Catalytic Applications of Pyridine-Containing Macrocyclic Complexes

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This work is dedicated to the memory of Flavia Roncalli

Abstract: The introduction of a pyridine moiety into the skeleton of a polyazamacrocyclic ligand affects both the thermodynamic properties and the coordination kinetics of the resulting metal complexes. These features have engendered a great interest of the scientific community in recent years. The field of application of pyridine-containing macrocyclic ligands ranges from biology to supramolecular chemistry, encompassing MRI, molecular recognitions, materials and catalysis. In this microreview we provide a perspective on the catalytic applications of metal complexes of pyridine-containing macrocycles, including an account of investigations from the authors' laboratories dealing with stereoselective C-C and C-O bond forming reactions. The increased conformational rigidity imposed by the pyridine ring allowed for the isolation and characterization of metal complexes in a high oxidation state and the study of their relevance in oxidation reactions. On the other hand, the very different conformations accessible upon the metal coordination and the easy tuneable synthesis of the macrocyclic ligands were exploited in stereoselective synthesis.

1. Introduction

The history of macrocyclic compounds dates a long time ago; in a certain way, they are ancients as life: porphyrins, corrins, chlorins are natural compounds with biological and vital roles both in animal (*i.e.* hemoglobin) and in vegetal world (*i.e.* chlorophyll). The strong importance of the biological occurring macrocycles directed most of the early synthetic studies to the mimicking of those species.[1] The natural ligands were taken as models in the synthesis, causing an initial predominance of nitrogen containing ligands[2] with respect to macrocycles bearing other heteroatoms. Fisher, "the father of porphyrin chemistry", reported the first total synthesis of etioporphyrin-III and octamethylporphyrin in 1926,[3] whilst the first non-natural macrocycle came to life "only" in 1960, when N. F. Curtis synthesized a nickel(II) complex from tris-ethylenediamine nickel(II) perchlorate and acetone.[4] Polyazamacrocycles are a common class of macrocyclic compounds, utilised across a number of fields, including, but not limited to, catalysis,[5] selective metal recovery and recycling,[6] therapy and diagnosis,[7] materials and sensors.[8] Worth of note is their ability to form stable complexes with a plethora of both transition, especially late, and lanthanide metal cations.[9] Deviation of the macrocycle donor atoms from planarity often leads to rather uncommon oxidation states of the coordinated metal.[10]

Both the thermodynamic properties and the complexation kinetics are affected by the introduction of a pyridine moiety into the skeleton of polyazamacrocycles by increasing the conformational rigidity and tuning the basicity.[11] Pyridine-containing ligands engendered great interest due to various potential field of applications and were successfully employed in biology,[12] Magnetic Resonance Imaging,[13] molecular recognition,[14] supramolecular chemistry[15] and self-assembly,[16] molecular machines[17] and mechanically interlocked architectures.[18] Among the numbers of reports dealing with pyridine-containing macrocycles, we wish to highlight here their metal complexes relevant to catalytic applications, with a focus interest on the role of the sp^2 nitrogen donor atom, which in turn tune up the structural features of corresponding metal complexes. Only macrocycles in which the pyridine ring is part of the macrocycle skeleton are covered and classical 1-(2'-pyridylnethyl)-4,7-triazacyclononane (PyTACN)[19] and 1-(2'-pyridylnethyl)-,4,8,11-tetraazacyclotetradecane (PyCyclam)[20] ligands bearing exocyclic pendant arms incorporating pyridine donor atoms have not been included. Schiff base derived complexes incorporating the pyridine moiety were recently object of a complete review by Rezaeivala and Keypour.[21] The excellent paper by Vigato and Tamburini covered synthetic pathways and structural aspects of cyclic Schiff bases.[22]

The work is subdivided in two main chapters. The first one is dedicated to catalytic oxidation reactions and systems relevant to the biomimetic oxidation of organic substrates, while in the second part we present an account of investigations from the authors' laboratories dealing with stereoselective C-C and C-O bond forming reactions.

However, given the high numbers of papers published on this topic, this microreview do not pretend to be comprehensive and we apologise with authors whose works have not been included.

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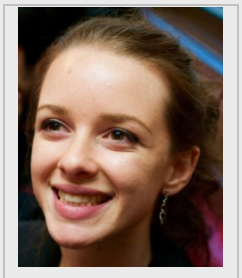
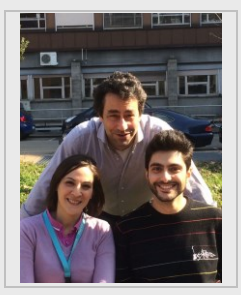


Flavia Roncalli was born in Italy in 1992. She received her bachelor's degree in chemistry in 2014, working on the synthesis of aminoacid derived tetraazamacrocyclic ligands and the catalytic applications of their Ag^I complexes under the supervision of prof. Alessandro Caselli. In 2016, for the thesis of the Master's degree, she joined our group with a project aimed at the direct synthesis of non-natural aminoacids starting from amines and alcohols. On the 29th of November 2016,

when she had only started to have some exciting results, Flavia passed away after contracting meningitis. We like to remember her with the dedication she had chosen for her bachelor's thesis: "*Sometimes it is better to get lost on the way to an impossible journey than never to leave*…and MINE has been a wonderful journey!"



Giorgio Tseberlidis was born in Italy in 1988. He received his master's degree in Chemical Science at the University of Milan (Italy) in 2013 under the supervision of Prof. Emma Gallo with a thesis focus on the synthesis of glycoporphyrin complexes to be used as catalysts in the amination reactions of sp^3 and sp^2 C–H bonds. He is currently PhD student at Milan University in Prof. Alessandro Caselli's group and his research activity is mainly devoted to the synthesis of new hybrid catalysts based on metal complexes of bio-inspired ligands for stereoselective reactions.

Daniela Intrieri received her PhD degree in Chemical Science at the University of Milan (Italy) under the supervision of Prof. Emma Gallo in 2014. Her PhD thesis focused on the synthesis of metal porphyrins complexes to be employed as catalysts for the functionalization of C–C and C–H bonds by carbene and nitrene transfer reactions. After her PhD she moved to the Trinity College of Dublin (Ireland) under the supervision of Prof. Mathias O. Senge to work in the field of organocatalysis and on the synthesis of highly substituted porphyrins. She is currently a post-doc researcher at Milan University in Prof. Emma Gallo's group.

Prof. Alessandro Caselli received his PhD under the supervision of Carlo Floriani at the University of Lausanne (Switzerland) in 2000. Than he moved to the Department of Organic and Industrial Chemistry at the University of Milano (Italy), as post-doc, under the supervision of Fulvia Orsini and in 2003 he became assistant professor in Sergio Cenini's research group. Currently he is Associate Professor and his research interest is centred on the synthesis of transition metal complexes with macrocyclic N-donor ligands and their use in homogeneous catalysis. His studies are focused also on mechanistic aspects and on heterogenisation techniques for chiral catalysts.

2. Stoichiometric and catalytic oxidations

Much effort in the use of macrocyclic pyridine containing ligands was devoted to the study of catalytic oxidation reactions. Early studies were inspired by Nature and the understanding of metallo-enzymes, which use molecular oxygen from air as the primary oxidant. Copper proteins like hemocyanin, the enzyme tyrosinase and catechol oxidase, and non-heme iron enzymes are very sophisticated catalysts and their reactions are fast and highly selective, under mild experimental conditions. The prospect of using model compounds for such metallo-enzymes as industrial oxygenation catalysts[23] has driven efforts to synthesize molecules capable to mimic the oxygen binding and activation in natural systems.[24]

2.1. Mononuclear iron complexes

The interest in understanding the structure and properties of iron complexes containing coordinated dioxygen has led the scientific community to explore ligands capable of stabilizing superoxo and/or μ-peroxo intermediates before their rapid autoxidation to Fe^{III}-oxo species, due to either the presence of water or to the oxidative dehydration of the ligands.[25] In a pioneering paper appeared in 1982, prof. Kimura and co-workers reported on a new pyridine-containing pentaaza macrocyclic ligand (Pyan), **1**, capable of stabilizing the O_2 adduct of its iron(II) complex in aqueous solutions at room temperature (Figure 1).[26] The presence of the pyridine ring into the macrocycle skeleton was of fundamental importance in the stabilization of the dioxygen adduct, by altering both the electronic and steric properties. On the one side, the oxidation of the Fe^{II} metal ion became more favourable in the presence of the pyridyl moiety, as deduced by cyclic voltammograms. The more rigid configuration imposed to the macrocycle by the presence of the pyridine ring in the μ-peroxo diiron(III) complex, proposed by the authors (Figure 1), rendered the complex kinetically inert by preventing the ligand dissociation. The kinetics were measured in Tris buffers (8.0 < pH < 9.5), to avoid any dissociation of the metal from the Fe^{II}-Pyan complex. At given pH the oxygenation reaction followed a first-order dependence in both [Fe^{II}-Pyan] and [O_2].

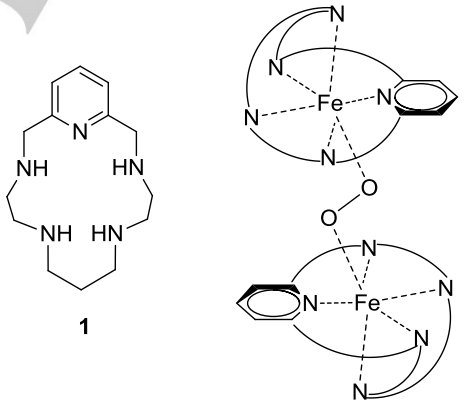
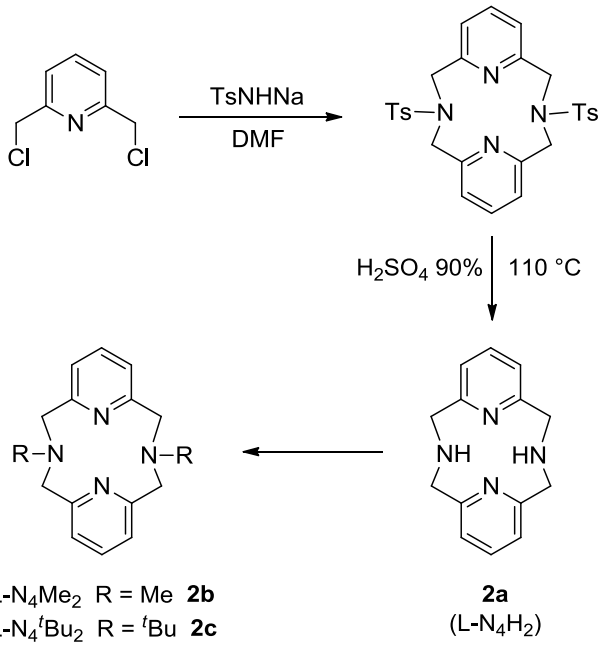


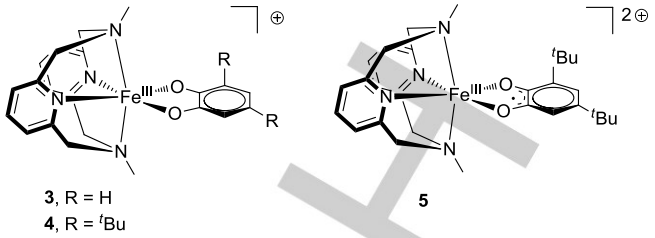
Figure 1. Ligand **1** (Pyan) and the proposed structure for the iron-dioxygen adduct.

Some years later, in the effort of modelling the intradiol cleavage of catechol dioxygenase, Koch and Krüger reported the structure and the catalytic reactivity of a Fe^{III} catecholate complex of a pyridinophane ligand.[27] Pyridinophane ligands were directly obtained in reasonable yields (53%) by the treatment of 2,6-bis(chloromethyl)pyridine with TsHNa (Ts = tosyl) in anhydrous DMF (Scheme 1).[28]



Scheme 1. Synthesis of pyridinophane ligands **2a-c**.

The reaction of ligand **2b**, (L-N_4Me_2), with iron(III) chloride, followed by the addition of catecholate anions in alcohol allowed the isolation of stable cationic complexes of formulae [Fe^{III}(L-N_4Me_2)(cat)]$^+$, **3**, and [Fe^{III}(L-N_4Me_2)(dbc)]$^+$, **4** respectively, which reacted with oxygen (cat^{2-} = catecholate, dbc^{2-} = 3,5-di-tert-buthylcatecholate, Scheme 2).[27a] The small cavity of the 12-membered macrocyclic ligand forced a distorted octahedral coordination geometry around the metal with the catecholate ligand bounded to *cis* coordination sites in the equatorial plane of the complex. The pronounced rigidity imposed that the ligand remained bound through all nitrogen donors to the iron centre during the complete catalytic cycle, even in the presence of large excesses of dbc^{2-}. During the course of the investigations it was shown that the intradiol cleavage product, 3,5-di-*tert*-butylmuconic anhydride, was the direct product of oxygenation reaction. The low-spin iron(III) semiquinonate complex **5** was stable in acetonitrile solution towards molecular oxygen. This finding indicated that most probably the intradiol cleavage catalysed by **4** did not occur through an initial electron-transfer step.[27b] Instead, the direct attack of the oxygen molecule to the iron(III) catecholate complex must occur. The system based on [Fe^{III}(TPA)(dbc)]$^+$ (TPA = tris(2-pyridylmethyl)amine) was approximately 40 time faster in the stoichiometric ring cleavage of catechols.[29]

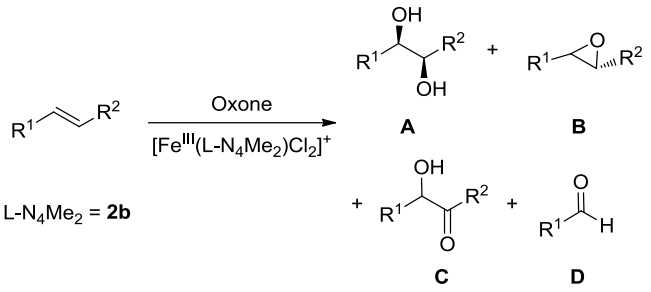


3, R = H
4, R = ^{t}Bu
5

Scheme 2. Iron(III) catecholate complexes **3** and **4**, semiquinonate complex **5** and proposed catalytic cycle for oxidative catechol cleavage.

By using less sterically hindered ligand **2a**, Banse, Girerd and co-workers synthesized [Fe^{III}(L-N_4H_2)Cl_2]$^+$ complex and were able to obtain a nearly 160-fold increase in the stoichiometric oxidative cleavage of catechol in CH_3CN.[30] This result suggested that the accessibility of molecular dioxygen to the iron centre, more than electronic factors, was the key parameter in order to achieve a fast ring cleavage of the substrate and in fact reaction rates comparable to those of the TPA system were measured.[29] Interestingly, in the oxidative cleavage of catechols catalysed by [Fe^{III}(L-N_4H_2)Cl_2]$^+$, products derived from extradiol cleavage were also observed.[30] This difference in reactivity could only be explained in terms of the increased steric hindrance of ligand **2b** that prevented the formation of a Fe^{III}-superoxo species, responsible for the extradiol cleavage observed with ligand **2a**.

Inspired by the previous work by Krüger, the group of professor Che, in the search for a robust iron catalyst, reported on the use of [Fe^{III}(L-N_4R_2)Cl_2]$^+$ in the selective *cis*-dihydroxylation of alkenes by potassium peroxymonosulfate (Oxone) (Scheme 3).[31] The use of ligand **2b**, endowed the iron catalyst with an enhanced stability, due to the absence of the secondary amine NH functionality of ligand **2a**, susceptible to oxidation. By using Oxone, a remarkable high selectivity in *cis*-diol, **A**, was obtained, keeping the alkene as limiting agent (up to 99% substrate conversion with 99% yield in *cis* diol when employing electron poor alkenes). On the other hand, H_2O_2 as the oxidant rendered the *cis*-dihydroxylation ineffective and the major product was the epoxide **B** (34%) instead. Despite the use of an oxidant excess, overoxidation products **C** and **D** were observed only in limited amounts. By replacing iron with osmium, Sugimoto and Itoh were able to obtain a selective *cis*-dihydroxylation catalyst in the presence of H_2O_2 as the terminal oxidant.[32] Hydrolysis of [Os^{III}(L-N_4Me_2)Cl_2]$^+$ yielded the hydroxo-aqua osmium(III) complex that was used as the catalyst. The absence of any dimer bearing μ-oxo bridge during the hydrolysis was noteworthy and it was again a proof of the peculiar properties of ligand **2b**, capable of forming very stable complexes with transition metals leaving two coordinative labile sites in *cis*. The system reported by Sugimoto and Itoh was extremely selective in *cis*-diol formation and overoxidation products were observed only in traces.



Scheme 3. *cis*-Dihydroxilation of alkenes catalysed by Fe^{III} complex of pyridinophane ligand **2b**.

The remarkable robustness toward oxidation of pyridinophane ligands, accompanied by their capability of binding strongly to metal ions was exploited also in the quest for water oxidation catalysts (WOCs). By using Oxone, but also $Ce(NH_4)_2(NO_3)_6$ (CAN) or $NaIO_4$, as oxidants, water oxidation catalysed by $[Fe^{III}(L\text{-}N_4Me_2)Cl_2]^+$ occurred under mild conditions.[33] When compared with other iron complexes bonded to other nitrogen donor ligands,[34] $[Fe^{III}(L\text{-}N_4Me_2)Cl_2]^+$ afforded a lower catalytic activity under the same reaction conditions and TON up to 32 in pure water were observed in the water oxidation by CAN and up to 113 in 0.1 M HNO_3 by Oxone. However, the strong donor properties of ligand **2b** were proposed to stabilize the *in-situ* generated Fe^V oxo species against demetalation and autooxidation and in fact, detailed spectroscopic studies accompanied by DFT calculations allowed for the proposal of a reactive $[Fe^V(L\text{-}N_4Me_2)(O)_2]$ species. Almost simultaneously to the work by Che, Sun and co-workers reported that $[Fe^{II}(L\text{-}N_4Me_2)(CH_3CN)_2](SO_3CF_3)_2$ was also a good pre-catalyst for water oxidation by CAN.[35] Substitution of non-coordinating triflate counter ions with chlorine anions resulted in a complex with a comparable catalytic activity. As expected, when comparing the structural data in the solid state for the Fe^{II} and the Fe^{III} complexes of ligand **2b**, the presence of an iron centre in +2 oxidation state resulted in much shorter Fe-N bond distances.

One attractive feature of pyridine-containing macrocycles is represented by the different synthetic paths to their synthesis that allows for an easy modulation of the substitution pattern of the macrocyclic skeleton. The one step synthesis of Schiff-base macrocyclic complex can be easily obtained via the template condensation between 1,2-diformyl- or 1,2-diacetylpyridine and an appropriate di-primary amine, in general a tripodal aliphatic amine such as 3,3'-diaminopropylamine.[21] However, metal complexes with those ligands experience a significant steric strain due to the rigid, planar, conjugated bis-iminepyridine fragment. On the other hand, the reduced macrocycles are by far more flexible and at the same time more chemically inert.[36] Even if this adds a further step in the ligand synthesis, the increased ligand flexibility can be exploited to accommodate metal ions with different conformations: from distorted tetrahedral to tetragonal-pyramidal and trigonal-bipyramidal, up to distorted octahedral geometry. Another feature is the presence of inequivalent nitrogen donor atoms, which can be used to introduce coordinating groups on the pendant arm.[37] In the search of non-heme iron complexes active as catalysts for oxygen and peroxide activation, it is important to prepare ligands that can fix the donor atoms in a square pyramidal (or square planar) geometry around the metal ion. The introduction of an aminopropyl pendant arm to a 14-membered pyridine-containing macrocycle allowed for that goal (Figure 2). The corresponding iron(II) complexes, in fact, resulted to be competent catalysts for the alkene epoxidation by H_2O_2.[38] The 14-membered macrocycle was perfectly suited for the equatorial coordination of its four nitrogen to an iron(II) ion while the flexible arm could be tuned for axial coordination by acid-base reactions.[37a] Iron(II) complexes with ligands **6b** and **6c** displayed a square-pyramidal geometry, the four N donor atoms of the macrocycle occupied the equatorial position while the fifth nitrogen of the pendant arm the axial position. No place was left for external solvent molecule or anions in the first coordination sphere of the metal ion, since the Fe^{II} atom was displaced from the macrocyclic plane towards the exocyclic amino group and the *trans* axial site was no longer available for an additional coordination. On the contrary, the iron(II) complex of ligand **7a** was found in a distorted octahedral geometry with the two axial positions occupied by solvent molecules (CH_3CN). The five coordinated complexes were catalytically inactive, but upon addition of a non-coordinating acid, high yields of epoxides were obtained (up to 89% for cyclooctene oxide and 76% for 1,2-epoxydecane with $[Fe^{II}$**6c**$](OTf)$ complex in the presence of triflic acid, TON = 19.6 and 15.2, respectively, Scheme 4, **A,**). This was ascribed to the protonation of the amine pendant, which freed the axial position for the hydrogen peroxide activation (Scheme 4, **B**). The enhanced catalytic activity was due to a spin state change of the iron centre from high to low spin. However, the axial position must be available for H_2O_2 coordination, since the addition of coordinating HCl hampered the reactivity (only 8% yield of cyclooctene oxide, TON = 1.6). The presence of the aminopropyl pendant played a role in the increased catalytic activity observed by shuttling an intramolecular proton transfer, since iron complexes of tetradentate ligands **7a** and **7b** showed lower conversions and selectivities.

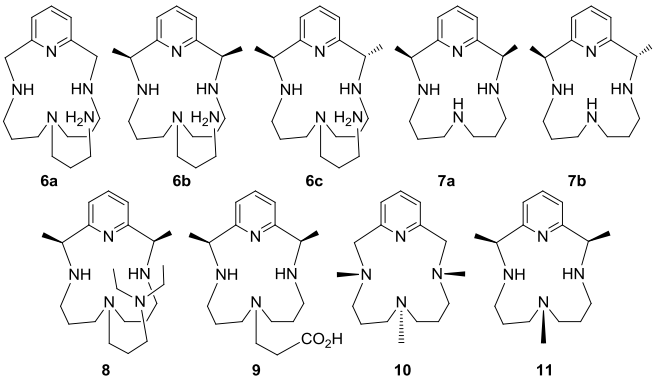
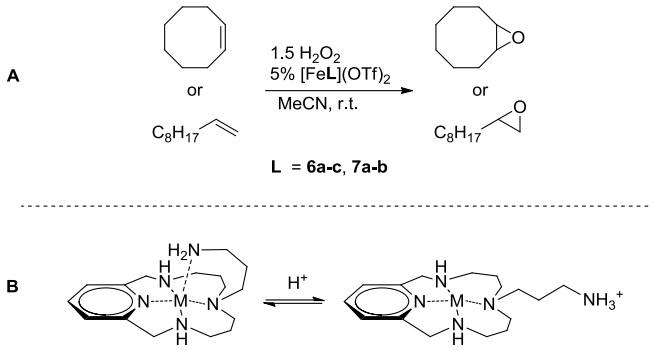


Figure 2. Tetradentate and pentadentate pyridine containing macrocycles **6-11** employed by Rybak-Akimova and co-workers.

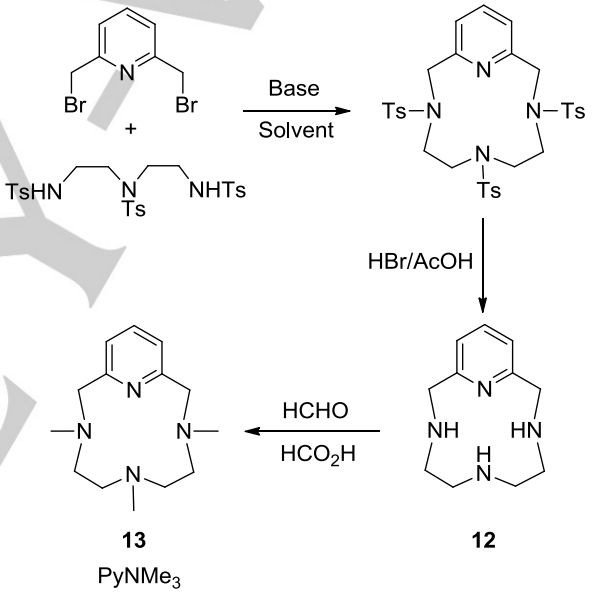


Scheme 4. Cyclooctene and 1-decene epoxidation reaction with H_2O_2 catalysed by iron complexes of ligands 6 and **7** (**A**) and the acid driven on-off coordination behaviour of the amine pendant (**B**).

Amino pendant arms were useful for studying the coordination behaviour of pyridine-containing macrocyclic ligands, but the presence of free N-H bonds rendered them sensitive to strong oxidants and affected the complex stability in oxidation reactions. The group of prof. Rybak-Akimova more recently showed that N-alkylated macrocyclic tetradentate ligand **10** was much more stable than **7b**. Depending on the coordinating abilities of the chosen anion, Fe^{II} complexes of ligand **10** adopted a distorted octahedral geometry, with weakly bonded *cis* triflate molecules, or a distorted square pyramidal geometry, with more strongly coordinating chlorine ion in the axial position.[39] N-alkylation of the macrocyclic ligand, caused a change in the spin state of the coordinated iron(II), favouring a high spin configuration, resulting in a lower catalytic activity (only 7% yield in the epoxidation of cyclooctene with H_2O_2 as terminal oxidant, TON = 1, in the absence of externally added mineral acid). Indeed, iron loss was observed during the catalytic experiments, consistent with a decreased thermodynamic stability of the oxidised iron complexes after N-alkylation of the ligand. The introduction of a strongly coordinating chloride ion suppressed completely the reactivity toward H_2O_2, showing the fundamental role of vacant or labile coordination sites. The increased ligand stability under oxidative conditions allowed for the generation of iron-peroxo and iron-oxo intermediates (isopropyl 2-iodobenzoate as terminal oxidant) and the latter was a competent oxidant for stoichiometric epoxidation of cyclooctene. An intermediate behaviour was observed for high-valent iron-oxo species of ligand **10,** compared with the reactivity of those supported by aminopyridine ligands[40] and by polyazamacrocycles.[41]. This clearly demonstrated that more electron-donating ligands stabilised the ferryl species hampering their reactivity, while the presence of electron-withdrawing pyridyl moieties, decreasing the stability of high-valent iron-oxo intermediates, increased their reactivity.

The observation that the N-H groups adjacent to the pyridine ring did not suppress the catalytic activity in oxidation reactions and that the most vulnerable site was the central N-H atom of the parent triamine led to the synthesis of the iron(II) complex of ligand **11**, bearing only one methylated N donor atom.[42] In this complex, the central low spin Fe^{II} atom was located in a distorted octahedral geometry with two acetonitrile molecules occupying the axial sites. The catalytic activity of this complex was still quite low (36% yield in the epoxidation of cyclooctene with H_2O_2 as the terminal oxidant, TON = 8, in the absence of externally added mineral acid), but the full characterization of a ferryl(IV) intermediate, competent in the epoxidation of cyclooctene, allowed to shed light on the catalytic oxidations of non-heme iron model complexes.[42]

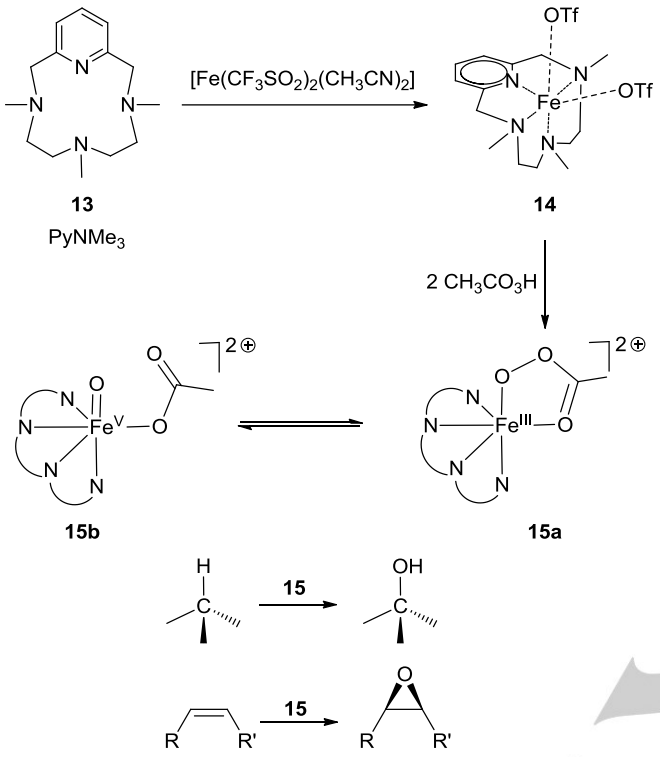
Another approach to the synthesis of pyridine-containing macrocyclic ligands consist in the modified Richman-Atkins procedure[43] by reaction of a N-tosyl protected polyamine with 2,6-bis(bromomethyl)pyridine, using K_2CO_3 as a base under heterogeneous conditions (CH_3CN as solvent).[11i] After the HBr promoted hydrolysis of the Ts (Ts = tosyl) protecting group, the free base ligand could be obtained in a reasonable yield (45%).[44] This synthetic scheme was followed to obtain mainly 12-membered macrocycles (Scheme 5).



Scheme 5. Synthetic path for the synthesis of twelve membered macrocycles **12** and **13**.

The iron(II) complex **14**, obtained by treating ligand **13** with $[Fe^{II}(CF_3SO_3)_2(CH_3CN)_2]$, possessed structural features very close to those described for the Fe^{II} bis-triflate complex of ligand **10**. The latter complex upon reaction with peracetic acid gave rise to the fastest non-heme oxoiron complex for cyclohexane oxidation reported to date.[45] EPR data of the product formed by oxidation of **14** with peracetic acid pointed out to the existence of two low spin species (S = ½) in rapid equilibrium, where the major component was proposed to be $[Fe^{V}(O)(OAc)(PyNMe_3)]^{2+}$, **15b** that was in equilibrium with the acylperoxoiron intermediate **15a** (Scheme 6). In addition of being a competent catalyst for C-H bond cleavage through an initial hydrogen atom transfer (HAT) mechanism, a remarkable feature of oxidant **15** was the

stereospecific and site-selective C-H hydroxylation reactivity which was related to electronic and steric parameters.



Scheme 6. Synthesis of Fe^{II} complex **14** and oxidation products **15a-b** obtained upon treatment with peracetic acid. C-H hydroxylation and epoxidation catalysed by oxidant **15**.

Complex **14** was also a competent catalyst in alkene epoxidations by peracetic acid.[46] All experimental evidences provided by Costas and co-workers were in agreement with complex **15** being the active species in oxygen atom transfer (OAT) reaction with alkenes. Active species **15** exhibited rates in OAT reactions with cyclooctene that were three to four orders of magnitude higher than those reported for the ferryl(IV) intermediates of ligands **10**[39] and **11**.[42] A Co(II) analogue of **14** (perchlorate salt) was recently reported.[47] Although this species was treated with H_2O_2 to gave a cobalt(III)-peroxo complex, no OAT and HAT reactivity was observed. Upon protonation a Co(III)-hydroperoxo was formed, which was capable of oxidizing Ph_3P to Ph_3PO.

A related iron(III) acylperoxo species based on the pyridinophane ligand **2c** was reported by Mirica and co-workers,[48] but, to the best of our knowledge, no reactivity studies in OAT reactions were performed.

Iron(II) complexes of 12-membered pyridine containing macrocyclic ligands were used to promote the direct Suzuki-Myaura reaction between N-heterocyclic compounds and arylboronic acids.[49] Fe^{II} oxalate was found to be the most efficient salt, and among the tetraazamacrocyclic ligands tested, pyridine-containing ligand **12** gave the best results. Noteworthy, the use of pyridinophane ligand **2a** yielded quite large amounts of phenol as the side-product. Oxygen was found to be of outmost importance for the C-H bond activation, since only traces of product were formed if the reaction was carried out under nitrogen atmosphere and preliminary mechanistic studies suggested that an oxoiron complex was the catalytically competent species.

Introduction of amide groups into the ring of pyridine containing macrocycles is expected to stabilize the high oxidation states of the coordinated metal. The synthesis of the macrocycle is quite straightforward and can be achieved by condensation reaction of the appropriate pyridinedicarboxylate with a suitable primary diamine. Following this approach, Zhou and co-workers reported the synthesis of Mn^{III} and Fe^{III} complexes of macrocyclic bis-pyridineamido ligand **16** (Figure 3) and their catalytic activity in epoxidation reactions.[50] Bot complexes failed to yield epoxides in good yields when employing H_2O_2 or NaClO as terminal oxidants. On the other hand, a 95% of epoxide (GC yield) was obtained by employing PhIO and a 5-fold excess of styrene in CH_3CN using the Mn complex (TON = 19). Iron was less reactive leading to a TON of 7.8. Interestingly, the manganese complex resulted in higher catalytic activities than related non-annular complexes.

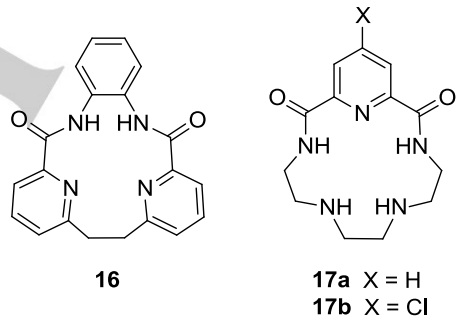


Figure 3. Bis-pyridineamido ligand **16**, pentadentate bisamido ligands **17a-b**.

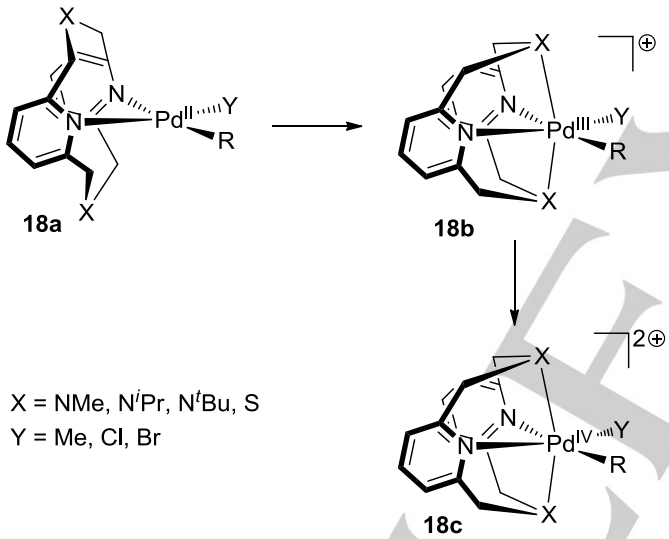
Iron(II) complexes of the pentadentate ligands **17a** and **17b** (Figure 3) were also reported,[51] and although not studied in catalytic reactions, the presence of an accessible proton was showed to alter the oxygenation reactions of these complexes and was reminiscent of the properties of iron(II) porphyrin complexes.

2.2. Mononuclear complexes of other metals

The tuneable steric properties of pyridinophane ligands were further explored by Smith and co-workers.[52] Investigation of the catalytic properties of $[Mn^{II}(L\text{-}N_4R_2)(H_2O)_2]^{2+}$ complexes with ligands **2a-c** demonstrated that a change in the steric properties of the ligand, accompanied by an increased donor strength in the series R = H, Me, *t*Bu, led to a change in the catalytic properties (Scheme 1). While the less steric demanding complexes of ligands **2a** and **2b** were active in H_2O_2 disproportionation,[53] the first one being more active but less

stable, the presence of bulkier *tert*-buthyl groups in ligand **2c** hampered this reactivity. Due to the easier access to higher oxidation states for the manganese ion, complex $[Mn^{II}(L\text{-}N_4{}^tBu_2)(H_2O)_2]^{2+}$ was an active catalyst for the electrochemical oxidation of water to molecular dioxygen. The stabilization of higher oxidation states by the pyridinophane ligands was investigated both experimentally and by DFT calculations.[54]

A systematic study on the oxidative C-C coupling promoted by palladium complexes of pyridinophane ligand was reported.[55] Remarkably, $[Pd^{II}(L\text{-}N_4R_2)Me_2]$, **18a**, was readily oxidised by either O_2 or peroxides to form a stable $[Pd^{III}(L\text{-}N_4R_2)Me_2]^+$ **18b** intermediate, from which a selective ethane formation was observed (Scheme 7). A change from the diamine bridge to a sulfur bridge resulted in a more flexible ligand, but also more sensitive to oxidative degradation.[56] It should be pointed out that, in the palladium series of complexes, the N(sp^3) or S donor atoms changed the denticity of the ligand as a consequence of the metal oxidation state. While for palladium(II) a k^2 conformation was preferred, in Pd^{IV} complexes the ligand adopted a tetradentate k^4 conformation (Scheme 7).



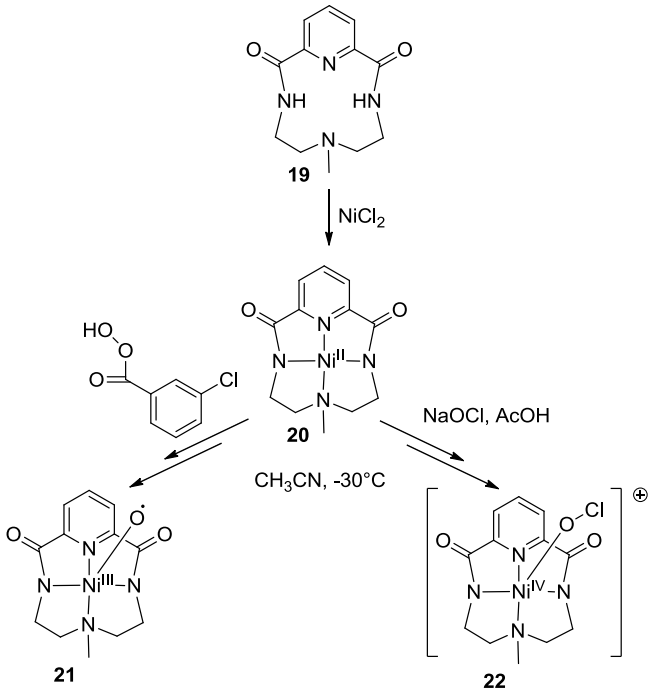
Scheme 7. Synthesis of $Pd^{II}(L\text{-}N_4)$, **18a**, $Pd^{III}(L\text{-}N_4)$, **18b**, and $Pd^{IV}(L\text{-}N_4)$, **18c**, complexes.

The coordinative flexibility of ligand **2c** was demonstrated by the formation of cationic complexes with late fist-row transition metal ranging from iron to zinc.[48] In all the $[M^{II}(L\text{-}N_4{}^tBu_2)L_2]^{2+}$ complexes, a distorted octahedral geometry with shorter equatorial M-N_{py} and longer axial M-N_{amine} distances were found, in striking difference with the Pd^{II} series. The use of pyridinophane ligand **2c** allowed the isolation and characterization of several Ni^{III}(aryl) complexes that were catalytically relevant in cross-coupling reactions.[57] Again, the ligand modification of the pyridinophane structure played a key role. When less bulky ligand **2b** was used instead, a square planar dialkyl complex of formula $[Ni^{II}(L\text{-}N_4Me_2)Me_2]$ was isolated, which in turn can be oxidised to a stable octahedral $[Ni^{III}(L\text{-}N_4Me_2)Me_2]^+$ cationic complex. This last was a competent catalyst for Kumada cross-coupling reactions.[58]

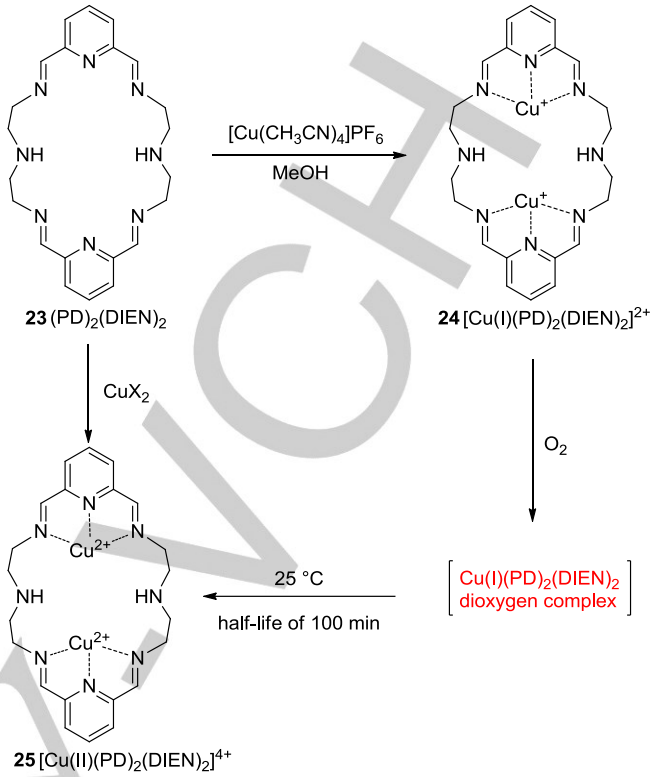
The group of prof. Rybak-Aikimova reported the peroxidase-like activity of the parent complexes of nichel(II) with ligands **6**-**7** and **8**-**9**, bearing either a tertiary amine, an amide or a carboxylic acid (Figure 2).[59] Worth to note, the Ni^{II} complex of ligand **8**, bearing a tertiary amine on the pendant arm, with weakly coordinating perchlorate counter ions, displayed a square planar geometry, where only the four nitrogen donor atoms of the ring were coordinated to the metal ion. This was ascribed to an increased steric hindrance due to the ethyl chains giving rise to structural features of the metal complex reminiscent of those of the protonated form of ligand **6b**. Proton-donating abilities at the pendant arm of the macrocycle played a fundamental role in the catalytic activity of the Ni^{II} complexes in the oxidation of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) by H_2O_2. Again, intramolecular proton transfers were likely to play a role in the H_2O_2 activation, facilitating the O-O bond cleavage.

Finally, formation of a potent oxidizing species by reaction of *meta*-chloroperbenzoic acid with the neutral nichel(II) complex of deprotonated ligand **19** (Scheme 8) was recently reported by Anna Company and co-workers.[60] Oxidation of olefins, sulphides and alkanes bearing strong C-H bonds could be triggered by this highly reactive compound, which based on experimental and theoretical evidences was proposed to be a Ni^{III}-oxyl species, **21**, that could be detected only at temperatures below -30 °C (half-life at -30 °C of 4.5 h). It should be pointed out that the reactivity of **21** exceeded that of previously reported well-defined nickel-oxygen species by several order of magnitude. The nickel complex **20** was also a particularly efficient catalyst in the chlorination and oxidation of C-H bonds using sodium hypochlorite as the terminal oxidant in the presence of AcOH (TON up to 53 for the chlorination/oxidation of cyclohexene at -30 °C). [61] A high valent Ni-hypochlorite species was trapped by reaction with NaOCl in the presence of acetic acid. Spectroscopic evidences supported by theoretical calculations indicated that, despite the formal oxidation state of the nickel in **22** is +4, one unpaired electron was most probably delocalised in the ligand.[61]

The square-planar Co(II) complex of ligand **19** was applied for the catalytic oxidation and deformylation of cyclohexanecarboxaldehyde using nitrous oxide as the terminal oxidant.[62] The nature of the cobalt species resulting from N_2O activation could not be determined, but this catalytic reaction was remarkable since this highly toxic gas is kinetically inert under mild conditions and N_2 was obtained as the sole by-product.



Scheme 8. Tetradentate dianionic ligand **19** and high valent nickel complexes reactive toward organic substrates.



Scheme 9. Synthesis of **23** by 2:2 condensation of pyridine-2,6-dicarboxaldehyde and 1,4,7-triazaheptane and dinuclear Cu(I), **24**, and Cu(II), **25**, complexes.[64]

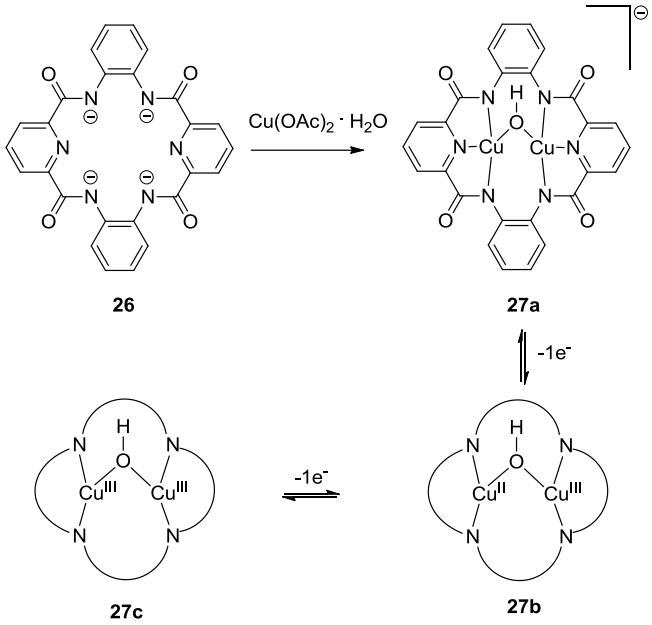
2.3. Dinuclear metal complexes

In the effort to find mechanistic proof for the active sites of many natural enzymes active in oxidation chemistry, the scientific community has often driven his attention to the synthesis of dinuclear complexes.

Both hemocyanin and tyrosinase enzymatic proteins possess a dinuclear copper(I) active site. Rockcliffe and Martell in 1995 reported on the stoichiometric and catalytic oxidation of hydroquinones, phenols and catechols, by dinuclear copper complexes.[63] The $[Cu^{I}_2(PD)_2(DIEN)_2]^{2+}$ complex, **24**, was found to react readily in the presence of O_2 to yield a thermally unstable dioxygen adduct, degrading to the $[Cu^{II}_2(PD)_2(DIEN)_2]^{4+}$ complex **25** (Scheme 9).[64] A kinetic study on the stoichiometric reaction of substrates with the dioxygen adduct of complex **24** and complex **25** revealed that copper(I) oxidation occurred faster than copper(II) oxidation. The highly distorted square pyramidal geometry proposed for complex **25** was suggested to be the reason for the effectiveness of the catalyst for the oxidation of catechols. When the initiator for the catalytic cycle was **24**, the essential steps are the oxygen uptake to form a peroxo complex, the coordination of the substrate followed by its oxidation, with the consequent formation of the desired product and the copper(II) complex **25**. Finally, substrate oxidation by the Cu^{II} restored the copper(I) complex.

A related approach to mimic the dinuclear type-3 site of copper proteins was reported by Driessen and Reedijk.[65] In their approach, a square pyramidal N_3O_2 coordination environment for the copper ions was provided by a macrocycle with built in pyrazole groups and two pendant pyridine groups.[66] Again, dioxygen uptake between two copper(I) ions to form a peroxo complex was observed, and the enhanced protective nature of the macrocyclic ligand slowed down the decomposition reaction. These complexes were competent catalysts for the oxidative coupling of 2,6-dimethylphenol (DMP). Full conversion of the substrate was never observed, probably because of the formation of inactive copper hydroxide species.[67]

Pyridine(dicarboxamide) are strongly electron-donating ligands, well known for the preparation of highly reactive copper complexes.[68] Cramer and Tolman, taking advantage of the macrocyclic ligand **26**, comprising two pyridine(dicarboxamide) units, recently reported a hydroxo-bridged dicopper(II,II) complex, **27a**, and its stepwise oxidation to mixed-valence Cu^{II}/Cu^{III}, **27b**, and Cu^{III}/Cu^{III}, **27c** (Scheme 10).[69] Identification of these species was relevant to the proposed mechanism of catalytic hydrocarbon oxidations promoted by copper sites in metallo-enzymes, and potential catalytic applications of the system can be sought of.

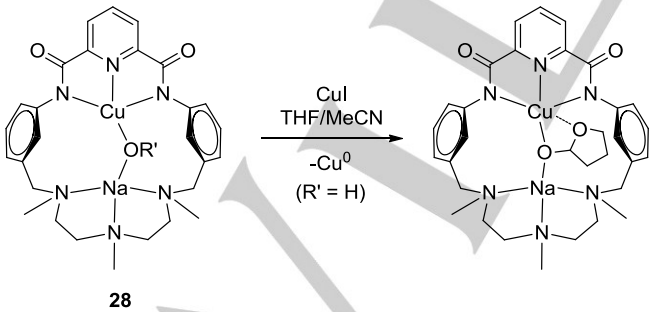


26 **27a** **27c** **27b**

Scheme 10. Macrocyclic ligand **26,** comprising two pyridine(dicarboxamide) units, and dicopper complexes **27a-c.**

A related ligand with ethylene linkers instead of the *orto*-phenylene bridges was reported to yield monocopper complexes instead. In this case, the X-ray analysis revealed the formation of hydrogen bonds between the free doubly protonated carboxamide groups and the copper(II) ion.[70]

A heterodimetallic macrocyclic complex, **28**, comprising a Cu^{II} ion coordinated to a pyridine(dicarboxamide) linked to Na^+ metal ion bound to a triamine fragment capable of promoting the hydroxylation of THF was also reported (Scheme 11).[71] Interestingly the C-H activation to give THF hydroxylation occurred with the involvement of the coordinated Na^+ ion kept in near proximity of the active Cu hydroxo unit.

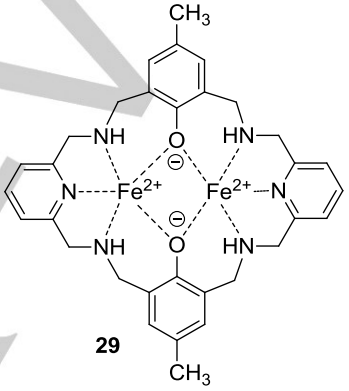


28

Scheme 11. Hydroxylation of THF promoted by the heterodimetallic complex **28**.

Dinuclear macrocyclic complexes of iron(II) proved to be efficient catalysts for the hydrocarbon oxidation by molecular oxygen.[72]

Again, the synthetic approach chosen by the Martell's group to the macrocyclic ligand involves a 2:2 condensation, but this time, before complex formation, the imine functionalities of the tetra Schiff base were hydrogenated. The presence of four relatively hard saturated nitrogen donor atoms interacting with the metal ion only through σ bond,[2] and of two phenolate donor groups capable of neutralizing and strongly coordinate divalent iron, allowed the isolation of dinuclear Fe^{II} complex **29**. A remarkable catalytic activity of complex **29** in hydrocarbon hydroxylation by molecular oxygen in the presence of H_2S, acting as a two electron reductant was observed (Scheme 12). The proximity of the two ferrous atoms, constricted by the 24-membered macrocyclic ligand, was proposed to favour the formation of a peroxo-bridged dinuclear Fe^{III} complex.[72a]



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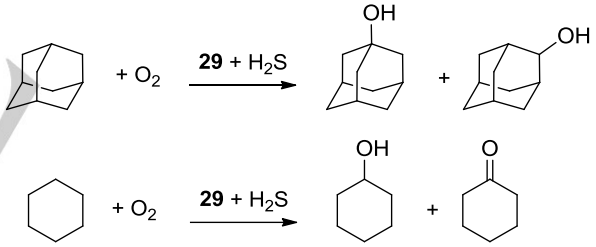


Scheme 12. Hydrocarbon oxidation reactions catalysed by the dinuclear Fe^{II} complex **29**.

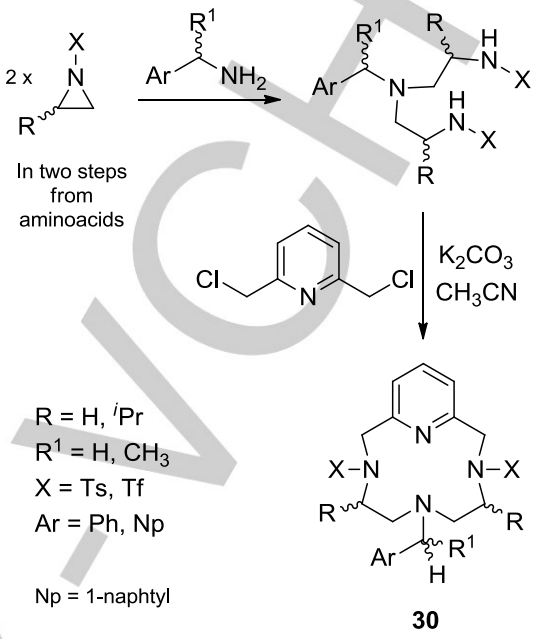
3. C-C and C-O bond forming reactions

Carbon-carbon and carbon-heteroatom bond forming reactions are of fundamental importance in their capability of generating molecular complexity.[73] In this context, transition metal catalyst plays a fundamental role serving as versatile tool to efficiently promote stereoselective C-C and C-X bond formations. The ligand design is of cornerstone value: ligands must be tailored not only for a given reaction, but also for each individual substrate because even small changes can affect the catalyst performance to a significant extent. In this respect, the quest for ligands that can be easily adapted through modular design is of high interest, since the effort required to adapt the ligand to the reaction are much smaller than for ligands with little structural variability.[74] Tetraazamacrocycles, such as cyclen (1,4,7,10-

tetraazacyclododecane) or its derivatives bearing functional groups on the nitrogen atoms, have attracted much attention in recent years due to their ability to form stable complexes with a wide range of metal ions. The macrocyclic framework can be adjusted by changing the nature of the donor atoms and the conformation flexibility of the ring system in order to obtain pre-organised ligands able to bind certain metal ions. Introduction of a pyridine ring in the skeleton of these tetraazamacrocycles was aimed at enhance the stereochemical rigidity of the resulting complexes, which could results in an increase of their thermodynamic stability. The pyridine moiety may also provide a suitable site for a further functionalization, which may facilitate the binding ability of the ligand itself. In the quest for a robust ligand, easy to modify, to form stable metal complexes in a plethora of different stereoselective C-C and/or C-X bond formation reactions, pyridine containing macrocyclic ligands can play a significant role.

3.1. 12-Membered Pyridine-Containing Ligands (Pc-L)

In the field of asymmetric catalysis, the synthesis of enantiomerically pure cyclopropanes is still a challenge, although many different approaches were designed and excellent results were achieved.[75] Caselli and co-workers became interested in the stereoselective synthesis of cyclopropanes several years ago when they reported the synthesis of a Co^{II} complex of a chiroporphyrin and its use in asymmetric carbene transfer reaction to alkenes.[76] Although very modest diastereo- and enantioselectivities were obtained, a careful design of the chiral porphyrin and the use of Ru^{II} and Fe^{III} allowed to improve the results and to obtain excellent *trans* diastereoselectivities, with good to very high *ee*.[77] Others metals in combination with different ligands were employed by the group as catalysts for cyclopropanation reactions.[78] In 2008, we reported the synthesis and characterization of copper(I) complexes of a new class of 12-membered pyridine-containing tetraazamacrocyclic ligands (Pc-L*) and we showed their ability to promote the asymmetric cyclopropanation of alkenes by ethyldiazoacetate (EDA).[79] The practical and efficient modular access to this class of macrocycles, together with the high yields obtained, was a key feature for the development of new synthetic methodologies in obtaining “tailored” ligands. The key step in the synthesis of the macrocyclic ligands, Pc-L*, **30**, was the assembly of the pyridine unit from the reaction of a 2,6 disubstituted methyl pyridine functionalised with a suitable leaving group with an opportunely designed non racemic bis(sulfonamide) under heterogeneous reaction conditions (yields up to 90%). The bis(sulfonamides) are obtained in good global yields and enantiomerically pure starting from a primary amine and an aziridine as outlined in Scheme 13. At the outset, N-tosyl (Ts = tosyl) protected aziridines were chosen as starting material for two major reasons: i) the tosyl protecting group has a dual role, both as a protecting group and as activating electron-withdrawing centre; ii) the resulting macrocycle possess two strongly coordinating N donor atoms and two less basic N-Ts donor atoms that can provide a more flexible coordination sphere around the metal (*vide infra*). Following that general approach, a small library of macrocyclic pyridine containing ligands with either C_1 or C_2 symmetry was synthesized.[80]



Scheme 13. Synthetic scheme for pyridine-containing ligands (Pc-L*) **30**.

X-ray diffraction studies conducted on the ligands, their protonated salts and Cu^{I} [80] and Ag^{I} [81] complexes, allowed the characterization of the very different conformations of the macrocyclic skeleton, which could be influenced by the substituents R, R’ and Ar, by the complexation to the metal or by the presence of a coordinating external ligand. When Ar was 1-naphtyl, it acted as a further coordination site for the metal ion, as shown for the copper(I) complex **31a** (Figure 4).[80] The crystal structure of this complex was better described as possessing a tetracoordinate copper(I) despite the presence of five potential coordination sites, with the metal ion shifted to one side of the macrocyclic cavity for steric reasons, resulting in a distance with one of the two N-Ts protected donor atom well above regular Cu-N bond distances. Addition of an external ligand such as CH_3CN caused a drastic change in the ligand conformation. The structure of complex **31b** showed the metal ion placed in the middle of the macrocyclic cavity and truly pentacoordinated in a strongly distorted trigonal bipyramidal geometry, with the two N-Ts donor atoms occupying elongated axial sites.[80] Bulkier silver(I) atom was instead found in a geometry closer to a regular square pyramid with a strong coordination to the CH_3CN external ligand and again weaker coordination to the N-Ts groups, as depicted for complex **32a**.[81] However, when the solvent molecule was water, two different molecules with different conformations and coordination modes were found in the asymmetric unit. One of the two independent molecules, shown in Figure 4 as complex **32b**, possessed again a distorted conformation of one N-Ts groups that brings one oxygen atom very close to silver, resulting in a distortion of the

ideal square pyramidal geometry and the coordination at the metal was extended to six.[81] All these structural features are particularly relevant to catalysis, since it may be assumed that the ligand can adapt its conformation to the coordination geometry required for a given transition state.

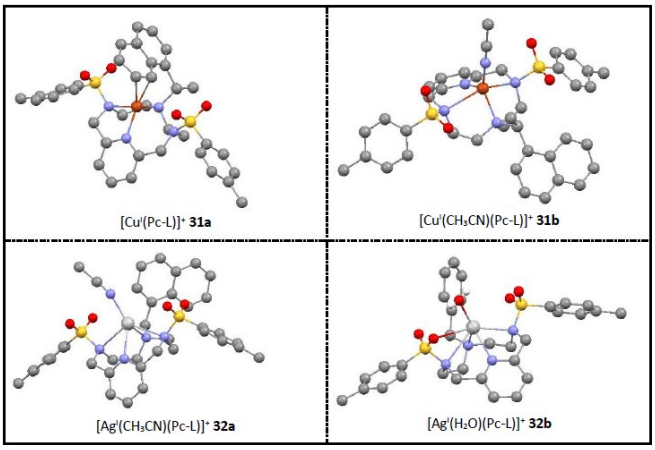
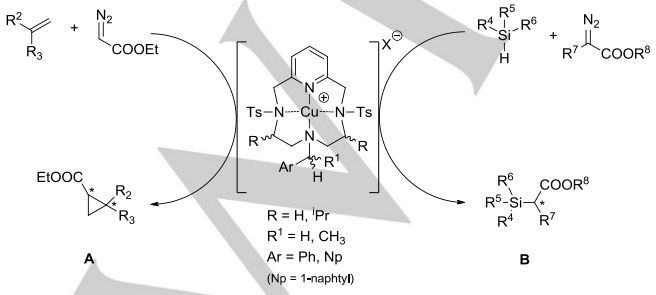


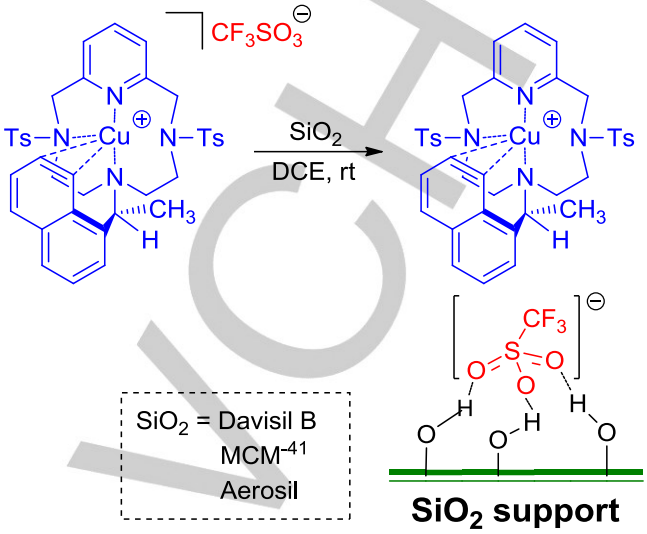
Figure 4. Structures of some copper(I) and silver(I) complexes of pyridine-containing ligands (Pc-L*), showing the very different conformations of the macrocyclic skeleton. In all cases, hydrogen atoms and the counter ions were omitted for clarity.

Copper(I) complexes of Pc-L ligands **30** were successfully applied as catalyst in the enantioselective cyclopropanation reaction of alkenes by EDA (Scheme 14, **A**).[80] Although with rather modest diastereoselectivities, high yields of cyclopropane products with up to 99% *ee* with both aliphatic and aromatic olefins were obtained.[80]

The presence of a triflate counterion in the copper(I) complexes of ligands was exploited to graft the catalysts on different ordered and non-ordered silicas trough supported hydrogen bond (SHB), as shown in Scheme 15. No need of ligand modification was required and the grafted complexes showed catalytic performances comparable or even higher to those observed in the homogeneous phase and a good recyclability (only after seven consecutive runs a decrease in activity was observed).[82] Commercially available silicas could be used as support, despite their acidity.



Scheme 14. General scheme for the Cu(I) catalysed cyclopropanation reactions (**A**) and Si-H bond insertion reactions (**B**).



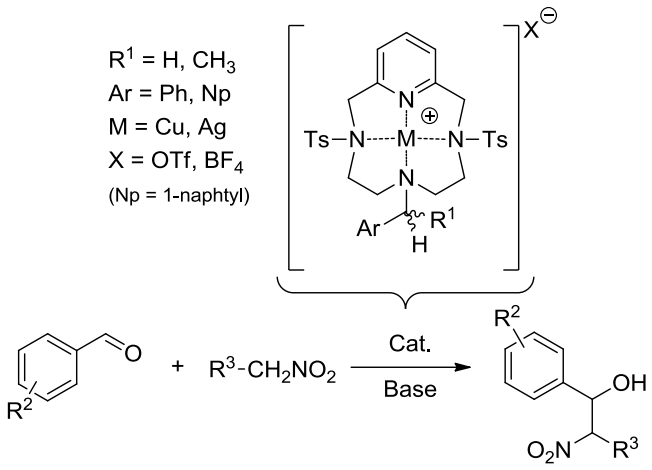
Scheme 15. General synthesis of supported catalysts (SHB).

It was shown that the copper site of the supported catalyst has a "solution like" behaviour and was fully accessible to small molecules. In order to shift to a more sustainable and greener solvent, cyclopropanation reactions were run in flow conditions employing carbon dioxide as a carrier.[83] The heterogeneised system under flowing CO_2 showed chemoselectivities comparable or even higher than those observed for the homogeneous counterpart. The catalyst activity was prolonged in time and it was shown that chemoselectivity increased upon prolonged time, probably due to the poisoning of the parasite active site (acidic silanols) of the non-innocent support, leaving "at work" only copper(I) single sites. In terms of enantioselectivity, very good results were obtained in particular with non-activated double bonds, such as that of 1-octene. Catalysts were stable and negligible copper leaching was observed, and TON up to 440 were obtained, just re-feeding the reactor with the reagents.

More recently, Caselli and co-workers also studied the reactivity of complex **31a** with diazocompounds to promote X-H bond insertion reactions.[84] Excellent results in terms of chemoselectivity were obtained with Si-H bonds, showing a broad scope and functional group as well as steric hindrance tolerance, accompanied with a remarkable robustness as indicated by high TON numbers (Scheme 14, **B**). The reactivity was also extended to N-H or O-H bonds of anilines and phenols. Unfortunately, the enantioselective outcome of the carbene insertion was very sensitive to the "carbene" steric hindrance, and when using bulkier disubstituted diazocompounds such as ethyl-2-diazo-2-phenyl acetate, only very modest *ees* were observed.

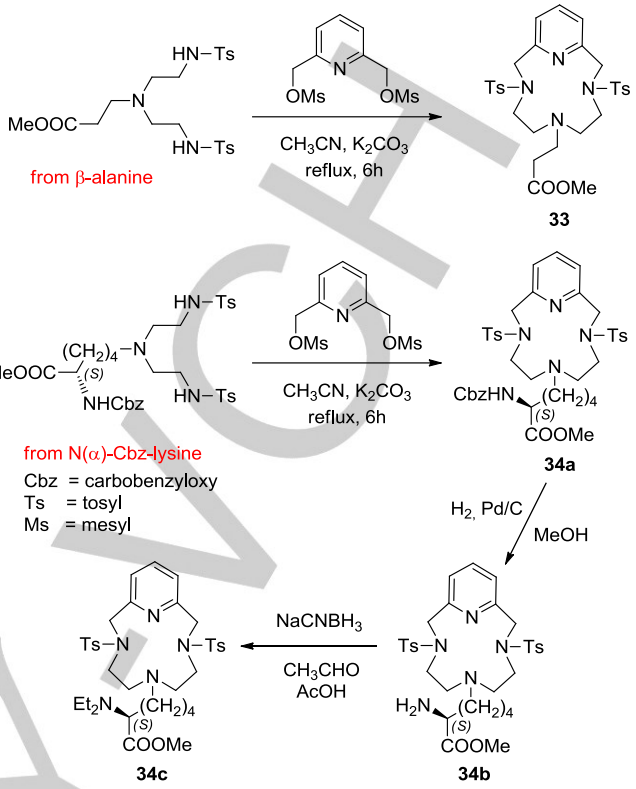
The Henry (or nitroaldol) reaction can be considered amongst the most valuable C-C bond forming reactions, since all the atoms of the starting reagents are found in the formed

product.[85] Copper(I) complexes of non-chiral Pc-L ligands showed a good efficiency in promoting the coupling of nitroalkanes with electron-poor, and to a lesser extent also electron-rich, aromatic aldehydes under mild conditions.[86] Surprisingly, very good catalytic activities were observed also with the related silver(I) complexes, and to the best of our knowledge this was the first report in which silver(I) complexes were used to promote the Henry reaction (Scheme 16).[87]



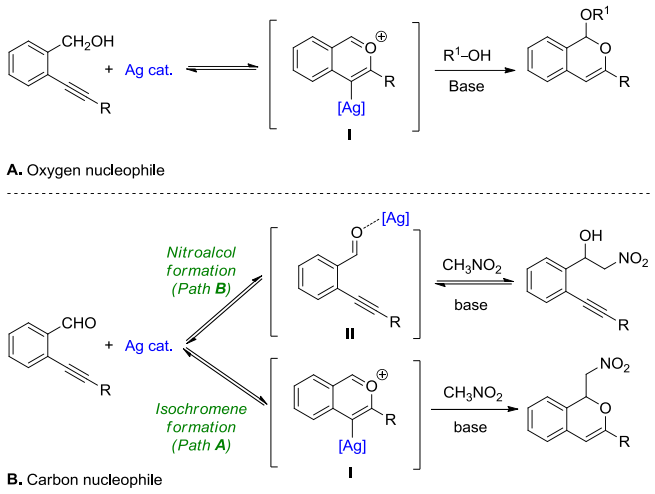
Scheme 16. General scheme for the Cu(I) and Ag(I) catalysed Henry reaction.

Results obtained compared well with the state of the art and, if weighted with Cu(I) Pc-L complexes, better yields in shorter reaction times were observed. In addition, a careful design of the ligand, allowed to introduce a suitable functional group embedded into the macrocycle framework. The free amine group of natural aminoacids was used for the synthesis of the ligands **33** and **34**, as depicted in Scheme 17. Metal complexes of ligand **34c**,[88] possessing a tertiary amine functionality as pendant arm were exploited as a bifunctional catalyst, and used to catalyse the Henry reaction in short reaction times without the need for an added external base.[87] Unfortunately, also in this case, control of the enanioselective reaction outcome proved to be more complex than for cyclopropanation reactions and further efforts devoted to structural modifications of the ligands will be needed in order to obtain products in good *ees*.

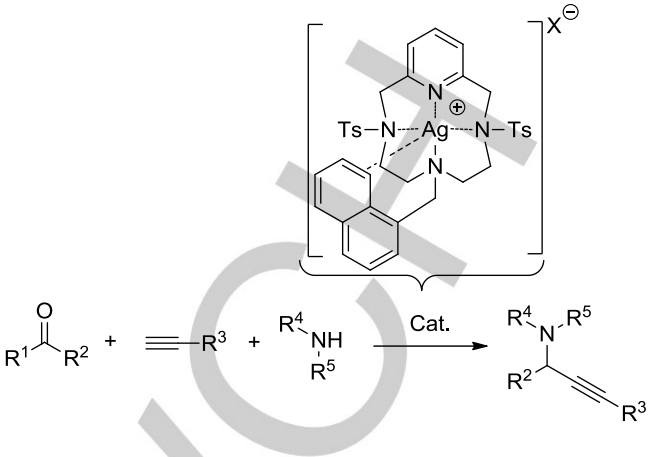


Scheme 17. Synthesis of aminoacid derived macrocyclic ligands **33** and **34**.

Silver(I) complexes are endowed with both a σ-philic and π-philic character.[81] Silver(I) triflate was reported to be quite effective in the domino intramolecular cyclisation of 2-alkynylacetophenones.[89] The increased solubility and the enhanced thermodynamic stabilities of macrocyclic complexes were exploited to synthesize in a stereoselective manner 3-substituted-1-alkoxyisochromenes starting from 2-alkynylbenzaldehydes and alcohols as nucleophiles in the presence of silver(I) complexes of Pc-L ligands **30**.[90] The absolute regioselectivity, the mild conditions employed and the excellent yields of pure products without the need of further purification steps were the major features of these silver(I) catalysed addition/cycloisomerisation reactions. An in-depth kinetic ^{1}H NMR study accompanied by an aimed trapping experiment allowed us to propose the silver(I) catalysed formation of an isochromenilium ion as main intermediate involved in the reaction mechanism (Scheme 18, **A**).



Scheme 18. Ag^{I} catalysed synthesis of isochromenes.



Scheme 19. General scheme for the Ag(I) catalysed A3-coupling.

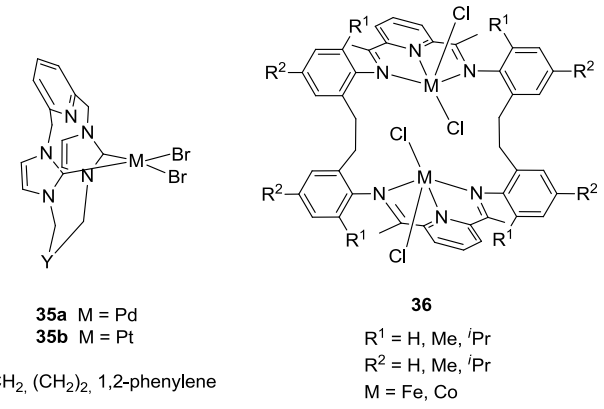
A logical consequence of these finding was the combination in a single domino sequence of the Henry reaction of a 2-alkynylbenzaldehyde and the cycloisomerisation to yield 1-(α-nitroalkyl)-isochromenes.[87] Although associated with strong limitations, we have shown that this cascade reaction can occur and that the mechanism again involves a preliminary silver(I) catalysed cycloisomerisation of the 2-alkynylbenzaldehyde to form an isochromenilium intermediate, followed by the attack of the nitronate anion. The chemoselectivity was low because of the competing formation of the nitroalcohol *via* the Ag(I) catalysed Henry reaction (Scheme 18, **B**).

Finally, in connection with the interest in the study of metal catalysed domino[91] and multicomponent[92] processes of alkynes, carbonyl compounds and amines, Caselli, Abbiati and co-workers showed that the well-defined silver(I) Pc-L complexes were able to efficiently promote the coupling among aldehydes, terminal alkynes and amines (A^3-coupling) to yield propargylamines (Scheme 19).[93] The use of microwave heating allowed a lower catalyst loading (3% mol), a reduced ratio between the three starting reagents in short reaction times (5 min) and a broad reaction scope, including aryl/alkyl aldehydes, aryl/alkyl acetylenes and secondary aliphatic amines. More challenging substrates, such as anilines and ketones were tested as reaction partners, although with modest results.

3.2. Miscellaneus

Recently, the group of prof. Biffis reported the synthesis of a chelating macrocyclic dicarbene ligand bearing a 2,6-lutidinyl bridge.[94] The palladium(II) and platinum(II) complexes were prepared and characterised. As expected, the pyridine nitrogen in square planar metal complexes **35a** and **35b** was found outside the coordination sphere, but close to the metal ion. Oxidation of the Pt^{II} centre to Pt^{IV}, caused a change in the coordination sphere assisted by the pyridil group to give an octahedral geometry (Figure 5). Furthermore, the pyridine N-donor atom was able to help in promoting the catalytic role of the Pd^{II} complex **35a** in copper- and amine-free Sonogashira reactions.

Dinuclear iron and cobalt complexes of a bifunctional macrocyclic ligand, possessing two bis(imino)pyridine groups, were prepared (**36**, Figure 5).[95] The iron(II) complex catalysed the ethylene polymerization under mild conditions to yield polymers with a relatively narrow molecular weight distribution.[96] The dinuclear complex showed a higher thermal stability and prolonged catalyst lifetime when compared to mononuclear complexes. A cooperative interaction between the growing polymer chain and the second metal centre was proposed to be the reason for the higher catalyst stability and the diminished tendency to give chain transfer.



35a M = Pd
35b M = Pt

Y = CH_2, $(CH_2)_2$, 1,2-phenylene

36

R^1 = H, Me, ^{i}Pr
R^2 = H, Me, ^{i}Pr
M = Fe, Co

Figure 5. Group 10 metal complexes of chelating bridging dicarbene ligands, **35**, and double decker type dinuclear metal complexes **36**.

4. Conclusion

The introduction of a pyridine moiety into the skeleton of macrocyclic ligands presents several advantages in terms of both thermodynamic stability and coordination kinetics of their metal complexes. These features were largely exploited in catalysis. On the one hand, high oxidation states are easily accessible, and this has allowed shedding light on the mechanism of oxidative reactions catalysed by metallo-enzymes, as well as the synthesis of extremely active oxidation catalysts. One feature that remains challenging is the stability of the ligand to the harsh oxidizing conditions employed during the catalysis. The recent progresses made showed that very robust metal complexes could be synthesized by taking advantage of simple synthetic procedures, if the more oxidation-fragile moieties (*i.e.* imine functionalities, N-H bonds) were suitably protected. When dealing with C-H bond oxidation reactions, a particular attention should be given to selectivity, but also in this respect, several metal complexes of pyridine-containing macrocyclic ligands were shown to be particularly capable.

Several different synthetic routes can be followed for the synthesis of that pyridine containing macrocycles, and for most synthetic paths, a large modularity is observed. This allows for the target synthesis of substrate and/or reaction specific ligands that can be exploited in steroselective synthesis. However, especially in this respect, progress should be made in order to address enantioselective catalysis, where a strict control of the transition state is needed and a too large conformational flexibility may be detrimental.

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Keywords: macrocycles • pyridine containing macrocyclic ligands • catalytic oxidations • C-C bond forming reactions • homogeneous catalysis

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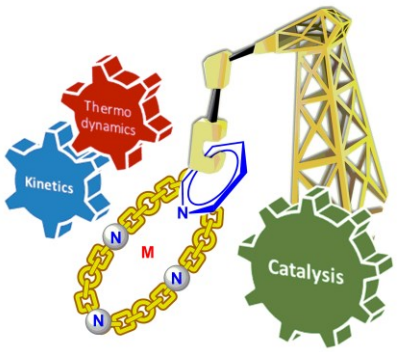

Pyridine containing Macrocyclic complexes

*Giorgio Tseberlidis, Daniela Intrieri, Alessandro Caselli**

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