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SCUOLA DI DOTTORATO DI RICERCA IN :SCIENZE MOLECOLARI
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CICLO XXIV

BIOMIMETIC CATALYSTS FOR OXYGEN TRANSFER REACTIONS

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Chapter 1

Introduction

1.1 Biomimetic chemistry

"Biomimetic chemistry", as defined by Breslow,[1] is the branch of organic and inorganic chemistry which attempts to imitate natural reactions and enzymatic processes as a way to improve the power of chemistry itself. In biological systems, complex reactions take place at very high rates and with elevated specificity. In general, pH and temperature conditions are mild as a consequence of the intervention of enzymes. The full comprehension of the mechanisms and of the role of the enzymes in these processes is essential for the development of biological, chemical and medical sciences. The enzymatic activity requires the concomitant intervention of several factors, such as the selective recognition and the consequent activation of the substrate, as well as the stabilization of both the transition state and the product. All these processes involve a high number of weak interactions, such as hydrogen bonds, Van der Waals, electrostatic and hydrophobic interactions, together with a precise spatial arrangement of the functional groups in the active site. The specificity is the outcomes of billions of years of evolution which have defined the complex tertiary and quaternary structures of the protein responsible of substrate binding in well-defined geometries.

A direct study of these systems is complicated by the large number of processes involved. A powerful approach is offered by "biomimetic chemistry", which relates to the design, synthesis and study of artificial systems that reproduce, in a simplified manner, the principal features of the "inspiring" biological system. This approach has the advantage of an easier validation of mechanistic hypotheses of the biological system in examination, together with the development of new compounds able to mantain the same functions, and possibly the same activity, of the enzyme-catalyzed process. "Enzyme models" are mimicking the basic functions of the enzyme itself, bearing suitable functionalities for the substrate, and in most of the cases the ability to operate in aqueous medium, at physiological pH and temperature. The results of this 'imitation of nature' are well known-improved rates and high selectivity with the respect of "classical" catalytic systems, and interesting examples are proposed in the literature by several groups all over the world.[2]

1.2 Metals in biological systems

Although biology is generally associated with organic chemistry, inorganic elements are also essential in life processes. Metals are commonly found as natural constituents of proteins. Nature has learned to use the special properties of metal ions to perform a wide variety of specific functions. Metalloproteins that perform a catalytic function are called *metalloenzymes*. Table 1 summarize most of the essential inorganic elements together with some their known roles in biology.

Table 1. Biological functions of selected metal ions in *metalloenzymes*.

Metal	Function
Magnesium	Hydrolase, isomerase
Vanadium	Nitrogen fixation, oxidase
Molybdenum	Nitrogen fixation, oxidase, oxo transfer
Tungsten	Dehydrogenase, oxo transfer
Manganese	Photosynthesis, oxidase
Iron	Oxidase, dioxygen transport and storage, electron transfer, nitrogen fixation
Cobalt	Oxidase, alkyl group transfer
Nickel	Hydrogenase, hydrolase
Copper	Oxidase, dioxygen transport, electron transfer
Zinc	Hydrolase

Metallonzymes can be classified according to their function, and usually, each reaction category can be catalysed by several different metals. The reason for this diversity comes from multiple factors: evolution, bioavailability of a given element in the biosphere and the need to exploit different biochemical pathways to secure the viability of critical cellular functions.

Many metalloenzymes catalyse redox transformation of a substrate. These reactions are generally *two-electron redox processes*, and often involve atom or group transfers as well, *e.g*. the addition of an oxygen atom to a substrate. Example of this class of enzymes are cytochrome P-450, tyrosinase and sulfite oxidase (Table 2).

Table 2. Two-electron redox reactions.

Enzyme	Metal	Reaction/Substrate
Cytochrome P-450	Fe	Oxiations of hydroarbons to alcohols
Tyrosinase	Cu	Ortho-hydroxylations of phenols
Sulfite oxidase	Mo	Oxidations of sulphites to sulphates

Other metalloenzymes, such as ribonucleotide reductase and nitrate reductase, remove oxygen atoms from a substrate. Dehydrogenation reactions constitute another class of two-electron redox processes, that involve liver alcohol dehydrogenase, which contains a Zn^{2+} and catalyse the formation of acetaldehyde from ethanol.

Metalloenzymes also participate in multielectron-pair transformations. For example, cytocrome *C* oxidase, an enzyme containing two copper and two heme iron centres, catalyse the reduction of oxygen to water. The reverse reaction,

oxidation of water to dioxygen, is catalyzed by the photosynthetic oxygen-evolving complex (OEC) of photosystem II, that in some known enzyme contains four manganese and one calcium atoms in its active site.
Nitrogenase is instead involved in nitrogen metabolism; its active site contains a unique iron-molybdenum cofactor (FeMoco), which is, at the same time, the N_2 coordination and the reduction site. The enzyme, which is made up of two proteins, uses a second protein that contains a Fe_4S_4 cluster, to transfer electrons to the iron-molybdenum protein.

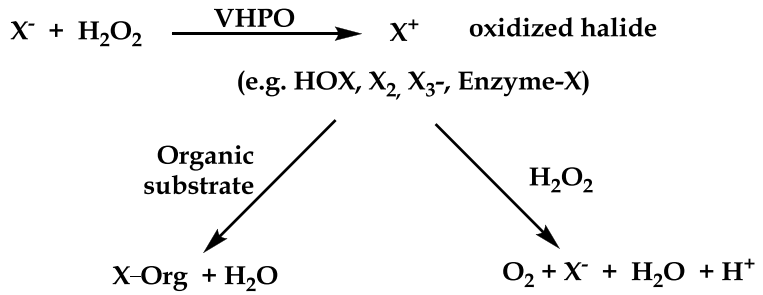
1.3 d^0 metals in biomimetic chemistry

In this very wide scenario, our main interest is focused on biomimetic chemistry and, in particular, on the catalytic opportunities offered by compounds which coordinate metals in high oxidation states and by their possibility to catalyse oxygen transfer processes. In the next sections vanadium(V), molybdenum(VI) and tungsten(VI) biomimetic metal complexes will be presented. The first part will be dedicated to vanadium compounds, which generally catalyse reactions without formal change in the metal oxidation number. The coordination chemistry and the catalytic activity of molybdenum and tungsten complexes will be reported in the second part of this introduction. Vanadium and molybdenum metal complexes usually perform catalytic cycles that involve a change of their oxidation states, generally from VI to IV and *vice versa*, but are also well known as catalysts for oxidations with peroxides.

1.4 Vanadium enzymes

Excluding the enzymes involved in nitrogen fixation, vanadium biochemistry is related to vanadium dependent peroxidase. Peroxidases are oxidases or oxygenases acting as electron acceptor on peroxides Three classes of peroxidases are usually distinguished: non-heme peroxidases, heme peroxidases (containing iron in a porphinogenic environment) and vanadate-dependent peroxidases. Whereas the last type were characterised only a quarter of a century ago, heme and non-heme peroxidases have a long-standing tradition. In contrast to the heme peroxidases, which are oxidatively deactivated by an excess of H_2O_2, the vanadate-dependent peroxidases, commonly known as vanadate-dependent haloperoxidases (VHPO), are surprisingly robust, i.e. they readily survive in excess of H_2O_2 as well as in organic solvents. VHPOs are widely distributed, mainly in marine brown algae. The first isolation of a vanadium haloperoxidase enzyme (VHPOs) from the marine algae *Ascophyllum nodosum* date back to 1984.[3] It is now known that these vanadium-dependent enzymes, found in most marine algae, seaweeds, and in some lichens[4] and fungi,[5] are able to oxidize halides "X^-" to the corresponding "X^+" species in the presence of hydrogen peroxide. Once

formed, oxidized halides can react with suitable organic substrates to form halogenated organic compounds (Scheme 1).[6] These products probably are part of the defence mechanisms of the organisms in which the VHPOs are found. For example, HOX (hypohalous acids) and some of the organohalogens produced by VHPOs may prevent fouling by microorganisms or may act as antifeeding system.[7]



Scheme 1. Summary of the general reactivity of VHPOs with halides (X^-).

The nomenclature for the haloperoxidases has traditionally been based on the most electronegative halide which can be oxidized by hydrogen peroxide, catalyzed by the enzyme. Thus chloroperoxidases (VCPOs) catalyze the oxidation of chloride, bromide and iodide; bromoperoxidases (VBPOs) catalyze the oxidation of bromide and iodide, while iodoperoxidases (VIPOs) catalyze the oxidation of only iodide. There are no fluoroperoxidases because hydrogen peroxide does not have the potential to oxidize fluoride.[8]

Four principal classes of enzymes able to perform halogenation of organic substrates in presence of a cofactor are known (Table 3).[9]

Table 3. Different classes of halo-peroxidase and halo-oxigenase and associated cofactors.

Enzyme	Cofactor	Oxidant	Co-Substrate
Haloperoxidase	Fe-heme	H_2O_2	Halogen
Haloperoxidase	Vanadium	H_2O_2	Halogen
Haloxygenase	$FADH_2$	O_2	Halogen
Haloxygenase	Fe-nonheme	O_2	Halogen, α-ketoglutarate

A variety of halogenated products have been isolated from natural organisms. Some of these compounds are simple, volatile halohydrocarbons (such as bromoform, dibromomethane, etc.), while others are more interesting halogenated indole or terpene compounds, possessing a variety of biological and pharmacological effects, such as antifungal, antibacterial, antiviral, anti-inflammatory or even anti-neoplastic activity.[10]

In the past, several studies have been carried out in order to reveal the nature of the active site and the mechanism of action. The first crystal structure of a vanadium chloroperoxidase enzyme was isolated from the fungus *Curvularia inaequalis* in 1996,[11] and a year later was published the X-ray analysis of the peroxo adduct that is the enzyme's active form.[12] In the native state, the vanadium ion is characterized by a trigonal bipyramidal geometry, where three oxygen atoms belong to the equatorial plane and one oxygen occupies an axial position. The other apical ligand is His496, which links the metal ion to the protein, whereas Lys353, Arg360, His404, and Arg490 are involved in hydrogen bonds with the oxygen atoms of the cofactor. In the peroxo derivative of the enzyme, the peroxide is bound side-on to the vanadium centre in a η^2-fashion and the cofactor is characterized by a strongly distorted tetragonal pyramidal geometry, with two oxygen atom types and one peroxo group in the equatorial plane, while His496 and the other oxo group occupy axial positions (Figure 1).[13]

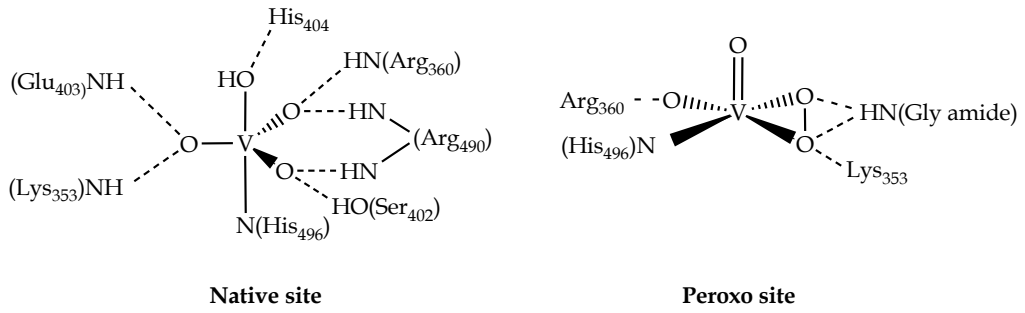


Figure 1. The native and peroxo vanadium site in VCPOs.

The active site of the enzyme is located on the top of the second four-helix bundle of the enzyme structure and a channel allows the entrance of hydrogen peroxide, X^- and a possible organic substrate.[1,14,15] At one side, the channel is composed of hydrophobic residues, while the other side is mainly hydrophilic.[1] However, the crystal structures of this type of enzymes revealed that VHPOs are composed of one or more subunits of around 60-70 kDa and have only one bounded vanadium atom for each subunit (Figure 2).[16]

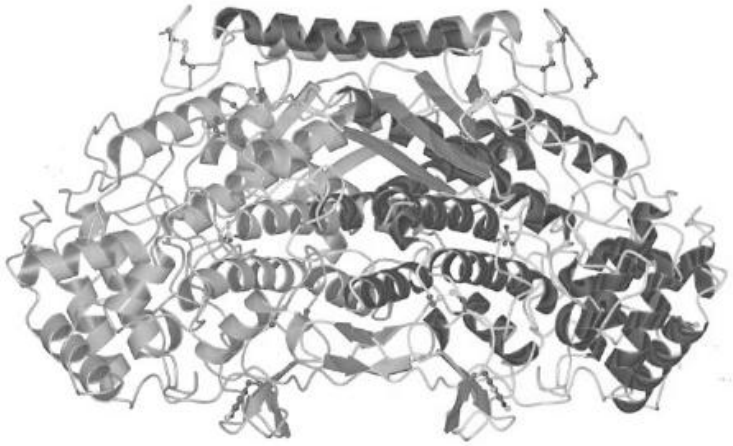
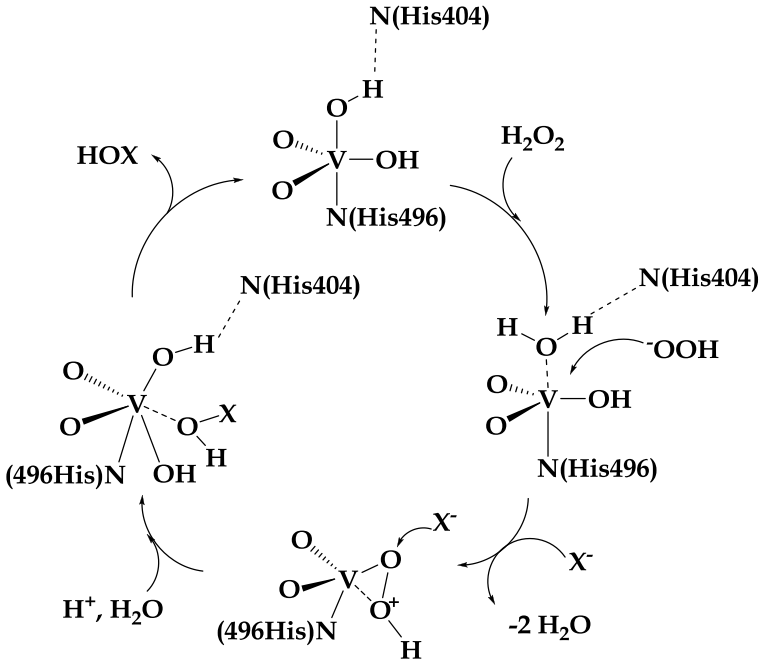


Figure 2. Ribbon-type representation of the VBPO dimer isolated from brown alga *Ascophyllum nodosum*. A vanadate group is present in each monomer.

The VHPOs require one equivalent of vanadium to perform their catalytic activity.[17] The vanadium centre does not appear to undergo redox cycling during turnover and is proposed to act as a Lewis acid towards the activation of the primary oxidant, i.e. hydrogen peroxide.

A general consensus currently exists for the mechanism of halide oxidations for VHPOs, which is a "ping-pong" mechanism: hydrogen peroxide coordinates to the vanadium centre, forming the peroxovanadate active specie. The rate-determining step in the catalytic cycle is the nucleophilic attack of the halide on the protonated protein-peroxide complex, generating a X^+ specie, which immediately reacts with the organic substrates, halogenating them. This step will generate singlet oxygen in the absence of a suitable organic substrate, and has been investigated in detail with Cl^-, Br^- and I^-.[18]

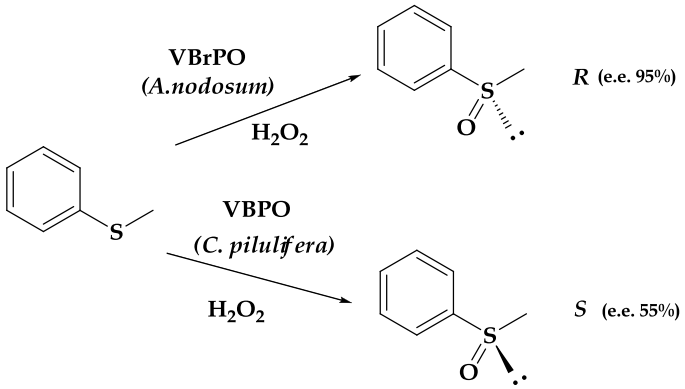
As mentioned above, the apical hydroxyl group of the enzyme is hydrogen bonded to a hystidine residue (His404) in a proteic environment. This hydrogen bond makes the OH^- group more nucleophilic. When a peroxide molecule approaches the active site, the OH^- unit is protonated with one of the peroxide H^+ and HOO^- is generated. The weakly bonded water molecule dissociates from vanadium ion and a side-on bound peroxide intermediate is formed after the departure of another water molecule. Subsequently, the attack of a chloride ion at a peroxidic oxygen and the uptake of a proton from a surrounding water molecule, leads to the generation of hypohalous acid (HOX) and restoration of the native state (Scheme 2).



Scheme 2. Proposed catalytic mechanism of VHPOs.[19]

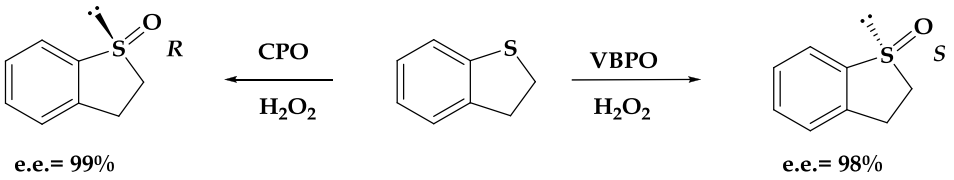
According to the literature, the oxygen transfer involves the attack of the substrate on the deprotonated peroxo oxygen: before the nucleophilic attack of the substrate, the peroxo moiety is protonated to hydroperoxo and Lys353 seems to polarize the peroxidic bound.[1] Besides, the oxidation reaction towards halides increases in velocity by adding acids and the spectroscopic data are consistent with the protonation of one or more sites of the peroxidic species.

In principle, every nucleophilic organic compound, which can gain access to the VHPOs active site and which have an oxidation potential lower than the reduction potential of hydrogen peroxide, could be oxidized by these enzymes. This is the case of sulfides. It was demonstrated that VHPOs are able to catalyze stereoselective sulfoxidations.[20] Depending on the substrate, up to 91% *e.e.* could be achieved. Moreover, different enzymes may produce opposite enantiomers, starting from the same substrate. As an example, the enzymes obtained respectively from *Ascophillum nodosum* and from *Corallina pilulifera* activate the hydrogen peroxide in the oxidation of thioanisole, affording the corresponding sulfoxide with high yields and selectivities, exceeding 95% enantiomeric excess of the (*R*)-enantiomer for the first enzyme, and 55% *e.e.* of the (*S*)-enantiomer for the second one (Scheme 3).[21]



Scheme 3. Stereoselective oxidation of thioanisole by two different VBPOs.

Complementary stereoselective sulfoxidation by means of different haloperoxidases can be reached using a heme-containing chloroperoxidase from marine fungus *Caldariomyces fumago*, and VBPO from *Corallina officinalis*: using hydrogen peroxide as the oxygen source, the enzymes can catalyze the oxidation of 2,3-dihydrobenzothiophene with excellent and opposite enantioselectivities, as shown in Scheme 4.[22]



Scheme 4. Stereoselective oxidation of 2,3-dihydrobenzothiophene by a heme-containing CPO and a VBPO.

1.4.1 Model chemistry

To get a better understanding of the mechanism of the VHPO enzymes and the role of vanadium a variety of vanadium compounds have been studied as functional models these enzymes.[23] These complexes are reactive towards the oxidation of sulfides and halides, in analogy with the VHPOs.[24] The role of the ligands in the VHPOs models is crucial: in fact, in the absence of ligands, which stabilize the monomeric complex, vanadium establishes a series of oligomeric and protonation equilibria depending on its concentration and on the acidic conditions. In recent years, several vanadium complexes with multidentate ligands containing O and N donor sites, were tested for catalysis in oxidation reactions.

In particular, different tripodal amine-based ligands have been largely employed to obtain monomeric V(V) complexes and they have been tested in the activation of hydrogen peroxide (Figure 3).[2,3] These ligands are ideal to model some of the donors that can be likely found in the active site of the enzymes, such as carboxylate, alcohol, amide, and pyridine donors.

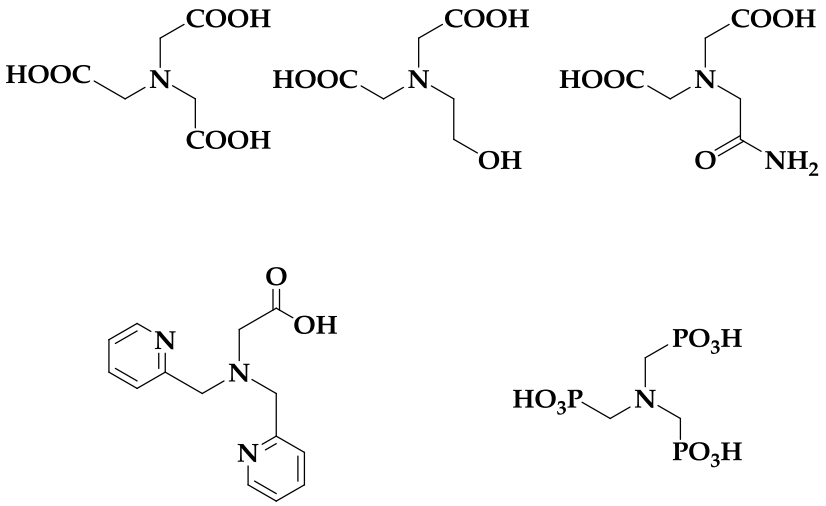
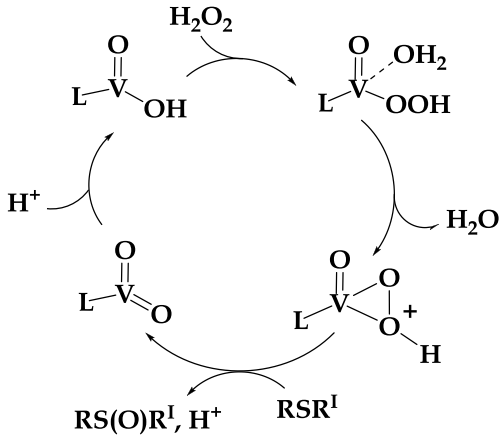


Figure 3. Ligands whose V(V) complexes have been tested for catalysis of bromide or sulfide oxidation.

For each ligand, the monomeric complex is obtained using a 1:1 ratio vanadium precursor/ligand. Addition of hydrogen peroxide affords a new monomeric metal peroxidic species, effective in halide oxidations and sulfoxidations. The sulfide oxidation has proven to be highly similar to halide oxidation by these complexes (Scheme 5).[25]

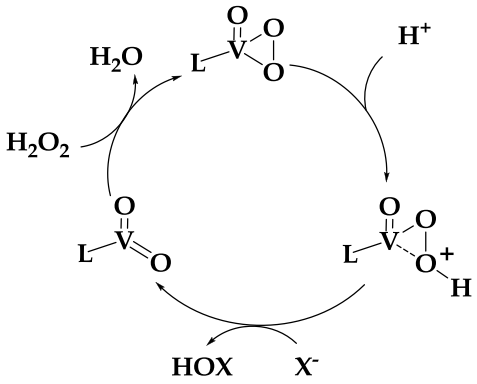


Scheme 5. Complete scheme for the catalytic cycle of sulfide oxidation by monoperoxovanadium(V) tripodal amine complexes.[25]

Once the initial oxoperoxo vanadium complex is protonated, the substrate perform a nucleophilic attack on the protonated peroxide ligand. The product

distribution displays almost exclusively sulfoxide products, with little presence of further oxidation products, points to an electrophilic rather than radical mechanism.

Scheme 6 reports a representation of the halide oxidation mechanism. The only difference, between the halide and sulfide oxidation mechanism, is the acid equivalent required for reactivity. In halide oxidation, the acid is consumed in each cycle, while in sulfide oxidation the acid is not necessary.

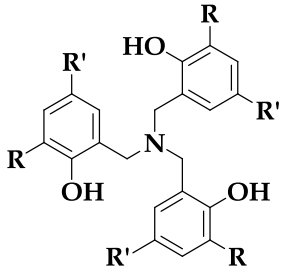


Scheme 6. Simplified halide oxidation mechanism.[25]

1.4.2 V(V)amine tri-phenolate complexes as functional and structural models of VHPOs

Triphenolamines (TPA) have emerged recently as a significant example, and in some extent, as an important opportunity in metal catalysis. In the last decade a considerable number of reports discuss about their complexation behaviour with a wide variety of transition metals and main group elements.

Steric and electronic factors can play an important role in the stability and catalytic activity of the complexes. As example, *ortho* groups to the phenol oxygen (R in Scheme 7), upon complexation with the metal ions, result in close proximity to the metal centre and can therefore be used as a control element towards the catalytic activity. On the other side, *para* groups (R' in Scheme 7) can modify the electronic properties of the ligand without affecting the steric demand of the system.



L_aH_3: R=R'=H
L_bH_3: R=R'=Me
L_cH_3: R=R'=*t*-Bu
L_dH_3: R=R'=Cl
L_eH_3: R=*t*-Bu; R'=Me
L_fH_3: R=Me; R'=*t*-Bu
L_gH_3: R=Adm; R'=*t*-Bu
L_hH_3: R=Me; R'=H
L_iH_3: R=*t*-Bu; R'=H
L_jH_3: R=Ph; R'=H

Scheme 7. Generic structure of a triphenolamine ligand.

Vanadium(V) complexes are reported to give trigonal bipyramidal (TBP) structures, even though, as in the case of Ti(IV), they can also adopt octahedral geometries to accommodate an extra ligand. Reaction of ligands L_bH_3 and L_cH_3 (Scheme 6) with VCl_3·THF led to the formation of C_3 symmetric TBP species in which a THF molecule occupies the apical position. When $V(O)(OR)_3$ species are used as metal precursors, TBP geometries are as well observed, in which the axial position *trans* to the nitrogen of the tripod ligand is occupied by the oxo moiety (Figure 4).[26] In these TPA-V(O) complexes, the V-N distances (from 2.416 to 2.4697 Å) are significantly longer than in V(III) (2.212-2.116 Å) or in Ti(IV) (2.172-2.334 Å) counterparts, due to the *trans* influence of a strong π-donor ligand (the V-oxo).

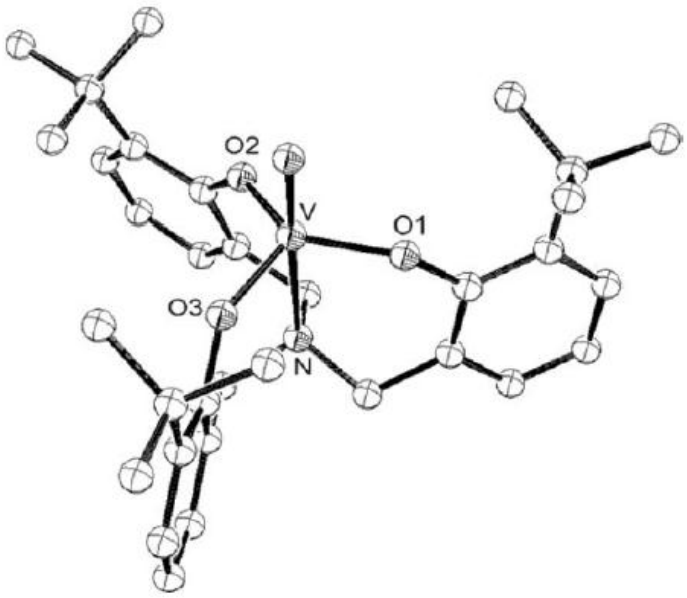


Figure 4. Molecular structure of $L_iV(O)$, complex **1**.[27]

In V(V) complexes different binding modes are found when highly electron-poor amine triphenolate ligands like L_dH_3 (R=R'=Cl, Scheme 7) are used. In this case, a hexa-coordinate octahedral complex is obtained, in which an oxo moiety occupies the axial position *trans* to the nitrogen and a molecule of water occupies an equatorial one. In this complex, the tripodal ligand does not present a propeller-like arrangement around the metal.

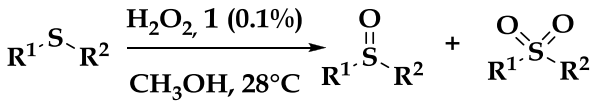
Good catalytic activities have been obtained using the V(V) complex $L_iV(O)$, **1**.

The renewed interest in vanadium(V) complexes arises from the possibility of these catalysts to work as mimic of vanadium-dependent haloperoxidase enzymes.[28] Goldschmidt, Kol and others firstly reported on the catalytic

activity of V(V) TPA complexes in oxidation.[26] They described preliminary results on the capability of these systems towards the oxidation of styrene. Employing 5 mol% of vanadium(V) complexes in a benzene solution of styrene/*tert*-butylhydroperoxide, styrene oxide was obtained. The rate of oxidation was slow (4-5 turnover per day) and additional products formed along the reaction.

More recently Licini reported on the catalytic activity of differently substituted V(V) catalysts. These systems are able to efficiently catalyze sulfoxidations at room temperature, using hydrogen peroxide as terminal oxidant yielding the corresponding sulfoxides in quantitative yields and high selectivities (catalyst loading down to 0.01%, TONs up to 9900, TOF up to 8000 h-1, Table 4). Moreover, to the best of our knowledge, the $L_iV(O)/H_2O_2$ system seems to be the most active VHPOs model so far reported.[29] The results in the oxidation of sulfides are by far superior of the analogous with Ti(IV) in terms of reactivity and selectivity. The solution behaviour under turnover conditions has been explored *via* ^{51}V NMR spectroscopy, demonstrating that the original singlet of the catalyst (at -396.2 ppm) is converted to a new species, very likely a diperoxo complex (at -649.3 ppm) in presence of an excess of hydrogen peroxide. The addition of the sulfide gave complete formation of the sulfoxide and regeneration of the original catalyst. Also in this case a range of substrates have been effectively oxidized in good yields and chemoselectivities, demonstrating the versatility of the catalyst (Table 4).

Table 4. Oxidation of sulfides by 30% aqueous H_2O_2 catalysed by **1**.[a]

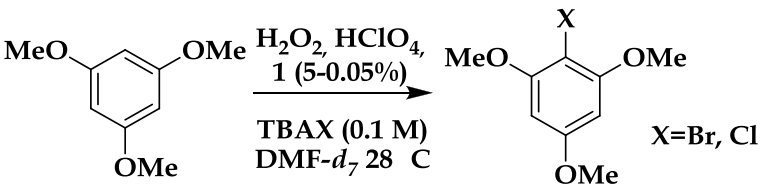


Entry	R^1	R^2	conv. (%)[b]	**SO**:**SO$_2$**[b]	Yield (%)[c]
1	Ph	Me	98	99:1	98
2	*p*-Tol	*n*-Bu	96	>99:1	94
3	Ph	Bn	99	>99:1	99
4	*n*-Bu	*n*-Bu	99	>99:1	91
5	*p*-MeO-C_6H_4	Me	98	>99:1	94
6	*p*-NO_2-C_6H_4	Me	98	97:3	70

[a] Reactions carried out at 28°C with a 1:1 molar ratio of substrate/aq. H_2O_2; 0.1% catalyst on 0.5 mmol scale. [b] Determined by ^1H NMR (CD_3OD, 300 MHz) and quantitative GC analysis on the crude reaction mixture after total oxidant consumption (iodometric test). [c] Isolated yields in sulfoxide.

The activity of complex **1** was tested also in halides oxidation under the reaction conditions described by Butler *et al.*[30] (Table 5).

Table 5. Halogenation (X=Br, Cl) of 1,3,5-trimethoxybenzene by H_2O_2 catalysed by **1**.[a]



Entry	X	**1** (%)	$[H_2O_2]_0$ (mM)	$[H^+]_0$ (mM)	TMBBr (mM)	$t_{½}$[b] (min)	Yield[c] (%)	TON
1	Br	5	20	20	17.3	17	87	17
2	Br	5	40	20	18.4	6	92	18
3	Br	0.5	20	20	17.3	33	87	173
4	Br	0.05	20	20	12.6	1440	63	1260
5	Cl	5	8	3	1.2	--	40[d]	1.2
6	Cl	5	40	20	1.1	--	5[d]	1.1

[a] Reactions were carried out in DMF-d_7 at 28°C using $[1,3,5\text{-trimethoxybenzene}]_o$= 20 mM, the *tert*-butylammonium salt $[TBAX]_0$ = 0.1 M, X=Br or Cl. [b] Time required for a 50% decrease of the initial concentration of oxidant. [c] Based on the limiting agent $HClO_4$ and determined by ^1H NMR (1,2-DCE as internal standard) on the crude reaction mixture after total oxidant consumption (iodometric test). [d] After 2 days.

Bromination of 1,3,5-trimethoxybenzene proceeds to the mono brominated 2,4,6-trimethoxybromobenzene with yields up to 92% and TONs up to 1260. In accordance with the stoichiometry of the reaction, one equivalent of acid and hydrogen peroxide are required. Chlorination of 1,3,5-trimethoxybenzene could be achieved as well even if the system affords only a single catalytic cycle (Table 5, entries 5 and 6).

1.5 Molybdenum and tungsten

The second part of this introduction deals with molybdenum and tungsten enzymes and their functions in living systems, which is mainly characterized by oxygen transfer processes. Coordination studies with TPA ligands are also reported, as well as the use of these complexes in oxidation catalysis with peroxides.

1.5.1 Molybdenum and tungsten enzymes

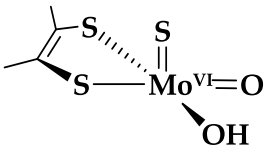
Metalloenzymes containing molybdenum and tungsten centers are present in almost all life forms. Tungsten is found almost exclusively in archaea, an ancient form of unicellular life forms. Molybdenum, instead, is found widely in all biological systems. Both molybdenum and tungsten have a chemical versatility that is useful to biological systems: they are redox-active under physiological conditions ranging between oxidation states VI an IV. Oxidation state V is also reachable, so these systems can act as transductors between bielectronic and mono electronic systems. The majority of molybdenum and tungsten enzymes are *oxotransferases* that catalyze the transfer of an oxygen atom to a substrate, using O_2 or H_2O assource of oxygen. These reactions involve a proton-coupled electron transfer (PCET) between the substrate and a Fe-S cluster, a heme group or a flavine.
Representative examples of reactions catalyzed by molybdenum enzymes are collected in Table 6.

Table 6. Representative Examples of the Reactions Catalyzed by Molybdoenzymes.

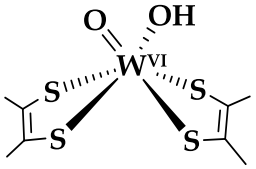
Enzyme	Reaction Catalyzed
Carbon monoxide oxidoreductase	$CO + H_2O \longrightarrow CO_2 + 2H^+ + 2e^-$
Dimethyl sulfoxide reductase	$Me_2SO + 2H^+ + 2e^- \longrightarrow Me_2S + H_2O$
Nitrate reductase	$NO_3^- + 2H^+ + 2e^- \longrightarrow NO_2^- + H_2O$
Arsenite oxidase	$H_2AsO_3 + H_2O \longrightarrow HAsO_4^{2-} + 3H^+ + 2e^-$
Sulfite oxidase	$SO_3^{2-} + H_2O \longrightarrow SO_4^{2-} + 2H^+ + 2e^-$
Xanthine oxidase	$xanthine + H_2O \longrightarrow uric\ acid + 2H^+ + 2e^-$
Aldehyde oxidoreductase	$RCHO + H_2O \longrightarrow RCO_2H + 2H^+ + 2e^-$

The group of molybdenum and tungsten dependent enzymes presents a common feature: the presence of the same ligand, called pterin (mpt). The complex formed by molybdenum and the pterin ligand is called molybdenum co-factor (Moco). Molybdenum- and tungsten-containing enzymes can be grouped as shown in Scheme 8.[31]

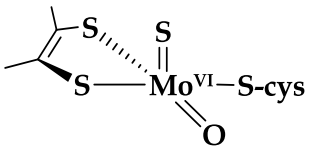
The xanthine oxidase family



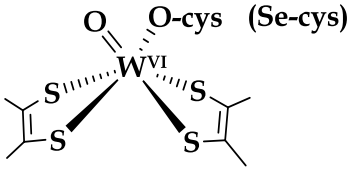
The aldehyde:ferredoxin oxidoreductase family



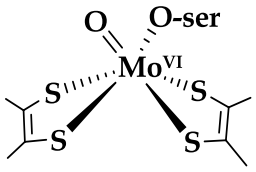
The sulfite oxidase family



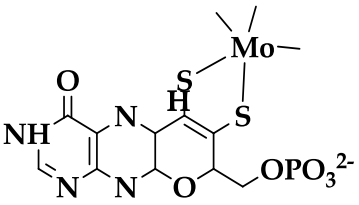
The formate dehydrogenase family



The DMSOreductase family



The pterin cofactor (mpt)



Scheme 8. Active-site structures of molybdenum- and tungsten-containing enzymes.

Molybdenum containing enzymes are divided into three families, each with a distinct active-site structure and type of reaction catalyzed. The first, which take its name from xanthine oxidase from cow's milk, has an Mo(VI)(mpt)OS(OH) core in the oxidized state, with one equivalent of the pterin cofactor coordinated to the metal. These enzymes typically catalyze the hydroxylation of carbon centers.[32] The second family includes sulfite oxidase (typically isolated from mammalian liver) and nitrate reductases (from plants that assimilate nitrate from the soil). The oxidized metal center has a single equivalent of the pterin cofactor, but as part of an Mo(VI)(mpt)O_2(S–Cys) core, with a cysteine ligand provided by the polypeptide. The members of this second family catalyze the transfer of an oxygen atom to a lone pair of electrons on the substrate, or *viceversa*. The third family is diverse in both structure and function, but all members have two equivalents of the pterin cofactor bound to the metal. The molybdenum coordination sphere is usually completed by a single Mo=O group and a sixth ligand in an Mo(VI)O$(mpt)_2$(X) core. The reactions catalyzed by the members of this last family frequently involve oxygen-atom transfer, but dehydrogenation reactions can also occur[33]
Tungsten-containing enzymes, all of which come from bacterial or archaeal sources, also fall into three groups.[34] The members of the first family catalyze the oxidation of aldehydes to carboxylic acids, with the reducing equivalents

being transferred to a [4Fe–4S] ferredoxin. In their active sites, tungsten is coordinated to two equivalents of the pterin cofactor present as the mononucleotide, but no ligand contributed by the polypeptide. Although there is considerable ambiguity at present,34 it is likely that the oxidized enzyme possess one W(VI)=O and one W(VI)–OH, analogous to the molybdenum center of arsenite oxidase; the reduced form probably has a single W^{IV}–OH.[35] The second family of tungsten-containing enzymes consists of the formate and *N*-formylmethanofuran dehydrogenases, both of which function physiologically to reductively fix CO_2 (into acetate and *N*-formylmethanofuran, respectively). The third family of tungsten-containing enzymes comprises a single enzyme, acetylene hydratase from *Pelobacter acetylenicus*,[36] which catalyzes the hydration of acetylene to acetaldehyde.

1.5.2 Model chemistry

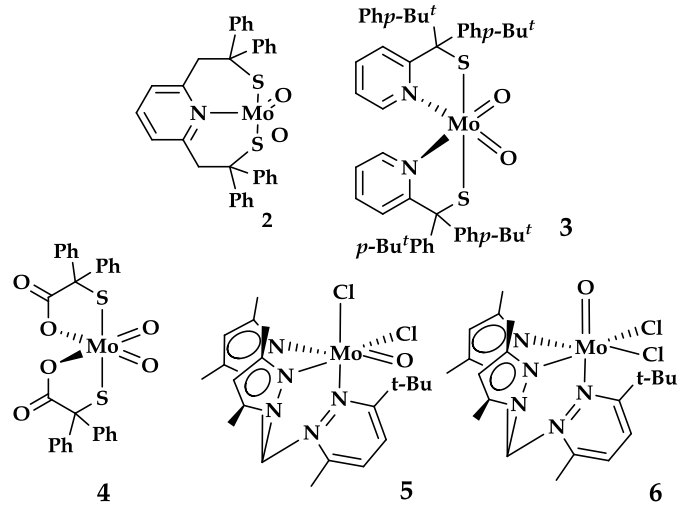
Crystallographic proof of the structure of molybdenum and tungsten active sites dates back to 1995. However the ene-1,2-dithiolate nature of the cofactor was proposed in 1982, since that time many complexes were synthesized to mimic the coordination sphere of these enzymes and research efforts were spent to study molybdenum-mediated oxo transfer, reaction (2). Systems were designed to suppress the irreversible μ-oxo "dimerization" reaction (3).

$$\mathbf{Mo^{IV}O + XO \rightleftharpoons Mo^{VI}O_2 + X} \qquad \mathbf{(2)}$$

$$\mathbf{Mo^{IV}O + Mo^{VI}O_2 \rightleftharpoons Mo^{V}_2O_3} \qquad \mathbf{(3)}$$

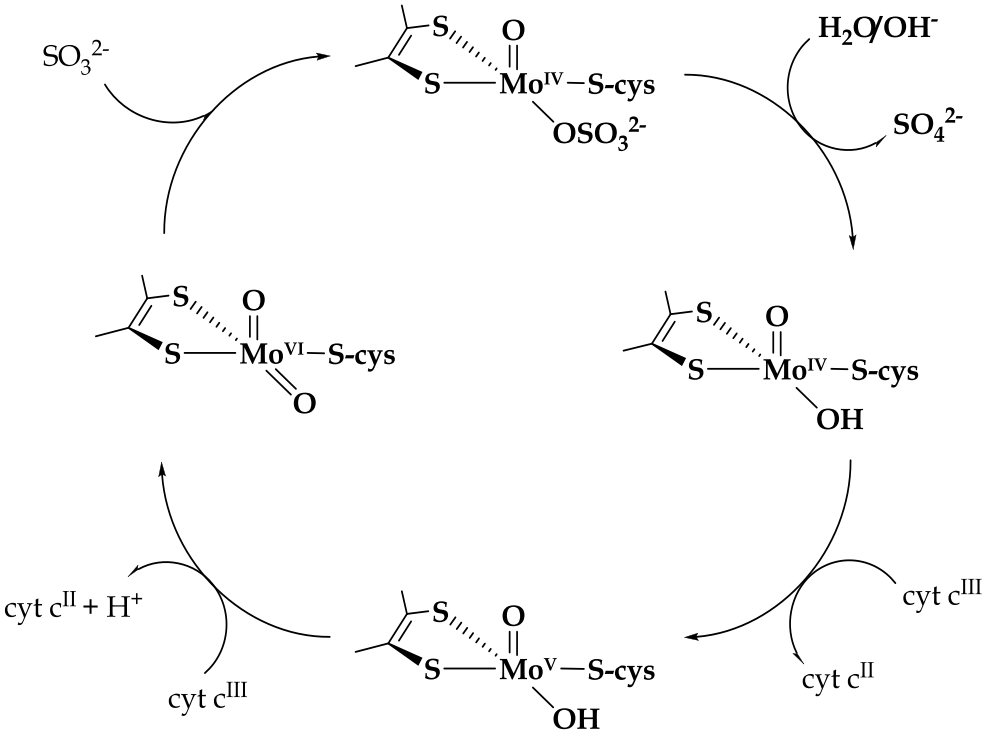
Other specific synthetic problems are the formation of the uncommon $Mo^{VI}OS$ group in the ligand environment of site and the stabilization of the five-coordinate $Mo^{VI}O_2$ center of sulfite oxidase in the presence of a strongly reducing ligand environment of three thiolates. These challenges also apply to the synthesis of analogues of tungstoenzyme sites. Chemical approaches to molybdenum and tungsten enzyme sites have been directed toward mimicking a portion of the structural center in order to ascertain the features of the coordination environment on the chemical reactivity and the spectroscopic properties of the metal center. Two different type of systems have been studied as model for molybdenum and tungsten containing enzymes. The first are molecules that contains one or two ene-1,2-dithiolate ligands and are closer to the sites described in scheme 9, and are called *dithiolene* systems. The second, called *non-dithiolene,* are systems in which coordination spheres contain non-physiological ligands and manifest the

effects of ene-1,2-dithiolate ligands on the electronic structure of the metal center. In this paragraph reactivity *non-dithiolene* analogues of sulphite oxidase are briefly described.



Scheme 9 . Structures of non-dithiolene oxo-molybdenum complexes.

In some respects the chemistry of the SO family should be relatively simple to mimic. The oxidation state changes proposed for the enzymic catalytic cycle are shown in scheme 10.



cyt = cytocrome, cys = cysteine

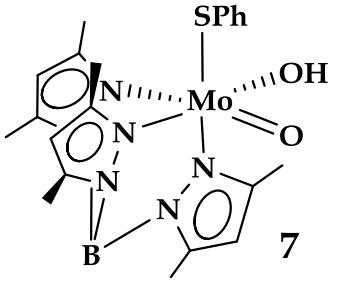
Scheme10. Proposed reaction cycle for sulfite oxidase.

Complexes with the $Mo^{VI}O_2$, $Mo^{V}O$, and $Mo^{IV}O$ groups are well known.[37] However, oxo-transfer chemistry between substrate and $Mo^{VI}O2$ or $Mo^{IV}O$ centers in the form of reaction **2** is complicated by competing comproportionation reaction **3** to form binuclear $Mo^{V}O$ species containing the $[Mo_2O_3]^{4+}$ core.[38] Similar dimerization reactions can occur for $Mo^{V}O$ centers in the presence of trace amounts of water.[39] Thus, an essential requirement for reactivity analogues of sulfite oxidase (and other molybdenum enzymes) is inhibition of the formation of dinuclear Mo^{V} centers. The general approach has been to incorporate steric constraints into the ligands to restrict the approach of the metal centers so that the equilibrium of reaction 3 will lie far to the left. One of the first sulfur-containing ligands to be specifically designed to favor oxygen-atom-transfer chemistry while inhibiting dimer formation was described by Berg and Holm.[40] Complex **2** cleanly oxidizes tertiary phosphines and catalyzes the oxidation of Ph_3P to Ph_3PO by Me_2SO. However, subsequent reinvestigation of this system has shown that reorientation of the ligands after oxygen atom transfer does enable a dinuclear Mo_2O_3 center to form, and that the overall stoichiometry of the oxidation of phosphines involves 2 equiv of 10 per equivalent of phosphine.[41]

The structures of six-coordinate $[Mo^{VI}O_2(ButL\text{-}NS)_2]$ (**3**) and five-coordinate $[Mo^{IV}O\text{-}(ButL\text{-}NS)_2]$ were both established by X-ray crystallography, and their

interconversion by oxo-transfer reaction 4 was demonstrated by ^{18}O labeling experiments. In nonpolar solvents, the $Mo^{VI}O_2$ and $Mo^{IV}O$ complexes did comproportionate to form $Mo^{V}_2O_3$ centers according to eq 3. However, in the polar solvents used for atom-transfer experiments there was no evidence for dimer formation.[42] This functional analogue system enabled oxo-transfer reactions to be investigated for a wide range of substrates X/XO, including Et_3P, S-oxides, N-oxides, and Ph_2-SeO, and contributed to the development of a thermodynamic scale for oxo transfer.

Hydrotris(pyrazolyl)borate complex is a family of ligands that minimize comproportionation. The most extensively studied compounds contain the readily accessible hydrotris(3,5-dimethylpyrazolyl) borate ligand (Tp*). Compounds of the type $[(Tp^*)Mo^{VI}O_2X]$ exhibit oxo transfer to phosphines for X) Cl, Br, OPh, and several thiolates.[43] For X) SPh, the resultant $[(Tp^*)Mo^{IV}O(SPh)(py)]$ complex has been isolated in the presence of pyridine and structurally characterized.



7

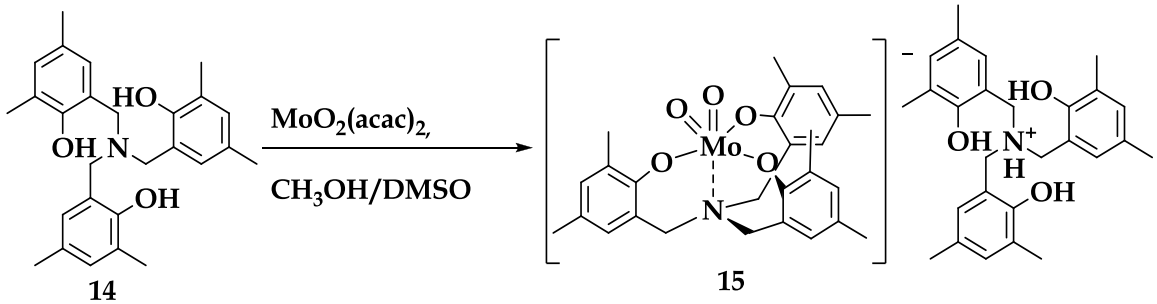
Scheme 11.

The $Mo^{IV}O$ species can be reoxidized upon addition of Me_2SO, and it has been shown that these compounds catalyze the oxidation of tertiary phosphines to phosphine oxides by Me_2SO.[44] Even more interesting than this reversible two-electron oxygen-atom-transfer chemistry is the cycle of reactions that is observed when phosphines are reacted with $[(Tp^*)MoO_2(SPh)]$ in the presence of small amounts of water. These conditions result in the formation of $[(Tp^*)Mo^{V}O(OH)(SPh)]$ (**7**), which can be detected by its EPR spectrum(Scheme 11). Oxidation regenerates the starting $Mo^{VI}O_2$ compound, which can then react with additional phosphine. When the reaction is carried out in labeled water, the label is incorporated into the phosphine. This analogue system remains the only one that catalyzes a two electron oxidation of the substrate by an oxygen atom-transfer reaction with the subsequent regeneration of the oxidized molybdenum center by incorporation of water and successive one-electron transfers, passing through Mo^{V}. Thus, this minimal system incorporates the key components of the reaction proposed for

SO (Figure 3), in that the oxygen atom that is incorporated into substrate ultimately comes from water and re oxidation of the molybdenum center proceeds through two sequential one-electron steps.

1.5.3 Mo(VI) and W(VI) amino triphenolate complexes

As described previously molybdenum and tungsten are essential elements in diverse biological systems. Molybdenum compounds are also used to catalyze industrial processes including the isomerization of allyl alcohols[45], olefin metathesis[46]], oxo transfer reactions [47] and the oxidation of propene in SOHIO process[48]. Both artificial and biological catalysts involve molybdenum and tungsten ions in high oxidation states, therefore many active systems can be modeled with isolated molybdenum-oxo species which are stabilized by hard donors, such as alkoxido and aryloxido ligands. Amine triphenols can react as tetradentate trianionic O_3N donor ligands with transition metals. At present, the chemistry of these ligands has been focused mainly on Group IV and Group V metals[27], whereas the reports on Group VI metal complexes with amine triphenolates are still rare.
Lehtonen firstly synthesized a molybdenum(VI) complex with an amino triphenolate ligand. A general approach to these compounds is a reaction of ligand precursor with appropriate metal halides or alkoxides. $MoO_2(acac)_2$ was used as metal precursor and reacted with two equivalent of ligand in various solvents, resulting in an intense yellow solution and rapid precipitation of yellow microcrystalline solid 63% yield (Scheme 12).



Scheme 12.

Isolated material was soluble in DMSO, but poorly soluble in alcohols, acetonitrile or chlorinated hydrocarbons, which indicates ionic or polymeric character of the solid product. Identical product was also obtained using a 1:1 stoichiometry, although in a smaller yield. The use of additional bases (pyridine, DABCO, Et_3N) has negligible effect on the reaction outcome. Molecular structure of the complex confirms that one half of the amine triphenol molecules have been triple deprotonated during the formation of the

anionic complex, whereas another half of H_3L molecules have behaved as a base forming corresponding ammonium ions. This is the first example of structurally characterized ionic atrane complexes. In the Mo centered unit, the phenoxide groups of the tetradentate ligand are bonded to cis-MoO_2, while the amino nitrogen completes the distorted octahedral coordination (Fig. 5). The amine nitrogen atom is also located trans to the oxo-ligand, thus it bonds to the Mo1 ion with a distance of 2.421(4) Å.

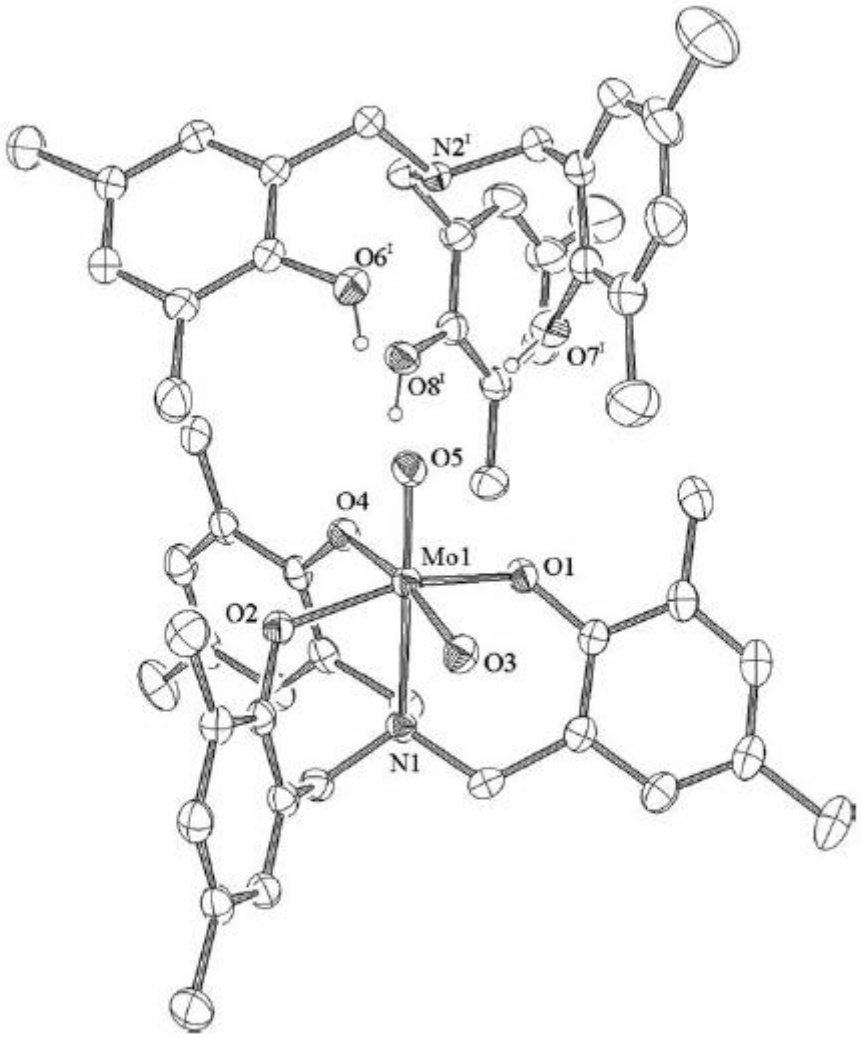
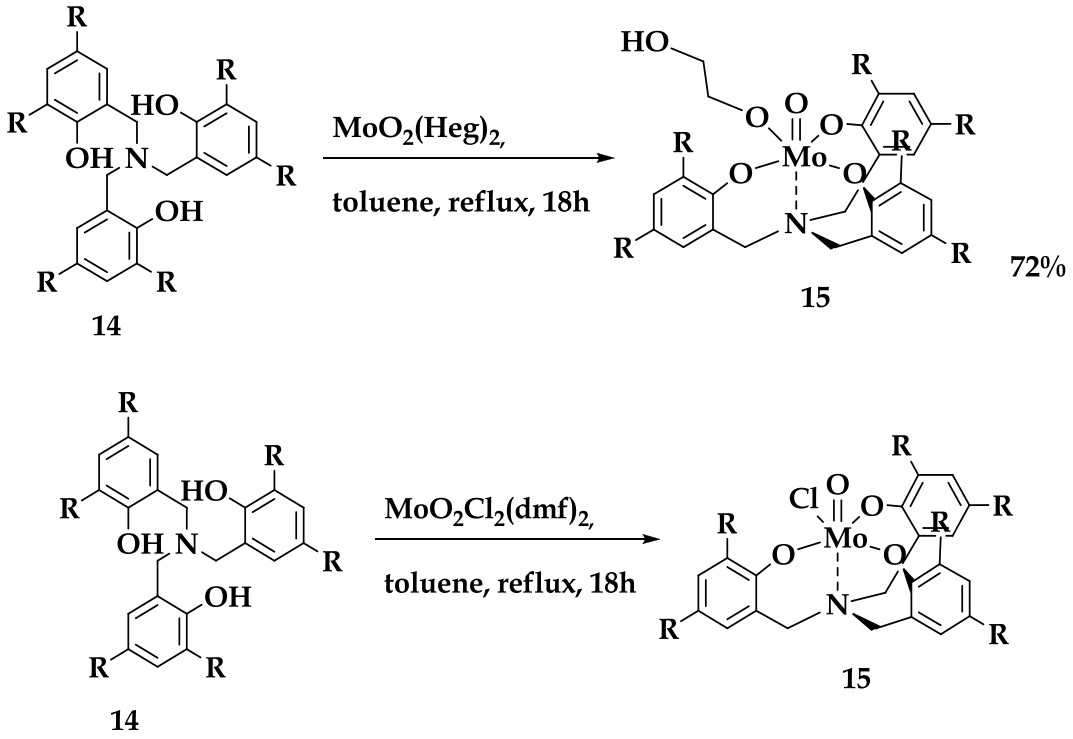


Figure 5. Structure of MO_2 ionic atrane complexes.

In another contribution Lehtonen reported that neutral octahedral complexes are obtained by reaction of TPA ligands with $MoO_2Cl_2(dmf)_2$ (dmf= *N*,*N*-dimethylformamide) or $MoO_2(OCH_2CH_2OH)_2$ (complex **14c**, Figure 14).[49] Ligand exchange reactions with high-boiling point alcohols and with TMSCl are possible.



Scheme 13.

Based on precedent literature for similar complexes, it was suggested that in the first step the ligand **14** is coordinated to the MoO_2(ethane-1,2-diol=Heg_2)$_2$ unit as a neutral nitrogen donor, which process is subsequently followed by an alcoholysis reaction and elimination of a Heg_2 molecule. Then, the reaction proceeds via an addition of one of the remaining OH functions across the Mo=O bond to form an intermediate MoO(OH)(Heg)(HLR), which then reacts to eliminate water and produce the final product.

All the structures own C_1 symmetry in the solid state, meaning that the tripodal ligand wraps around the metal in a propeller-like conformation. However, as pointed out for octahedral Ti(IV) complexes, a C_s-average symmetry is observed in solution because of fast racemization in the NMR time scale.

TPA tungsten complexes have been obtained from $W(OCH_2CH_2O)_3$ or $W(O)Cl_4$.[50] They present similar structural characteristics to molybdenum complexes, though, in cases of important steric clash, loss of the propeller-like arrangement is observed.

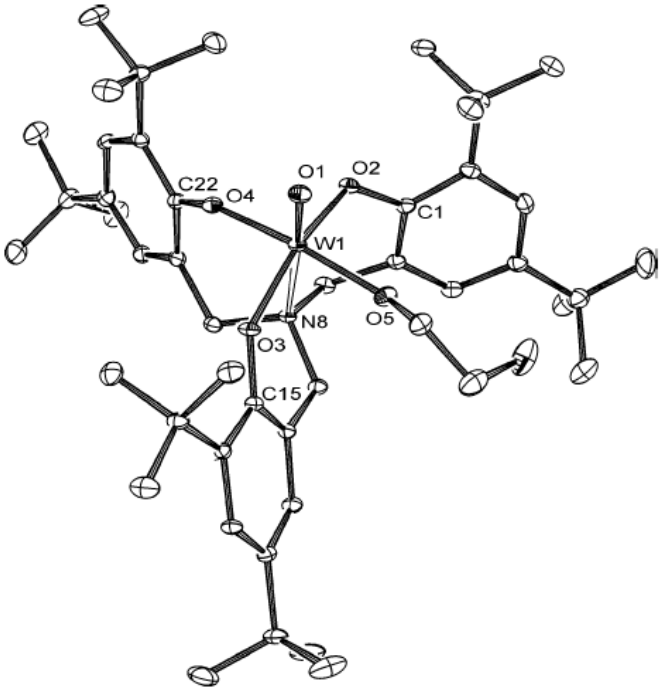


Fig. 6 Molecular structure of $W^{VI}(O)(OCH_2CH_2OH)$ complex.[49]

1.6 Aim of the thesis

The work described in this thesis concerns oxygen transfer processes mediated by metal complexes, new synthetic procedures to functionalize TPA ligands in order to explore new reactivity and routes to recycle of the catalyst. V(VI) TPA's precedent studies about biomimetic activity in haloperoxidase reactions prompted us to synthesize new Mo(VI) and W(VI) TPA complexes.

In this respect, Chapter 2 describes the reactivity of two new Mo(VI) complexes in oxidations reactions towards various substrates such as sulfide, olefines and halides using *tert*-butyl hydroperoxide and hydrogen peroxide.

Chapter 3 is dedicated to the synthesis of new W(VI) complexes and their catalytic activity towards activation of hydrogen peroxide in oxidations of sulfides, olefins and halides. A comparison of the catalytic activity towards olefins epoxidations in presence of hydrogen peroxide of Mo(VI) and W(VI) complexes bearing the same ligand has also been carried on.

In Chapter 4 various synthetic strategies to functionalized TPA ligands are described. Various techniques to achieve catalyst recycle are introduced and in particular 'catalytically active membrane' are underlined. In this respect a new TPA ligand bearing three fluorinated alkyl chains has been synthesized and

the formation of two complexes with V(VI) and Mo(VI) is reported. **1.7 References and notes**

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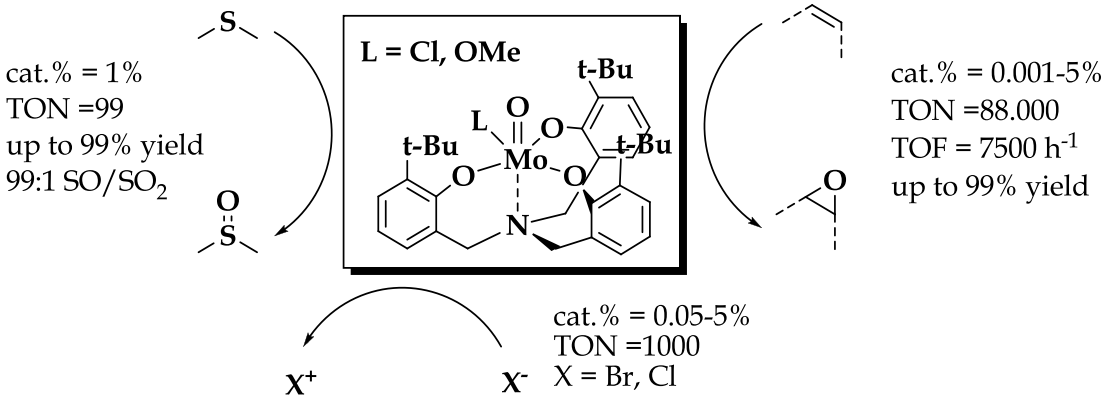
Chapter 2

Molybdenum(VI) amino triphenolate complexes: synthesis, characterization and catalytic activity

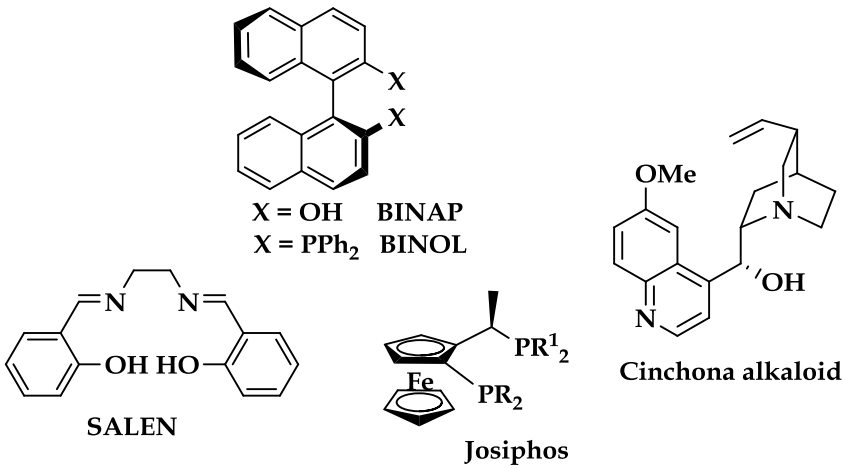


The coordination chemistry and catalytic activity in oxidation transfer reactions of molybednum(VI) amino triphenolate complexes have been investigated. In particular, Mo(VI)-oxo chloride triphenolate amino complex **1** has been synthesized and it proved to be an air and water tolerant complex that efficiently catalyzes, in high yields and selectivities, the oxidation of sulfides, olefins and halides. In particular, high TOF and TON have been observed for the oxidation of *cis*-cyclooctene (catalyst loading down to 0.001%, TONs up to 88.000 and TOFs up to 7500 h^{-1}).

Part of the work described in this chapter has been published:
F. Romano, A. Linden, M. Mba, C. Zonta, and G. Licini, "Molybdenum(VI) Amino Triphenolate Complexes as Catalysts for Sulfoxidation, Epoxidation and Haloperoxidation", *Adv. Synth. & Cat.* **2010**, 17, 2937 -2942.

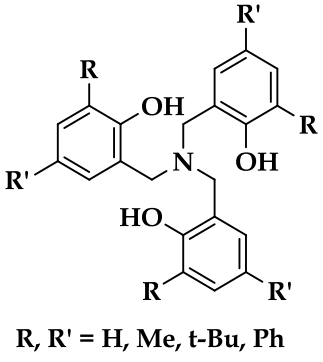
2.1 Introduction

Ligands can modulate the electronic and steric properties around a metal center controlling its catalytic properties. While a considerable number of ligands is known, few of them are able to express their reactivity across different metals. These ligands have been defined as "privileged" and outstanding examples, especially concerning their applications in stereoselective catalysis, are 1,1'-bi-2-naphthols (BINOLs) and 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyls (BINAPs), together with Josiphos, Salen and cinchona alkaloid ligands,[1] Scheme 1.



Scheme 1. Examples of "privileged" ligands.

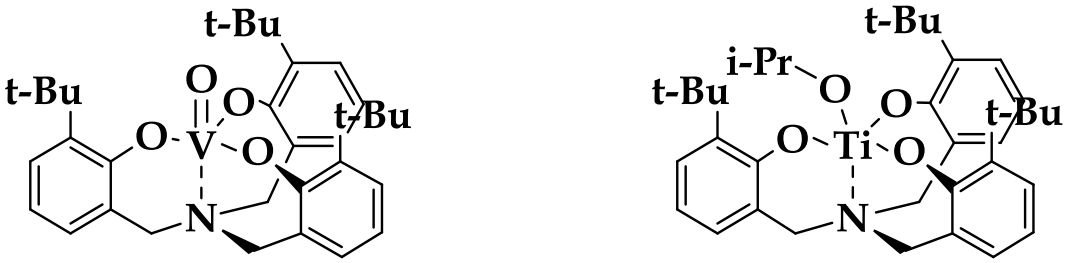
The possibility of developing "unique" classes of ligands able to form stable complexes with a variety of metals, while also being catalytically active towards a variety of reactions, is of considerable interest. In this scenario, amino triphenolate ligands, Scheme 2, have attracted attention because they give robust complexes with transition metals and main group elements, and, when highly symmetric, they facilitate the study of the coordination chemistry and reactivity, by reducing the number of possible species.



Scheme 2. Chemical structure of amino triphenolate ligands (TPAs).

Indeed, in the last decade a considerable number of reports discuss about their complexation behavior with a wide variety of transition metals and main group elements[2], and these studies report that the highly tuneable nature of the phenol moieties, associated to the three-fold symmetry and tetradentate nature of the system, allow to obtain a large family of stable complexes. More importantly, steric and electronic factors can play a key role in the stability and catalytic activity of the complex. As example, by introducing bulky groups in *ortho* position to the phenol oxygen (R), Scheme 2, it is possible to protect the metal center from hydrolysis reactions. Another possibility is offered by side *para* groups (R') which can modify the electronic properties of the ligand without affecting the steric demand of the system. In this position is possible to introduce electron withdrawing/donor groups tuning the Lewis acidity of the metal center.

Recently a series of publications have been reported about the catalytic performances of this robust class of complexes. Catalytic studies have focused mainly on polymerization reactions,[3] Diels–Alder reactions[4] and oxygen transfer processes.[5] Regarding the latter, the group were this work has been carried on has recently shown that the amino tris-*tert*-butylphenolate titanium(IV) complex (Scheme 3) has noteworthy catalytic properties towards the oxidations of sulfides and secondary amines,[5a,b] while the corresponding vanadium(V) complex effectively catalyzes the oxidation of sulfides and halides, and has proved to be a structural and functional model of vanadium-dependent haloperoxidases.[5c]



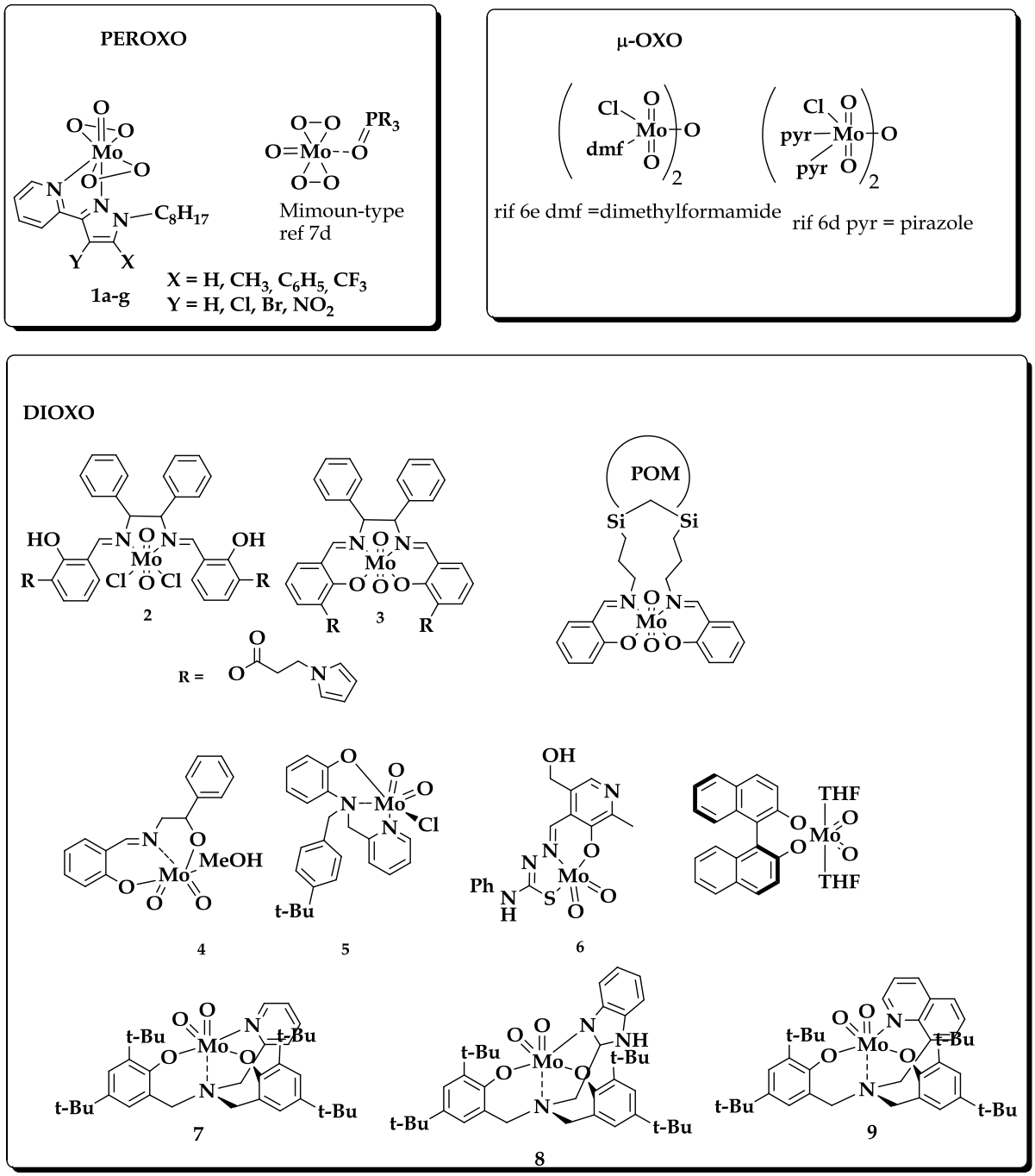
Scheme 3. Structures of tris-*tert*-butylphenolate vanadium(V) and titanium(IV) complexes.

What emerged from these studies is that while the tetradentate nature of the ligand is important for the stability and geometry of the complex, the presence of *tert*-butyl substitutions *ortho* to the phenol group has an impressive influence on its stability

under turnover conditions. During the catalytic cycle, the *tert*-butyl groups shield the metal from the formation of multinuclear species and they prevent the hydrolytic degradation, thus increasing the catalyst life.

As part of the work of these thesis we decided to extend the investigation to the catalytic properties of amino tris-*tert*-butylphenolate metal complexes of molybdenum(VI). In fact, Mo(VI) complexes are in general known to be effective catalysts in oxygen transfer reactions.[6] In particular, a wide interest in these catalysts arose in the 1960s when Atlantic Richfield (ARCO) and Halcon reported on the olefin epoxidation catalyzed by Mo(VI) compounds in the homogenous phase.[7] The two companies independently developed processes for the production of epoxides using an alkyl hydroperoxide in the presence of homogeneous catalysts based on molybdenum, tungsten, titanium, niobium, tantalum, rhenium, selenium, chromium, zirconium, tellurium, uranium and vanadium[8]. From all the referred metals, molybdenum, tungsten and titanium were found to be most efficient. The inventors suggested the utilization of the molybdenum catalyst in the form of organic salts, oxides, chlorides, oxichlorides, fluorides, phosphates, sulfide and molybdic acid. Molybdenum catalysts gave the highest rate and selectivity when used with *tert*-butyl hydroperoxide (TBHP) or ethylbenzene hydroperoxide. In this process, *tert*-butanol and 1-phenyl ethanol, which are obtained as by-products of the epoxidation process, are finally converted into methyl *tert*-butyl ether (MTBE), and styrene, both of them being versatile bulk products.[9] As example, MTBE can be used as an octane booster in gasoline.

Following this seminal study, in order to obtain high turnovers and information on the catalytic process, a significant number of Mo(VI) coordination compounds were synthesized, including Mo-oxo, Mo-dioxo and Mo-peroxo complexes, with different ligands (Scheme 4). Mo-dioxo compounds take inspiration from enzymes and metal surfaces where they are commonly encountered, and are in general the more studied at the moment.



Scheme 4. Mo-oxo, Mo-dioxo and Mo-peroxo complexes, with different ligands.

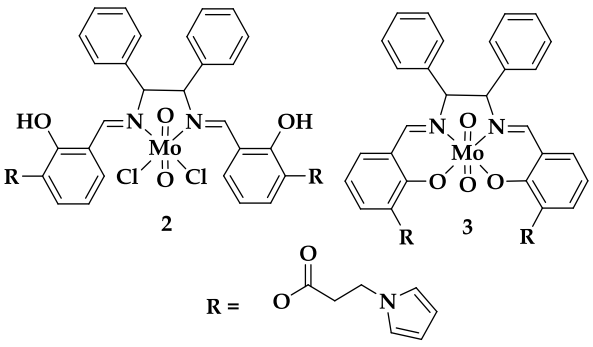
Great part of the initial studies on molybdenum epoxidation chemistry has been carried using Mimoun type complexes **7d.** From this seminal studies several groups took inspiration. As example this is the case of a study of Eppinger and Thiel on a library of aromatic bidentate ligand made of the same core but with different substituents on the ring.[10] This system has been synthesized and tested towards epoxidation of *cys*-cyclooctene with the purpose of understand the influence of substituents in the reactivity. Turnover frequencies (TOF), which are compared in Table 1, highlight the strong influence of the substituent on the reactivity. Complex **1g** is the more active, confirming that a reduced electronic density around the metal,

consequence of the electron withdrawing group on the imidazole ring, can be translated in a higher reactivity-.

Table 1. Experimental initial turnover frequencies (TOF) for the catalytic epoxidation of cyclooctene with the bisperoxo complexes **1a-g**.

Ligand	Y	X	TOF(h^{-1})
1a	H	H	3420
1b	H	CH_3	3160
1c	H	C_6H_5	4040
1d	H	CF_3	5710
1e	Cl	H	4930
1f	Br	H	5200
1g	NO_2	H	6470

The group of Gonçalves has extensively studied the correlation between structure and reactivity in molybdenum complexes. Besides studing the reactivity of μ-oxo complexes,[11] great part of her work has been dedicated to the study of dioxo complexes, and in particular on how ligand can tune the reactivity of this metal center. As example, interesting is the comparison between a classical MoO_2Cl_2(N-N) complex **2** and a tetradentate Salen-type complex **3** (Scheme 5).



Scheme 5. Mo(VI) complexes with a tetradentate Salen-type ligands (**3**) and a bidentate MoO_2Cl_2(N-N) (**2**).

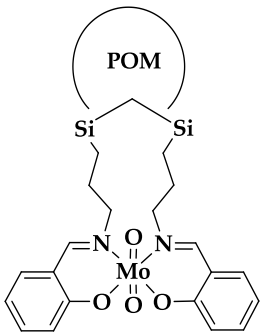
The epoxidation reaction results much faster in the presence of **2** than of **3** (Table 2), with initial TOF of 280 and 12·h^{-1}, respectively. The higher activity of **2** is probably a consequence of the interplay of steric hindrance of the **R** group in **3** and the higher electronic density around the metal. Interestingly, for *cis*-cyclooctene epoxidation using TBHP in decane without additional co-solvents, the catalysts were successfully separated from the reactants and products by adding *n*-hexane to the reaction

solution after a catalytic run of 24 h. The resultant solids can be reused in a second run, without losing their activity. While product selectivity remained unchanged for both systems, epoxide yield at 24 h decreased in the second run to 88% for **2** and to 57% for **3**.[12]

Table 2. Olefin epoxidation catalyzed by tetradentate complexes reported in Scheme 4.[a]

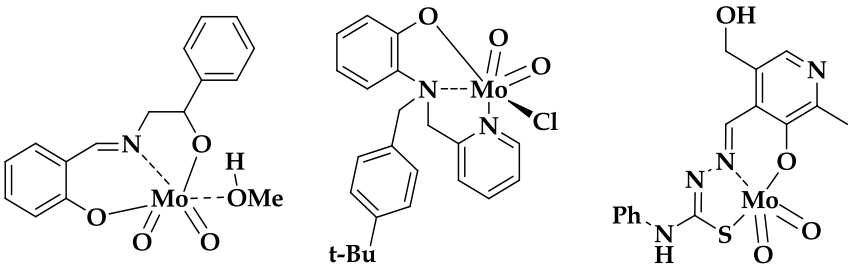
Substrate	Catalyst	Epoxide Yield (%)
cis-cyclooctene	**3**	81
cis-cyclooctene	**2**	100
Styrene	**3**	2
Styrene	**2**	22

More in particular, as suggested by the authors, the observed reactivity can be linked to the Lewis acidity of dioxomolybdenum(VI) complexes **2** and **3.** As for similar d_0 metal centers, it is suggested that the major role of the Mo(VI) center is to coordinate the peroxide, and to withdraw electrons from the peroxidic oxygen making it more susceptible to be attacked by nucleophiles such as olefins. It has been shown that Lewis Acidity is one of the most important characteristics that determines the catalytic performance in olefin epoxidation.[7a,13] TOFs are often associated with a low electron density at the metal center.[7a] Salen-type Mo(VI)-dioxo complexes have also been reported to be efficient epoxidation catalysts when covalently attached to a polyoxometalate (Scheme 6)[14]. Styrene was efficiently converted to styrene epoxide by this heterogeneous system, with 86% yield.



Scheme 6. Salen-type Mo(VI)-dioxo covalently attached to a polyoxometalate.

Recently, a growing interest in also tridentate ligands, with different structures than that of salen-type, has emerged, because it has been shown that the increasing stability leads to lower amounts of catalyst loading and, hence, to a higher turnover number. [15,16]

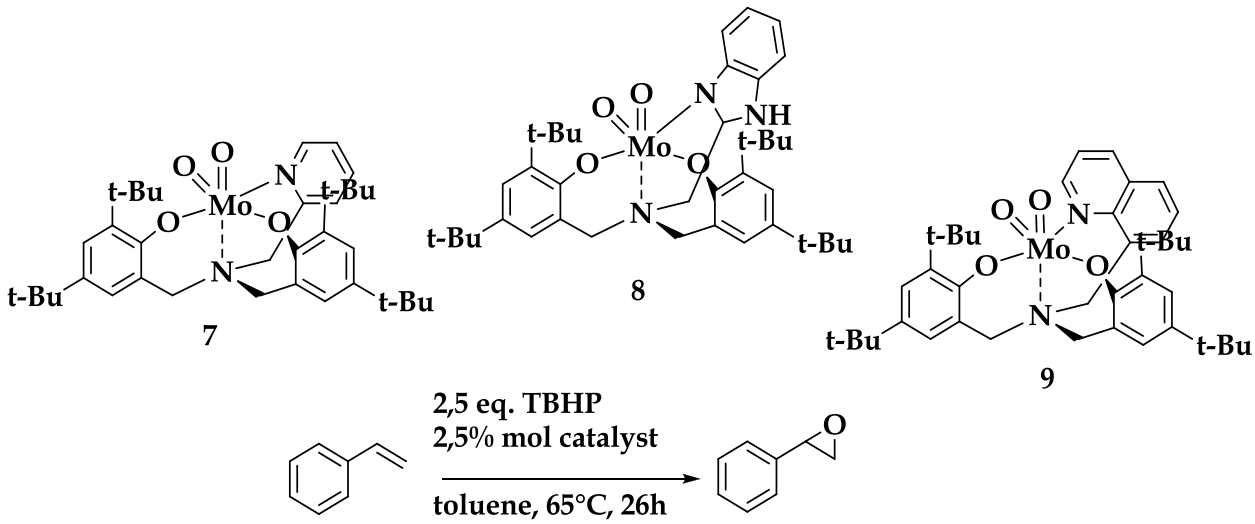


Scheme 7. Selected examples of tridentate Mo(VI) complexes.

Catalyst **4** (Scheme 7) is reported to achieve quantitative conversion of *cis*-cyclooctene to the correspondent epoxide in 45 minutes, when used with 2 equivalents of TBHP at 80°C in 1,2-dichloroethane (DCE), with a catalyst/substrate ratio of 1:100. Also less reactive aliphatic terminal alkenes were oxidized by this complex in high yields and selectivities.[17]

Concerning tetradentate Mo(VI) complexes as catalysts for oxygen atom transfer reactions, there are very few examples available in literature, with the exception of Salen-type complexes.

Dilworth *et al.* reported the catalytic activities of tetradentate dioxo complexes (**7, 8, 9**) in towards epoxidation of styrene.[18] Reactions were performed in toluene, with 2.5 mol% catalyst and 2.5 eq. of *tert*-butyl hydroperoxide under N_2 at 65°C for 26 h (Scheme 8).

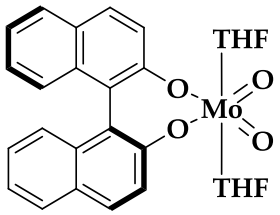


Scheme 8. Tetradentate complexes for Mo(IV) dioxo complexes.

Complexes **7**,**8** are active towards oxidation of styrene to styrene oxide, but with moderate reaction yields in 56% for **7** and 42% for **8**, **Errore. Il segnalibro non è definito.** Catalytic activities of **9** was not examined due to its limited solubility in toluene. A straightforward relationship between the catalytic activities of **7**,**8** and **9** dioxo complexes and the properties (both steric and electronic) of the supporting ligands was not discernible, other factors such as solubility of the complexes may also contribute to a difference in their catalytic behaviour.

Thus, apparently catalytic performances of Mo(VI) complexes do not depend on the number of chelating sites, but mainly on the electronic and steric characteristics of the ligands themselves, because they are responsible for both the overall Lewis acidity and the accessibility of the metal center itself.

There have been also attempts to use chiral ligands for molybdenum dioxo complexes. This is the case of the group of Royo which reported the catalytic activity of MoO_2(*S*-BINOL)$(THF)_2$ complex (Scheme 9), which is an active catalysts in the sulfoxidation of methyl phenyl sulfide and, in a minor extent, in olefin epoxidation.[19] However, this complex was found to give poor ee , <5%.



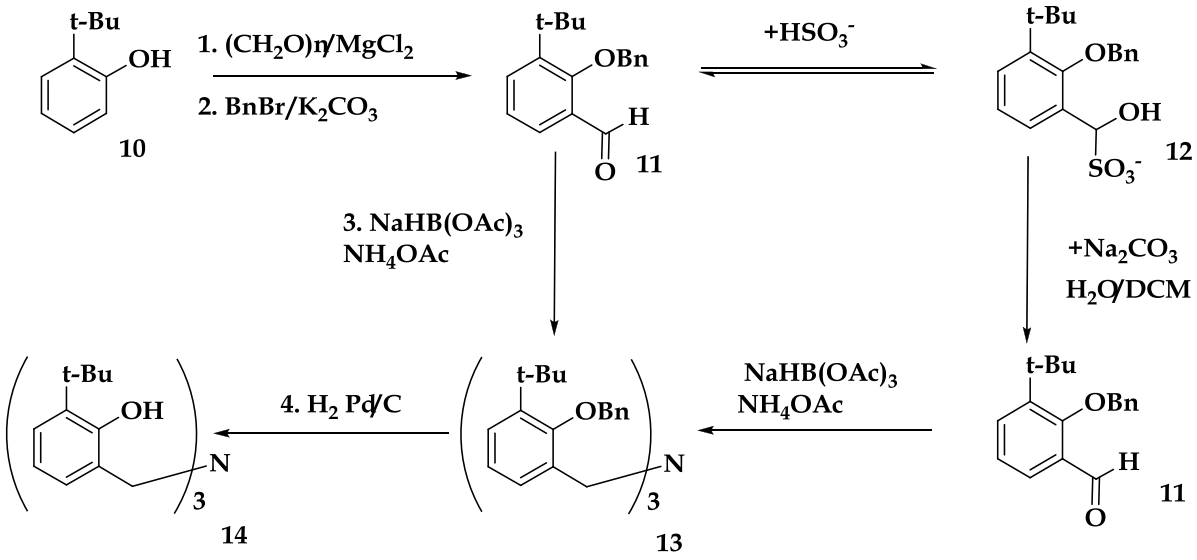
Scheme 9. A chiral MoO_2(*S*-BINOL)$(THF)_2$ complex.

However, a major drawback for the existing Mo(VI)-based catalysts is the formation, under turnover conditions, of polymeric species, which are much less active. Hence, the maintenance of a monomeric structure results of pivotal importance. With this aim, a careful study of the ligand system in the coordination sphere of the metal is required. For this reason, we thought the aminotriphenolate ligand can have the correct electronic and steric effects that can be suitably modulated. The preparation and characterization of these complexes will be described in the next paragraph.

2.2 Mo(VI)amine tri-phenolate complexes: synthesis and structural studies

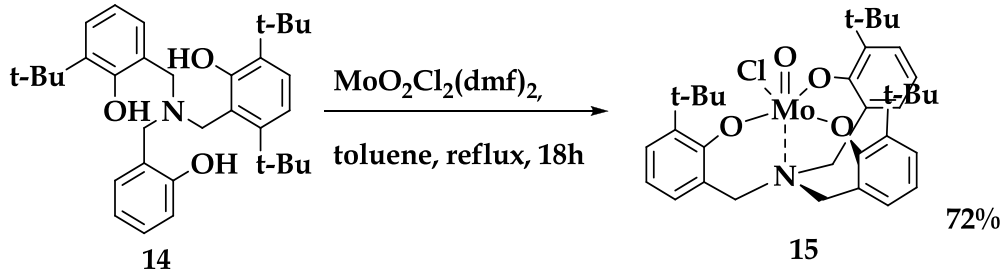
Compound **14** was prepared using a synthetic strategy developed in our group, based on a threefold reductive amination of the corresponding substituted salicyl aldehyde **10**.[20] The reductive amination need to be performed on the protected aldehyde **11**, which is readily synthesized from the corresponding phenol in high yield. This synthetic route, which have been used successfully in the past year, offers the possibility to access to a large class of functionalized ligand in high yields.

However, if we planned a multigram synthesis, this route had the disadvantage to need high-pressure chromatographic purifications, hence the overall process was limited to a few grams scale. To overcome this problem, we improved the purification steps avoiding the use of chromatography. Our aim was to use a synthetic strategy which will use the purification of the products *via* extraction, distillation or crystallization techniques(Scheme 10). The limiting purification step was the purification of this aldehyde **11** which is obtained as an oil. To avoid the chromatography, the aldehyde was mixed with a solution of $NaHSO_3$ and ethanol to obtain the bisulfite adduct **12**.[21] This compound is soluble in water and separable from the reaction mixture. The aqueous phase is then basified and the aldehyde **7** re-obtained *via* re-extraction with CH_2Cl_2. With this purification, it has been possible to obtain 74 g (0.29 mol) of ^{1}H-NMR pure aldehyde **11**, which was used for the subsequent two steps. The following steps, the reductive amination and the deprotection of phenol group *via* Pd/C catalysed hydrogenolysis, are carried out in multigram scale performing the purification using re-crystallization techniques.



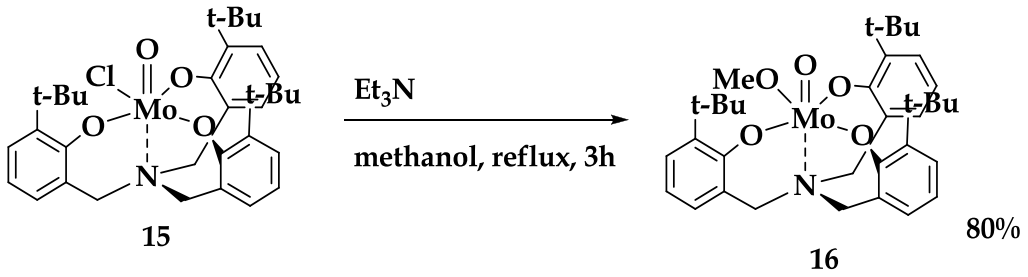
Scheme 10. Synthesis of the amino tri-*tert*-butylphenolate ligand **10**.

The molybdenum complex was synthesized using a recent procedure reported by Lehtonen[22] *et al.* for similar systems which uses MoO_2Cl_2 as the metal source. After dissolving solid MoO_2Cl_2 with stoichiometric amounts of **14** in toluene, the resulting mixture was kept at reflux temperature to obtain an intense purple solution (Scheme 11). The decourse of the reaction can been followed using TLC monitoring, and after 18 hours the reaction mixture was purified by flash chromatography on SiO_2 using toluene as eluent obtaining Molybdenum complex **11** in 72% yield.



Scheme 11. Synthesis of Mo(VI) complex of the amino tri-*tert*-butylphenolate ligand **14**.

Displacement of the chloro ligand in favor of a methoxy group can easily be achieved by refluxing complex **15** in methanol in the presence of one equivalent of triethylamine (Scheme 12). Compound **16** was also purified using flash chromatography and obtained in 80% yield as an intense purple solid.



Scheme 12. Synthesis of Mo(VI) complex **16**.

The compounds are wet and air stable and they can be characterized with various techniques. The ^{1}H NMR spectra of the oxo molybdenum complex **16** and the corresponding ligand **14** show the maintenance of the high symmetry of the ligand into the complex. The benzylic protons of the ligand become diastereotopic in the complex, resulting as three groups of signals: two doublets and one singlet (Figure 1).

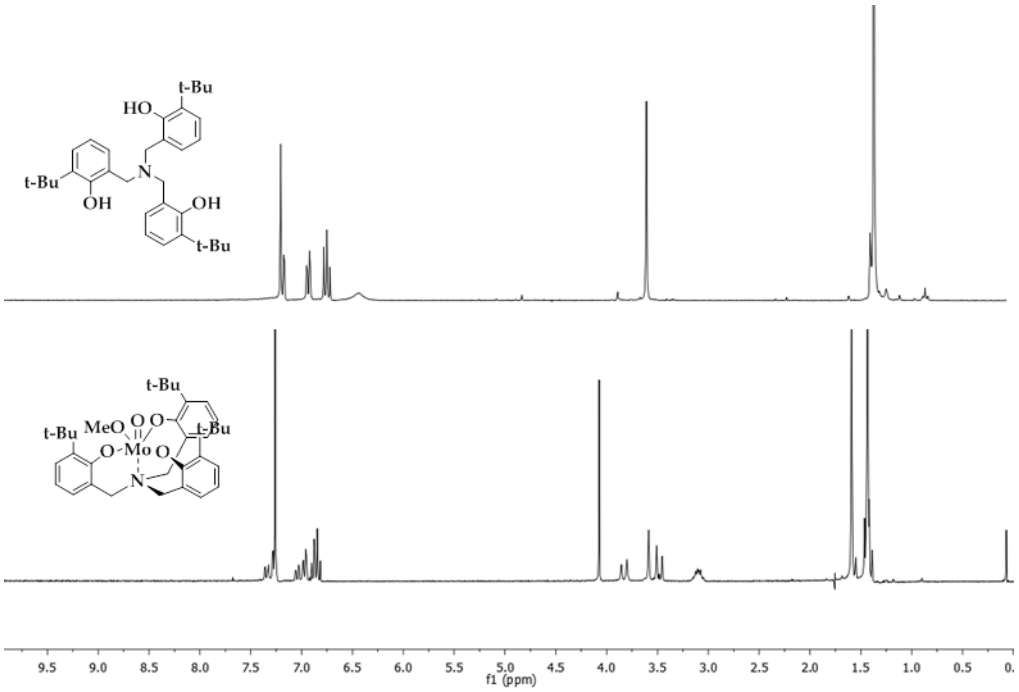


Figure 1. ^{1}H NMR spectra (250 MHz, $CDCl_3$) of the free ligand **10** and Mo(VI) complex **12**.

In particular, an octahedral coordination geometry can be established by symmetry considerations on the basis of variable temperature (VT) ^{1}H NMR spectra.

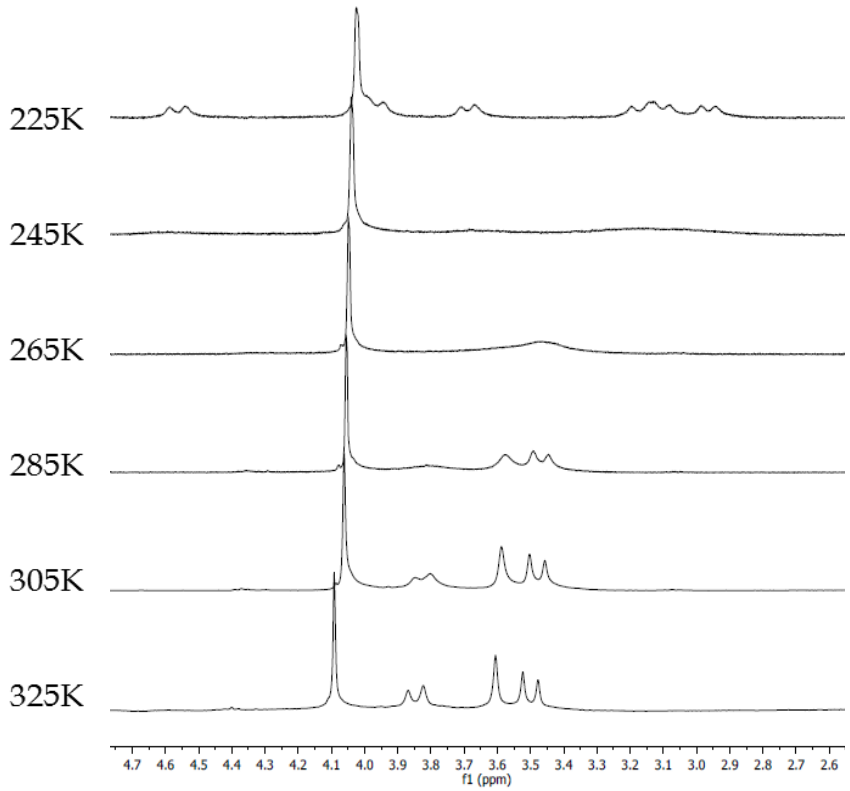


Figure 2. Temperature dependence of the benzylic CH_2 protons chemical shift of complex **12**.

At room temperature, both **11** and **12** show a symmetrical ^{1}H NMR spectrum with three sets of signals for the diastereotopic benzylic protons, consistent with a C_S average symmetry of the system caused by fluxional processes. At lower temperatures (225 K) the benzylic proton resonances resolve into five sets of signals, consistent with a C_1 symmetry of the complexes. This has been confirmed by the X-ray crystal structure of **11**, crystallized from chloroform. The solid-state structure reveals a monomeric complex, which adopts a distorted octahedral geometry, with the oxo function occupying the axial position located *trans* to the nitrogen atom. The molybdenum center is set slightly above the phenolate oxygens plane, pointing towards the oxo function (Figure 3).

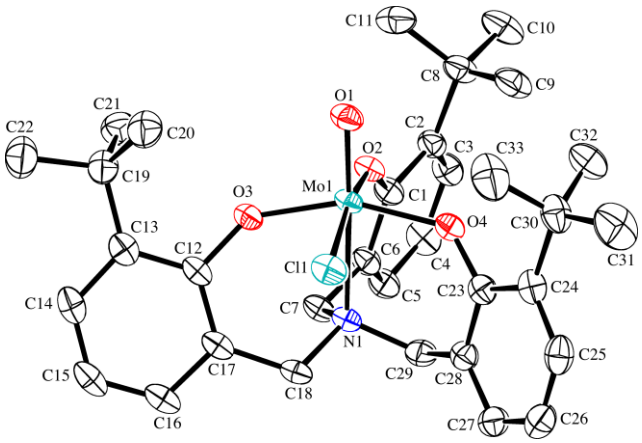


Figure 3. Displacement ellipsoid representation of the molecular structure of **11**.

The distance between the Mo atom and the oxo oxygen is 1,68 Å, which are typical for mononuclear cis-dioxomolybdenum(VI) species;[23] while length of the Mo—N bond is 2,48 Å due to the *trans* effect of the strong π-donor oxo ligand. Due to the propeller-like arrangement adopted by the coordinated three arms of the ligand, the complex is chiral and it is present in the crystal cell in the two enantiomeric forms. Another confirmation of the coordination of the molybdenum is coming by the IR-spectrum of **15** which exhibits typical Mo=O stretching modes as a pair of strong absorption bands at 887 and 878 cm^{-1}, these values are similar to those exhibited by other Mo(VI) amino triphenolate complexes.[24]

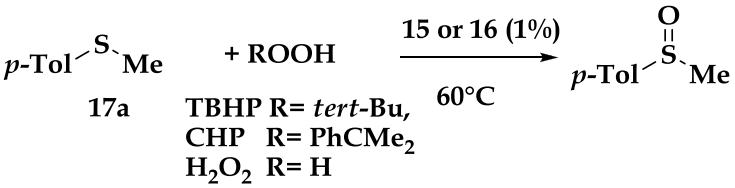
2.3 Mo(VI)amine tri-phenolate complexes: catalytic activity

Reactivity of complexes **15** and **16** were examined in sulfides, olefins and halides oxidation.

2.3.1 Oxidation of sulfides to the corresponding sulfoxides

The first catalytic studies were performed on the oxidation of sulfide to sulfoxides. The oxidations were performed using alkyl peroxides (cumyl hydroperoxide, CHP or *tert*-butyl hydroperoxide, TBHP) and the more environmentally friendly hydrogen peroxide as terminal oxidants. Sulfides oxidation was performed under homogeneous conditions and the reaction course was followed by ^{1}H NMR. *p*-tolyl methyl sulfide **17a** was used as test substrate and 1% of complexes **15** and **16** as catalysts (Table 3). In the presence of both complexes, **17a** was selectively oxidized to the corresponding sulfoxide in high yields and with complete consumption of the oxidant. The best results in terms of reactivity were obtained using the **15**/H_2O_2 system (Table 3, row 5). However, the observed rates resulted slower with the respect of the analogous reaction catalyzed by amino tri-*tert*-butylphenolates of both titanium(IV)[25] and vanadium(V).[26]

Table 3. Oxidation of *p*-tolyl methyl sulfide **17a** at 60°C. Effect of the catalyst and oxidant.[a]

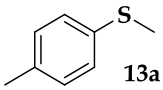
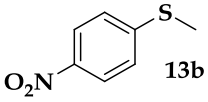
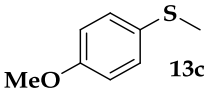
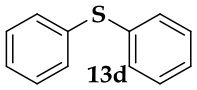
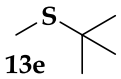
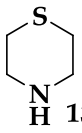
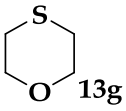


ROOH	Solvent	Catalyst	$t_{1/2}$, min[b]	Sulfoxide Yield, %[c]
CHP	$CDCl_3$	**15**	47	90
CHP	$CDCl_3$	**16**	60	91
TBHP	$CDCl_3$	**15**	30	83
TBHP	$CDCl_3$	**16**	135	65
H_2O_2	CD_3OD	**15**	12	99
H_2O_2	CD_3OD	**16**	20	99

[a] Reaction conditions: 60 °C, [**17a**]$_0$=[ROOH]$_0$=0.1 M, [**15**]= [**16**]=0.001 M. [b] Time required for a 50% decrease of the initial concentration of sulfide. [c] Determined by ^{1}H NMR analysis on the crude reaction mixture after complete oxidant consumption (iodometric test).

The scope of the reaction was explored towards different sulfides. Yields are high (71-99%) for all the substrates either they are aromatic or aliphatic; the selectivities sulfoxide/sulfone (SO : SO_2) are almost complete towards the sulfoxide (Table 4).

Table 4. Oxidation of sulfides **17a-g** by aqueous hydrogen peroxide (35%) catalysed by **15**.[a]

	Substrate	Yield (%)[b]	SO : SO_2
1	 **13a**	99	99 : 1
2	 **13b**	99	92 : 4
3	 **13c**	99	98 : 2
4	 **13d**	90	99 : 1
5	 **13e**	98	99 : 1
6	 **13f**	82	99 : 1
7	 **13g**	71	99 : 1

[a)] Reaction conditions: 60°C; [**17a-g**]$_0$=[H_2O_2]$_0$=0.1 M; [**15**]=0.001 M in CD_3OD. [b)] Determined by ^{1}H NMR analysis on the crude reaction mixture after complete oxidant consumption (iodometric test).

While these catalytic systems have shown an high selectivity towards the first oxidation and good conversion of the oxidant is observed, the slow rate of reaction does not make these catalyst good candidate for this reaction. In fact, molybdenum catalysts in general are well known to perform well in the oxidation of olefins or halides.

2.3.2 Olefin epoxidation

Epoxidation reactions were carried out using *cis*-cyclooctene **18a** as the test substrate, in $CDCl_3$ or CD_3OD depending on the oxidant employed, and the reaction courses were followed via ^{1}H NMR and GC analysis. Cyclooctene epoxide is used in virtue of its stability toward secondary reactions. This is due to the steric hindrance of the ring in the formed epoxide which prevent for overoxidation or nucleophlyic substitution. Both **15** and **16** complexes catalyze the oxygen transfer to *cis*-cyclooctene in the presence of alkyl peroxides, while they failed when hydrogen peroxide was used in methanol solution. The complex **15** shows shorter induction time due, probably, to a less coordination strength of the chloride moiety respect of the methoxy group; and this aspect reflex also in higher final yields(Figure 4).

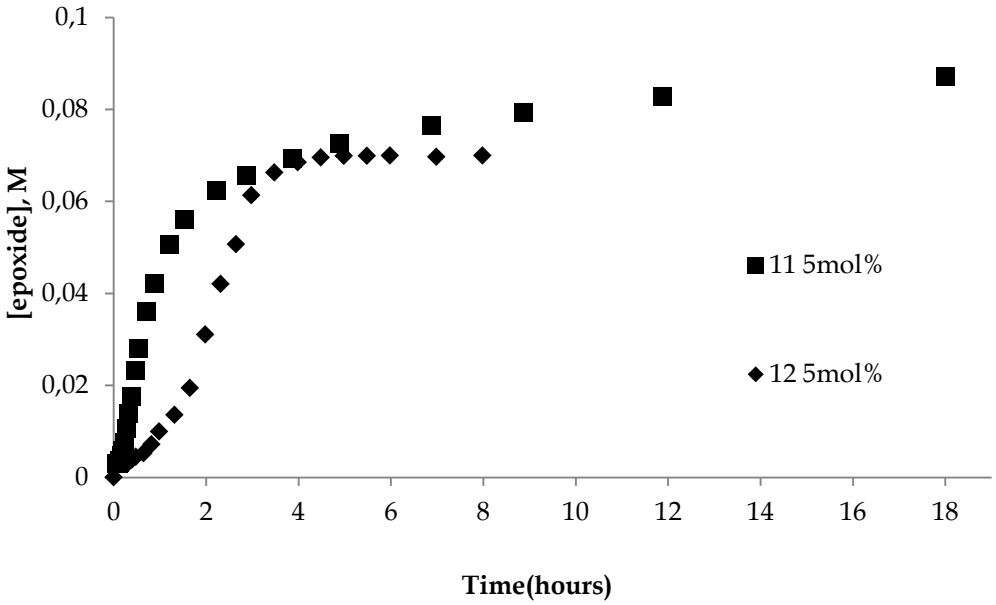
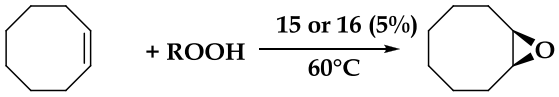


Figure 4. Kinetic profile of the cys.cyclooctene epoxidation in presence of 1 equivalent of CHP.

Table 5. Oxidation of *cis*-cyclooctene **18a** at 60°C catalyzed by **15** or **16**. Effect of catalyst and solvent.[a]



18a **TBHP R= *t*-Bu, CHP R= $PhCMe_2$ H_2O_2 R= H** **18b**

ROOH	Solvent	Catalyst	$t_{1/2}$[b] (min)	**18b** Yield (%)
CHP	$CDCl_3$	**11**	80	95
CHP	$CDCl_3$	**12**	130	80
TBHP	$CDCl_3$	**11**	52	99
TBHP	$CDCl_3$	**12**	105	83
H_2O_2	CD_3OD	**11**	--	--
H_2O_2	CD_3OD	**12**	--	--

[a)] Reaction conditions: 60 °C, [**18a**]$_0$=[oxidant]$_0$=0.1 M, [**15**]=[**16**]=0.005 M. [b)] Time required for a 50% decrease of the initial concentration of olefin. [c)] Yield determined by ^{1}H NMR analysis on the crude reaction mixture after complete oxidant consumption (iodometric test). Complete selectivity towards the epoxide has been observed.

The best results, as far as reactivity and chemical yields are concerned, were obtained using the **15**/TBHP system, and the catalytic activity for this system has been explored more in detail (Table 6).

Table 6. Oxidation of *cis*-cyclooctene **14a** by **11** at 60°C. Effect of the catalyst loading.[a]

#	$[\mathbf{14a}]_0$	**TBHP** (1 equiv)		**TBHP** (2 equiv)	
		% cat	Yield %[b]	% cat	Yield %[b]
1	0.1	5	99	5	99
2	1	0.5	99	0.5	99
3	1	0.05	94	0.05	99
4	1	0.01	94	0.01	97
5	1	0.001	67	0.001	88

a) Reactions were carried out at 60°C in $CDCl_3$. In the absence of the catalyst, conversions lower than 10% are observed after 24 hours. b) Yield determined by ^1H NMR analysis on the crude reaction mixture after 24 hours. Complete selectivity towards the epoxide is observed.

At this point the effect of the substrate/catalyst concentrations rate was studied. Developing a catalyst that is still active and gives fast reaction time in low concentrations is needed in order to obtain an efficient system. Kinetic epoxidations experiments were performed keeping the concentrations of the substrate and oxidant constant, while the concentration of the catalyst was lowered by several order of magnitude. The catalyst loading could be reduced down to 0.01% without affecting the efficiency of the system. A further lowering to 0.001% led to lower yields with one equivalent of TBHP, however high yields can be restored using two equivalents of oxidant. Under the best conditions (Table 6 entry 5), a TON of 88,000, with a TOF around 7500 h^{-1} were obtained. These values are significantly high, especially if compared to other epoxidation catalysts, confirming an exceptional stability and reactivity of the catalyst under turnover conditions.

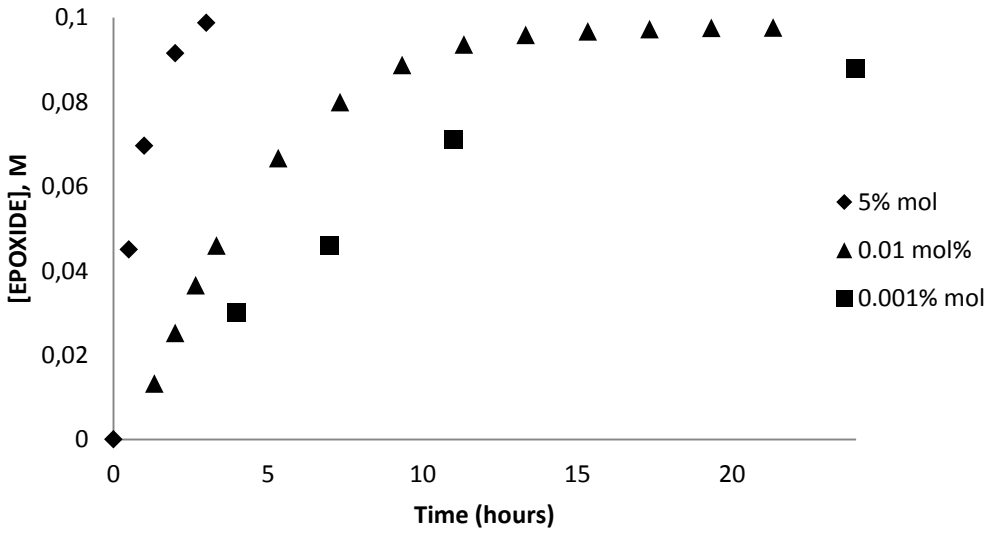
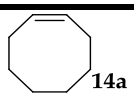
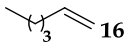
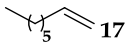
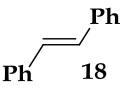
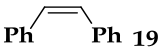
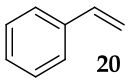
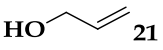


Figure 5. Kinetic profiles of the epoxidation of *cis*-cyclooctene (0.1 M) with 2 equivalent of TBHP in $CDCl_3$ at 60°C, with catalyst **11,** at 5% mol(♦), 0.01% mol(▲), and 0.001% mol(■).

The kinetic profile of the *cis*-cyclooctene epoxidations with different catalyst loading is reported in Figure 5. For a good assessment of a catalytic system a range of alkenes has to be tested. Terminal epoxides are generally quite stable towards ring opening, but, on the other hand, the corresponding olefinic substrate is less reactive. Instead, as a result of the electronic influence of the aromatic ring, styrene oxide is highly reactive and oxidation usually led to benzaldehyde as the major product. Hence, the scope of the reaction was explored towards different olefins using one and two equivalents of TBHP (Table 6). The different olefins are oxidized in fairly high yields. While complete conversion to the corresponding epoxide is observed for *cis*-cyclooctene **14a** and methylcyclohexene **15** (Table 6, entries 1 and 2), lower conversions, even if with very good selectivities, are observed for terminal olefins such as 1-hexene **16** and 1-octene **17** (Table 6, entries 3 and 4). In these cases, using an excess of the oxidant (2 equivalents) allows the conversions to be increased up to 75%, maintaining high selectivities (Table 6, entries 3 and 4). Comparable conversions are obtained for *trans*-stilbene **18**, *cis*-stilbene **19**, allyl alcohol **20** and styrene **21**, even if, in these cases, the corresponding epoxides are more reactive and unstable under the reaction conditions and they generally undergo consecutive ring opening, thereby decreasing the selectivity of the process. Furthermore, *trans*- and *cis*-stilbene (**18** and **19**) afford only the *trans*- and *cis*-epoxide respectively, indicating that this is a stereospecific concerted oxygen transfer process.

Table 6. Oxidation of olefins at 60°C using **11**/**TBHP**.[a]

	Substrate	**TBPH**, 1 equiv.		**TBPH**, 2 equiv.	
		Conv. (%)	Sel. (%)	Conv. (%)	Sel. (%)
1	 **14a**	99	99	99	99
2	 **15**	99	99	99	99
3	 **16**	50	95	77	95
4	 **17**	45	97	73	96
5	 **18**	78	52	86	75
6	 **19**	73	54	75	98
7	 **20**	75	44	72	26
8	 **21**	58	70	76	80

[a)] Reaction conditions: 60°C, [**14a-21**]$_0$, [**TBHP**]$_0$=0.1-0.2 M, [**11**]=0.005 M. [b)] Conversion and selectivity determined by ^{1}H NMR analysis using an internal standard (1,2-dichloroethane, DCE) on the crude reaction mixture.

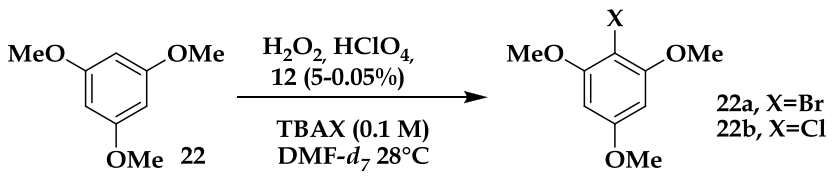
2.3.3 Oxidation of halides

Due to the remarkable stability shown by complexes **11** and **12** under turnover conditions, we also tested their catalytic performances in haloperoxidation reactions, where the catalyst has to be stable under aqueous highly acidic conditions.[27] Mononuclear C_3 vanadium(V) amine triphenolate complex were previously found to effectively catalyze the oxidation of sulfides and bromide ions, and thus proved to be both a structural and a functional model of vanadium haloperoxidase.

Catalyst **12** was examined in order to avoid contamination with the chloride ligand present in **11**. Reactions were performed under Butler's standard reaction conditions.[28] This translates into the use of tetrabutylammonium bromide (TBABr) and tetrabutylammonium chloride (TBACl) as halogen sources in the presence of 1,3,5-trimethoxybenzene **22** as test substrate. These reaction conditions allow for a comparison with previously developed catalysts. Reactions are followed by checking change of ^{1}H-NMR chemical shifts of the aromatic protons of the trimethoxy benzene and are performed in screw-cap NMR tube. The bromination reaction proceeds with high yields based on the limiting reagent (H^+) when a 5% loading of **12** was used (Table 7, entries 1–3). While the time required for the reaction is longer than that with the corresponding vanadium(V) complexes,[29] yields are generally higher. Catalyst loading could be decreased down to 0.05% (Table 7, entry 7) and the product **22a** could be obtained in 50% yield with TON = 1000. The metal precursor MoO_2Cl_2 is also an active catalyst, but it displays much lower reactivity than **12** (Table 7, entries 4 and 8), especially when used at low catalyst loadings. Reactions were also carried out in the presence of chloride ions. Slow chlorination of **22** could be achieved (**12** loading = 5%) obtaining **22b** in 20% yield after two days (Table 7, entry 9).

The obtained yields indicate that the system is catalytically active and can perform four catalytic cycles. Our previous results on V(V) complexes showed that this system could also oxidize chloride ions, but only a single catalytic cycle was obtained.[29]

Table 7. 22a or **22b** formation as a function of [H^+], [H_2O_2], and of Mo(VI) catalysts (**12** or MoO_2Cl_2).[a]



	X	**Catalyst** (%)	$[H_2O_2]_o$ (mM)	$[H^+]_o$ (mM)	$t_{½}$[b] (min)	Yield[c] (%)
1	Br	**12** (5)	8	3	< 5	90
2	Br	**12** (5)	20	20	57	88
3	Br	**12** (5)	40	20	24	99
4	Br	**MoO_2Cl_2** (5)	40	20	24	99
5	Br	--	20	20	--	11
6	Br	**12** (0.5)	20	20	80	90
7	Br	**12** (0.05)	20	20	1440	50
8	Br	**MoO_2Cl_2** (0.05)	20	20	--	38
9	Cl	**12** (5)	40	20	--	20

[a)] Reaction conditions: DMF-*d*7, 28 °C using [**22**]$_0$=20 mM, [**TBAX**]$_0$=0.1 M, X=Br or Cl. [b)] Time for a 50% decrease of $[H_2O_2]_0$. [c)] Based on the limiting agent $HClO_4$ and determined by ^{1}H NMR (DCE as internal standard) on the crude reaction mixture after total oxidant consumption (iodometric test).

The obtained yields indicate that the system is catalytically active and can perform four catalytic cycles. Our previous results on V(V) complexes showed that this system could also oxidize chloride ions, but only a single catalytic cycle was obtained.[29]

2.4 Conclusions

In conclusion, amino tris-*tert*-butylphenolate molybdenum complexes **11** and **12** have proven to be active and efficient catalysts in the oxidation of sulfides, olefins and halides, using alkyl hydroperoxides or hydrogen peroxide as primary oxidants. Conversion of the primary oxidant is, in most of the cases, quantitative and the optimisation of the reaction conditions allows the attainment of the products in good yields and with high turnover numbers, especially in the case of olefin epoxidation (TON up to 88,000 and TOF up to 7500 h^{-1} for cyclooctene). These results, in combination with the results reported previously for the corresponding Ti(IV) and V(V) complexes, reinforce the knowledge that amino tris-*tert*-butylphenolate is a versatile ligand for the formation of very stable and active metal catalysts. Moreover, the same ligand, in combination with three different metals Ti(IV), V(V) and Mo(VI),

offers the possibility of preparing complexes which are able to oxidise efficiently a large range of functional groups.

2.5 Experimental

General remarks

All chemicals and dry solvent have been purchased from Aldrich or Fluka and used as provided, without further purifications; 70% aqueous $HClO_4$ was purchased from Carlo Erba.

Flash chromatographies have been performed with Macherey-Nagel silica gel 60 (0.04-0.063 mm, 230-400 mesh). The NMR spectra have been recorded on a Bruker AC 250 (^{1}H: 250.13 MHz; ^{13}C: 62.9 MHz), a Bruker AV 300 (^{1}H: 300.13 MHz; ^{13}C: 75.5 MHz) spectrometer and a Bruker AV 200 (^{1}H: 300.13 MHz; ^{13}C: 75.5 MHz) spectrometer. Chemical shifts (δ) have been reported in parts per million (ppm) relative to the residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR; CD_3OD: 3.31 ppm for ^{1}H NMR and 49.05 ppm for ^{13}C NMR). The following abbreviations have been used to explain the multiplicities: s = singlet, d = doublet, t = triplet, dd = double doublet, m = multiplet, br = broad. ^{13}C NMR spectra have been recorded with complete proton decoupling. Analytical gas chromatography analysis has been carried out on a Shimadzu GC-2010 gas chromatograph with a FID detector and a capillary column EQUITY™-5 using decane as internal standard. Injector temperature has been set to 250 °C, detector temperature has been set to 280 °C and the carrier gas is He (1 mL/min) with a HP-5MS column. APCI-MS spectra have been obtained on a LC/MS Agilent series 1100 spectrometer in both positive and negative modes, by direct flow injection using methanol as mobile phase, with ESI-ion trap mass detector. IR spectra have been recorded on a Nicolet 5700 FT-IR, with range 4000-400 cm^{-1} and resolution 4 cm^{-1}, using KBr pellets. Elemental analysis

General procedure for purification of 7 via formation of a bisulfite adduct

120 grams of aldehyde **7** and 300 mL of a 40% $NaHSO_3$ solution were stirred for two hours with 300 mL of ethanol, the bisulfite adduct **8** is soluble in water and separable from the reaction mixture. The aqueous solution was then basified and the aldehyde re-obtained via extraction with three portions of 100 mL of CH_2Cl_2, with an overall yield of 62%; the starting material can also be recovered, characterized as the precedent substrate and reused.

^{1}H-NMR (250 MHz, $CDCl_3$) δ 10.42 (s, 1H, C*H*O), 7.84 (dd, 1H, *J* = 7.6, 1.7 Hz, *H*Ar), 7.70 (dd, 1H, *J* = 7.8, 1.7 Hz, *H*Ar), 7.62 – 7.38 (m, 5H, *H*Ar), 7.24 (t, 1H, *J* = 7.8 Hz, *H*Ar), 5.12 (s, 2H, C*H*$_2$Bn), 1.53 (s, 9H, C*H*$_3$).

Synthesis of Molybdenum(VI) complex (11)

MoO_2Cl_2 (200 mg, 1 mmol) and the ligand precursor **10** (503 mg, 1 mmol) were mixed with toluene (50 mL) and the stirred suspension was heated to reflux for 18 h. The resulting intense purple solution was filtered through a short pad of silica and evaporated to afford complex **10** as a violet solid; yield: 500 mg (72%).
^{1}H NMR (250 MHz, $CDCl_3$): δ =7.40 (dd, 1H, *J*=7.8 and 1.4 Hz, ArH), 7.34 (dd, 2H, *J*=7.8 and 1.8 Hz, ArH), 7.15 (dd, 3H, *J*=9.2 and 1.4 Hz, ArH), 6.98 (m, 3H, ArH), 3.99 (d, 2H, *J*=11.5, NCH_2), 3.6 (d, 2H, *J*=21.1 Hz, NCH_2), 3.49 (s, 2H, NCH_2), 1.59 (s, 9 H), 1.47 (s, 18H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 159.84 (C), 141.40 (C), 140.4 (CH), 128.71 (CH), 128.11 (C), 125.61 (CH), 60.23 (CH) 35.45 (CH), 35.43 (CH), 30.54 (C), 30.40 (C); ESI-MS: *m/z* = 672.2 ($M + Na^+$), 650.2 ($M + H^+$), 614.3 ($M-Cl^-$); Elemental analysis (CHN): calculated for $C_{33}H_{42}NO_4ClMo$: C 61.16%, H 7.00%, N=2.16%; found: C 61.64%, H 6.93%, N 2.18%.

Synthesis of Molybdenum(VI)complex (12)

Complex **11** (100 mg, 0.15 mmol) was dissolved in methanol and triethylamine (42 mL, 0.30 mmol) was added. The solution was stirred for three hours at reflux temperature. The resulting dark red solution was filtered through a short pad of silica and evaporated to afford complex **12** as a dark red solid; yield: 70 mg (80%).
^{1}H NMR (250 MHz,$CDCl_3$): δ = 7.34 (dd, 1H, *J*=7.8 and 1.4 Hz, ArH), 7.27 (dd, 2H, *J*=7.8 and 1.4 Hz, ArH), 7.03 (dd, 2H, *J*=7.8 and 1.4 Hz, ArH), 6.98 (dd, 3H, *J*=7.4 and 1.8 Hz, ArH), 6.86 (m, 3H, ArH), 4.07 [s, 3H, (CH_3)], 3.82 (d, 2H, *J*=13.3 Hz, NCH_2), 3.58 (s, 2H, NCH_2), 3.47 (d, 2H, *J*=13.3 Hz NCH_2), 1.59 [s, 9H, $C(CH)_3$], 1.43 [s, 18H, $C(CH)_3$]; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ =158.85 (C), 141.57 (C), 140.56 (CH), 128.67 (CH), 128.14 (C), 126.87 (CH), 60.65 (CH), 35.66 (CH), 35.20 (CH), 30.60 (C), 30.31 (C); ESI-MS: *m/z* = 646.2 ($M + H^+$), 614.3 ($M - MeO^-$); Elemental analysis (CHN): calculated for $C_{34}H_{45}NO_5Mo$: C 63.45%, H 7.04%, N 2.18%; found: C 63.92%, H 6.96%, N 2.21%.

X-ray crystallographic data collection and structure refinement for 11

In order to obtain crystals suitable of crystallographic analysis, in a screw-capped vial, 1 mmol of **11** was dissolved in 1.0 mL of chloroform. After standing for two weeks, dark purple crystals of **11** were collected. Crystallographic parameters are given in Table 8.

Table 8. Crystallographic experimental details for complex **11**.

Crystallised from	$CHCl_3$	
Empirical formula	$C_{34}H_{43}Cl_4MoNO_4$	
Formula weight [g mol^{-1}]	767.43	
Crystal colour, habit	purple, prism	
Crystal dimensions [mm]	0.15 ´ 0.25 ´ 0.33	
Temperature [K]	160(1)	
Crystal system	monoclinic	
Space group	$P2_1/n$ (#14)	
Z	4	
Reflections for cell determination	84347	
2q range for cell determination [°]	4 – 55	
Unit cell parameters	a [Å]	9.4045(1)
	b [Å]	19.1507(2)
	c [Å]	19.9729(1)
	a [°]	90
	b [°]	98.7715(5)
	g [°]	90
	V [Å^3]	3555.10(6)
F(000)	1584	
Dx [g cm^{-3}]	1.434	
m(Mo Ka) [mm^{-1}]	0.705	
Scan type	f and w	
2q(max) [°]	55	
Transmission factors (min; max)	0.810; 0.903	
Total reflections measured	88965	
Symmetry independent reflections	8148	
Rint	0.061	
Reflections with $I > 2s(I)$	6837	
Reflections used in refinement	8146	
Parameters refined	407	
Final	$R(F)$ [$I > 2s(I)$ reflections]	0.0439
	$wR(F^2)$ (all data)	0.1155
Weights:	$w = [s^2(F_o^2) + (0.0516P)^2 + 6.0508P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$	
Goodness of fit	1.059	
Secondary extinction coefficient	0.0029(4)	
Final Dmax/s	0.001	
Dr (max; min) [e Å^{-3}]	1.88; -1.48	
$s(d$(C – C)) [Å]	0.004 – 0.005	

General Procedure for Monitoring the Oxidation Reactions Catalyzed by 11 or 12 (Tables 2-6).

A screw-cap NMR tube was charged with a solution of the Mo(VI) catalysts (in $CDCl_3$, CD_3OD or DMF-d_7), the internal standard (1,2-dichloroethane, DCE), the oxidant (35% aqueous H_2O_2, 80% cumene hydroperoxide or 80% *tert*-butyl hydroperoxide) and the substrate were added up to a final volume of 0.6 mL. The NMR tube was kept at 60°C. Concentrations of reagents and products, were monitored by integration of ^{1}H NMR resonances in respect of the internal standard DCE (3.78 ppm).

Typical Epoxidation Procedure with 11/TBHP (Table 4-6).

In a 25 mL screw-cap vial, under nitrogen, complex **11**, (0.05 mmol) was dissolved in 10 mL of DCE followed by TBHP (1.0 or 2.0 mmol) and, after 30 min, by the substrate (1.0 mmol). The solution was heated at 60°C and the reaction course was monitored via TLC and GC-MS. After the disappearance of the oxidant (iodometric test), the solvent was removed under vacuum and the reaction mixture was purified directly via radial chromatography over silica gel (gradient: ethyl ether/petroleum ether). Products were identified by comparison of ^{1}H NMR and mass spectral data with those reported in the literature (**12**,[15a] **13**,[15a] **14**,[15a] **15**,[15a] **16**,[15b] **17**,[15b] **18**,[15a] **19**[15c]).

General procedure for bromination and chlorination reactions catalysed by 12 using aqueous H_2O_2 as oxidant (Table 7).

A screw-cap NMR tube was charged with a solution of the complex **12** in DMF-d_7 (0.0006 mmol), 1,3,5-trimethoxybenzene (0.012 mmol), TBABr or TBACl (0.06 mmol) and DCE as internal standard. An appropriate volume of 35% aqueous H_2O_2 and 70% aqueous $HClO_4$ were added, as reported in Table 7, to a final volume of 0.6 mL. Reactions were performed at room temperature and monitored via ^{1}H NMR (concentrations of trimethoxybenzene **22**, TMB, and halogenated product were detected by integration of the aromatic CH: **22** (6.11 ppm), **22a** (6.38 ppm) and **22b** (6.40 ppm). Final yields were determined by ^{1}H NMR after complete H_2O_2 consumption (iodometric test) with the respect of the internal standard DCE (3.78 ppm). Mono halogenation of the substrate has been confirmed via ^{1}H NMR and GC-MS analyses, that match those already reported in the literature.

2.6 References and notes

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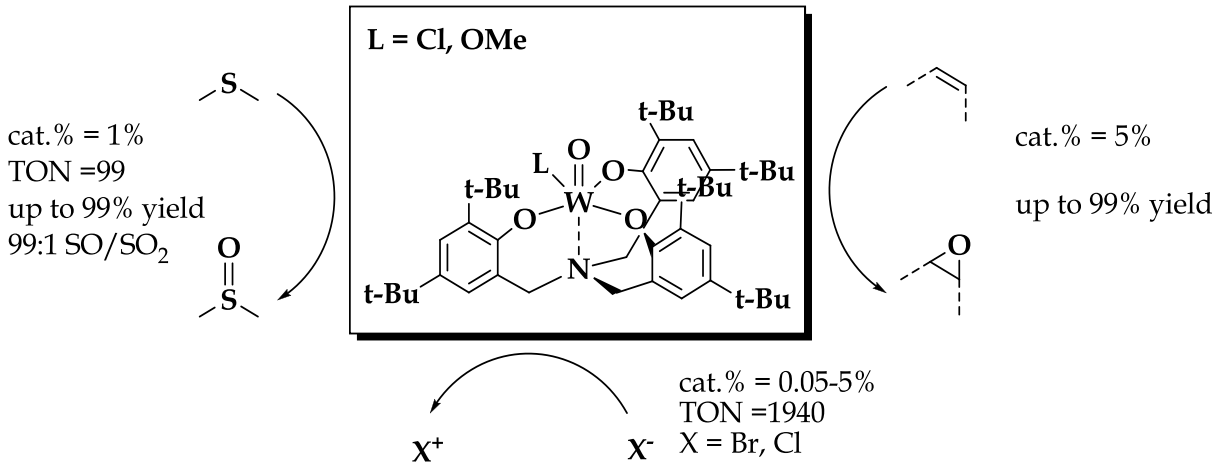
Chapter 3

Tungsten(VI) amino triphenolate complexes: synthesis, characterization and catalytic activity



The coordination chemistry and catalytic activity in oxidation of tungsten(VI) amino triphenolate complexes have been investigated. In particular, W(VI)-oxo amino triphenolate complexes have been synthesized and have proved to be air and water tolerant catalysts that efficiently catalyze, in high yields and selectivity, the oxidation of sulfides, olefins and halides. In particular, high turnover frequencies (TOFs) and turnover numbers (TONs) have been observed for the bromination and chlorination of 1,3,5-trimethoxybenzene (catalyst loading down to 0.05%, TONs up to 1940 for Br and 120 for Cl).

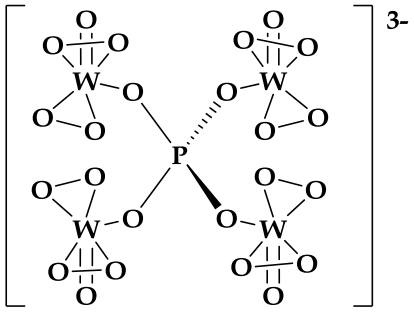
3.1 Introduction

3.1.2 W(VI) oxygen transfer catalysts: general overview

The use of W(VI) based catalysts for the epoxidations of olefin dates back to the late 40's[1] and since that time has proved to be useful for the oxidation of a variety of carbon-carbon double bonds, like in simple olefins[2] and α,β-unsaturated acids.[3] Heterogeneous W(VI) compounds, W-oxo cluster complexes, and tungstate WO_4^{2-} derivatives gained significant interest in oxidation catalysis, mainly with H_2O_2 as the oxidizing agent.[4] In this specific case, it is assumed that the actual oxidant specie is a η^2-peroxotungsten complex. Pertungstic acid and pertungstates are known to give highly stable aqueous solutions, and the tungstate ion itself has been shown to be quite superior to molybdate and vanadate in epoxidation reactions with H_2O_2, since the 'transition metal ion-induced decomposition' of hydrogen peroxide is much slower, and a broader pH range (up to 6-7) can be used. Moreover, many Mo(VI)-based catalysts reported in the literature failed to activate H_2O_2.[5]

On the other hand, W(VI)/H_2O_2 systems does not have the same broad synthetic utility as other transition metal/alkyl hydroperoxide systems,[6] *e.g.* Mo(VI)/TBHP. These latters are in fact still used in industries (*e.g.* in the ARCO-Halcon process, cfr. Chapter 2), despite their high costs and the environment pollutants and global warming agents they generate. Obviously, replacement of alkyl hydroperoxides by H_2O_2 as oxidant is more advisable,[7] in order to guarantee eco-sustainability to the whole process, since hydrogen peroxide only produces water as by-product.

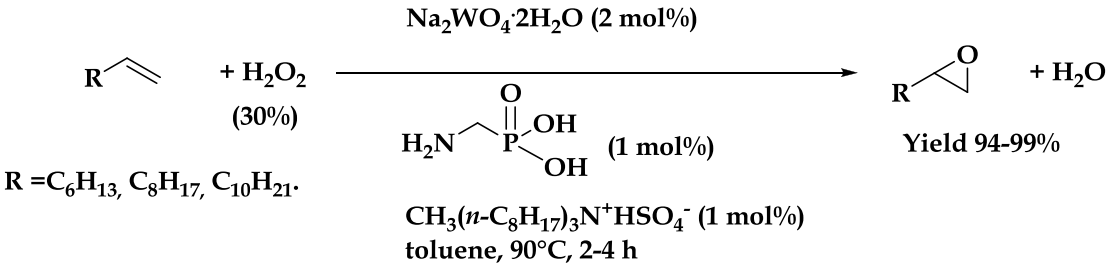
To date, tungsten(VI) complexes are probably the best transition-metal catalysts for epoxidation reactions of alkenes with hydrogen peroxide, even if sometimes the epoxides formed tend to hydrolyze to the corresponding glycols. However, good yields of epoxides can be obtained when the water is removed from the reaction medium.[8] One of the most known epoxidation system using W(VI) and H_2O_2 was reported by Venturello *et al.*[9] His work showed that a mixture of tungstate and phosphate in the presence of a tetraalkylammonium salt as the phase transfer catalyst, catalyzed olefin epoxidations with H_2O_2 in a biphasic 1,2-dichloroethane/water medium. Since its discovery in 1983, this system has been extensively studied in particular with regard to the exact nature of the active catalyst.[10] The structure of the actual active oxidant consists in a tetranuclear phosphotungstate, bearing η^2-peroxo ligands, as reported in Scheme 1.



$PW_4O_{24}^{3-}$

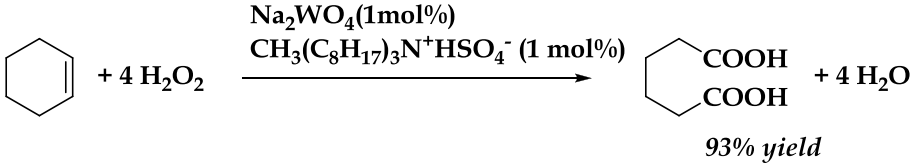
Scheme 1. Structure of the active oxidant in the Venturello-system.

More recently, Noyori and co-workers[11] reported a significant improvement of the original system. An appropriate choice of phase transfer catalyst, containing a sufficiently lipophilic tetraalkylammonium cation and a hydrogensulfate (HSO_4^-) anion, in combination with catalytic amounts of $H_2NCH_2PO_3H_2$ and sodium tungstate produced an effective system for the epoxidation of olefins with H_2O_2 in toluene/water or in the absence of an organic solvent (Scheme 2).



Scheme 2. Noyori's halogenated solvent-free biphasic epoxidation using 30% H_2O_2.

Subsequently, the same system was shown[12] to be effective in the oxidative cleavage of cyclic olefins to dicarboxylic acids (Scheme 3) using 4 equivalents of H_2O_2, *via* the intermediate formation of the epoxide. For example, cyclohexene afforded adipic acid in 93% isolated yield, thus providing a "green route" to this product that is a key intermediate in the synthesis of nylon. Although the economics of the whole process may be prohibitive, owing to the consumption of 4 equivalents of H_2O_2, the method has general utility for the selective conversion of a variety of cyclic olefins to the corresponding dicarboxylic or keto-carboxylic acids.



Scheme 3. Synthesis of adipic acid with the Noyori system.

BASF patents [13] using Mimoun-type [14] diperoxo-tungsten complexes further encouraged the studies on W(VI)-based catalysis in the area of olefin epoxidation. For example, Mizuno *et al.* [15] recently reported a silicotungstate compound (n-$Bu_4N)_4[\gamma$-$SiW_{10}O_{34}(H_2O)_2]$ as epoxidation catalyst using H_2O_2 as oxidant in CH_3CN medium, claiming that their catalyst showed the highest efficiency and selectivity among the known epoxidation catalysts.

3.1.2 W(VI) homogeneous mononuclear W(VI) complexes

The literature regarding homogeneous mononuclear tungsten(VI) complexes as oxidation catalysts is poor and sparse, and the majority of the articles concerning tungsten encloses also molybdenum complexes. Herein it is reported the evolution from firstly synthesized solvent coordinating compounds to more complex bi-, tri- and tetra-dentate ligands.

Mononuclear W(VI) complexes with general formula $W(O)_2(Cl)_2L_2$ (L_2 = bidentate ligands, such as 2,2′-bipyridyl or 2,2′-phenanthroline) were reported for the first time by Brisdon in 1967.[16] An analogous complex, namely $W(O)_2(CH_3)_2$(2,2′-Bipyridyl), was instead reported by Schrauzer *et al.* in 1990 and represented in Figure 1.[17]

In several cases, the literature procedures for the syntheses of $W(O)_2(Cl)_2L_2$ complexes are either complicated or have low yields, so that improved synthetic strategies were necessary.[18] The variety of the reported L_2 ligands was quite small, since it was essentially limited to solvent molecules (e.g. dimethoxyethane) or bidentate ligands (such as 2,2′-bipyridine and 2,2′-phenanthroline), sometimes used in excess, in order to synthesize more soluble $W(O)_2L_4$ complexes. This family of tungsten complexes with general formulae $W(O)_2L_4$, $W(O)_2(Cl)_2L_2$ and $W(O)_2(R)_2L_2$, were not investigated in great detail with respect to applications in homogeneous oxidation.[19]

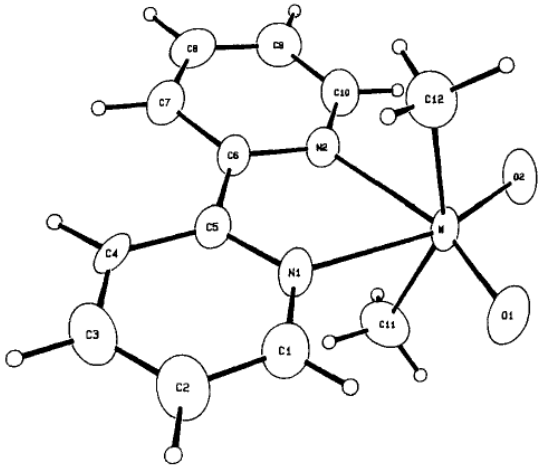
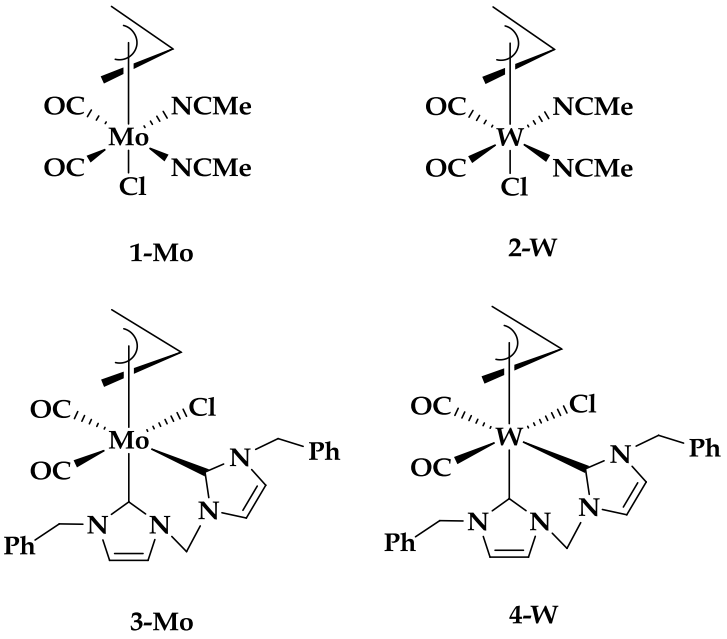


Figure 1. Perspective view of $W(O)_2(CH_3)_2$(2,2′-bipyridyl) complex.

Recent studies compared the catalytic activity in the oxidation of thiophene derivatives with W and Mo complexes of $[Cp^*_2W_2O_5]$ (Cp* = pentamethyl cylopentadiene) .[20] By using H_2O_2 as oxidant in acetonitrile solution, the W compound was found to be more active than the Mo analogue by approximately two orders of magnitude.

The group of Royo recently synthesized molybdenum and tungsten η^3-allyl dicarbonyl complexes (**3-Mo, 4-W**) bearing *N*-heterocyclic carbene (NHC) ligands $[M(\eta^3\text{-}C_3H_5)Cl(CO)_2(\text{bis-NHC}^{Bn})]$ (M = Mo or W; bis-NHC^{Bn} = 1,10-dibenzyl-3,30-methylenediimidazoline-2,20-diylidene, Scheme 4), from the corresponding acetonitrile precursors (**1-Mo, 2-W**) $[M(\eta^3\text{-}C_3H_5)Cl(CO)_2(NCMe)_2]$ by treatment with free carbene.[21]



Scheme 4. Mo(VI) and W(VI) complexes bearing *N*-heterocyclic carbene (NHC) ligands.

Their catalytic performance towards the epoxidation of *cis*-cyclooctene using H_2O_2 as oxidant has been studied. All complexes can be used as catalysts, displaying complete selectivity for the formation of cyclooctene oxide. The tungsten acetonitrile precursor $[W(\eta^3\text{-}C_3H_5)Cl(CO)_2(NCMe)_2]$, **2-W**, displayed the highest catalytic activity achieving quantitative conversion of epoxide in 30 min (Figure 2).

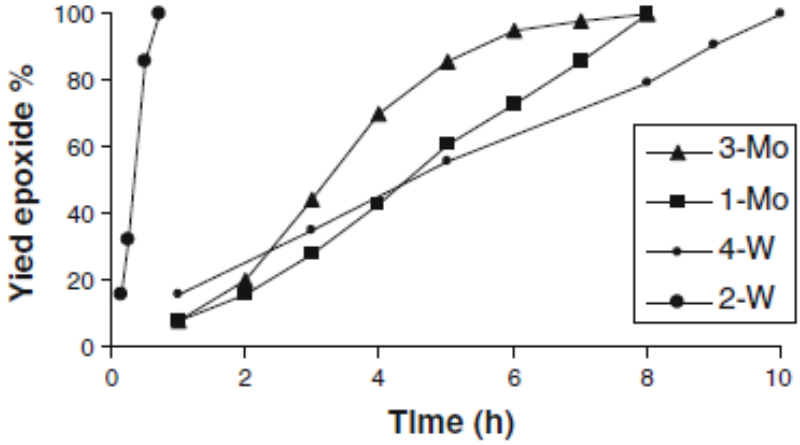
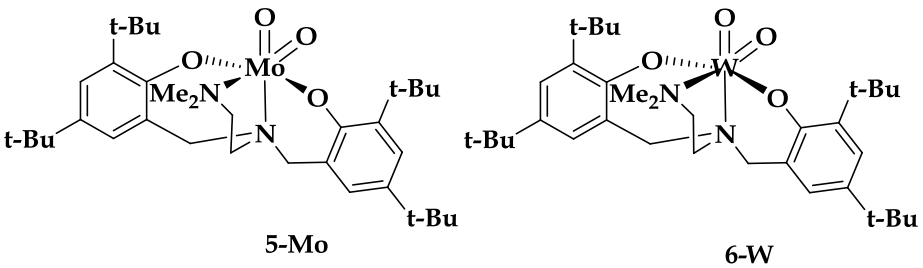


Figure 2. Kinetic profiles of *cis*-cyclooctene epoxidation with H_2O_2 in the presence of complexes **1–4**.

Among different systems, metal complexes constituted by amine and diamine *bis*-phenolate ligands have attracted considerable attention over past decades due to their properties as catalysts for olefin polymerization and ring-opening polymerization of lactones and lactides.[22] There are few reports on molybdenum and tungsten complexes supported by this family of ligands and their application in epoxidation catalysis has been scarcely investigated.



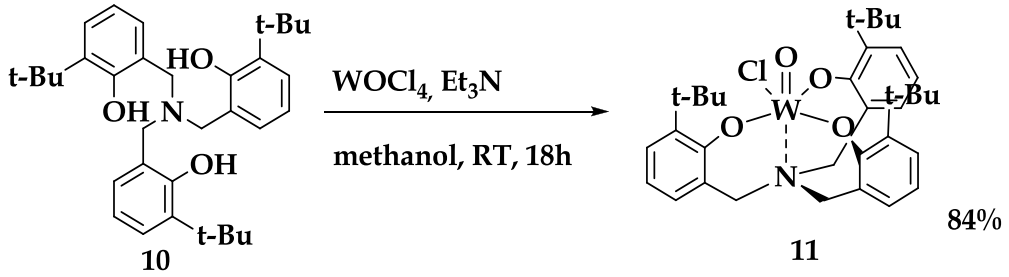
Scheme 5. Molybdenum, tungsten complexes with amine *bis*-(phenolate) ligands.

However, catalytic performance of amino bisphenolate complexes **5-6** (Scheme 5) was investigated using *cis*-cyclooctene as model substrate. In particular, when 2 equivalents of H_2O_2 as terminal oxidant and 1 mol% of catalyst were used selective conversion to the epoxide was observed in the first hour with a 43% yield in the case of the W complex. The epoxide product at the end of the run was 84%. Control experiments showed that no epoxide was formed in a measurable extent in this reaction conditions in the absence of catalyst. Conversely, the molybdenum analogue, **5-Mo**, presented no significant conversion. The inactivity of this octahedral $Mo(O)_2X_2L_2$ complex in the epoxidation of olefins with H_2O_2 as oxidant is in agreement with previous reports[23] and likely reflects the instability of molybdenum complexes to hydrolysis.

The high stability towards hydrolysis of amino triphenolate Ti(IV), V(V) and Mo(VI) complexes previously synthetised in the group were this work was carried, prompted us to extend our research towards W(VI) TPA complexes. In this work, tetradentate tungsten amino triphenolate complexes have been synthesized with a new and optimized methodology and catalytic studies have been carried out towards oxidations of sulfides, olefins and halides.

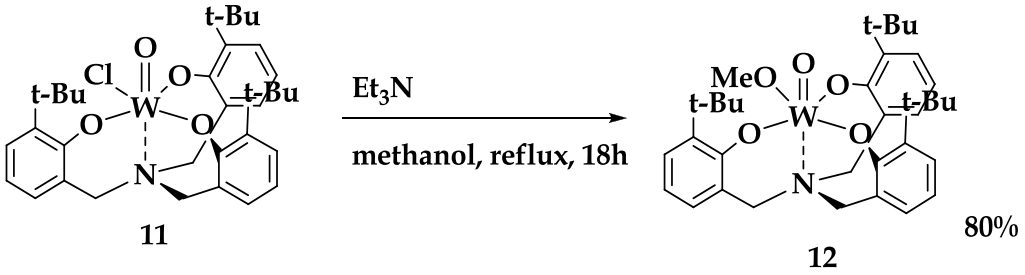
3.2 W(VI) amine triphenolate complexes: synthesis and structural study

As already mentioned, several amino triphenolate ligands were successfully synthesized in our laboratories, with an optimized synthetic strategy based on a threefold reductive amination of a substituted salicyl aldehyde (cfr. Paragraph 2.2). Tungsten(VI) complexes of the amino tri-*tert*-butylphenolate ligand **10** were synthesized using a new methodology developed in our laboratories, which uses $WOCl_4$ as the metal precursor (Scheme 6). In a glove-box, the solid $WOCl_4$ was dissolved in methanol in the presence of stoichiometric amounts of **10** and five equivalents of triethylamine. The resulting mixture was stirred at room temperature overnight to obtain an intense red solution. The solution was washed with a 4 N HCl solution, then extracted with dichloromethane and purified by flash chromatography on SiO_2 using toluene as the eluent obtaining pure complex **11**.



Scheme 6. Synthesis of W(VI) complex of the amino tri-*tert*-butylphenolate ligand **10**.

Displacement of the chloro ligand in favor of a methoxy group can be achieved by refluxing complex **11** in methanol in the presence of one equivalent of triethylamine. Compound **12** was also purified using flash chromatography (Scheme 7).



Scheme 7. Synthesis of W(VI) amino tri-*tert*-butylphenolate complex **12**.

The formation of mononuclear, six coordinated complexes was confirmed by ESI-MS and ^{1}H NMR studies. ESI-MS spectrum of **11** shows two groups of peaks: the first is referred to the complex without the apical group (m/z 700) and the second (m/z 740) to the complex coordinating an acetonitrile molecule (Figure 3). In both the groups the isotopic pattern of a tungsten complex is clearly recognizable.

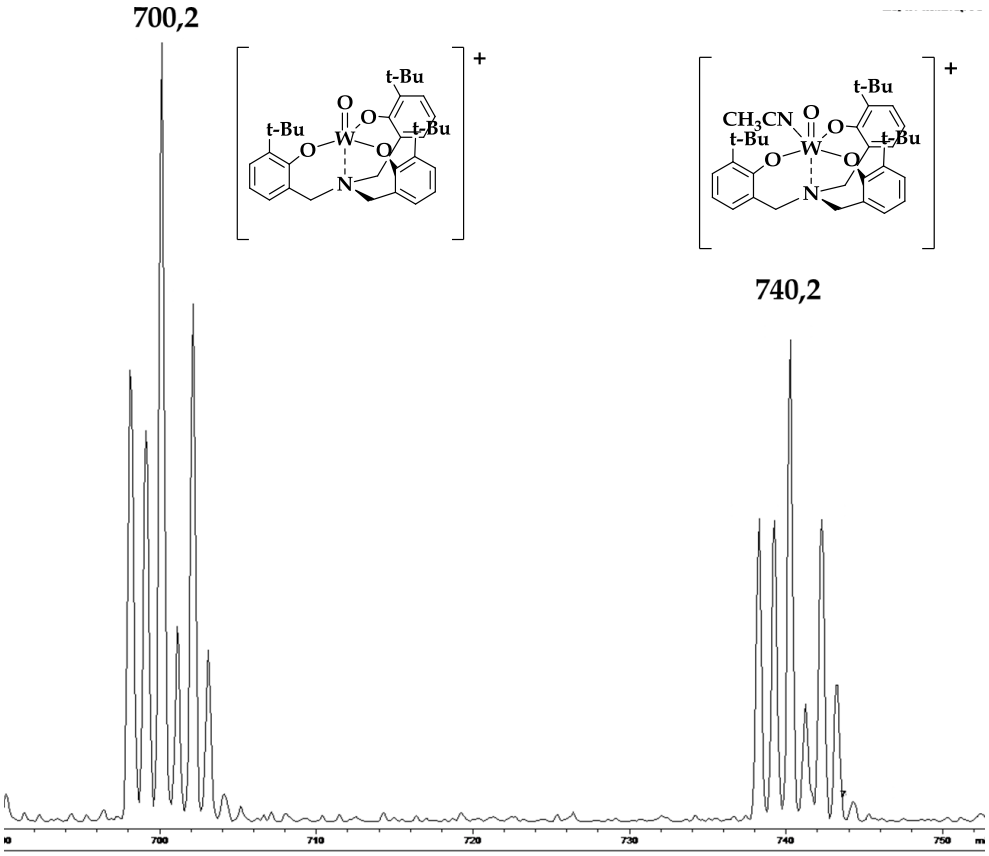


Figure 3. ESI-MS spectrum of **11**, performed in positive mode with flow injection analysis**.**

The ^{1}H NMR spectra of the oxo tungsten complex **11** shows that the benzylic protons of the ligand as a consequence of the complex symmetry become diastereotopic in the complex, resulting in three groups of signals: two doublets and a singlet (Figure 4).

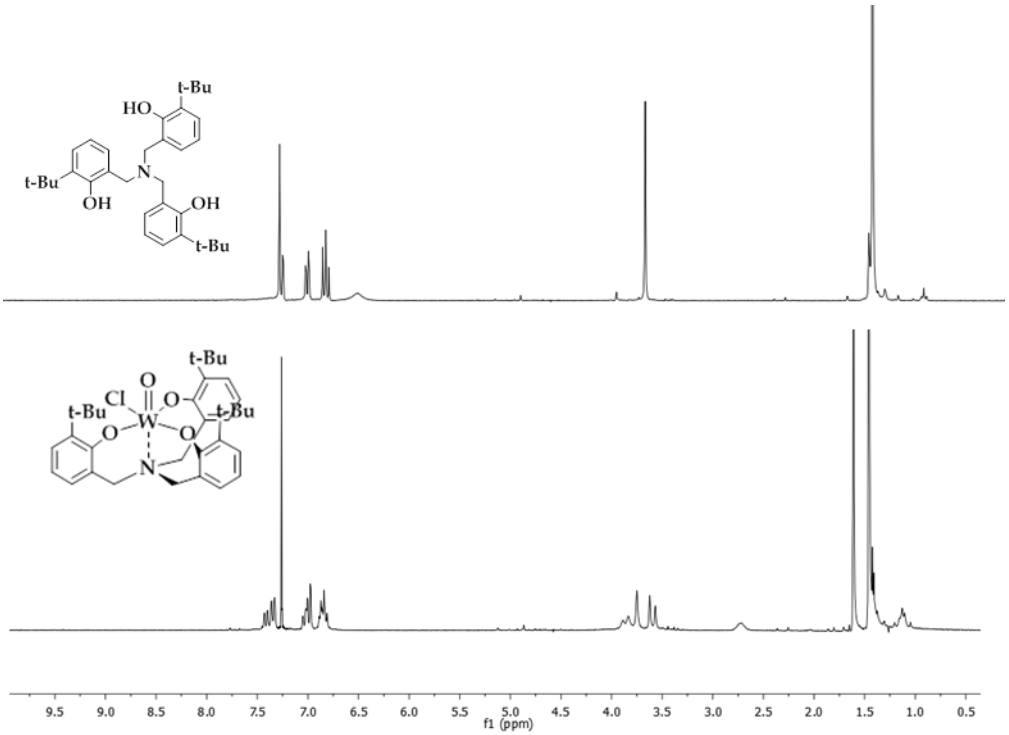


Figure 4. ^{1}H NMR spectra (250 MHz, $CDCl_3$) of the free ligand **10** and the complex **11** respectively.

3.3 Catalytic activity of W(VI)amine triphenolate complexes

The precedent use of multidentate amine triphenolate ligands for complexation of molybdenum(VI) afforded high stable metal complexes, which allowed either to lower catalyst concentrations (without losing catalyst integrity) and to obtain high TONs and TOFs in the oxidation of different substrates (cfr. Chapter 2). With this background, W(VI) complexes **11** and **12** were tested as catalysts for sulfides, olefins and halides oxidation. Oxidation of secondary and tertiary amines, alcohols, and hydroxylation of ethyl benzene and benzene were explored, but no adequate results were obtained. The results obtained are reported and discussed in the following paragraphs.

3.3.1 Oxidation of sulfides to the corresponding sulfoxides

Complex **11** was tested as catalyst in the oxidation of sulfides using H_2O_2 as the terminal oxidant. In these reactions, **11** can activate hydrogen peroxide already at room temperature, affording quantitative yields of the sulfoxides. This behavior is

different from the corresponding Mo(VI)Cl-based system, for which a reasonable reactivity was observed only after heating at 60°C.

In Figure 5, reaction profiles of the oxidation of methyl-*p*-tolyl sulfide (sulfoxide formation) are reported. The figure shows a comparison between the activity of complex **11** (1%) with hydrogen peroxide and *tert*-butyl hydroperoxide (TBHP). Higher yield and shorter reaction time with hydrogen peroxide are, as expected, consistent with other data reported in literature.

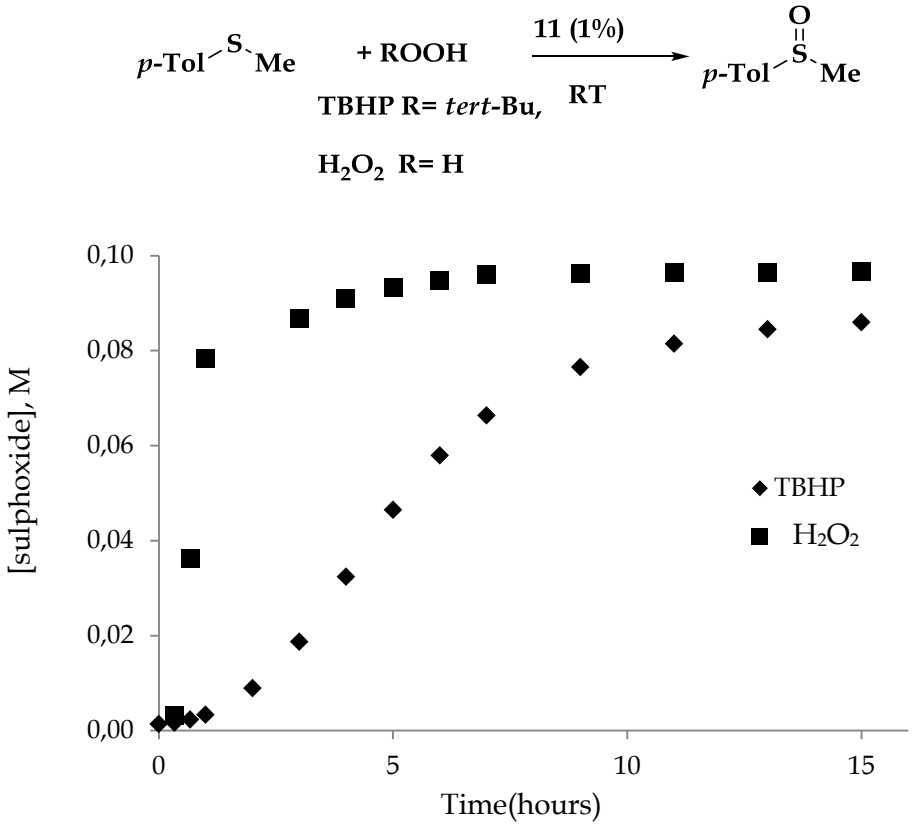
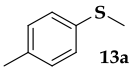
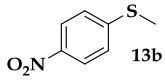
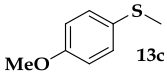
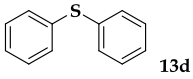


Figure 5. Oxidation of methyl-*p*-tolyl sulfide with H_2O_2 (■) and TBHP (◆). Reaction conditions: 25°C; $[sulfide]_0=[oxidant]_0$=0.1 M; [**11**]=0.001 M; solvent = CD_3CN (with H_2O_2) or CD_3Cl (with TBHP).

The scope of the reaction was explored towards different sulfides. Yields are high for all the substrates either they are aromatic or aliphatic; the selectivity rates sulfoxide/sulfone ($SO:SO_2$) are very high towards the production of sulfoxide (Table 1).

Table 1. Oxidation of sulfides **13a-g** by 35% aqueous hydrogen peroxide catalyzed by **11**.[a]

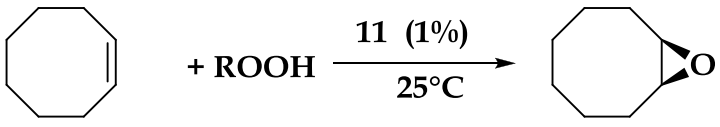
	Substrate	Yield (%)[b]	SO : SO_2
1	 **13a**	98	99 : 1
2	 **13b**	100	75 : 12
3	 **13c**	89	99 : 1
4	 **13d**	72	99 : 1
5	 **13e**	99	82 : 9
6	 **13f**	99	60 : 20
7	 **13g**	77	/

a) Reaction conditions: 25°C; $[sulfide]_0=[H_2O_2]_0=0.1$ M; [**11**]=0.001 M in CD_3OD. b) Determined by ^1H NMR analysis on the crude reaction mixture after complete oxidant consumption (iodometric test).

3.3.2 Olefin epoxidation

The epoxidation reaction using *cys*-cyclooctene as model substrate using hydrogen peroxide as the benign oxidant was tested using the same procedures described in Chapter 2. We found that using acetonitrile as the solvent can enhance the rate of hydrogen peroxide activation in olefin epoxidations. The data regarding the effect of different solvents and oxidants on the overall yield of the reaction are reported in Table 2.

Table 2. Oxidation of *cis*-cyclooctene **14a** at 60°C catalyzed by **11** (5%). Effect of the oxidant and solvent.



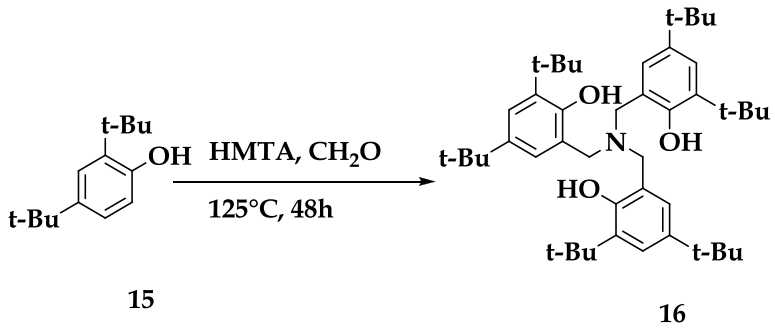
14a **TBHP R= *t*-Bu,** **14b**

H_2O_2 R= H

ROOH	Solvent	$t_{1/2}$[b] (min)	Epoxide Yield (%)
TBHP	$CDCl_3$	-	45
H_2O_2	CD_3OD	240	57
H_2O_2	CD_3CN	33	63

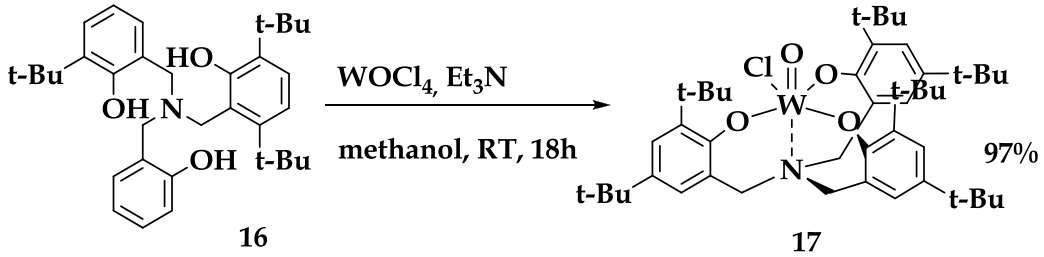
a) Reaction conditions: 25°C; $[sulfide]_0=[H_2O_2]_0=0.1$ M; [**11**]=0.001 M in CD_3OD. b) Determined by ^1H NMR analysis on the crude reaction mixture after complete oxidant consumption (iodometric test).

Using acetonitrile as solvent, the epoxide yield goes up to 63%, with a half-time of 33 minutes. While the results in term of yields were good, extensive decomposition of the catalysis is observed by ^{1}H-NMR experiments in the course of the kinetic experiments. Decomposition can arise from an oxidation of the ligand, followed by hydrolysis of the metal complex. In order to enhance the stability of the complex, a new ligand was synthesized, bearing a second *tert*-butyl group in *para* position to the phenol group. Ligand **17** was synthesized with a one-step methodology using a Mannich-type reaction, starting with 2,4-di-*tert*-butylphenol (**15**), in the presence of hexamethylenetetramine and 37% aqueous solution of formaldehyde[24] (Scheme 8). The resulting solid is crystallized from diethylether and methanol and **16** obtained as colorless crystals, in 75% yield.



Scheme 8. Synthesis of ligand **17** *via* hexamethylen tetraamine (HMTA) aromatic formylation.

Complex **17** was isolated as solid and characterized similarly to complex **11** . These analyses confirm the structures.



Scheme 9. Synthesis of W(VI) amino tri-(3,5-di-*tert*-butyl)phenolate complex **17**.

Complex **17** was then used in catalysis, using same conditions used for **11** to verify if a stability enhance could be achieved. Interestingly, in the same reaction conditions epoxide yield was raised from 63% to 80%. The increased in the yield prompted us to test the effect of the catalyst **17** concentration was tested (Figure 7). As shown in Table 3 and Figure 6, the catalyst loading could be reduced down to 1% without

affecting the final yield. This is possible when two equivalents of H_2O_2 are used. A further lowering to 0.1% does results in a decreased epoxide yields and, with an excess of the oxidant, complete decomposition of the catalyst was observed.

Table 3. Effect of catalyst loading on the cys-cyclooctene epoxidation reaction.

Entry	Cat.(%)	$[H_2O_2]_{0,}$ M	Yield(%)
1	5	0.2	98
2	5	01	80
3	1	0.2	94
4	1	0.1	62
5	0.1	0.2	46

Reaction conditions: 60°C; [cys-cyclooctene]0=0.1 M; [H2O2]0=0.1-0.2 M; [17]=0.005-0.0001 M in CD_3CN.

It is possible that, lowering down the concentration of the catalyst results in the formation of unstable diperoxo species, or in longer reaction times that compromises the stability of the catalyst.

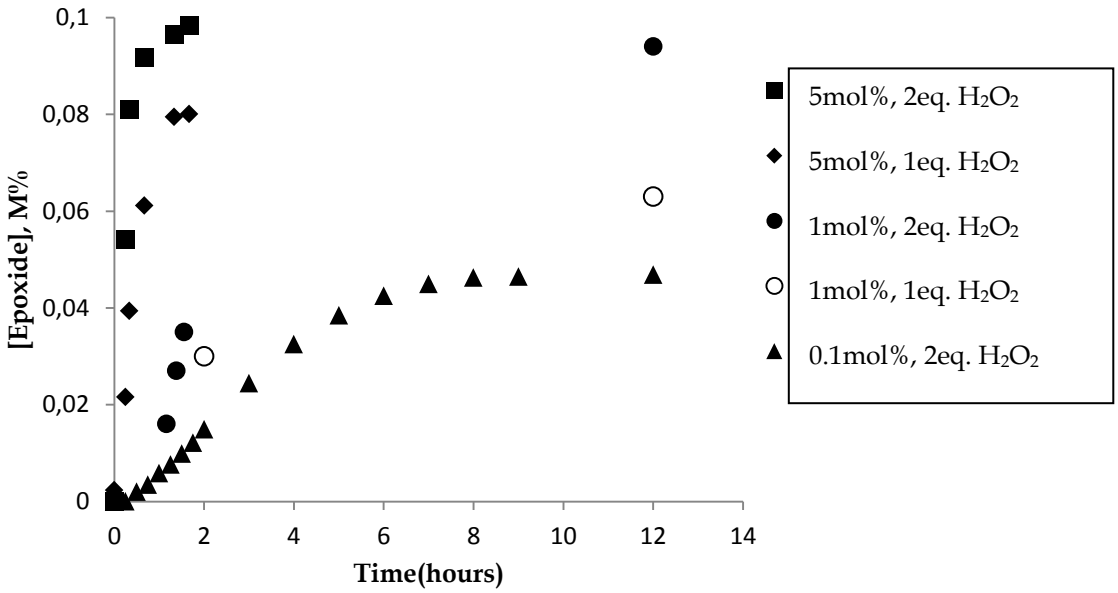


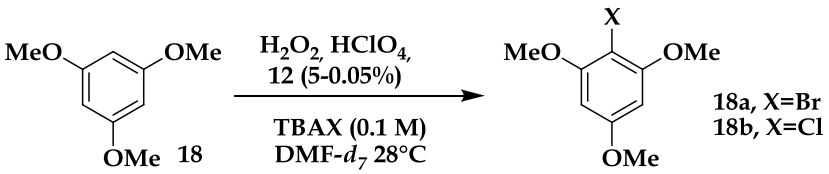
Figure 6. Kinetic profiles of oxidation of *cys*-cyclooctene with H_2O_2 and different catalyst **18** loading. Reaction conditions: 60°C; [*cys*-cyclooctene]$_0$=0.1 M; $[H_2O_2]_0$=0.1-0.2 M; [**18**]=0.005 M

in CD_3CN. The scope of the reaction was tested towards styrene and 1-octene and *trans*-/*cis*-stylbene, however, even if various reaction conditions have been testes, no epoxides formation was observed. Possibly, the lower reactivity of this olefins combined with the low stability of the tungsten complex results in strong decomposition of the catalyst. The results so far indicates that W(VI) TPA complex **18** is a good catalyst for epoxidations of *cys*-cyclooctene but more thorough studies need to be carried out in order to elucidate the extent of the catalyst decomposition in presence of excess of hydrogen peroxide..

3.3.3 Oxidation of halides

The catalytic activity of W(VI) amino triphenolates **12** was also tested in the haloperoxidation reaction. The oxidative halogenation of organic substances including alkenes, alkynes and aromatics is one of the most important chemical transformations, because the halogenated products can be used as important intermediates for substitution and cross-coupling reactions, yielding pharmaceuticals, agricultural and specialty chemicals. Complex **12** was used for these experiments in order to avoid the possible interference of the chloride ligand present in **11**. The reactions were performed under Butler's standard reaction conditions. As described before, this translates into the use of tetrabutylammonium bromide (TBABr) or chloride (TBACl) as halogen sources in the presence of 1,3,5-trimethoxybenzene **20** as the test substrate. The bromination reaction proceeds in high yields (calculated on the limiting reagent, i.e. H^+) with a 5% of **12** (Table 4, entries 1–3). While the reactions are slower than the analogues catalyzed by vanadium(V) amino triphenolate complexes, the yields are generally higher with **12**. These results can also be compared to the ones obtained for the bromination in the presence of the molybdenum analogue **15**. In this case, we observed a similar catalytic activity of the two complexes (cfr. Chapter 2). Moreover, catalyst loading could be decreased down to 0.05% (Table 4, entry 7) and the 1-bromo-2,4,6-trimethoxybenzene could be obtained in 97% yield with TON = 1940. The metal precursor $WOCl_4$ also resulted an active catalyst under the same conditions.

Table 4. Formation of **18a** or **18b** as a function of [H^+], [H_2O_2], and of W(VI) catalysts (**12** or **$WOCl_4$**).[a]



Entry	X	Cat (%)	$[H_2O_2]_0$ (mM)	$[H^+]_0$ (mM)	$t_{1/2}$ (min)	Yield (%)
1	Br	**12** (5)	8	3	135	71
2	Br	**12** (5)	20	20	52	94
3	Br	**12** (5)	40	20	18	96
4	Br	**$WOCl_4$** (5)	40	20	22	92
5	Br	/	20	20	-	11
6	Br	**12** (0.5)	20	20	60	96
7	Br	**12** (0.05)	20	20	300	97
8	Br	**$WOCl_4$** (0.05)	20	20	300	94
9	Cl	**12** (5)	40	20	720	70
10	Cl	**12** (0.5)	40	20	1440	60

a) Reaction conditions: RT, [**20**]$_0$ = 20 mM, $[H_2O_2]_0$ = 20-40 mM; [**12**] = 5-0.05%mol in d_7-DMF. b) Determined by ^{1}H NMR analysis on the crude reaction mixture after complete oxidant consumption (iodometric test).

Chlorination of 1,3,5-trimethoxybenzene could also be achieved (**12** loading = 5%) obtaining the 1-chloro-2,4,6-trimethoxybenezene in 70% yields after 24 hours (Table 4, entry 9). These results indicate that the system is able to complete at least 14 catalytic cycles. In the presence of V(V) and Mo(VI) amine triphenolate complexes, we could respectively obtain a single and four catalytic cycles in 48 hours. The kinetic profile of the reaction is reported in Figure 8.

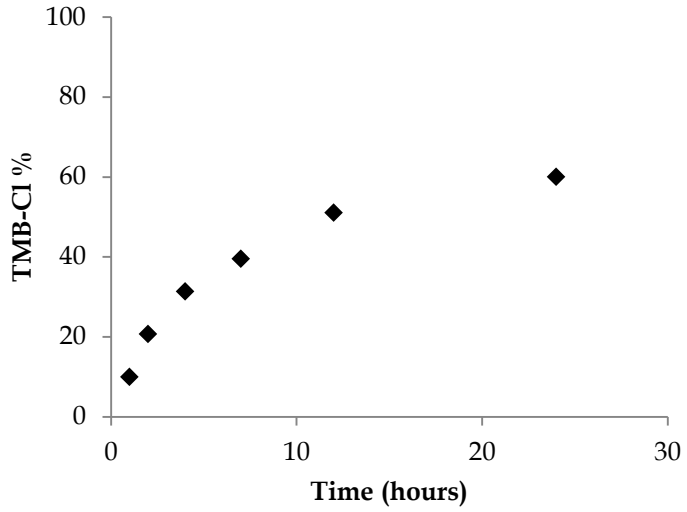


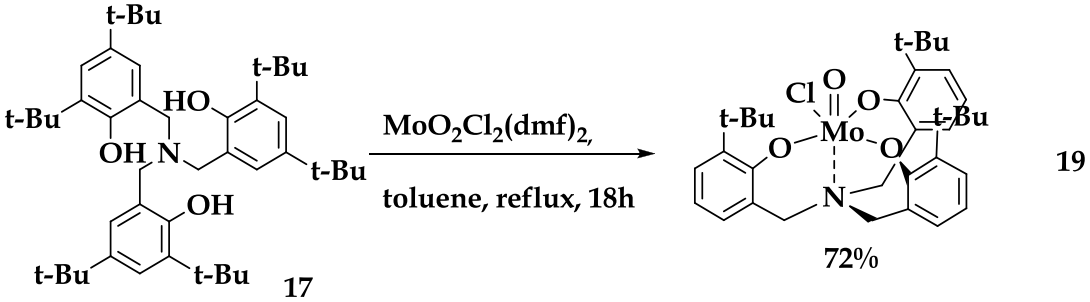
Figure 8. Kinetic profiles of chlorination of 1,3,5-trimethoxybenzene with H_2O_2, catalyzed by **12**. Reaction conditions: RT, [**18**]$_0$ = 20 mM, [H_2O_2]$_0$ = 40 mM; [**12**] = 5%mol in d_7-DMF.

This result prompted us to test the behavior of the system with catalyst loading lowered down to 0.5% while the reaction is slower, 60% conversion is observed which corresponds to 120 cycles for the catalysts a value (Table 4, entry 10).

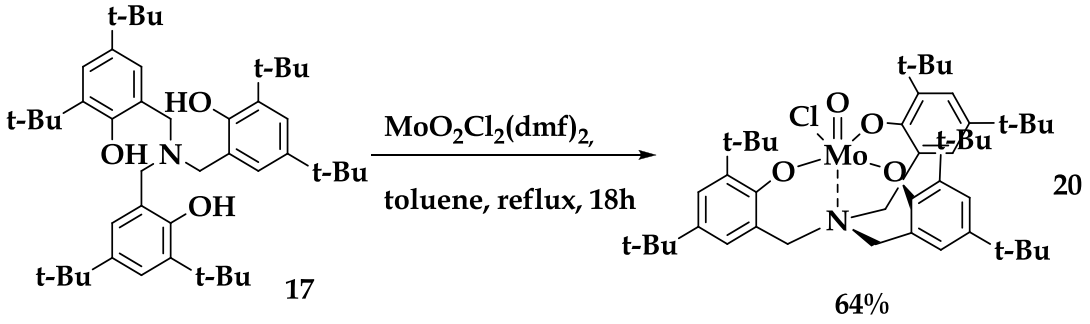
The use of d_7-DMF was necessary in order to have a direct comparison with previously tested systems, but **12** can oxidize chloride ions also in the less expensive acetonitrile, leading to quantitative formation of 1-chloro-2,4,6-trimethoxybenezene. Moreover, the reactions could be carried out also using more benign and cheaper chloride sources, like NaCl and LiCl, with no significant loss of reactivity.

3.3.4 Comparison of catalytic performances with H_2O_2 between Mo and W TPA

The yields and selectivity obtained in epoxidation obtained with complex **18** prompted us to synthesize the molybdenum analogue and to check its catalytic activity. Compound **20** was synthesized with precedent developed synthesis for analogous molybdenum complex **19** reported before.



Scheme 10. Synthesis of catalyst **19** for more information please see chapter 2.

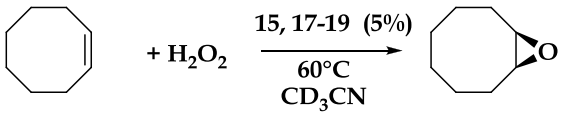


Scheme 11. Synthesis of complex **20**.

The data regarding the epoxidation of *cis*-cyclooctene with H_2O_2 catalyzed by complexes **11**, **17, 19** and **20** are reported in Table 3.The best results in terms of epoxide yield were obtained where the W(VI) catalyst **18** was used in CD_3CN in the presence of 2 equivalents of the oxidant.

The analogous molybdenum complex (the MoOCl-amino tri(*tert*-butylphenolate) reported in Chapter 2, hereafter defined as compound **19** (Scheme 20) was also used in catalytic epoxidation tests in the presence hydrogen peroxide in CD_3CN. Preliminary studies showed that low *cys*-cyclooctene conversion, using one equivalent of H_2O_2 were obtained with both Mo(VI) and W(VI) complexes (*vide infra*, Table 3). The use of a second equivalent of oxidant restored the yield only for the tungsten complex **11**.

Table 3. Oxidation of *cis*-cyclooctene **14a** at 60°C catalyzed by complexes **11**, **17**, **19** and **20**.



Entry	Complex	$[H_2O_2]_0$, M	Yield (%)
1	**20**	0.1	32
2	**20**	0.2	38
3	**19**	0.1	23
4	**19**	0.2	34
5	**17**	0.1	64
6	**17**	0.2	94
7	**11**	0.1	80
8	**11**	0.2	98

a) Reaction conditions: 60°C; [*cys*-cyclooctene]$_0$=[H_2O_2]$_0$=0.1 M; [**catalyst**]=0.005 M in CD_3CN. b) Determined by ^1H NMR analysis on the crude reaction mixture after complete oxidant consumption (iodometric test).

The best catalyst towards activation of hydrogen peroxide in terms of activity and selectivity is complex **17**. More studies have to be carried on in order to increase stability. A great chance in this contest could be offered by the heterogeneization of the catalyst, as will be explained more forward in Chapter 4.

3.4 Conclusions

In conclusion, tris-*tert*-butylphenolate tungsten complexes **11**, **12** and **18** have proven to be active catalysts in the oxidation of sulfides, olefins and halides using hydrogen peroxide as primary benign oxidants. In the sulfides oxidations, conversion of the primary oxidant is, in most of the cases, quantitative and highly selective towards the formation of the sulfoxide. Epoxidation of *cis*-cyclooctene was also carried out very efficiently, since the optimization of the reaction conditions allows the attainment of the epoxide product in quantitative yield, when two equivalents of the oxidant were used.

Oxidative bromination and chlorination of a model aromatic compound were also efficiently performed using complex **12**, with interesting yields and turnover numbers up to 120 for the chlorination of 1,3,5-trimethoxybenzene with 0.5% of catalyst loading. These results, in combination with the results reported previously for the corresponding Ti(IV), V(V) and Mo(VI) complexes, reinforce the knowledge that amino triphenolates are versatile ligands for the formation of very stable and active metal catalysts, able to oxidize efficiently a large range of functional groups.

3.5 Experimental

General remarks

All chemicals and dry solvent have been purchased from Aldrich or Fluka and used as provided, without further purifications; 70% aqueous $HClO_4$ was purchased from Carlo Erba. Triphenolamines were synthesized as previously reported.[25]

Flash chromatographies have been performed with Macherey-Nagel silica gel 60 (0.04-0.063 mm, 230-400 mesh). The NMR spectra have been recorded on a Bruker AC 250 (^1H: 250.13 MHz; ^{13}C: 62.9 MHz), a Bruker AV 300 (^1H: 300.13 MHz; ^{13}C: 75.5 MHz) spectrometer and a Bruker AV 200 (^1H: 300.13 MHz; ^{13}C: 75.5 MHz) spectrometer. Chemical shift (δ) have been reported in parts per million (ppm) relative to the residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR; CD_3OD: 3.31 ppm for ^1H NMR and

49.05 ppm for ^{13}C NMR). The following abbreviations have been used to explain the multiplicities: s = singlet, d = doublet, t = triplet, dd = double doublet, m = multiplet, br = broad. ^{13}C NMR spectra have been recorded with complete proton decoupling. Analytical gas chromatography analysis has been carried out on a Shimadzu GC-2010 gas chromatograph with a FID detector and a capillary column EQUITY™-5 using decane as internal standard. Injector temperature has been 250 °C, detector temperature has been 280 °C and the carrier gas has been He (1 mL/min) with a HP-5MS column. APCI-MS spectra have been obtained on a LC/MS Agilent series 1100 spectrometer in positive mode, by direct flow injection using methanol as mobile phase, with ESI-ion trap mass detector. FT-IR spectra have been recorded on a Nicolet 5700 FT-IR, with range 4000-400 cm^{-1} and resolution 4 cm^{-1}, using KBr pellets.

All oxygen or moisture sensitive compounds have been handled under controlled atmosphere (nitrogen) in a glovebox Mbraun MB 200MOD, equipped with a MB 150 G-I recycling system.

Synthesis of Tungsten(VI) complex (11)

In a glove-box $WOCl_4$ (136 mg, 0.40 mmol) and the ligand precursor 10 (200 mg, 0.39 mmol) were mixed with methanol (50 mL) and the stirred suspension was heated at room temperature for 18 h. The resulting intense orange-red solution was filtered through a short pad of silica using $CHCl_3$:CH_3:4:1. The fractions collected were evaporated and washed with HCl/H_2O and then extracted with CH_2Cl_2. The organic fraction was evaporated to afford complex 11 as a intense orange–yellow solid; yield: 79.5% ^1H NMR (300 MHz, CD_3OD) δ 7.18 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 7.06 (dd, J = 7.7, 1.3 Hz, 2H, ArH), 6.88 – 6.76 (m, 3H, ArH), 6.55 (t, J = 7.5 Hz, 3H, ArH), 3.81 (d, J = 13.5 Hz, 2H, NCH_2), 3.66 (s, 2H, NCH_2), 3.56 (d, J = 13.5 Hz, 2H, NCH_2), 1.50 (s, 9H), 1.28 (s, 18H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ =159.84 (C), 141.40 (C), 140.4 (CH), 128.71 (CH), 128.11 (C), 125.61 (CH), 60.23 (CH) 35.45 (CH), 35.43 (CH), 30.54 (C), 30.40 (C); ESI-MS: m/z=740.2 (M^+CH_3CN), 700.2 ($M\text{-}Cl^-$); elemental analysis (CHN): calculated for $C_{33}H_{42}ClNO_4W$: C 53.85%, H 5.75%, N=1.90%; found: C 61.64%, H 6.93%, N 2.18%.

Synthesis of Tungsten(VI) complex (12)

Complex 11 (200 mg, 0.22 mmol) was dissolved in methanol (10 mL) and triethylamine (62mL, 0.44 mmol) was added. The solution was stirred for three hours at reflux temperature. Solvent was evaporated and solids were solved in a minimal volume of methanol and purified with chromatography (eluent : 1,2-dichloromethane: methanol 4:1). Eluents were evaporated to afford complex **12** as a pale yellow solid; after re-crystalization from methanol to yield, 115 mg (72%). ^1H NMR (250 MHz,$CDCl_3$): δ 7.34 (dd, 1H, *J*=7.8 and 1.4 Hz, ArH), 7.27 (dd, 2H, *J*=7.8 and 1.4 Hz, ArH), 7.03 (dd, 2H, *J*=7.8 and 1.4 Hz, ArH), 6.98 (dd, 3H, *J*=7.4 and 1.8

Hz, ArH), 6.86 (m, 3H, ArH), 4.07 [s, 3H, (CH_3)], 3.82 (d, 2H, *J*=13.3 Hz, NCH_2), 3.58 (s, 2H, NCH_2), 3.47 (d, 2H, *J*=13.3 Hz NCH_2), 1.59 [s, 9H, $C(CH)_3$], 1.43 [s, 18H, $C(CH)_3$]; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ =158.85 (C), 141.57 (C), 140.56 (CH), 128.67 (CH), 128.14 (C), 126.87 (CH), 60.65 (CH), 35.66 (CH), 35.20 (CH), 30.60 (C), 30.31 (C); ESI-MS: m/z=646.2 ($M+H^+$), 614.3 ($M-MeO^-$); elemental analysis (CHN): calculated for $C_{34}H_{45}NO_5Mo$: C 63.45%, H 7.04%, N 2.18%; found: C 63.92%, H 6.96%, N 2.21%.

Synthesis of tris(2-hydroxy-3,5-di-*tert*-butyl-benzyl)amine (16)

In a round-bottomed flask 2,4-*tert*-butylphenol (8.25g, 0.039mol), hexamethylenetetramine (0.47g, 0.082mol) and a 37% aqueous solutions of formaldehyde (1.18 mL, 0.35mol) were stirred for 48 hours at 125°C. $CHCl_3$ (100 mL) were added and the solution was washed with water (3x100 mL). The organic phases were reunited and dried ($MgSO_4$). The solvent was evaporated and the solid was recrystallized from diethyl ether and methanol. Yield 75%(3.82 g).

Synthesis of Tungsten (VI) complex (17)

In a glove-box $WOCl_4$ (136 mg, 0.40 mmol) and the ligand precursor 10 (200 mg, 0.39 mmol) were mixed with methanol (50 mL) and the stirred suspension was heated at room temperature for 18 h. The resulting intense orange-red solution was filtered through a short pad of silica using $CHCl_3$:CH_3:4:1. The fractions collected were evaporated and washed with HCl/H_2O and then extracted with CH_2Cl_2. The organic fraction was evaporated to afford complex 11 as a intense orange–yellow solid; yield: 79.5% ^1H NMR (300 MHz, CD_3OD) δ 7.18 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 7.06 (dd, J = 7.7, 1.3 Hz, 2H, ArH), 6.88 – 6.76 (m, 3H, ArH), 6.55 (t, J = 7.5 Hz, 3H, ArH), 3.81 (d, J = 13.5 Hz, 2H, NCH_2), 3.66 (s, 2H, NCH_2), 3.56 (d, J = 13.5 Hz, 2H, NCH_2), 1.50 (s, 9H), 1.28 (s, 18H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ =159.84 (C), 141.40 (C), 140.4 (CH), 128.71 (CH), 128.11 (C), 125.61 (CH), 60.23 (CH) 35.45 (CH), 35.43 (CH), 30.54 (C), 30.40 (C); ESI-MS: m/z=740.2 (M^+CH_3CN), 700.2 ($M-Cl^-$); elemental analysis (CHN): calculated for $C_{33}H_{42}ClNO_4W$: C 53.85%, H 5.75%, N=1.90%; found: C 61.64%, H 6.93%, N 2.18%.

Synthesis of Molybdenum (VI) complex (20)

MoO_2Cl_2 (200 mg, 1 mmol) and the ligand precursor **16** (503 mg, 1 mmol) were mixed with toluene (50 mL) and the stirred suspension was heated to reflux for 18 h. The resulting intense purple solution was filtered through a short pad of silica and evaporated to afford complex **20** as a violet solid; yield: 500 mg (64%).

^1H NMR (250 MHz, $CDCl_3$): δ =7.40 (dd, 1H, *J*=7.8 and 1.4 Hz, ArH), 7.34 (dd, 2H, *J*=7.8 and 1.8 Hz, ArH), 7.15 (dd, 3H, *J*=9.2 and 1.4 Hz, ArH), 6.98 (m, 3H, ArH), 3.99 (

d, 2H, *J*=11.5, NCH_2), 3.6 (d, 2H, *J*=21.1 Hz, NCH_2), 3.49 (s, 2H, NCH_2), 1.59 (s, 9 H), 1.47 (s, 18H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 159.84 (C), 141.40 (C), 140.4 (CH), 128.71 (CH), 128.11 (C), 125.61 (CH), 60.23 (CH) 35.45 (CH), 35.43 (CH), 30.54 (C), 30.40 (C); ESI-MS: *m/z* = 672.2 ($M + Na^+$), 650.2 ($M + H^+$), 614.3 ($M-Cl^-$); Elemental analysis (CHN): calculated for $C_{33}H_{42}NO_4ClMo$: C 61.16%, H 7.00%, N=2.16%; found: C 61.64%, H 6.93%, N 2.18%.

General Procedure for Monitoring Catalyzed Oxidation Reactions by (Table 3, 4 and 5).

A screw-cap NMR tube was charged with a solution of catalyst (in $CDCl_3$, CD_3OD or DMF-d_6), the internal standard (1,2-dichloroethane, DCE), the oxidant (35% aqueous H_2O_2, 80% cumene hydroperoxide or 80% tert-butyl hydroperoxide) and the substrate were added up to a final volume of 0.6 mL. The NMR tube was maintained at 60°C. Concentrations of reagents and products, were monitored by integration of ^1H NMR resonances in respect of the internal standard DCE (3.78 ppm).

Typical Epoxidation Procedure with 11/TBHP (Table 6).

In a 25-mL screw-cap vial, under nitrogen, complex 11, (0.05 mmol) was dissolved in 10 mL of DCE followed by TBHP (1.0 or 2.0 mmol) and, after 30 min, by the substrate (1.0 mmol). The solution was heated at 60°C and the reaction course was monitored via TLC and GC-MS. After the disappearance of the oxidant (iodometric test), the solvent was removed under vacuum and the reaction mixture was purified directly via radial chromatography over silica gel (gradient: ethyl ether/petroleum ether).

General procedure for monitoring the bromination and chlorination reactions catalyzed by 12 using aqueous H_2O_2 as oxidant (Table 7).

A screw-cap NMR tube was charged with a solution of the complex **1f** in DMF-d_7 (0.0006 mmol), 1,3,5-trimethoxybenzene (0.012 mmol), TBABr or TBACl (0.06 mmol) and DCE as internal standard. An appropriate volume of 35% aqueous H_2O_2 and 70% aqueous $HClO_4$ were added, as reported in Table 7, to a final volume of 0.6 mL. reactions were performed at rt and monitored via ^1H-NMR (concentrations of TMB and halogenated product were detected by integration of the aromatic CH: **5** (6.11 ppm), BrTMB **18a** (6.38 ppm) and ClTMb **18b** (6.40 ppm). Final yields were determined by ^1H-NMR after complete H_2O_2 consumption (iodometric test) in respect of the internal standard DCE (3.78 ppm). Mono halogenation of the substrate has been confirmed via ^1H-NMR and GC-MS analysis that match those already reported in the literature.[26]

Synthesis of 1-chloro-2,4,6-trimethoxybenzene chloride (18b)

A round bottomed flask was charged with 1,3,5-trimethoxy benzene (1 g, 5,94 mmol), TBA Cl^- (4,1 g, 14.86 mmol), 70% $HClO_4$ (851 μL, 5.94 mmol), complex **11** (53.6 mg, 1% mmol) and acetonitrile (60 mL). H_2O_2 was added (520 μL, 5.94 mmol) and the mixture was stirred at room temperature for 24 hours. The reaction mixture was washed with toluene and water, dried over $MgSO_4$ and solvents were evaporated. This methodology afforded 836 mg (70%)of 1-chloro-2,4,6-trimethoxybenzene chloride. ^1H NMR (200 MHz, $CDCl_3$) δ 6.19 (s, 2H, ArH), 3.88 (s, 6H, OCH_3), 3.81 (s, 6H, OCH_3).

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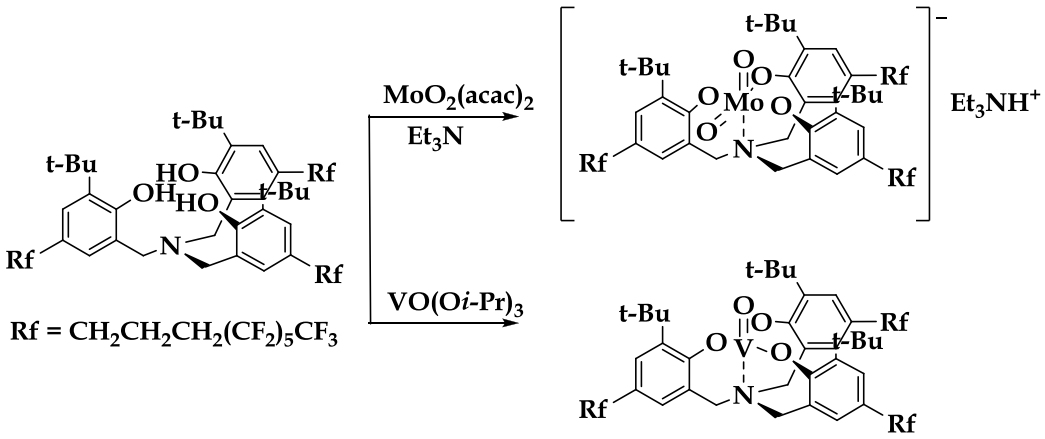
Chapter 4

Synthesis of new fluorinated Mo(VI) and V(V) amino triphenolate complexes, for the production of "Catalytically active" membranes



Tetradentate amino triphenolate (TPA) ligands are well-known to provide highly stable Mo(VI) and V(V) homogeneous complexes. In the presence of alkyl hydroperoxides and hydrogen peroxide, such species are able to catalyze epoxidations, sulfoxidations and haloperoxidations, with high chemical yields and good selectivities. These catalysts were also shown to be robust under the reaction conditions, i.e. in the presence of large quantities of peroxides and water, as well as in acidic conditions. These results inspired the synthesis of new fluorinated analogue complexes suitable to be either embedded in polymeric fluorous membranes or dissolved in fluorous solvents.

4.1 Introduction

A key target for contemporary chemistry is eco sustainability. For this reason, *recovery* and *recycle* are growing topics for both academics and industrial chemists. Catalyzed reactions are fundamental for developing new technologies since they produce a lower amount of waste compared to stoichiometric reactions. Hence, they are often more selective, allowing to save raw material and energy. An efficient catalytic system should guarantee the complete removal of the catalyst from the reaction mixture at the end of the reaction, in order to avoid contamination of the products with heavy metals.[1] One of the possible ways to achieve this goal is the employment of heterogeneous catalysts which are easily recoverable at the end of the reaction and, eventually, reusable in further cycles thus reducing the costs of the process. Great efforts in catalysis research have been devoted in recent years to the introduction and application of effective and safe heterogeneous catalysts. A useful strategy for heterogeneizing a homogenous catalyst has been the anchoring of the catalyst itself to insoluble organic or inorganic supports.[2] Such catalysts are usually as active as their homogeneous counterparts, while having distinguished characteristics of being (i) easily separable from the reaction media, (ii) recyclable, (iii) more selective and stable (sometimes), (iv) easier to handle, (v) cheaper.

As mentioned above, catalyst embedding in a target material can be obtained by the preparation of hybrid polymeric films. Shaped as a membrane, polymers can offer specific advantages to catalytic processes, as they are able to improve them by combining reaction and separation. [3] Polymer-based catalytic membrane applications can be divided in two major classes. In "catalytically active" membranes, the catalyst is incorporated in the polymer or deposited on it. They can be subdivided in membrane encapsulated catalysts and heterogeneous or homogeneous catalysts embedded in a polymeric matrix. A well-chosen polymeric environment can regulate beneficially the selective sorption of reagents and products.[4,5] The catalyst activity should remain guaranteed over the whole membrane preparation process. Moreover, a stable suspension (in the case of a heterogeneous catalyst) or good dissolution (in the case of a soluble catalyst) should exist. Additives can be co-incorporated to promote reaction yields. When embedding a homogeneous catalyst in a polymeric membrane, catalyst heterogeneization is simultaneously realized, even if catalyst leaching still remains a challenge.[3]

The second class consists of "membrane-assisted processes", also referred to as "inert catalytic membrane reactors" (CMRs) where "catalytically passive" membranes are used, since the membrane merely retains the catalyst in the reactor volume. The membrane thus simply serves as a barrier to drain off reactants and/or to supply products. An appropriate selection of polymer materials or the

implementation of small modifications (such as cross-linking) allows the use of polymeric membranes in many chemical reactions (Figure 1).[3]

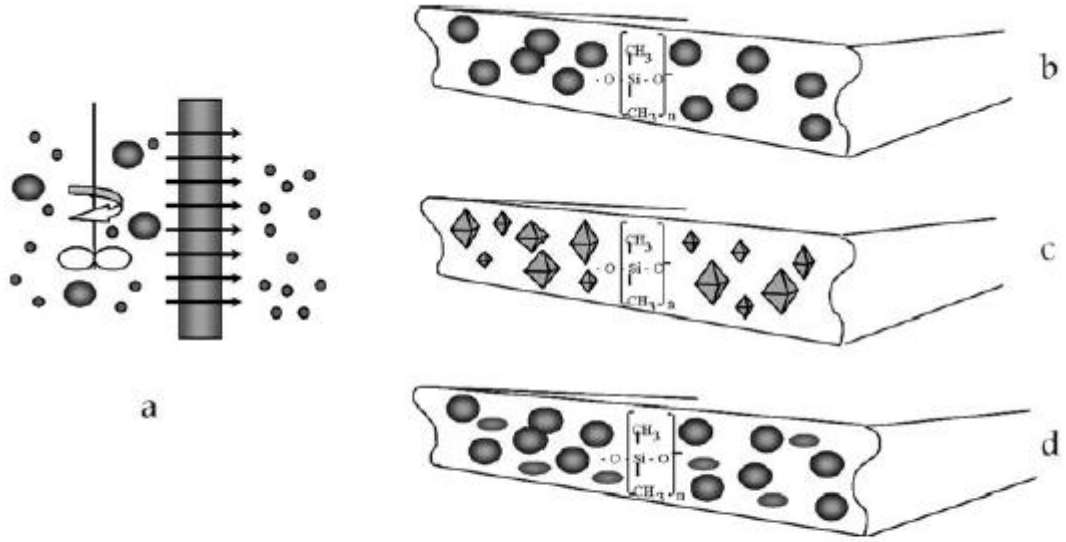


Figure 1. Catalytically passive (**a**) and catalytically active membranes: homogeneous (**b**), heterogeneous (**c**) and homogeneous with additive (shown as ellipses) (**d**).

The design of new catalytic membranes can be tuned by a proper choice of both the polymeric material and the catalyst precursor in order to guarantee structure integrity, good dispersion, hydrothermal and chemical stability and active site accessibility. Also hydrophobic/hydrophilic surface properties of the membrane can be modified in order to optimize its affinity towards target reagents. On the other hand, catalytic membranes can achieve also selective transport properties, thus allowing their reuse in phase transfer catalysis and selective supply/removal of solvents, reagents, products and by-products.

Membrane technology in oxidation reactions has received increasing attention during recent two decades. Most investigations on catalytic membranes have focused on the use of inorganic membranes because of their excellent thermal stability at high reaction temperatures. Although applications of this type of membranes concerned small molecules or decomposition reactions at high temperature, polymeric membranes can be applied in the case of low-temperature reactions with versatile applicability.[6] Most polymeric membranes can be easily manufactured in different shapes (*e.g.* hollow, spiral wound, flat sheet); they are elastic, show satisfactory diffusion and sorption coefficients and can be produced with incorporated catalysts as nanosized dispersed metallic clusters, zeolites, activated carbon or metallic complexes. The ability to produce a well-defined porous matrix to be used as a support for a wide variety of catalytic materials gives an interesting contribute to the production of single-site catalysts in which every active site closely resemble to the

others.[7] The membrane can select the passage of molecules of reactants across its structure, control the feeding of reactant and improve the contact between reactants and catalyst. Polymeric membranes show different affinities for different chemicals, therefore they can drive a reaction modulating the adsorption and diffusion of some components of the reaction mixture. Catalytic polymeric membranes can be prepared controlling the mechanical, chemical and thermal stabilities to yield the desired permeability and affinity for reagents and products.[8] Indeed a good porous membrane must have high permeability and excellent chemical resistance to the feed stream, as well as a thin separating layer thickness.

All the advantages of polymeric *vs.* inorganic membranes can be exploited in various catalytic applications in a wide range of temperature. For example, the one-step production of phenol in mild condition by direct hydroxylation of benzene is a recent subject of studies by several groups in the world.[9] Also inorganic membranes, such as Pd membrane reactor, at a reaction temperature of 433 K,[10] have been tested. A recent work by Molinari *et al.* reported the developing of this process employing a membrane reactor working in milder conditions.[11] The oxidation reaction has low selectivity, since the phenol is more reactive towards oxidation than benzene, and substantial formation of by-products (such as biphenyl) and further oxidation compounds was found. The control of contact time of phenol with the catalyst can avoid by-products formation. An innovation, with respect to the previous tested membrane reactor configuration, is the control of reactivity by inclusion of the catalyst in polymeric membranes and permeating the oxidant solution, containing the substrate, at different permeate flow rates. In this work, the polymer used as membrane material is polyvinylidene fluoride (PVDF) because of its excellent chemical resistance, particularly the oxidant resistance. The catalytic PVDF asymmetric membranes(Figure 2) were prepared by using the phase inversion method induced by non-solvent, filled with a CuO nanopowder catalyst. Phenol productivity of 72.5 $g_{phenol}\ g_{cat}^{-1}\ h^{-1}$ and a phenol yield of 2.3% were obtained in a single pass using a contact time with the catalyst of 19.4 s at 35°C.

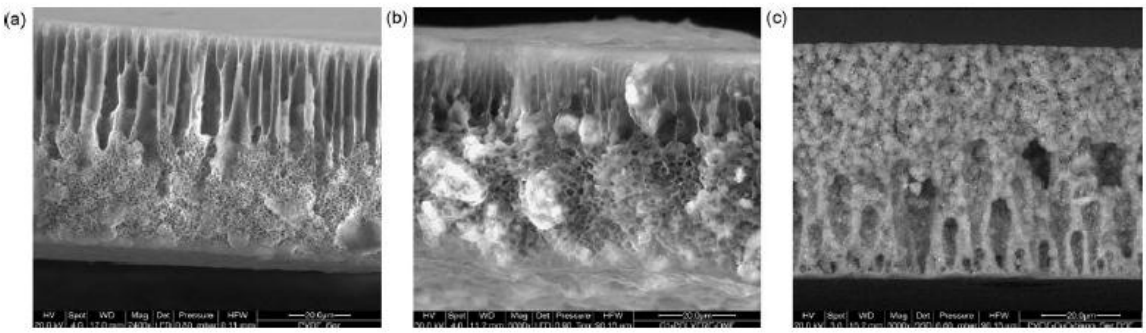
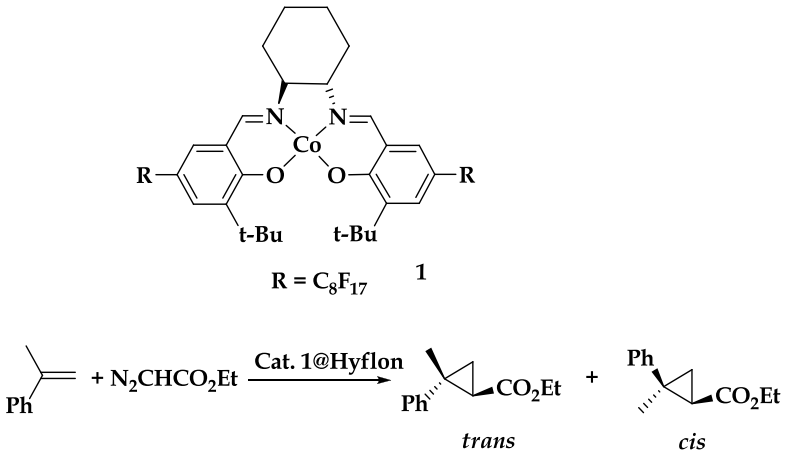


Figure 2. Cross section image of PVDF membranes with DMF with copper oxide nanopowder catalyst showing the so-called asymmetric structure.

A specific problem that can occur in liquid-phase reactions with homogeneous catalysts occluded in membranes is the leaching of the complex out of the polymer into the liquid reaction phase. While the absence of strong interaction forces between the catalyst and the polymer is one of the practical advantages of this kind of heterogeneization, this renders at the same time the system more susceptible of leaching. The catalyst/polymer interaction is the result of van der Waals forces and steric constraints of the polymer chains on the complex. Leaching can be minimized by placing bulky groups on the catalyst or by increasing its affinity for the polymer. As an example, Co(II)–salen complexes, a class of catalysts that has found a remarkable success in the cyclopropanation of olefins by diazoacetates, have been embedded into polymeric membranes, affording new catalytic membranes[12] (Scheme 1).



Scheme 1. Perfluorinated Co(II) salen complex was embedded in a Hyflon membrane and used as heterogeneous catalyst in cyclopropanation reactions .

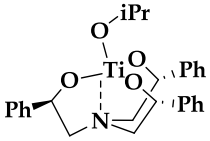
The Co(II)–salen complex was opportunely functionalized with perfluorinated substituents, that should guarantee a higher affinity for the Hyflon membrane. Indeed, when the catalytic membrane was kept under vacuum at 90°C to remove the solvent (Galden HT) used for its preparation, the amount of **1** leached was below the detectability limit. The catalytic activity in cyclopropanation reactions was then tested, and the results reported in Table 1. The heterogeneous catalyst could be recovered and reused for following cycles. However, its catalytic activity is reduced after every cycle and the time needed for the quantitative conversion of the starting ethyl diazoacetate (EDA) almost doubled (Table 1).

Table 1. Cyclopropanation of ethyl diazoacetate catalysed by a perfluorinated Co(II) salen embedded in a Hyflon membrane.

Run	Time (h)	Conversion	Yield %	*cis*/*trans*	Catalyst leached (mol/L)
1st run	48	>99	99	2:1	$<10^{-6}$
2nd run	96	80	75	2:1	$<10^{-6}$
3rd run	96	50	25	1:1	$<10^{-6}$

Moreover, a quite fast degradation of the catalytic membrane, probably due to partial oxidation of the cobalt metal ions, was observed and, already at the third recycle, the membrane was much less active and selective. This can be explained with a catalyst deactivation, but any attempt to recover it from the membrane after its use, failed and mixtures of cobalt difficult to characterize were obtained. While the activity of the catalyst seems to be the major problem, leaching is not, showing that there is a good interaction between the polymeric material and the organic ligand.

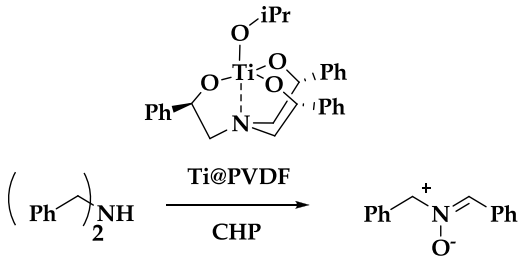
Licini *et al.* recently reported a heterogeneous oxidation catalysts, performing in presence of an alkyl hydroperoxide, i.e. cumyl hydroperoxide (CHP), constituted by a Ti(IV) trialkanolamine complex (Scheme 2) embedded within a polyvinylidene fluoride (PVDF) membrane.



Scheme 2 Ti(IV) trialkanolamine complex embed in PVDF membrane.

The performance of the Ti@PVDF catalytic membrane towards the oxidation of dibenzilamine to nitrone was evaluated on the basis of system recycling.[13] A series of experiments were performed to examine this membrane's activity along five oxidation runs. After each experiment, the membrane was removed from the reaction vessel, washed in chloroform to remove adsorbed reagent or products, and recycled. The results are reported in Table 2.

Table 2. Oxidation of dibenzylamine with cumylhydroperoxide (CHP), catalyzed by Ti@PVDF. Catalyst recycling: $[substrate]_0$ = 0.1 M; $[CHP]_0$ = 0.4 M, [catalyst] = 0.01 M; *T* = 60°C, $CDCl_3$, molecular sieves = 250 mg/mol in run 1, 500 mg/mol in run 2-5.[a]



run	$t_{1/2}$ (min)	Nitrone (%)
1st run	39	92
2nd run	10	90
3rd run	14	90
4th run	14	90
5th run	23	90

[a] In the recycling, the presence of twice amount of molecular sieves proved to be beneficial in decreasing the formation of benzaldehyde.

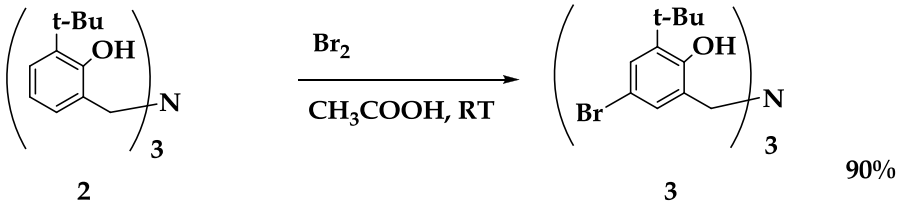
It is noteworthy that the catalytic activity of the Ti@PVDF membrane was maintained for all five runs, affording comparable yields in nitrone (90%). Interestingly, reaction rates were higher in the recycling experiments than in the initial experiment. This increased reactivity could originate from modifications of the polymeric membrane that make available a larger quantity of the catalytic sites or enhance the Lewis acidity of the metal complex.

In order to extend this heterogeneization protocol also to amino triphenolate complexes, attempts to immobilize vanadium(V) amino triphenolate complexes in these membranes failed, as catalyst leaching was extensive. Therefore, a modification of the catalysts structure is required in order to favour their embedding in the solid support. Based on the literature, the functionalization of TPA complexes with fluorinated ponytails should enhance the affinity for the membrane fluorous phase. The optimized synthesis of fluorinated amino triphenolate ligands, their complexation with molybdenum(VI) and vanadium(V) will be described in the following paragraphs.

4.2 Synthesis of *para* substituted amino trisphenolate ligands: introducing a versatile anchoring site

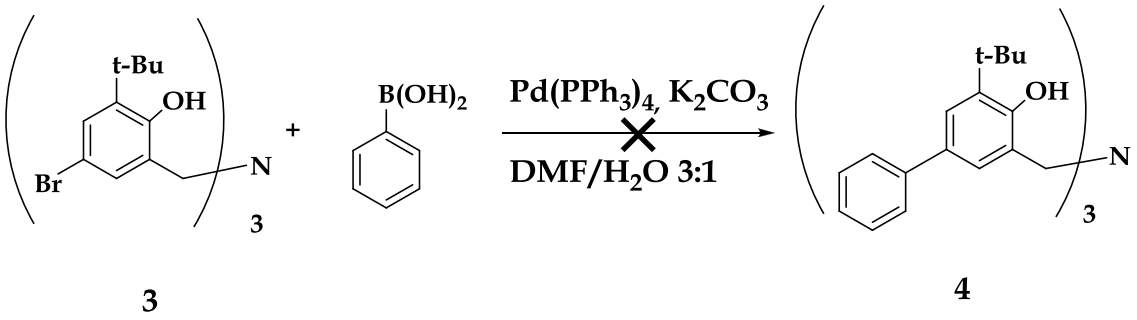
The introduction of an efficient anchoring site into amino trisphenolate ligands is one of the aim of this thesis work. The choice of the appropriate group could lead to a large number of possible ways to recycle these metal complexes, using the same ligand, with the advantage of keeping the same environment around the metal, thus preserving the features of the catalyst.

The first attempt focussed on the introduction of fluorinated ponytails on the amino triphenolate ligand using as key step palladium catalysed coupling chemistry. This strategy needs the introduction of a bromide atom in the aromatic ring which should act as leaving group for further Pd-catalyzed coupling reactions. Thus, ligand **3**, bearing a bromide in *para* position to the phenol moiety, was firstly synthesized (Scheme 2). The problem to overcome in this bromination step is the high reactivity of the benzylic hydrogens towards molecular bromine. In order to avoid this reaction, ligand **2** was dissolved in glacial acetic acid to protonate the tertiary amine thus making the benzylic protons less reactives. The addition of three equivalents of molecular bromine lead to the formation of the tri-substituted product **3**. The product precipitate from the solution as a yellow solid in good yield, 90% (Scheme 3).



Scheme 3. Synthesis of brominated ligand **3**.

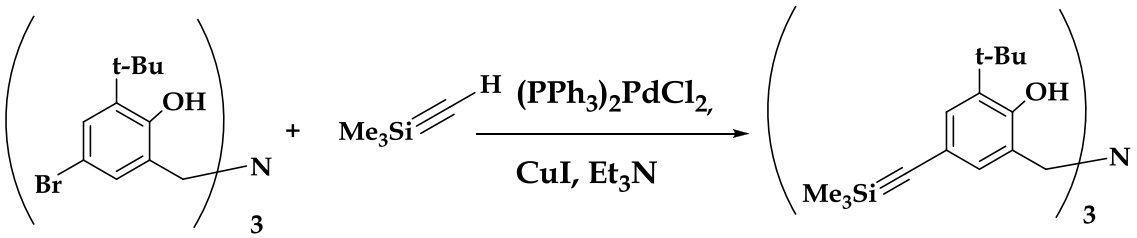
The bromine offers the possibility to exploit the palladium chemistry and, one of the most known and versatile reactions for the formation of a new C—C bond is the Suzuki coupling.[14] This reaction takes place in the presence of both a palladium catalyst and a base, to form a new C—C bond between a carbon atom next to a bromide atom and the one of an organo-boronic acid. The advantage of this couplings is that a wide variety fo functionalised aromatic rings can be linked. The feasibility of this strategy was tested with phenyl boronic acid as a model substrate (Scheme 4). However, even if various reaction conditions have been tested, the coupling product was not found in the reaction mixture.



3 4

Scheme 4. Pd-catalyzed Suzuki coupling between ligand **3** and phenylboronic acid.

Thus, a second synthetic strategy, involving the use of a Sonogashira coupling reaction,[15] was tested. This reaction consists in the formation of a new carbon-carbon bond between a terminal alkyne and an alkyl or an aryl halide; it is catalyzed by a palladium complex, in the presence of a copper co-catalyst and an aminic base.[16] The insertion of an alkyne functionalization will allow the extension to the 'click chemistry' for the direct linking with properly functionalized polymer with an azide group We tested this reaction with ligand **3** in presence of trimethylsilylacetylene (Scheme 5).

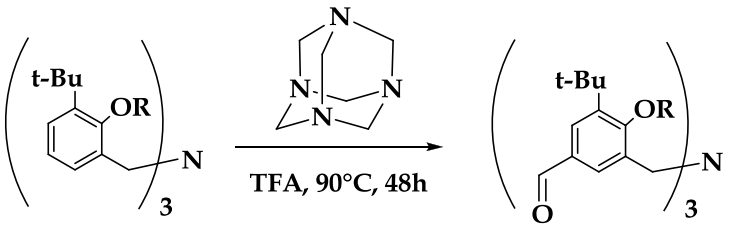


3 5

Scheme 5. Pd-catalyzed Sonogashira coupling between ligand **3** and trimethylsilylacetylene.

While the formation of the tri-alkyne substituted ligand **5** indeed take place, a mixture of mono-, bi- and tri- alkyne substituted compounds was obtained and detected with ESI-MS spectrometry. Optimization of the reaction conditions, using of microwave heating and consequently shorter reaction times allowed to obtain the mono-substituted ligand as the major product, although it was not possible to isolate with chromatographic techniques.

An alternative route to the introduction of a suitable anchoring site involves the formylation in *para* position to the phenol moiety. A modified Duff reaction, using hexamine (hexamethylenetetramine) as the formylating agent in acidic conditions (trifluoroacetic acid, TFA, as the solvent and proton source) was used (Scheme 6).

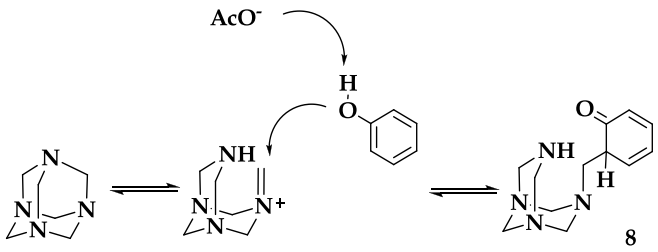


2 R = H
6 R = Bn

7 R = H (90%)
8 R = Bn (none)

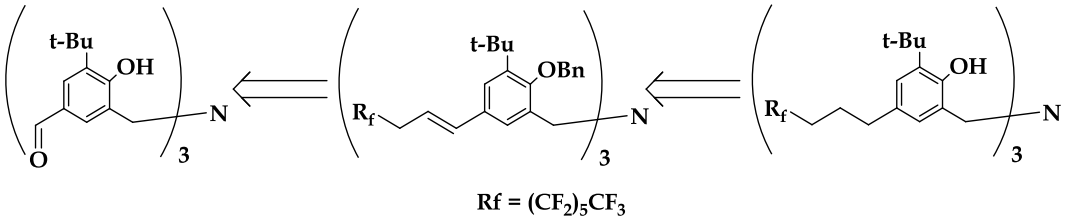
Scheme 6. Formylation on ligand **2**. And protected 6

The product is easily obtained as a white precipitate after the hydrolysis, in presence of 3 N HCl, of the intermediate iminium salt formed.[17] This reaction was carried out on both the ligand with free hydroxyl (**2)** or benzylated (**6)**. The desired formylated product was obtained only using **2**, probably because the protected ligand **6** is not activated for the reaction as shown in the reaction mechanism in Scheme 7.



Scheme 7. Formation of intermediate in the Duff reaction.

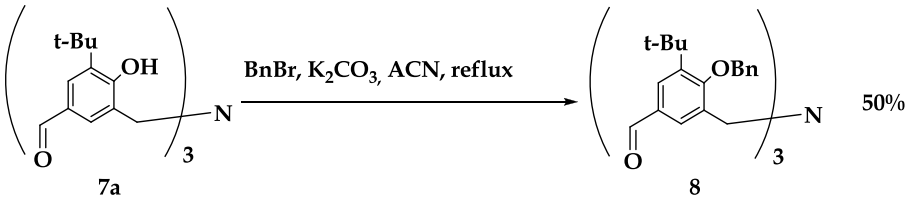
At this point, the presence of an aldehyde in para position opens the possibility to functionalised the ligand using different reactivities. As a proof of concept, it was decided to introduce a perfluorinated alkyl chain into the amino triphenolate ligand using the Wittig chemistry. In Scheme 8, the retrosynthetic procedure to yield these fluorinated ligands (R_f -TPA) is reported. Three steps are involved in the synthesis: the protection of the phenol moiety with a benzyl group, a Wittig reaction and the following reduction of the C—C double bond and the deprotection of the benzyl group. The two latter step can be carried out simultaneously.



Rf = $(CF_2)_5CF_3$

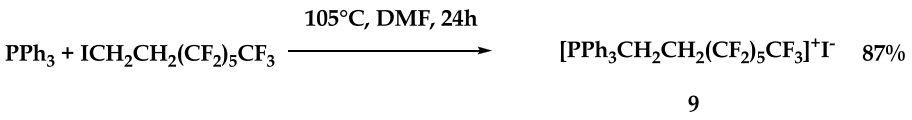
Scheme 8. Retrosynthetic scheme for the synthesis of perfluorinated TPA ligand.

Attempts to perform the Wittig reaction directly on the un–protected ligand gave very low conversion (<5%), so the formylated ligand **7a** was firstly benzylated. The formylated ligand **7a** was directly transformed into the corresponding tri-benzyl alcohol **8** (50% yield), after the reaction with benzyl bromide in presence of K_2CO_3 (Scheme 9).



Scheme 9. Benzylation of ligand **7a** in order to protect the OH functions.

A Wittig reaction was then performed in order to link the perfluorinated alkyl chain. 1,1,1,2,2,3,3,4,4,5,5,6,6,tridecafluoro-8-iodoctane was used to prepare the corresponding phosphonium salt, using reaction conditions reported by Gladysz (Scheme 10)**.** [18] Forcing conditions were required owing to the attenuated SN_2 reactivity of the iodides.[19]



Scheme 10. Synthesis of the phosphonium salt of 1,1,1,2,2,3,3,4,4,5,5,6,6,tridecafluoro-8-iodoctane.

The formation of phosphonium salt **9** was confirmed by ESI-MS spectrometry (Figure **3**) as the only reaction product, and it was obtained in high purity and yield (87%) as a white solid with no need of further purifications.

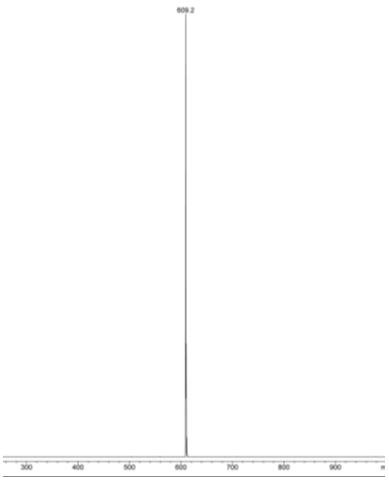
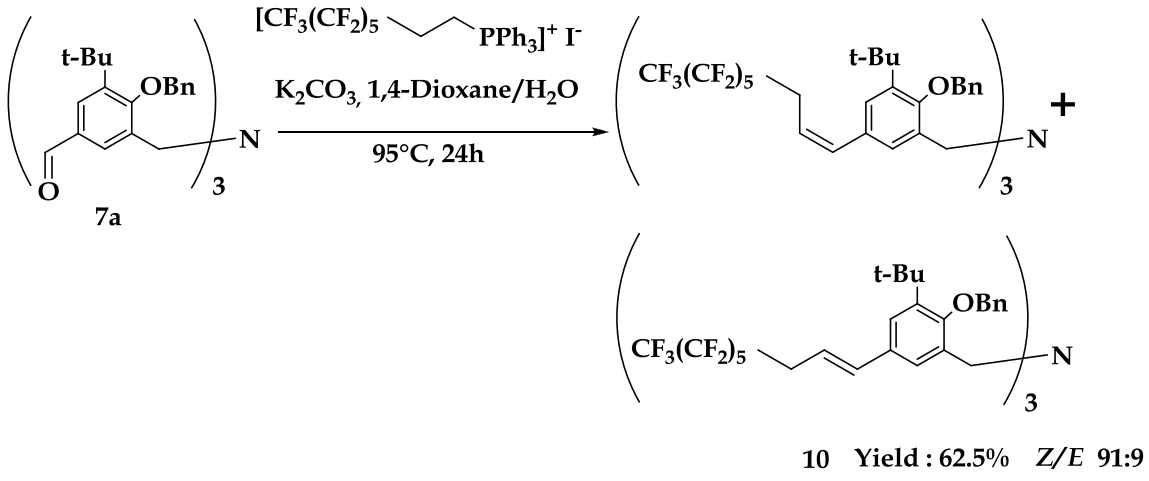


Figure 3. ESI-MS spectrum of **9**.

In the following step, ligand **7a**, the phosphonium ylide **9** and K_2CO_3 were stirred at 95°C in a 1,4-dioxane/water (10:0.3) solution for 24 hours.As expected, the Wittig reaction gave the corresponding olefin as a *Z/E* mixture with a 91:9 ratio (Scheme 11). The reaction was monitored following the ^{1}H-NMR aldehyde proton signal. After complete disappereand volatiles were removed and product **10** was obtained as a colourless oil (62%).



Scheme 11. Wittig reaction on ligand **7a**.

Classical stereo-selection shown by Wittig reactions was found with the predominant formation of the *Z* isomer (Z/E 91:9). Both the isomers are well recognisable by ^{1}H NMR (Figure 4).

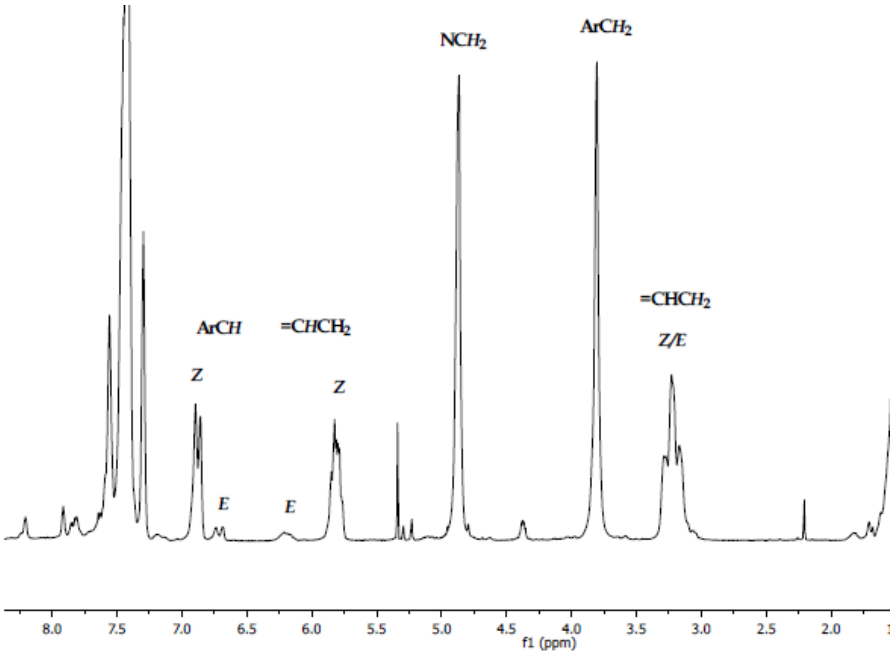
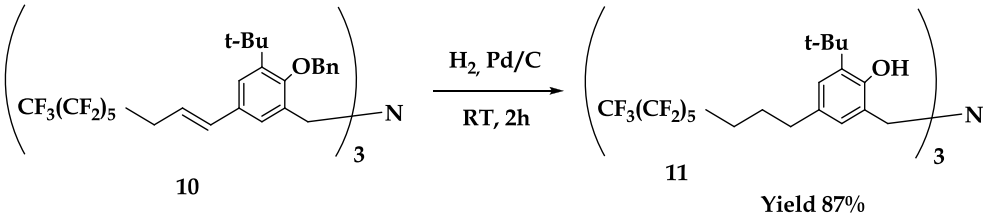


Figure 4. ^{1}H NMR of the product **10** as a *Z/E* mixture.

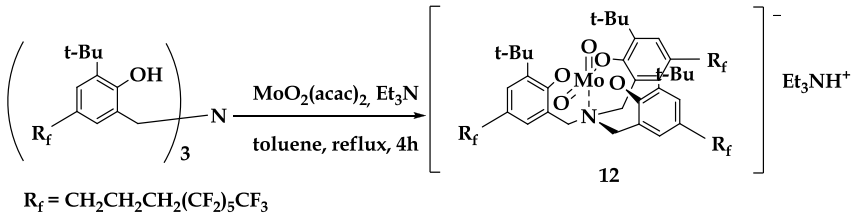
The final skeleton is at this point present in the molecule, however the double bond need to be reduced in order to avoid oxidation or other undesired reactions during catalysis. This offers the possibility to remove at the same time via hydrogenolysis the bezyl protection. The reaction was carried out under H_2-atmosphere with Pd/carbon catalyst in ethyl acetate, and the progression was followed *via* ^{1}H NMR. After 4 hours, the reaction mixture was filtered through celite, the solvent evaporated and the product obtained as an orange oil in 87% yield, with no further purification needed. Both the saturation of the alkyl chain and the removal of the protecting group took place completely (Scheme 12), thus yielding the desired perfluorinated ligand (**R_f–TPA**, **11**).



Scheme 12. Hydrogenolysis step yielding the perfluorinated ligand **11**.

4.3 Synthesis of molybdenum(VI) and vanadium(V) complexes with R_f -TPA

Molybdenum and vanadium were chosen for the preparation of fluorinated complexes, since amino triphenolate complexes of Mo(VI) and V(V) gave the best results as catalyst in oxygen transfer reactions, and their coordination behaviour is well known in our research group.[20a,b] First attempt to synthesize the Mo/R_f -TPA complex using the standard conditions with $MoO_2Cl_2(DMF)_2$ lead to a mixture of the molybdenum dioxo (MoO_2)- and oxo-chloride (MoOCl)- R_f -TPA complexes, that were difficult to isolate with chromatography. Thus, the complexation reaction was carried out with a different precursor, $MoO_2(acac)_2$, which is reported to give Mo-dioxo complexes as the only product.[21] The metal precursor was prepared according to literature[22] reacting the ammonium molybdate salt $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ together with acetyl acetone and 10% nitric acid in water. The resulting $MoO_2(acac)_2$ precipitates as a yellow solid and is obtained after filtration.With this new procedure Mo-dioxo R_f -TPA complex **12** was obtained as the only product (an intense red solid), after filtration through a short pad of silica. ESI-MS experiment show the presence of a complex in negative mode with a mass peak of 799(M+1) giving us the evidence af the anionic nature of **12**which carries a triethylammonium molecule as counter cation as shown also by the ^{1}H-NMR (Scheme 13).



Scheme 13. Synthesis of the Mo(VI)O_2-R_f-TPA complex **12**.

The anionic nature of **12** was confirmed *via* ESI-MS operating in negative mode (registered *m/z* = 1710 = $[M]^-$), while ^{1}H NMR analysis revealed that the metal coodination sphere is the same of the analogous non-fluorinated complex (Figure 5).

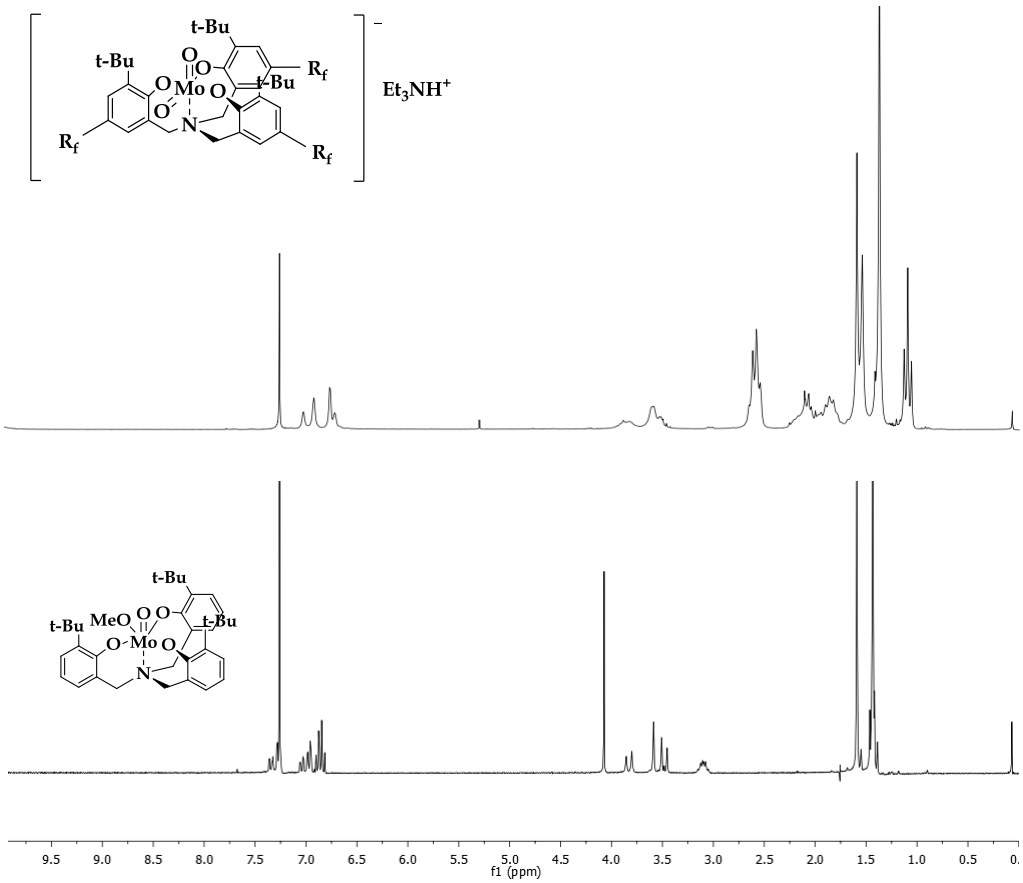
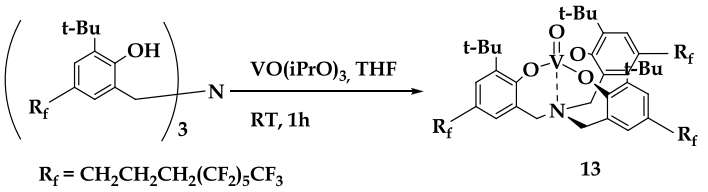


Figure 5. ^{1}H NMR spectra of Mo(VI)O_2-R_f–TPA and of the non-fluorinated analogous Mo(VI)O_2-TPA.

Vanadium(V)-R_f-TPA complex was prepared using the standard procedure previously reported by Licini *et al.* (Scheme 13).[23] The reaction of the fluorinated ligand **11** with VO(O*i*-Pr)$_3$ in dry tetrahydrofuran in glove box yielded complex **13** as deep-red crystalline solid in high yield (88%). The reaction mixture was stirred at room temperature for 1 hour and complex was obtained after solvent removal with vacuum pump.



Scheme 14. Synthesis of the V(V)O_2-R_f-TPA complex **13**.

Complex **14** is air and moisture stable and can be easily handled and stored in open air. Its identity was confirmed by ^{1}H, ^{13}C and ^{51}V NMR spectroscopies. In particular, in Figure 6 the ^{51}V NMR spectrum of **13** is reported; it shows a single peak at 370,78 ppm consistent with previously reported spectra of analogous vanadium compounds.

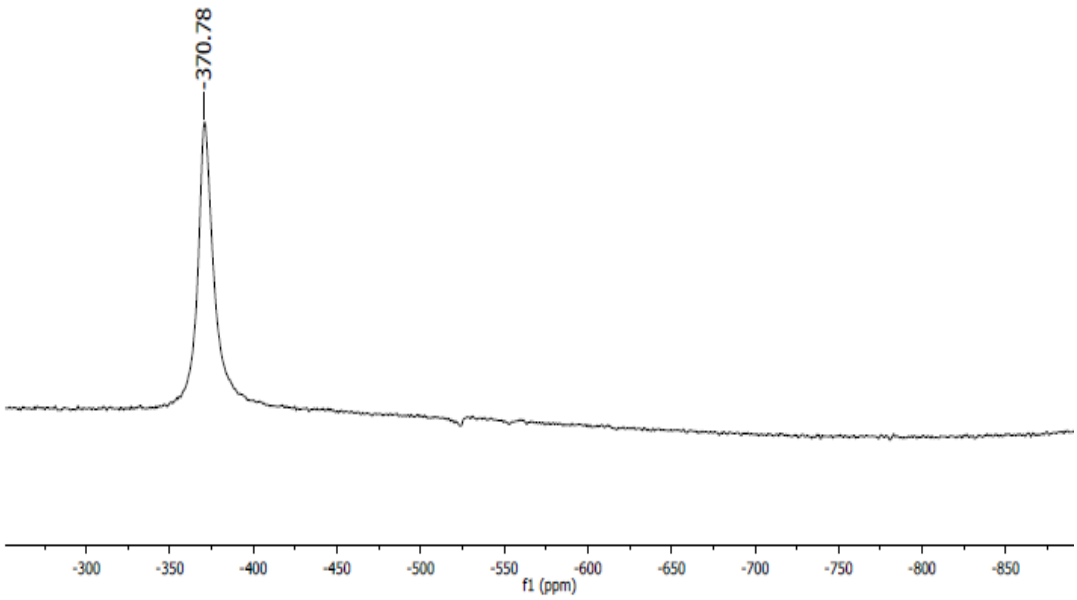


Figure 6. ^{51}V NMR spectrum of V(V)O_2-R_f–TPA complex **13**.

4.4 Conclusions

In order to obtain heterogeneization of TPA based catalysts functionalization with fluorous alky chains has been achieved.

Two different routes have been studied: Pd-coupling and formylation. The first route was pursued brominating the TPA with in acidic conditions, and using this

function for the Pd catalysed C—C couplings. Suzuki and Sonogashira couplings . This have been object of our studied and, while the Suzuki did not furnish any product, the second methodology lead to desired compound in low yields. It was not possible to set the reaction conditions in order to obtain the desired ligand pure and in high yileds. However, this coupling strategy remains interesting for the development of the click chemistry around the TPA.

Very interesting results have been obtained using formylation reaction. The formyl group opens the way to a number of further reactions that can be exploited to change the ligand features. As a first attempt, aldehyde functionalised TPA was subjected to Wittig reaction in presence of a fluorinated phosphonium ylide to obtain perfluorinated TPA ligand. Simultaneous deprotection of the benzyl protecting group and reduction of the C=C double bond permitted to obtain the desired ligand in a three-step methodology. Subsequently complexation reactions lead to Mo(VI) and V(V) complexes, that have been characterized as previously studied complexes.

This project will be continued in order to study the embedding of the perfluorinated complexes here reported and their behaviour in heterogeneous catalysis.

4.4 Experimental

General remarks

All chemicals and dry solvent have been purchased from Aldrich or Fluka and used as provided, without further purifications; 70% aqueous $HClO_4$ was purchased from Erba. Triphenolamines were synthesized as previously reported.[24]
Flash chromatographies have been performed with Macherey-Nagel silica gel 60 (0.04-0.063 mm, 230-400 mesh). The NMR spectra have been recorded on a Bruker AC 250 (^{1}H: 250.13 MHz; ^{13}C: 62.9 MHz), a Bruker AV 300 (^{1}H: 300.13 MHz; ^{13}C: 75.5 MHz) spectrometer and a Bruker AV 200 (^{1}H: 300.13 MHz; ^{13}C: 75.5 MHz) spectrometer. Chemical shift (δ) have been reported in parts per million (ppm) relative to the residual undeuterated solvent as an internal reference ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR; CD_3OD: 3.31 ppm for ^{1}H NMR and 49.05 ppm for ^{13}C NMR). The following abbreviations have been used to explain the multiplicities: s = singlet, d = doublet, t = triplet, dd = double doublet, m = multiplet, br = broad. ^{13}C NMR spectra have been recorded with complete proton decoupling.

^{51}V NMR spectra have been recorded at 301K with 10000 scans at 78.28 MHz with a broadband probe, using $VO(O_2)$ picolinate ($5\ 10^{-3}$ M, water, pH = 1) as external standard. APCI-MS spectra have been obtained on a LC/MS Agilent series 1100 spectrometer in positive mode, by direct flow injection using methanol as mobile phase, with ESI-ion trap mass detector.

All oxygen or moisture sensitive compounds have been handled under controlled atmosphere (nitrogen) in a glovebox Mbraun MB 200MOD, equipped with a MB 150 G-I recycling system.

Synthesis of tris-(2-hydroxy-3-*tert*-butyl-5-bromo-benzyl)amine (3)

Ligand **2** (2 g, 3.97 mmol) was dissolved in glacial acetic acid (80 mL), then bromine (1.75 mL, 39.7 mmol) was added carefully and the suspension formed was stirred for 12 hours. The reaction was stopped by pouring the suspension into cold water and a precipitated was suddenly formed. The solid was washed with a K_2CO_3 solution and hexane. The organic phase was dried with $MgSO_4$, filtered and evaporated. The solid **3** was weighted for a final yield of 65% (1.9 g, 2.58 mmol). ^1H NMR (250 MHz, $CDCl_3$): δ 7.47 (d, 3H, *J* = 2.2 Hz, ArH), 7.17 (d, 3H, *J* = 2.1 Hz, ArH), 4.18 (s, 6H, CH_2N), 1.47 (s, 27H, CH_3) ppm. ESI-MS: *m/z* = 741 ($M+H^+$).

Synthesis of tris-(2-hydroxy-3-*tert*-butyl-5-formyl-benzyl)amine(7)

In a Schlenk flask, a mixture of 503 mg (1 mmol) of tris-(2-hydroxy-3-*tert*-butyl-benzyl)amine ligand, 140.2 mg (6 mmol) of hexamethylenetetramine and 30 mL of trifluoroacetic acid was stirred for 12 hours at 90°C. The solvent was distilled off to obtain an orange oil. 60 mL of 3 N HCl were then added to the oil and the resulting mixture was stirred at 80°C for three hours. The white precipitate was filtered off, washed with water, recrystallized from ethanol, and dried. The final product **7** was obtained in 95% yield (552 mg). ^1H NMR (250 MHz,$CDCl_3$): δ 9.81 (s, 1H, C*H*O), 7.81 (d, 1H, *J* = 2.0 Hz, *H*Ar), 7.59 (d, 1H, *J* = 1.9 Hz, *H*Ar), 4.04 (s, 1H, CH_2N), 1.41 (s, 1H, CH_3) ppm. ^{13}C NMR (200 MHz, $CDCl_3$) δ 191.00 (CHO), 159.66 (C), 138.76 (C), 131.50 (C), 131.18 (C), 129.54 (CH), 121.49(CH), 56.65 (CH_2), 34.72 (C), 29.81 (CH_3) ppm. ESI-MS: *m/z* = 588 ($M+H^+$). Elemental analysis (CHN): calculated for $C_{36}H_{45}NO_6$: C 73.57%, H 7.72%, N 2.38%; found: C 63.92%, H 6.96%, N 2.21%.

Synthesis of tris-(2-hydroxybenzyl-3-*tert*-butyl-5-formyl-benzyl)amine (8)

In a three-neck round-bottomed flask, tris-(2-hydroxy-3-*tert*-butyl-5-formyl-benzyl)amine (3 g, 5.11 mmol) are stirred in presence of benzyl bromide (1.84 g, 18.4 mmol) and 12 equivalents of K_2CO_3 at reflux temperature for 15 hours. The product is filtered through celite, dissolved with EtOAc (100 mL) and washed with 1 M HCl

(80 mL). The organic phase is then dried with $MgSO_4$ and filtered. The solvent is evaporated at reduced pressure, and the product **8** obtained as a white solid (1.3 g, 50% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.88 (s, 1H, CHO), 7.98 (d, 1H, *J* = 1.8 Hz, ArH), 7.79 (d, 1H, *J* = 1.8 Hz, ArH), 7.30 (broad signal, 5H, HAr), 4.77 (s, 2H, CH_2Bn), 3.70 (s, 2H, CH_2N), 1.38 (s, 9H, CH_3) ppm. ^{13}C NMR (200 MHz, DMSO) δ 191.74 (CHO), 162.53 (C), 144.51 (C), 136.67 (C), 133.25 (C), 132.29 (C), 131.92 (C), 128.78 (C), 128.11 (C), 126.86 (C), 76.18(CH_2), 52.53 (CH_2), 35.56 (C), 30.96 (CH_3) ppm. ESI-MS: *m/z* = 588 ($M+H^+$). Elemental analysis (CHN): calculated for $C_{57}H_{63}NO_6$: C 79.78%, H 7.40%, N 1.63%; found: C 63.92%, H 6.96%, N 2.21%.

Synthesis of 1,1,1,2,2,3,3,4,4,5,5,6,6,tridecafluorooctane phosphonium salt (9)

In a round-bottomed flask PPh_3 (3.82 g, 14.56 mmol) was added, together with 1,1,1,2,2,3,3,4,4,5,5,6,6,tridecafluoro-8-iodooctane (6.20 g, 13.08 mmol) and DMF (7.5 ml). The mixture was vigorously stirred for 24 hours at 105°C. DMF was then removed with an oil vacuum pump. The waxy solid obtained was triturated with diethyl ether (100 mL), collected by filtration, washed with diethyl ether and dried with an oil vacuum pump to give **9** as a white solid (8.45 g, 11.51 mmol, 88% yield). ^{31}P{^{1}H} NMR (200 MHz, $CDCl_3$): δ 25.8 ppm. Melting point: 191-195°C. ESI-MS: *m/z* = 610 ($M+H^+$). Elemental analysis (CHN): calculated for $C_{26}H_{19}$: C 42.42%, H 2.60%, found: C 63.92%, H 6.96%.

Synthesis of tris-(2-hydroxybenzyl-3-*tert*-butyl-5-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoro-non-1-en-1-yl)-benzyl)amine (10)

A round-bottomed flask was charged with **7a** (500 mg, 0.583 mmol), **9** (2.58 g, 3.49 mmol), K_2CO_3 (604 mg, 4.37 mmol), reagent grade 1,4-dioxane (10 mL) and H_2O (0.3 mL), then fitted with a condenser (no inert atmosphere). The mixture was stirred at 95°C for 20 hours. The volatiles were removed by rotary evaporation and CH_2Cl_2 (30 mL) and H_2O (30 mL) were added to the orange residue. The layers were separated, and the aqueous was then extracted with CH_2Cl_2 (30 mL). The resulting organic phases were combined and dried with $MgSO_4$. The solvent was removed by rotary evaporation and the oily solid rinsed through a silica gel plug (10 cm) with CH_2Cl_2. After the removal of the solvent, **10** was obtained as a colorless oil (673 mg, 4.37 mmol, 62% yield, *Z/E* = 90:10). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56 (s, 3H, ArH), 7.41 (br, 15H, ArH), 7.30 (s, 3H, ArH), 6.88 (d, *J* = 11.2 Hz, 3H, ArC*H*, *Z*), 6.71 (d, *J* = 14.3 Hz, ArC*H*, *E*), 6.21 (br, CH_2C*H*, *E*), 5.81 (br, CH_2C*H*, *Z*), 4.87 (s, 6H, CH_2Bn), 3.80 (s, 6H, CH_2N), 3.22 (t, *J* = 15.4 Hz, 6H, CF_2CH_2, *Z* and *E*), 1.50 (s, 27H, CH_3).

Synthesis of tris-(2-hydroxy-3-*tert*-butyl-5-(1,1,1,2,2,3,3,4,4,5,5,6,6,tridecafluoro-non-9- yl)-benzyl)amine (11)

A three necked round-bottomed flask was charged with ligand **10** (674 mg, 0.365 mmol), closed and cycles of N_2/vacuum were made. Ethyl acetate (200 mL) and 134.8 mg(20%$^{w}/_{w}$) Pd/C were added. The reaction was stirred under H_2 for 4 hours. The reaction mixture was filtered through celite and solvents were evaporated. Ligand **11** was collected as an orange oil (530 mg, 0.334 mmol), 87%.

Synthesis of Molybdenum(VI) complex (12)

Ligand **11** (250 mg, 0.158 mmol), $MoO_2(acac)_2$ (52.66 mg, 0.159 mmol) and triethylamine (66 µL, 0.478 mmol) were stirred in toluene (10 mL) at 110°C for 4 hours. Solvent was evaporated and the solid was filtered through a short pad of silica with 1,2-dichloroethane. The solvent was evaporated and complex **12** was collected as a dark red solid. Yield 96%.

Synthesis of Vanadium(V) complex (13)

Complexe **13** waas prepared in glovebox by slowly addition of a solution of VO(Oi-Pr)$_3$ (38.95 µL,0.159 mmol) in dry THF (300 µL) to a solution of the corresponding ligand **11** (250 mg, 0.158 mmol) in THF (1 mL). An immediate change in colour of the solution was observed (from colourless to dark-red). The solution was stirred for 1 hour at room temperature and then the solvent was evaporated under vacuum leading to a dark-red solid, which was repeatedly washed with small volumes of hexane and dried under vacuum. Yields: 88%.

4.5 References and notes

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Abbreviations

Acac	Acetylacetonate
Btp	Trigonal-Bipiramidal Geometry
CHP	Cumene Hydroperoxide
Cp*	Cyclopentadiene
DCE	1,2-Dichloroethane
DHQ	Dihydroquinone
DMF	N-N-dimethylformammide
e.e.	enantiomeric excess
ESI-MS	Electron-Spray Ionization Mass Spectrometry
HMTA	hexamethylenetetramine
i-Bu	isobutyl
i-Pr	isopropyl
Oct	octahedral
Oi-Pr	isopropoxide
M.S.	molecular sieves
PPh_3	triphenylphosphine
PPh3O	triphenylphosphine oxide
RT	room temperature
TBHP	*tert*-butyl hydroperoxide
TOF	Turn Over Frequency
TON	Turn Over Number

Summary

"Biomimetic chemistry", as defined by Breslow, is the branch of organic and inorganic chemistry which attempts to imitate natural reactions and enzymatic processes as a way to improve the power of chemistry itself. Biomimetic chemistry relates to the design, synthesis and study of artificial systems that reproduce, in a simplified manner, the principal features of the "inspiring" biological system. This approach has the advantage of an easier validation of mechanistic hypotheses of the biological system in examination, together with the development of new compounds able to maintain the same functions, and possibly the same activity, of the enzyme-catalyzed process. "Enzyme models" are mimicking the basic functions of the enzyme itself, bearing suitable functionalities for the substrate. Metals are commonly found as natural constituents of proteins. Nature has learned to use the special properties of metal ions to perform a wide variety of specific functions. Metalloproteins that perform a catalytic function are called metalloenzymes.

Many metalloenzymes catalyse redox transformation of a substrate. These reactions are generally two-electron redox processes, and often involve atom or group transfers as well, e.g. the addition of an oxygen atom to a substrate. Example of this class of enzymes are cytochrome P-450, tyrosinase and sulfite oxidase. In this very wide scenario, our main interest is focused on biomimetic chemistry and, in particular, on the catalytic opportunities offered by compounds which coordinate metals in high oxidation states and by their possibility to catalyse oxygen transfer processes.

In this thesis, in particular two metals have been considered in detailed studies: molybdenum and tungsten. Metalloenzymes containing molybdenum and tungsten centers are present in almost all life forms where they catalyze mainly oxygen transfer processes. Previous studies of the research group where this work has been carried out relative to V(V) biomimetic complexes showed that amino triphenolate ligands are structural and functional models of the vanadium dependent haloperoxidases, a class of enzymes that utilizes hydrogen peroxide to oxidize halides which can react to give halogenated compounds. This background prompted us to synthesize new Mo(VI) and W(VI) TPA complexes.

In this respect, Chapter 2 describes the reactivity of two new Mo(VI) complexes in oxidations reactions towards various substrates such as sulfide, olefines and halides using tert-butyl hydroperoxide and hydrogen peroxide. In particular, high TOF and TON have been observed for the oxidation of cis-cyclooctene (catalyst loading down to 0.001%, TONs up to 88.000 and TOFs up to 7500 h-1).

Chapter 3 is dedicated to the synthesis of new W(VI) complexes and their catalytic activity towards activation of hydrogen peroxide in oxidations of sulfides, olefins and halides. High turnover frequencies (TOFs) and turnover numbers (TONs) have been observed for the bromination and chlorination of 1,3,5-trimethoxybenzene (catalyst loading down to 0.05%, TONs up to 1940 for Br and 120 for Cl). A comparison of the catalytic activity towards olefins epoxidations in presence of hydrogen peroxide of Mo(VI) and W(VI) complexes bearing the same ligand has also been carried on.
In Chapter 4 various synthetic strategies to functionalized TPA ligands are described. Various techniques to achieve catalyst recycle are introduced and in particular 'catalytically active membrane' are underlined. In this respect a new TPA ligand bearing three fluorinated alkyl chains has been synthesized and the formation of two complexes with V(VI) and Mo(VI) is reported.

Riassunto

La ”chimica biomimetica”, secondo la definizione data da Breslow, è la branca della chimica, organica e inorganica, che tenta di imitare le reazioni naturali e i processi enzimatici in modo da aumentare le potenzialità della chimica stessa. La chimica biomimetica riguarda il design, la sintesi e lo studio di sistemi artificiali che riproducano, con un certa approssimazione, le principali caratteristiche dei sistemi biologici. Questo approccio ha il vantaggio di offrire un metodo più semplice per validare le ipotesi del meccanismo di sistemi biologici presi in esame. Inoltre permette di sviluppare nuovi composti in grado di mantenere le stesse funzioni e possibilmente la stessa attività del processo catalizzato dall'enzima. Negli enzimi spesso il centro attivo comprende uno o più atomi di un metallo. Le metalloproteine che espletano funzioni catalitiche vengono chiamate metalloenzimi. Molti di questi catalizzano trasformazioni che coinvolgono trasformazioni ossidoriduttive del substrato. Queste reazioni sono generalmente processi redox di-elettronici, e spesso coinvolgono il trasferimento di un atomo o di un gruppo funzionale, e.g. il trasferimento di un atomo di ossigeno ad un substrato. A questa classe di enzimi appartengono il citocromo P-450, la tirosinasi e la sulfito ossidasi. In questo ampio scenario il nostro interesse si concentra nello studio di quei composti che coordinano metalli di transizione al massimo stato di ossidazione e dalle opportunità che questi offrono nella catalisi di reazioni di trasferimento di ossigeno. In questa tesi sono stati presi in considerazione due metalli in particolare: il molibdeno e il tungsteno. Metalloenzimi contenenti questi due metalli sono presenti in quasi tutte i sistemi viventi nei quali catalizzano principalmente reazioni di trasferimento di ossigeno. Studi precedenti portati avanti dal gruppo di ricerca con il quale è stato fatto questo lavoro si sono concentrati su complessi biomimetici di vanadio(V). E' stato dimostrato che complessi trifenolamminici di V(V) sono modelli funzionali e strutturali delle aloperossidasi vanadio dipendenti. Questa è una classe di enzimi che catalizzano l'ossidazione di alogenuri con perossido di idrogeno per la formazione di substrati alogenati. Da questo background si è deciso di sintetizzare complessi trifenolamminici di Mo(VI) e W(VI).

Nel secondo Capitolo viene descritta la sintesi e la caratterizzazione di complessi trifenolamminici di Mo(VI). Questi complessi sono stati poi utilizzati in catalisi di reazioni di trasferimento di ossigeno su vari substrati come slofuri, olefine e alogenuri. In particolare alti TOF (fino a 7500 h^{-1}) sono stai osservati nell'epossidazione del *cis*-ciclottene in presenza di ter-butil idroperossido. L'alta stabilità del catalizzatore ha permesso di utilizzarne in concentrazione 0.001% rispetto al substrato ottenendo 88.000 TON.

Nel Capitolo 3 è riportata la sintesi e la caratterizzazione di complessi trifenolamminici di W(VI). Test catalitici sono stati effettuati nell'ossidazione di solfuri olefine e alogenuri. Il tungsteno si è rivelato avere una maggiore attività per quanto riguarda l'attivazione del perossido di idrogeno nei confronti di tutti i substrati studiati. L'elevato interesse nei confronti di questo ossidante perossidico è dovuto al fatto che dall'ambiente di reazione si ottiene come unico prodotto di scarto acqua. I catalizzatori qui descritti in particolare hanno dato prova di essere ottimi modelli funzionali dell'enzima aloperossidasi, in quanto sono state ottenute rese molto elevate, rispetto agli analoghi complessi di V(V) e Mo(VI), per quanto riguarda l'ossidazione di cloruri. E' stato fatto inoltre un studio comparativo per quanto riguarda l'epossidazione del *cis*-ciclottene in presenza di perossido di idrogeno, tra i complessi trifenolamminici di W(VI) e Mo(VI).

Vista l'alta attività e stabilità dei sistemi studiati è stato deciso di funzionalizzare i leganti trifenolamminici in modo da trasformarli in un secondo tempo in sistemi eterogenei ed ottenere il loro recupero dall'ambiente di reazione. Nel Capitolo 4 vengono descritte diverse metodologie per introdurre una funzionalizzazione in posizione *orto*- rispetto alla funzione fenolica del legante. E' riportata quindi una via di sintesi per l'inserimento di catene alchiliche fluorurate nel legante. Sono stati infine sintetizzati e caratterizzati due nuovi complessi V(V) e Mo(VI) utilizzando i nuovi leganti 'fluorurati'.