:p %)*	Yields	*m/o*
	**[DPI(H)]$_2$Fe**	40%	6:16 (*m* + *p*)	22	–
	[DPI(Ar')]$_2$Fe	29%	5:13 (*m* + *p*)	18	–
	[DPI(Ar")]$_2$Fe	53%	< 1:12 (*m* + *p*)	13	–
	**[DPI(H)]$_2$Fe**	53%	4.0:3.5:3.5	11	0.88
	[DPI(Ar')]$_2$Fe	38%	2.0:3.5:2.5	7.5	1.5
	**[DPI(H)]$_2$Fe**	41%	8.5:6.0:11.5	26	0.70
	[DPI(Ar')]$_2$Fe	35%	2.5:3.0:4.5	10	1.2
	[DPI(Ar")]$_2$Fe	46%	3.0:4.0:6.0	13	1.3

[a] 100:1 substrate/catalyst ratio, H_2O_2 2.5 mol equiv. with respect to substrate added during the first 30 min of reaction; solvent CH]CN; concentration of substrate: 0.320 M; T = 25 °C; reaction time: 90 min.

recognition was observed. The origin of such preference was ascribed to steric factors due to the increased hindrance around the iron center of these two new catalysts.

To further explore the role of steric factors in the mechanism of action of the imine-based catalyst **[DPI(H)]$_2$Fe**, two new ligands endowed with bulky substituents were synthesized.[34]

The increased steric hindrance around the metal core is obtained with the introduction of one (**[DPI(Si)]$_2$Fe**) or two ((**[DPI(Si$_2$)]$_2$Fe**) triisopropylsilyl groups on the ligand (Figure 9).

Again, the self-assembly of the parent compounds led to the complete formation of the complexes, in 45 min (**[DPI(Si)]$_2$Fe**) and 75 min (**[DPI(Si$_2$)]$_2$Fe**). A full characterization of the complexes afforded data perfectly matching with those of complex **[DPI(H)]$_2$Fe**, the only differences lying in the grown steric hindrance. When **[DPI(Si)]$_2$Fe** and **[DPI(Si$_2$)]$_2$Fe** were tested as catalysts for the H_2O_2 oxidation of a series of alkylaromatic compounds, their catalytic activity was found to be similar to that of **[DPI(H)]$_2$Fe**. This behaviour is in accordance with the strong decrease of the steric hindrance around the iron center after detachment of a pyridine arm in the formation of the active species, as reported in Scheme 4.

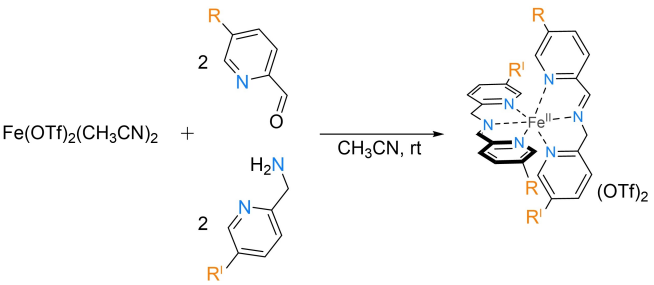


Figure 9. In situ preparation of complexes (**[DPI(Si)]$_2$Fe** (R=Si(CH(CH$_3$)$_2$)$_3$, R^I=H) and **[DPI(Si$_2$)]$_2$Fe** (R=R^I=Si(CH(CH$_3$)$_2$)$_3$).

4. Conclusions

The results described along this perspective article and originating from intensive research carried out within the Interuniversity Consortium Chemical Reactivity and Catalysis (CIRCC) show how complex the activation of a small and rather inert molecule like H_2O_2 can be and how the design and use of proper homogeneous catalysts can result in the development of efficient and sustainable processes. The described catalysts, developed in our research groups, proved to be versatile, robust and highly reactive in rather different oxidation processes, affording selectively the desired processes with high TONs, TOFs and low catalyst loadings under relatively mild reaction conditions.

Disclaimer

The opinions expressed in this publication are the view of the author and do not necessarily reflect the opinions or views of the European Journal of Inorganic Chemistry, the Publisher, Chemistry Europe, or the affiliated editors.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: hydrogen peroxide · hydroxylation · oxidations · oxygen-transfer reactions · peroxometallo complexes · transition metals

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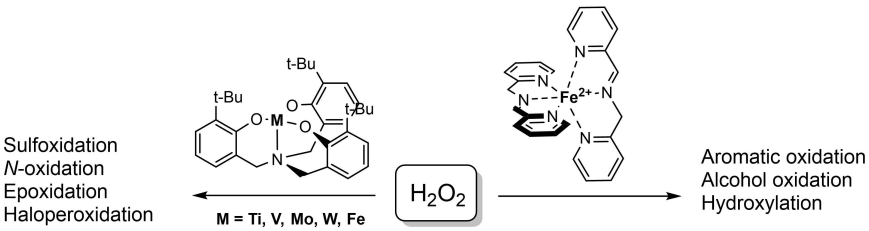

Dr. C. Sappino, Prof. S. Di Stefano, Prof. O. Lanzalunga, Prof. C. Zonta, Prof. G. Licini**

1 – 11

Transition Metal Catalysts Bearing Multidentate Ligands for Efficient and Environmental Benign Oxidations by H_2O_2

In this perspective, we summarize the catalytic performances of a series of Ti, V, Mo, W, Fe complexes bearing multidentate ligands developed in two of the CIRCC Consortium research groups. The catalysts have been successfully applied for the efficient and environmental benign H_2O_2 activation for a wide variety of oxidative processes (*N*- and *S*-oxidations, epoxidations, haloperoxidation, alcohol oxidation, hydroxylation).