Universitat de Girona

NEW RUTHENIUM COMPLEXES CONTAINING N, P AND S-DONOR TYPE OF LIGANDS: COORDINATION CHEMISTRY, CHARACTERIZATION AND APPLICATION TO ASYMETRIC AND NON-ASYMETRIC CATALYSIS

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New Ruthenium Complexes Containing N, P and S-Donor Type of Ligands: Coordination Chemistry, Characterization and Application to Asymmetric and non-Asymmetric Catalysis

PhD Dissertation presented by

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Els sotasignants Antoni Llobet i Dalmases i Montserrat Rodríguez Pizarro, Professor Catedràtic i Professora Agregada de l'Àrea de Química Inorgànica de la Universitat de Girona respectivament,

CERTIFIQUEM que la memòria que porta per títol "New Ruthenium Complexes Containing N, P and S-Donor Type of Ligands: Coordination Chemistry, Characterization and Application to Asymmetric and non-Asymmetric Catalysis" aplega el treball realitzat sota la nostra direcció per en Xavier Sala Román, llicenciat en Química, i constitueix la seva memòria per optar al grau de Doctor en Química.

I perquè consti a efectes legals, signem aquest certificat.

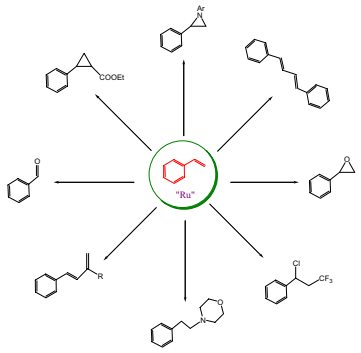
Girona, 5 de Desembre de 2006

Prof. Dr. Antoni Llobet i Dalmases

Dra. Montserrat Rodríguez Pizarro

Graphical Abstracts

Chapter 1. General Introduction (pages 1 – 34)

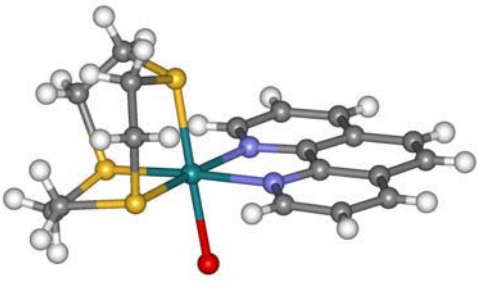


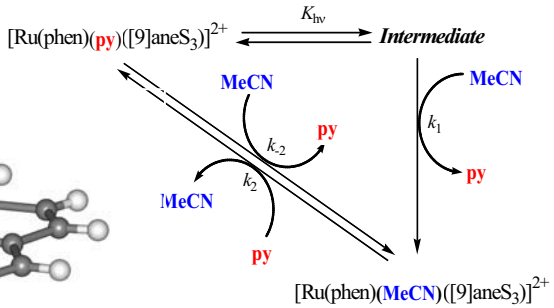
Situate the reader in the field of study of the thesis is the aim of this chapter. General aspects, major breakthroughs and recent advances in ruthenium coordination chemistry are described. Within the wide range of applications reported for these compounds, asymmetric catalysis and molecular-level machines will be central matters in the following chapters and, therefore, specially highlighted here.

Chapter 2. Objectives (pages 35 – 40)

Chapter 3. Papers A and B (pages 41 – 70)

Synthesis, Structure, Redox Properties and Substitution Mechanism of new Ru(II) Complexes containing the 1,4 7–Trithiacyclononane and 1,10–Phenantroline ligands

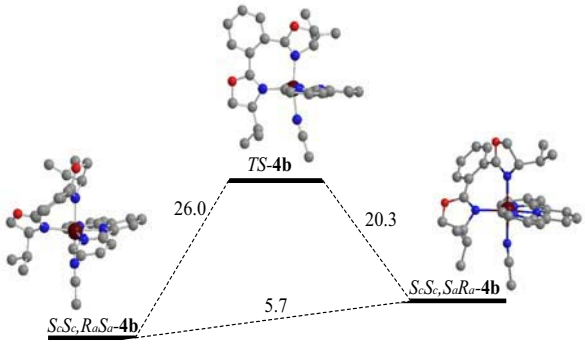




The synthesis, spectroscopic characterization and redox properties of a new Ru-H_2O complex containing 1,10-phenantroline and the soft [9]aneS_3 ligand are reported. Even though its higher oxidation states are not stable, they are sufficiently reactive to rapidly oxidize benzyl alcohol to benzaldehyde. Furthermore, the substitution pathways of a new Ru-py complex, $[Ru(phen)(py)([9]aneS_3)]^{2+}$, to form the corresponding Ru-NCMe complex, $Ru(phen)(MeCN)([9]aneS_3)]^{2+}$, have been established through kinetic analysis with and without irradiation. Electronic effects exerted by the [9]aneS_3 macrocycle on the Ru center are responsible for the relatively high rates of substitution obtained, and have allowed the kinetic establishment of a reaction intermediate.

Chapter 4. Papers C and D (pages 71 – 116)

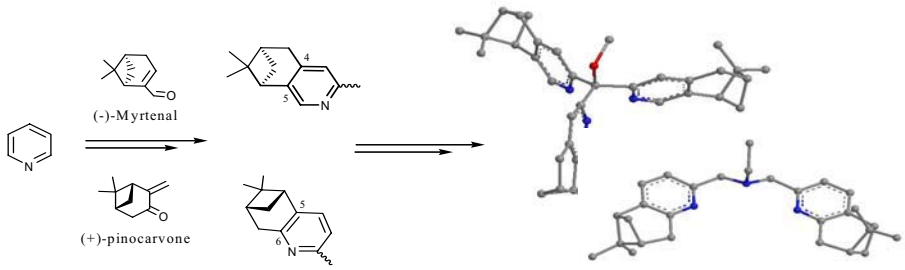
New Ru(II) Complexes Containing a Chiral Didentate Oxazolinic Ligand. Synthesis, Redox Chemistry and Atropisomeric Discrimination



A new family of Ru(II) complexes containing the chiral 1,2-bis(oxazolinyl) benzene ligand is described and thoroughly characterized. Rotationally restricted isomers are produced upon coordination to a ruthenium metal centre. These isomers show significantly different energy values due to steric effects between the oxazolinic and the auxiliary ligands, thus allowing the direct synthesis of pure atropisomers.

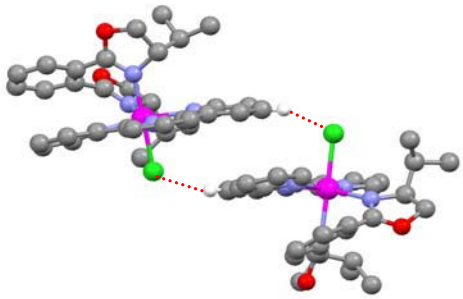
Chapter 5. Papers E, F and G (pages 117 – 186)

Ruthenium Catalysts for Asymmetric Oxidations and Reductions: Ligand Synthesis, Coordination Chemistry and Catalytic Performance



New synthetic routes towards chiral "pineno-fused" N-donor ligands are described here. A wide set of Ru(II) complexes containing different combinations of this and other chiral/achiral N-/P-donor ligands is also reported and their catalytic ability to reduce and oxidize C=C double bounds is evaluated. The enantioselective hydrogenation of a challenging enamide (N-(3,4-dihydro-2-naphthalenyl)-acetamide, **1**) has been performed using *cis-fac*-Δ-[Ru^{II}Cl{(*R*)-(bpea)}{(*S*)-(BINAP)}]BF_4, *cis-fac*-Δ-(*R*)-(*S*)-**3**, as catalyst achieving good conversions and enantioselectivities up to 74%. Also, promising results in styrene asymmetric epoxidation have been achieved using [Ru^{II}Cl(tpmOMe)(*bpy*)](BF_4), **5**, with ee up to 36%.

Chapter 6. Results and Discussion (pages 187 – 220)



A general view of the work presented in Chapters 3-5 is provided here. Extra information not included in the papers but relevant for purposes of comparison is also added and discussed. As is intended, this chapter tries to provide linkage between the previously proposed objectives (Chapter 2) and the experimental results obtained in the laboratory, being a way to enter in the general conclusions of this thesis (Chapter 7).

Chapter 7. Conclusions and Future Work (pages 221 – 226)

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Glossary of Terms and Abbreviations

ν (in IR):	frequency (units: cm^{-1})
δ:	chemical shift (units: ppm)
μ	ionic force
abs:	absorbance
AcO	Acetate
bpy	2,2'-bipyridine
COSY	correlation
cod	cyclooctadyene
CV	cyclic voltammetry
dmso	dimethyl sulfoxide
dppe	1,2-diphenylfosphineethane
E°	standard redox potential
$E_{1/2}$	half-wave potential
$E_{p,a}$	anodic peak potential
$E_{p,c}$	cathodic peak potential
ESI-MS	electrospray ionization mass spectroscopy
EtOAc	ethyl acetate
FT-IR	fourier transform infrared spectroscopy
HETCOR	heteronuclear chemical shift correlation
J	coupling constant
m (in IR)	medium
m/z	mass-to-charge ratio
Me	methyl
MLCT	metal-to-ligand charge-transfer
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser spectroscopy
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	Phenyl
py	pyridine
s (in IR)	strong
sh (in UV-vis)	shoulder
TBAH	tetrabutylammonium hexafluorophosphate
TMS	tetramethylsilane
trpy	2,2' :6', 2"-terpyridine
vs	versus
w (in IR)	weak

Chapter 1

General Introduction

This chapter provides the motivation for the research presented in this thesis and is intended to situate the reader in the field of study, coordination chemistry. General aspects and recent advances in ruthenium coordination compounds are discussed. Ruthenium complexes find application in most of the areas where coordination chemistry is present. Therefore, its relevance in such different fields as molecular switches and catalytic asymmetric oxidations and reductions are described and its major breakthroughs highlighted.

1.1 Coordination Chemistry

Since Werner's pioneering work, coordination chemistry has maturated in a continuous way, being bioinorganic and bio-mimetic chemistry and the growing interest in materials its latest driving forces. Nowadays, coordination compounds are involved in an unbelievable wide range of applications that can be divided in the following areas: (i) use of coordination complexes in all types of catalysis; (ii) applications related to the optical properties of coordination complexes, which covers fields as diverse as solar cells, nonlinear optics, display devices, pigments and dyes, and optical data storage; (iii) hydrometallurgical extraction; (iv) medicinal and biomedical applications of coordination complexes, including both imaging and therapy; and (v) use of coordination complexes as precursors to semiconductor films and nanoparticles. If nothing else, such an extensive list of applications can be employed, as suggested by Professor Ward in last edition of *Comprehensive Coordination Chemistry*,[1] as a suitable answer to the eternally irritating question that everyone involved in this field get asked at parties when we reveal what we do for a living: "But, what's it for?"

1.1.1 Ruthenium Coordination Chemistry

The electronic configuration of ruthenium, $4d^7\ 5s^1$, makes this metal, together with osmium, unique among all the elements in displaying the widest range of oxidation states in their complexes, i.e., from oxidation state -2 in $[Ru(CO)_4]^{2-}$ to +8 in RuO_4, corresponding to d^0 to d^{10}. Consequently, ruthenium complexes are redox-active and their application as redox reagents in many different chemical reactions is a topic of much current interest. Other general characteristics of ruthenium's coordination compounds are their high electron transfer capacity[2] and their ability to stabilize reactive metal species like oxo-metals[3] and metal-carbene complexes.[4]

Ruthenium complexes are an example of how coordination compounds can find application in many different fields, compressing most of the areas listed above. Clear correlations can be observed between their properties and the nature of the ligands

bounded to the central metal ion. Therefore, ruthenium complexes with π-conjugate ligands or systems that enable electronic delocalization have shown specific properties in nonlinear optics,[5] magnetism,[6] molecular sensors[7] or liquid crystals.[8] Ruthenium sulfoxide complexes have been extensively studied due to their relevant usefulness in chemotherapy.[9] Ruthenium complexes with heterocyclic N-donor ligands, definitely the most employed ones, have received much attention owing to their interesting spectroscopic, photophysical and electrochemical properties, which lead to potential uses in diverse areas such as photo sensitizers for photochemical conversion of solar energy,[10] molecular electronic devices[11] and photoactive DNA cleavage agents for therapeutic purposes.[12]

Synthetic versatility, high oxidation states easily available and a robust character of its first coordination sphere are suitable characteristics that make ruthenium complexes perform also particularly well as catalysts. Above all, polypyridyl complexes of ruthenium with aqua ligands have been extensively employed in oxidation reactions of organic substrates, and multiple oxidative pathways have been detected including atom transfer, C-H insertion, and proton-coupled electron transfer.[3b] Other ligands like carbonyl, tertiary phosphines, cyclopentadienyl, and arenes and dienes have proven to serve effectively as the activating factors such as in hydrogen abstraction or generation of coordinative unsaturated species through the liberation of ligands.

1.2 Catalysis

As above mentioned, one of the main fields where coordination compounds find application is catalysis. This term, derived from the Greek words *kata*, which stands for down, and *loosen*, which means to split or break, was coined by Berzelius more than 150 years ago. Later, in 1895, William Ostwald was the first to write down a definition of a catalyst: 'A catalyst is a substance that changes the rate of a chemical reaction without itself appearing in the products'. Therefore, the current definition is slightly more accurate, though close to Ostwald's proposal: 'A catalyst is a substance that increases the rate of approach to thermodynamic equilibrium of a chemical reaction without being substantially consumed'.

Nowadays, the importance of catalysis to our society and our quality of life is unquestionable. The growing environmental concern due to the increase in chemical products demand forces the development of 'green' production methods. In this context, 'green' processes can be described as chemical conversions that consume a minimal amount of energy and resources, and produce the least waste. Catalysts make it possible. Its ability to change the reaction path, accelerating only the one with lower activation energy leads to the desired products with minimal input of energy. Therefore, today, almost 70% of all chemicals that are produced have been in contact with a catalyst somewhere in their synthesis process.[13] However, we are still far from nature's catalysts, the enzymes. They show us how amazingly efficient catalysts can be (making possible essentially all biological reactions) and, by comparison with today's technology, they show how much opportunity there is for improvement.

1.2.1 Homogeneous Catalysis

A catalytic system in which the substrates for a reaction and the catalyst are mixed together in one phase, most often the liquid phase, is known as homogeneous catalysis. Part of the work described in this thesis will focus on metal-complexes functioning as oxidation/reduction homogeneous catalysts. However, we should bear in mind that there are many interesting and important reactions carried out by metal-free homogeneous catalysts.

Ligand effects are crucial in homogeneous catalysis by metal complexes.[14] The catalytic properties of a given transition metal can be tuned through the nature of the ligands bonded to the metal centre. Therefore, one metal can give a variety of products from a single substrate simply by changing the ligands around it. As example, Figure 1.1 shows the different products that can be obtained from styrene with various ruthenium catalysts (not shown).

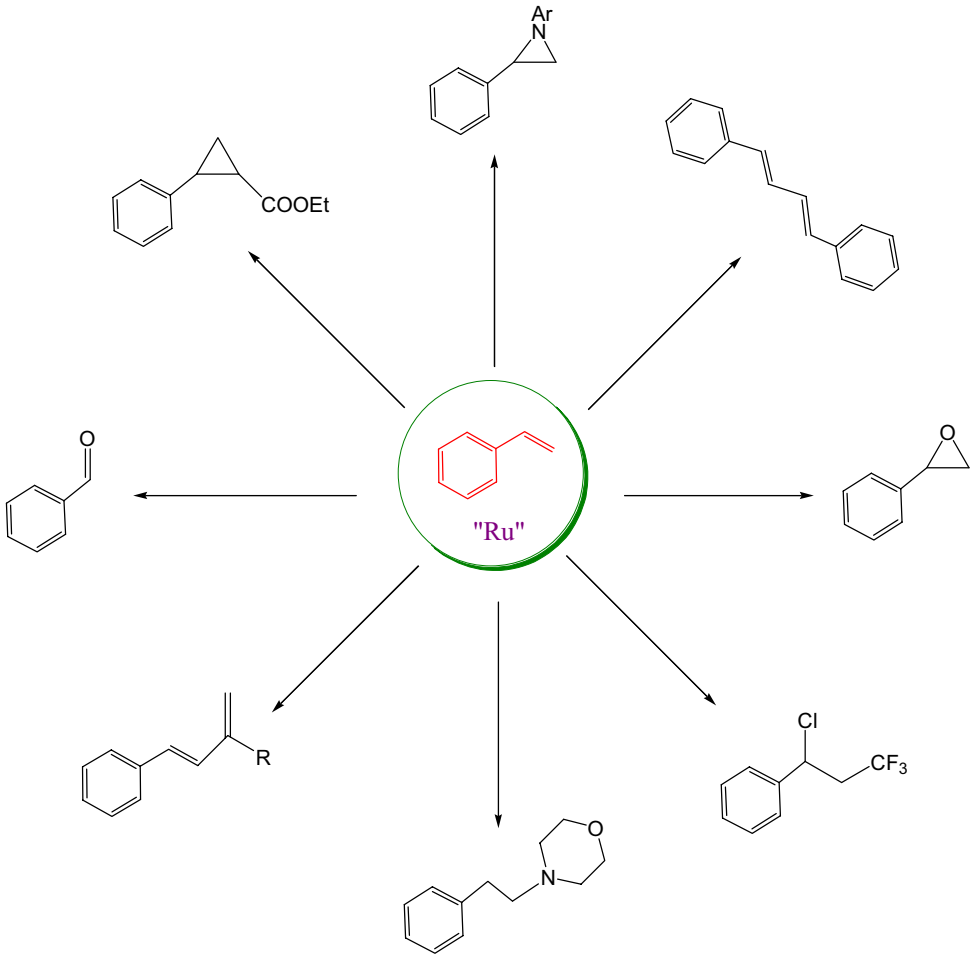


Figure 1.1 Ruthenium-catalyzed reactions of styrene.

Extraordinarily different reaction products can be reached from a single substrate through a correct election of the metal surrounding ligands. This exemplifies the key importance of knowing how electronic/geometric properties of the ligands can tune metal reactivity. Only this knowledge will enable us to rationally design better catalysts and achieve levels of effectiveness and selectivity comparables to the ones provided by nature's enzymes.

1.2.2 Ruthenium-Catalyzed Reactions

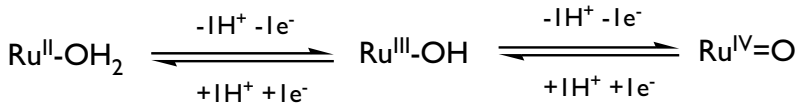
Until 1980s the reported useful synthetic methods using ruthenium reagents and catalysts were limited to a few reactions which include oxidations with RuO_4,[15] hydrogenation reactions[16] and hydrogen transfer reactions.[16] However, as the coordination chemistry of ruthenium complexes has progressed the same has occurred with its scope of applications. The great influence of this metal on organic transformations in recent years has now elevated its importance to the same level as palladium. Cyclopropanation, isomerization, metal-promoted radical reactivity, oxidation, hydrogenation, C-H and C-Halogen bond activation, olefin metathesis or metal-catalyzed bond cleavage are clear examples of the fascinating synthetic versatility feasible with ruthenium metal catalysts. Since excellent reviews[17] and books[18] exist covering all these topics, this introduction will mainly focus on the central aspects and recent advances of ruthenium-catalyzed oxidations and reductions, the reactions of choice along this thesis.

Ru-polypyridyl Aqua Complexes as Catalysts

Along the decades between 1940 and 1960 an extraordinary set of scientific papers was published by the Australian coordination chemist Frances P. Dwyer.[19] These contributions represented the beginning of the synthetic chemistry of polypyridyl ruthenium complexes. Then, and until now, the synthetic procedures firstly described in these initial publications have been used, expanded and improved enormously. In the late 1960s, Thomas J. Meyer and collaborators started a systematic study of these complexes and drew attention to their relevant reactive properties based in their accessibility to long-lived excited states and oxidation states varying form M(II) to M(VI).[20]

A particularly interesting situation within the redox chemistry of these complexes emerges when a water molecule is directly bounded to the metal centre, because redox properties of these Ru-aqua complexes are affected by proton exchange. As

shown in Scheme 1.1, the successive oxidations from Ru(II) to Ru(IV) are accompanied by a sequential proton losing favoured by the enhanced acidity of the bonded aqua ligand.



Scheme 1.1

A typical characteristic of these aqua complexes is the pH dependence of its redox potentials. Thus, Ru(III/II) and Ru(IV/III) transitions are shifted to lower potentials when a drop in the medium acidity takes place, attributable to the fact that higher oxidation states tend to be more acidic. The Nernst equation correlates pH with redox potential in such a way that, for a monoprotic and monoelectronic transfer, the redox coupling diminishes in 59 mV by every pH unit increased. The redox equilibria combine with the acid-base equilibria of all species involved and the dependence of the half wave redox potential, $E_{1/2}$, with respect to the complete pH range is represented in the so-called *Pourbaix* diagrams.

To illustrate the redox singularity of these ruthenium aqua complexes, Scheme 1.2 shows the corresponding Latimer diagrams of two sets of ruthenium complexes containing (2) and not containing (1) a water molecule directly bonded to the metal centre. The added electronic configurations make an important point. In these redox processes, electrons are gained and lost from $d\pi$ levels, no changes in the electron content occur in the σ-bonding framework. This is the reason for coordinative stability in three consecutive oxidation states and explains why these complexes have been so valuable in the study of electron transfer and redox reactions in general.

$$\underset{(d\pi^4)}{cis\text{-}[Ru^{IV}(bpy)_2(Cl)_2]^{2+}} \xrightarrow{1.7\ V} \underset{(d\pi^5)}{cis\text{-}[Ru^{III}(bpy)_2(Cl)_2]^{+}} \xrightarrow{0.0\ V} \underset{(d\pi^6)}{cis\text{-}[Ru^{II}(bpy)_2(Cl)_2]^{o}} \quad (1)$$

$$\underset{(d\pi^4)}{cis\text{-}[Ru^{IV}(bpy)_2(py)(O)]^{2+}} \xrightarrow{0.78\ V} \underset{(d\pi^5)}{cis\text{-}[Ru^{III}(bpy)_2(py)(OH)]^{2+}} \xrightarrow{0.67\ V} \underset{(d\pi^6)}{cis\text{-}[Ru^{II}(bpy)_2(py)(H_2O)]^{2+}} \quad (2)$$

(V versus NHE, μ = 0.1 at pH = 7)

Scheme 1.2 Latimer diagrams of Ru polypyridyl complexes containing (2) and non-containing (1) a water molecule

The example shown in eq 1 is typical for Ru polypyridyl couples with oxidation of Ru(II) to Ru(III) occurring at easily accessible potentials. The 1.7 V increase in potential for the Ru(IV/III) couple is due to the increase in charge and oxidation state compared to the Ru(III/II) couple.[21] In the couples shown in eq 2, the anionic Cl^- ligands are replaced by the neutral pyridine (py) and H_2O ligands. The increase in charge and changes in bonding increase the potential for oxidation of cis-$[Ru^{II}(bpy)_2(py)(H_2O)]^{2+}$ (Ru^{II}-OH_2^{2+}) to cis-$[Ru^{III}(bpy)_2(py)(OH)]^{2+}$ (Ru^{III}-OH^{2+}) by over 0.6 V compared to the analogous couple in cis-$[Ru^{II}(bpy)_2(Cl)_2]$.[22] The surprising point in eq 2 is the much smaller difference between the Ru(IV/III) and Ru(III/II) couples, 0.11 V compared to 1.7 V in (1). These data point to a dramatic stabilization of Ru(IV) in the aqua-containing coordination environment, causing the near overlap of Ru(IV/III) and Ru(III/II) potentials. There is an important implication for reactivity in this closeness of the redox potentials: thermodynamically, Ru(IV) is nearly as good a two-electron oxidant as a one-electron oxidant at pH 7. $d\pi_{Ru}$-$2p_{\pi,O}$ multiple-bond interaction is the key for the Ru(IV) stabilization.[23]

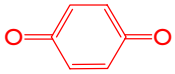
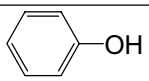
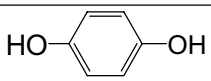
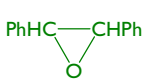
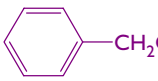
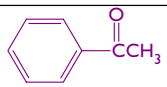
Ru=O Reactivity

The Ru^{IV}=O group transmits to its complexes a set of specific properties that enable them to operate as efficient oxidants for a wide range of substrates. Firstly, as mentioned above, the oxo groups stabilize high oxidation states and make them accessible at fairly low redox potentials. Furthermore, from a mechanistic point of view, its ability to accept two electrons can avoid radicalary reaction pathways of high energy and reactivity, [24] usually generated in monoeletronic transfers. Finally, the robust character of its first coordination sphere makes possible the easy exchange between Ru^{II} and Ru^{IV} without any dramatic change in the catalyst basic structure, being only the oxo group the one that modifies its composition.

The chemical versatility of these oxo complexes allows them to act following a wide variety of mechanistic pathways. Thus, Table 1.1 shows a compilation of oxidative pathways identified for cis-$[Ru^{IV}(bpy)_2(py)(O)]^{2+}$, probably the most paradigmatic and studied complex inside this family.[22, 25-33, 34] The mechanisms cited in this table are the result of a lengthy and exhaustive series of mechanistic studies through UV-visible and Infrared data, isotopic labeling, observation of intermediates, and kinetic isotope effects. The table lists the reductant, the oxidized product, the mechanistic pathway, rate constant information, and comments about the mechanism.

A really interesting point of these high oxidation state oxo complexes is the feasible modulation of its reactivity by tuning the redox potentials, modifying the accompanying ligands. This characteristic, jointly with the growing interest of the fine chemical industry to acquire selective catalysts for oxidation reactions, have promoted a huge number of systematic studies focused on the redox properties of these catalysts containing ligands of different natures.[35,36] The most relevant electrochemical information extracted from this extensive work is shown in Table 1.2 where the strong ligand effect over the Ru(IV/III) and Ru (III/II) redox couples can be clearly appreciated.

Table 1.1 Mechanistic Summary for cis-$[Ru^{IV}(bpy)_2(py)(O)]^{2+}$

Reduced Form	Oxidized Form	Pathway[ref]	k (25°C)[a] M^{-1} S^{-1}	Comment
$[Os^{II}(bpy)_3]^{2+}$	$[Os^{III}(bpy)_3]^{3+}$	Outer-sphere e^- transfer[26a]	$< 1 \times 10^3$ [b]	Slowed by intitial formation of cis-$Ru^{III}(bpy)_2(py)(O)^{2+}$
 Hydroquinone	 Benzoquinone	Proton-coupled e^- transfer[25]	9.6×10^5 [b]	$^kH_2O/^kD_2O = 30$
H_2O_2	O_2	Proton-coupled e^- transfer[26(b-c)]	1.7 [b]	$^kH_2O/^kD_2O = 22$
 Phenol	 Hydroquinone [c]	Electrophilic ring attak[27]	1.9×10^{-2}	$^kH/^kD = 5.5$ (C_5D_5OH)
$(CH_3)_2SO$	$(CH_3)S_2O$	O transfer[28]	17	Bound Sulfoxide observed
$(CH_3)_2SO$	$(CH_3)SO_2$	O transfer[28]	0.14	-
PPh_3	$O{=}PPh_3$	O transfer[29]	1.8×10^5	Bound Ru(II) and $O{=}PPh_3$ observed
Cis-, trans estilbè PhHC=CHPh	Cis-, trans- 	O transfer[30]	0.28 *trans* 2.5×10^{-3}, *cis*.	Bound Ru(II) epoxide observed
$PhCH_2OH$	PhCHO	H^- transfer[31]	2.4	$^kH/^kD = 50$
HCO_2^-	CO_2	H^- transfer[32]	4.2	$^kH/^kD = 19$
		C-H insertion[33]	0.6	$^kH/^kD = 18$ Bound Ru(II) ketone observed
		C-H insertion[34]	6.6×10^{-2}	Bound Ru(III) ketone observed

[a] In CH_3CN except where indicated. [b] H_2O (μ = 0.1). [c] Followed by rapid oxidation to the quinone. [d] Through an intermediate, bound alcohol complex that undergoes further oxidation.

The Ru (III/II) couple is, in general, strongly influenced by the ligands in such a way that Ru(II) is stabilized by $d\pi$-π^*(L) back-bonding in the presence of ligands (such as PPh_3 and CH_3CN, entries 17 and 18) having low-lying acceptor levels. However, electron-donating ligands as $acac^-$ or C_2O_4 (entries 2 and 3) clearly stabilize the Ru(III) oxidation state.[35c]

Table 1.2 Electrochemical Parameters for Aqua Complexes of Ru[a]

Entry	Complex	$E_{1/2}$ (V)			$\Delta E_{1/2}$ [c]
		$Ru^{III/II}$	$Ru^{IV/III}$	$Ru^{IV/II}$ [b]	
1	$[Ru(NH_3)(OH_2)]^{2+}$	-0.33	0.35	0.01	0.68
2	$[Ru(tpy)(acac)(OH_2)]^{+}$	0.19	0.56	0.38	0.37
3	$[Ru(tpy)(C_2O_4)(OH_2)]^{+}$	0.16	0.45	0.31	0.29
4	$[Ru(tpy)(OH_2)_3]^{2+}$ [c]	0.35	0.64	0.50	0.29
5	Trans-$[Ru(tpy)(pic)(OH_2)]^{+}$	0.21	0.45	0.33	0.24
6	Cis-$[Ru(tpy)(pic)(OH_2)]^{+}$	0.38	0.56	0.47	0.22
7	Cis-$[Ru(6,6'\text{-}Me_2\text{-}bpy)_2(OH_2)_2]^{2+}$ [d]	0.57	0.73	0.65	0.16
8	$[Ru(tpy)(tmen)(OH_2)]^{2+}$	0.36	0.59	0.48	0.13
9	$[Ru(tpy)(phen)(OH_2)]^{2+}$	0.50	0.60	0.55	0.10
10	Cis-$[Ru(bpy)_2(py)(OH_2)]^{2+}$	0.43	0.53	0.48	0.11
11	$[Ru(tpy)(bpy)(OH_2)]^{2+}$	0.49	0.62	0.56	0.13
12	Cis-$[Ru(tpy)(4,4'\text{-}((CO_2Et)_2bpy)(OH_2)]^{2+}$	0.66	0.80	0.73	0.13
13	Cis-$[Ru(tpy)(4,4'\text{-}Me_2\text{-}bpy)_2(OH_2)]^{2+}$	0.47	0.61	0.54	0.14
14	Cis-$[Ru(bpy)_2(AsPh_3)(OH_2)]^{2+}$	0.50	0.67	0.59	0.17
15	Cis-$[Ru(bpy)(biq)(PEt_3)(OH_2)]^{2+}$	0.45	0.63	0.54	0.18
16	$[Ru(tpm)(4,4'\text{-}(NO_2)_2\text{-}bpy)(OH_2)]^{2+}$	0.56	0.75	0.66	0.19
17	Cis-$[Ru(bpy)_2(Pet_3)(OH_2)]^{2+}$	0.46	0.67	0.57	0.21
18	Cis-$[Ru(bpy)(biq)(PPh_3)(OH_2)]^{2+}$	0.48	0.70	0.59	0.22
19	Cis-$[Ru(bpy)_2(PPh_3)(OH_2)]^{2+}$	0.50	0.76	0.63	0.36
20	Cis-$[Ru(bpy)_2(P(i\text{-}Pr)_3(OH_2)]^{2+}$	0.45	0.68	0.57	0.23
21	Cis-$[Ru(bpy)_2(SbPh_3)(OH_2)]^{2+}$	0.52	0.80	0.66	0.28
22	$[Ru(tpy)(dppene)(OH_2)]^{2+}$ [e]	1.17	1.53	1.35	0.36

[a] In H_2O at pH 7.0, T = 22 ± 2 °C, I = 0,1 M vs SSCE. [b] $E_{1/2}$ values for the Ru^{III}-OH/Ru^{II}-OH_2, Ru^{IV}=O/Ru^{III}–OH, and Ru^{IV}=O/Ru^{II}-OH_2 couples. [c] $\Delta E_{1/2} = E_{1/2}(Ru(IV/III) - E_{1/2}(Ru(III/II)$. [d] pH 4.0. [e] In CH_2Cl_2/H_2O (3:1). Abbreviations: biq = 1,1'-biquinoline; tmen = N,N,N,N-tetramethylethylenediamine; dppene = cis-1,2-bis(diphenylphosphino)ethylene; pic: picolinate anion. Acac = acethyl acetonate anion.

The Ru(IV/III) couples are in geneal far less sensitive to ligand variations than are the Ru(III/II) couples. This is illustrated for instance by comparing the complexes in entries 2 and 11 or in entries 3 and 9, where changes in the ligands produce only a slight modification in the potential of the Ru(IV/III) couple whereas the Ru(III/II) couple is strongly influenced. This behaviour is due to the control of the π-bonding exerted by the oxo ligand through a $d\pi_{Ru}$-p_o interaction in the Ru(IV) species.

On the whole, the set of properties stated in this section convert this complexes with the Ru=O group in excellent oxidants, in a catalytic or stoichiometric way, for organic[37] and inorganic[38] substrates.

1.2.3 Asymmetric Catalysis

Biological systems, in most cases, recognize a pair of enantiomers as different substances, and the two enantiomers will elicit different responses. For example, the L-enantiomer of some α-aminoacids such as leucine, phenylalanine, tyrosine and tryptophane taste bitter, whereas their corresponding D-enantiomers taste sweet.[39] Also the active molecules of many drugs are single enantiomers of chiral compounds and, in some cases, the opposite enantiomer may behave antagonistically and/or cause undesired side effects.[40] The sad example of thalidomide is well known.[41] Therefore, the development of synthetic methods for the production of single enatiomers of chiral compounds is highly valuable. Several techniques are used nowadays to obtain enantiopure materials which can be divided in two broad groups: optical resolution[42] and asymmetric synthesis.[42, 43] The major disadvantage of the former group is that half of the product is the undesired enantiomer. Therefore, asymmetric synthesis, defined as the conversion of an achiral starting material to a chiral product in a chiral environment, is presently the most powerful and commonly used method for chiral molecule preparation. Up until now, most of the best asymmetric syntheses are catalyzed by enzymes, and the challenge before us today is to develop chemical systems as efficient as the enzymatic ones. Accordingly, during the last decades, several strategies have grown to achieve this target: (a) using chiral natural products ("chiral pool" approach);[43] (b) employing chiral auxiliaries;[44] and (c) through the development of chiral catalysts for asymmetric catalysis.[43]

The chiral pool method is limited to natural-occurring chiral compounds and often only one of the enantiomers is available, e.g. D-sugars, α-aminoacids. On the other hand, The chiral auxiliary in method (b) has to be used in stoichimetric amounts and, after reaction, its removing requires additional steps. By contrast, an asymmetric catalytic reaction with a turnover number of 1000 means that 1000 new chiral

molecules can be generated from only one molecule of chiral catalyst, which leads to higher economy and efficiency. Also the work-up is often relatively simple, as only a small amount of catalyst is used. In the past 20 years, asymmetric catalysis has become one of the most important areas of research and major breakthroughs have been achieved.[43b] Such a statement is undoubtedly fully confirmed by the award of the 2001 Nobel Prize in Chemistry to W. S. Knowles,[45] R. Noyori,[46] and K. B. Sharpless[47] for their work on asymmetric hydrogenation and oxidation reactions.

1.2.3.1 Chiral Ligands

Most asymmetric catalysts that have been developed so far are metal complexes with chiral organic ligands. The chiral ligand modifies the reactivity and selectivity of the metal center in such a way that one of two possible enantiomeric products is formed preferentially. However, of the thousands of chiral ligands prepared so far, only few of them can be applied to a broad range of reactions and substrates.[48] Examples of these "privileged" chiral ligands and their applications are shown in Figure 1.2. Therefore, ligand design and synthesis is a central challenge in asymmetric catalysis.

Among these prominent ligand classes, chiral phosphines emerged first (in the late 1960s) as useful compounds for asymmetric catalytic reactions. However, it was in the 1980s, with Noyori's Binap synthesis (**1**, Figure 1.2), that a real expansion of chiral phosphine ligand applications took place. The axial chirality in this biaryl ligands results from a restricted rotation about the central single C-C bond and the highly skewed position of the naphthyl rings has been suggested as the determining factor in its effectiveness in asymmetric catalytic reactions.[49] More recently, bisoxazolinic ligands have emerged as paradigmatic compounds in the development of nitrogen donor ligand based homogeneous asymmetric catalysis.[50] Their wide applicability can be by far explained looking at their basic characteristics: (a) easy chelatation to metal centers; (b) chiral carbons close to the metal center upon coordination; (c) generally uncomplicated synthesis and (d) availability of the two possible enatiomers.

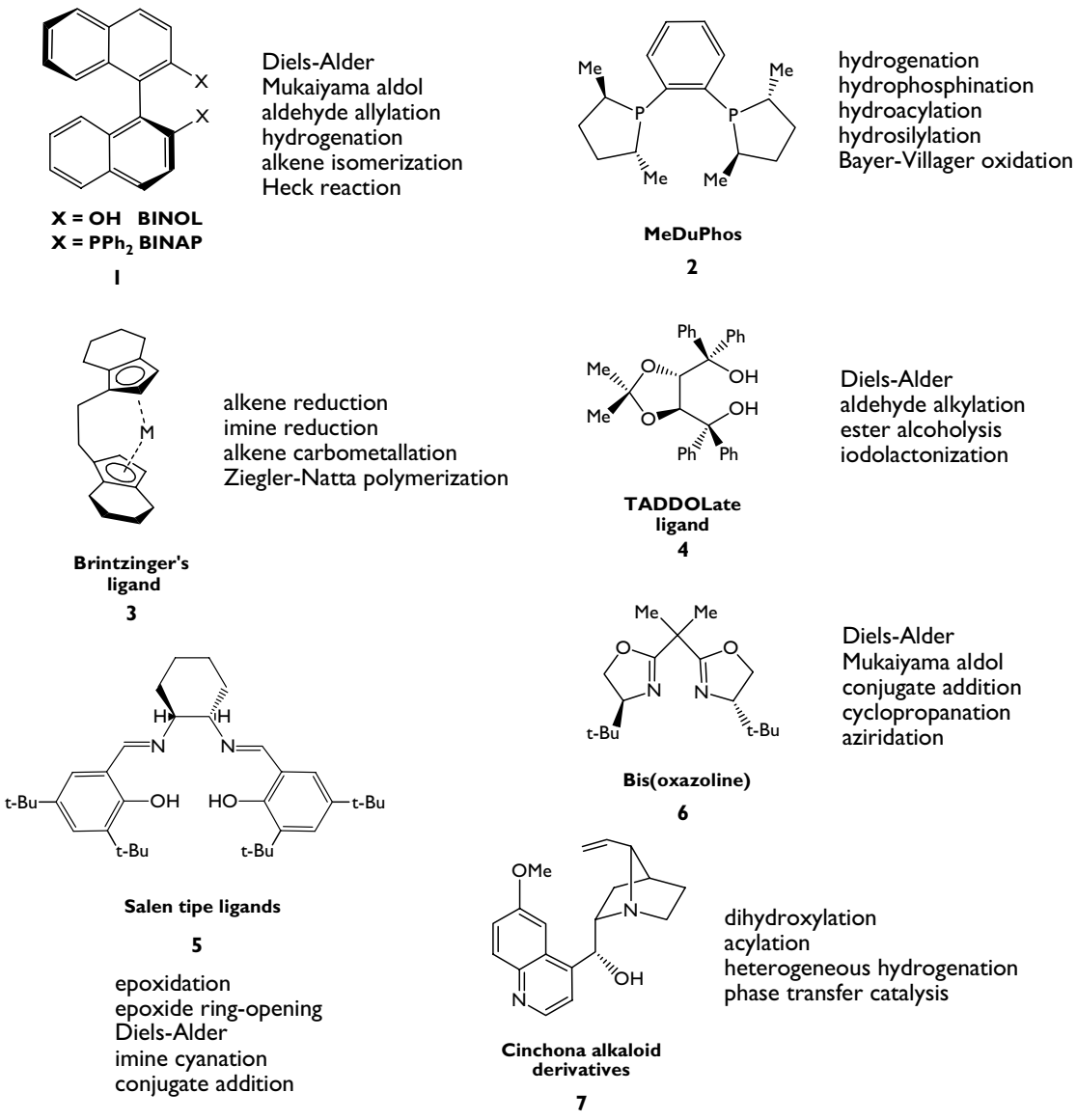


Figure 1.2 Privileged Chiral Ligands and catalytic applications of their complexes

Aside from these successful chiral inducers, polypyridylic ligands (Figure 1.3) can be viewed as another potentially promising group, since they can be rendered chiral by appending additional substituents (**8-11** in Figure 1.3(a)). However, despite their rich coordination chemisty, chiral polypyridylic derivatives have received relatively little attention in asymmetric catalysis owing to the difficulties associated with their conversion into chiral molecules and their chemistry has emerged only during the last decade.[51] Since the introduction of a chiral α-pinene moiety into bipyridine ligands by Hayoz[52] in 1992, a pretty large number of such pineno-annellated ligands[53] have been

synthesized. These ligands are easily accessible in enantiomerically pure forms starting from commercially available (-)-α-pinene, or (-)-myrtenal, respectively (**12**, **13** in Figure 1.3).

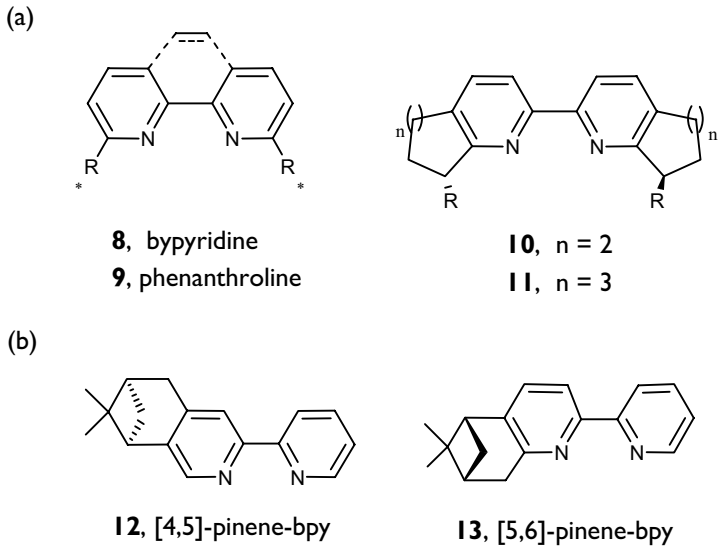


Figure 1.3 Examples of chiral polypyridylic ligands. (R = chiral substituents)

These chiral polypyridylic "pineno-fused" ligands have found application in a wide range of asymmetric transformations as Pd(0)-catalyzed allylic substitution,[54] Ni/Cr-catalyzed Kishi coupling,[55] Cu-catalyzed cyclopropanation,[56] and Ru-catalyzed epoxidation.[69c]

1.2.3.2- Ru-catalyzed Asymmetric Epoxidation

Chiral epoxides are versatile building blocks for syntheses of numerous natural products and biological active substances.[57] Among the various possibilities for their preparation, asymmetric catalysis constitutes an elegant and efficient tool for the synthesis of enantiomerically pure epoxides. In the past, transition metal complexes based on titanium[58] and manganese[59] were used most successfully as catalysts for the enantioselective epoxidation of olefins. Ru complexes, well known as useful catalysts for oxidation reactions as mentioned above, have been also employed in epoxidation reactions.[60] Ru-porphyrin,[61] Ru-bisamide,[62] Ru/Schiff base,[63] unsymmetrical Ru/Schiff base,[64] [Ru(salen)],[65] Ru-sulfoxide[66] and Ru-bis(oxazoline)[67] complexes, as well as [Ru(PPz)(bpy)][68] (PPz = 2,6-bis[(4S,7R)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-

methanoindazol-2-yl]pyridine) and [Ru(pydyc)(T*)][69] (pydyc = pyridinedicarboxilate anion, T* = chiral tridentate ligand), are relevant examples of asymmetric epoxidation catalysts (Figure 1.4).

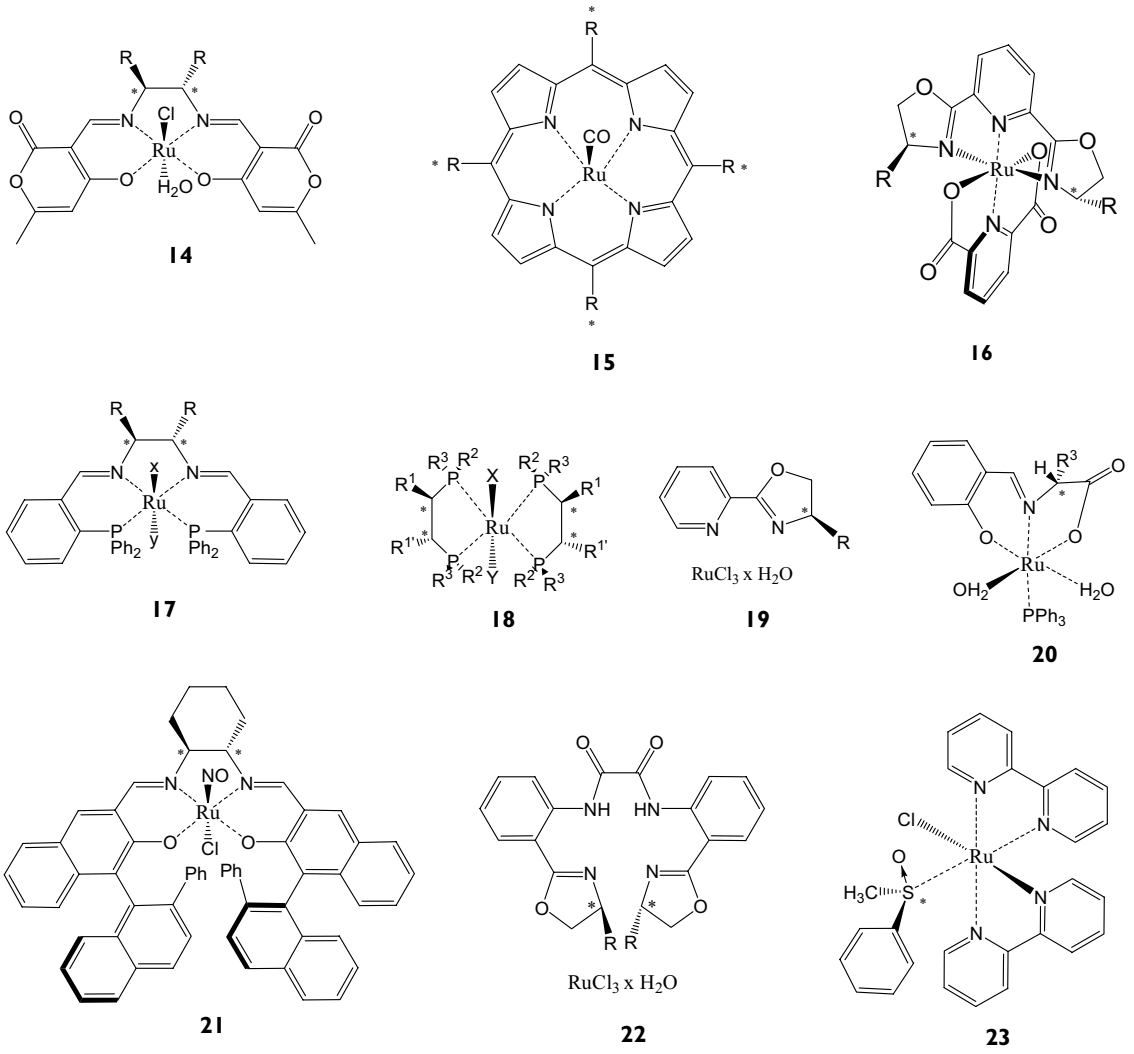
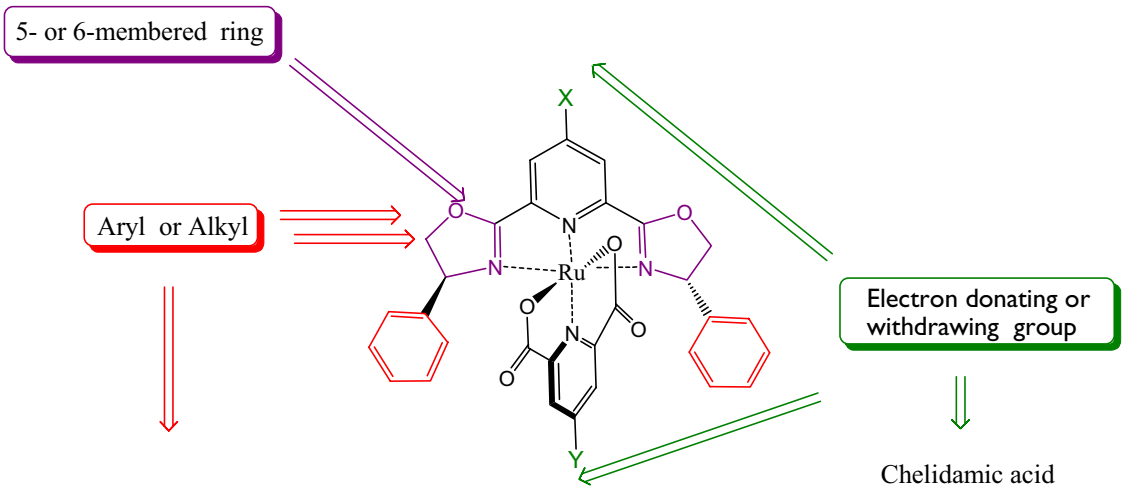


Figure 1.4 Useful Ru-catalysts for asymmetric epoxidation

Among them, the [Ru(pydyc)(T*)] complexes merits particular attention. Nishiyama's complex [Ru-(pyridinebisoxazoline)(pyridine-dicarboxylate)][67] (**16** in Figure 1.4), able to epoxidize *trans*-stilbene with approximately 70% ee, was the starting point of these promising catalytic systems. However, the method had important drawbacks (unfortunately, frequent features in Ru-catalyzed asymmetric epoxidation) such as low

reactivity (96 h were needed for full conversion) and the limited scope of the catalyst (only *trans*-stilbene was epoxidized). Taking Nishiyama's system as starting point, Beller et al. started, a few years ago, a thorough study in order to overcome the above mentioned shortcomings and apply this kind of complexes in a more general sense.[69] As shown in Scheme 1.4, systematic variations of steric and electronic parameters of the corresponding tridentate ligands were easily realizable.



Scheme 1.4 Beller's modifications to Nishiyama's epoxidation catalyst

Through the systematic variations showed above, a large number of different N,N,N-tridentate pybox and pyboxazine ligands were synthesized and a collection of 35 new ruthenium(II) complexes fully characterized. This interesting toolbox allowed the authors to develop a general ruthenium-catalyzed asymmetric epoxidation of olefins procedure using hydrogen peroxide as co-oxidant. High yields and chemoselectivities were obtained for the first time with six different classes of olefins and enantioselectivities up to 84% were achieved.

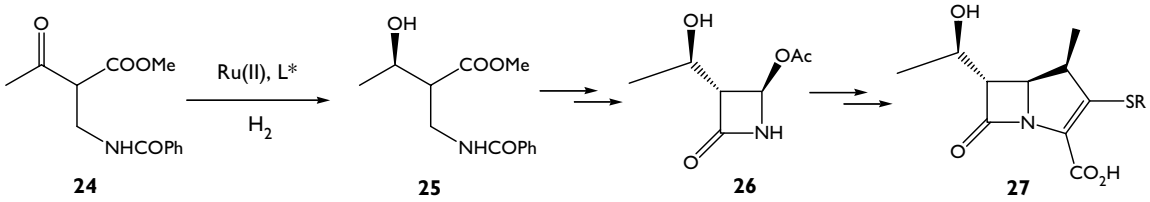
1.2.3.3 Asymmetric Hydrogenation.

Historical Overview

Asymmetric saturation of alkenes, ketones and imines by hydrogen or organic hydrogen donors provides an ideal access to chiral alkanes, alcohols and imines, respectively, important building blocks for the synthesis of biologically active compounds such as pharmaceuticals, agrochemicals, flavours and fragrances. Asymmetric hydrogenation, probably the most powerful and successful process in asymmetric catalysis, has emerged since the late 1960s as the method of choice for the production of these chiral saturated compounds.

In the first studies of homogeneous asymmetric hydrogenation, a modification of the achiral, triphenhylphosphine-containing, Osborn-Wilkinson's catalyst was used in the hydrogenation of prochiral alkenes. Horner et al.[70] and Knowles and Sabacky[71] replaced triphenylphosphine by a chiral phosphine having the phosphorus atom as a stereogenic center, and very modest optical yields were obtained. Subsequently, Kagan and Dang[72] demonstrated that a chiral phosphorus atom is not necessary if a chiral ligand is used, such as the C_2-symmetric diphosphine DIOP. This discovery was extended then to all homogeneous asymmetric catalysis.

Noyori's well-defined mononuclear Ru-Binap catalysts (see Figure 1.2) were the next real breakthrough, exhibiting an incredible range of efficiency and opening new ways for the asymmetric hydrogenation of many new classes of olefins.[73] Also this reaction could be further extended successfully to many types of keto groups.[74] Furthermore, Noyori's group developed an impressive technology by combining asymmetric hydrogenation with dynamic kinetic resolution which together led to an important process developed by *Tekasago* for the production of acetoxyazetidinone (150 tons/year, Scheme 1.5, **25**), a key intermediate in the synthesis of antibiotics (Scheme 5, **27**).[75]



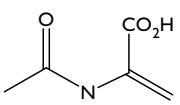
24 25 26 27

Scheme 1.5 *Tekasago* acetoxyazetidinone production

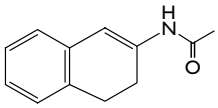
But this is not an isolated example. Today, the increasing number of industrial processes where asymmetric hydrogenation plays a key role clearly demonstrates its efficiency and its practicability.[76]

Current challenges

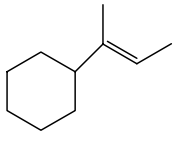
A recent perspective paper published in *Science* by Martin Willis, focused on asymmetric hydrogenation,[77] states "A quick inspection of the literature may lead one to the mistaken conclusion that asymmetric hydrogenation is a solved problem, as the number of reported catalysts now runs into the thousands.[78] However, a close reading of the literature reveals a more complex reality." Therefore, despite an enormous variety of chiral phosphine ligands has been developed during recent decades and great progress has been achieved, there are still important challenges in this field. To illustrate this assertion, Scheme 1.6 shows different substrate types and the corresponding feasibility of their asymmetric reduction. Thus, for example, while substrate **28** can be easily hydrogenated by means of a wide range of catalysts, substrate **29**, also with an enamide group, is a much more difficult example. Only a few Rh- and Ru-catalysts are able to hydrogenate **29** with good ee's and conversions.[79]



28: Relatively symple substrate lots of catalysts available



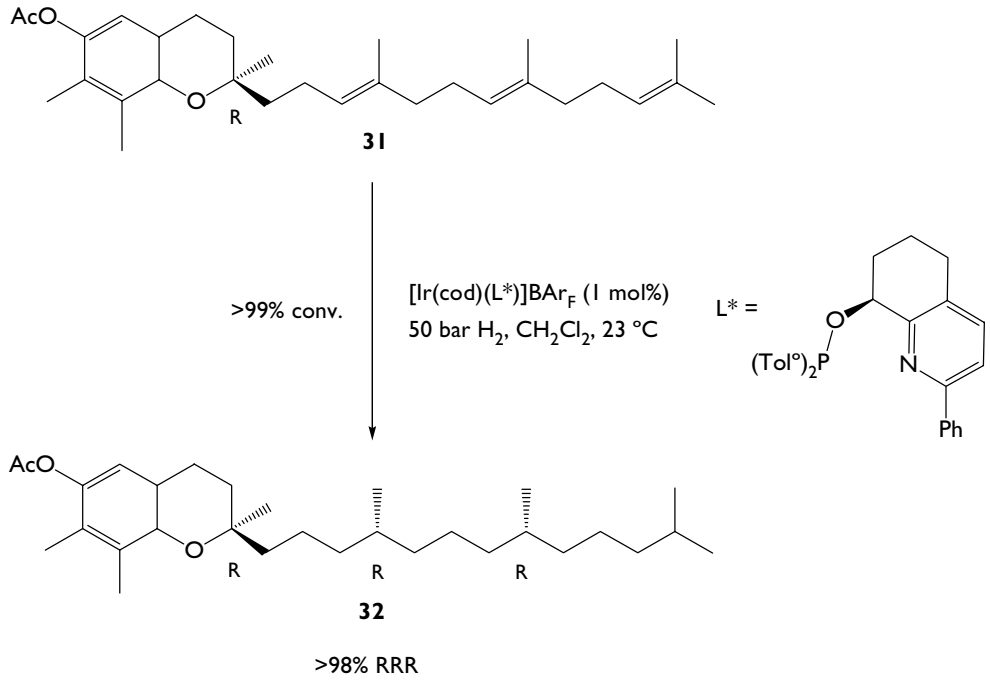
29: Chalenging substrate few catalysts available



30: Very Chalenging substrate only one catalyst available

Scheme 1.6

A still more challenging case is the one of unfunctionalized alkenes (**30**, scheme 1.6), in which the C=C double bond is flanked by only hydrocarbon groups. Indeed, until the recent report of Bell et al.[80] no practical method for their asymmetric hydrogenation had been reported at all. This lack of methods should not suggest that such substrates are uninteresting. Indeed, their reduction provides many target molecules of biological and medicinal importance like tocopherols, the principal components of vitamin E.[81] Bell et al. demonstrated the effectiveness of their iridium catalysts to an unprecedented one step tris-alkene reduction of one of these important substrates (Scheme 1.7).[80] This process hugely simplifies the stereoselective synthesis of an important and structurally complex series of target molecules.



Scheme 1.7 Hydrogenation of γ-tocotrienyl acetate

Examples like the one above show that there is still room for large improvement in asymmetric hydrogenation and justify the ongoing intensive research efforts in this area.

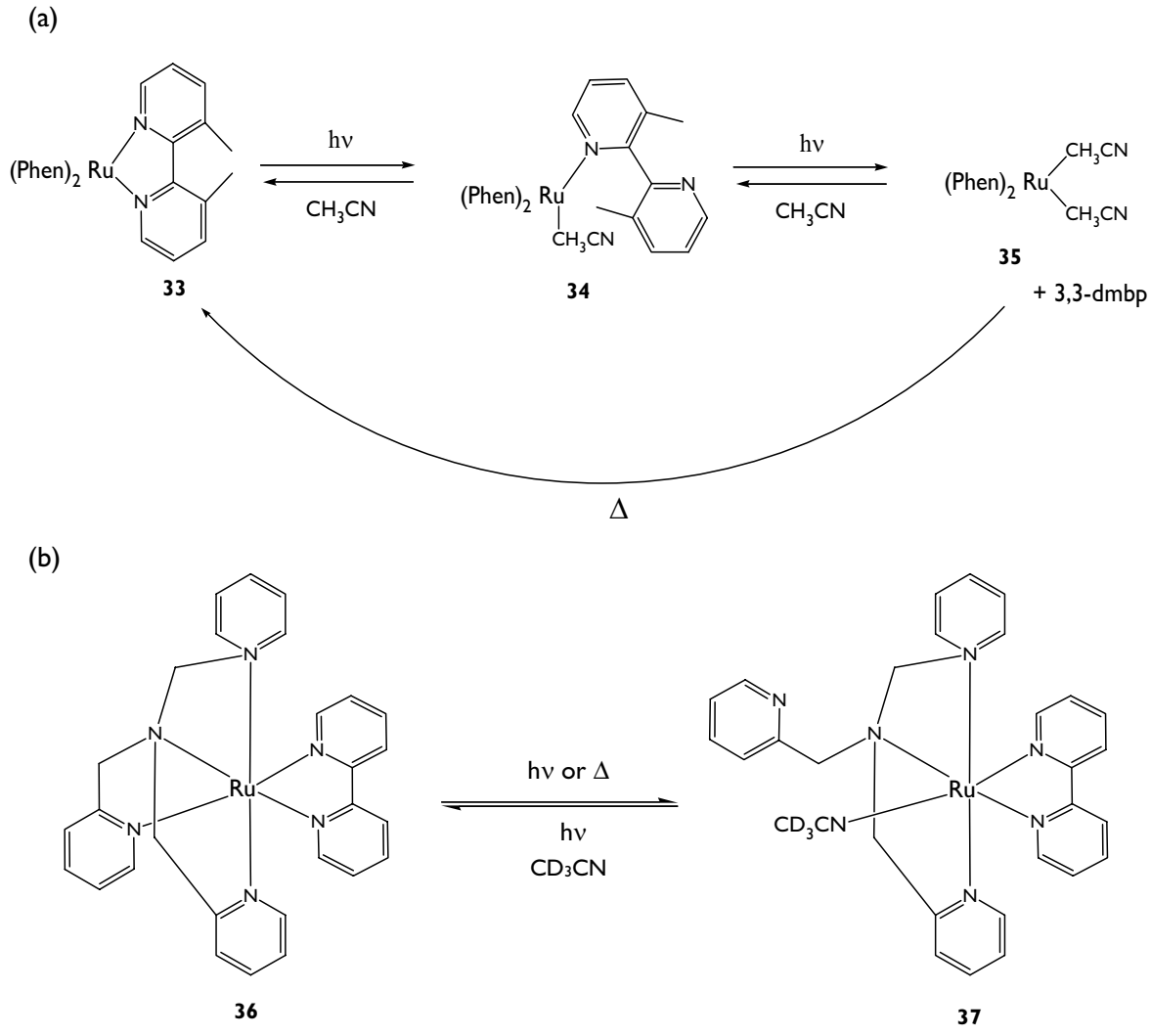
1.3 Molecular Machines.

"There's Plenty of Room at the Bottom" affirmed Richard P. Feynman,[82] Nobel Laureate in Physics, in his famous talk to the American Physycal Society in 1959. This was the first proposal that molecular-level machines could be constructed and useful not only for basic research but also for the growth of nanoscience and nanotechnology. The *top-down* approach currently used in today's production of miniaturized silicon-based transistors[83] may be reaching its limit and a new approach able to handle vast amounts of information on the nanometer scale is needed. Thus, Feyman was proposing a *bottom-up* approach, starting from atoms and molecules. However, only with the advent of supramolecular chemistry in the last decades of 20th century is now, at the beginning of the 21st, when we are able to construct large and intricate, yet highly ordered, functioning molecular and supramolecular entities.[84] Therefore, nowadays, the concept of machine can be extended to the molecular level,[85] defined as an assembly of a discrete number of molecular components designed to perform mechanically-like movements (output) as a consequence of appropriate external stimuli (input). Again, since comprehensive reviews[86] and books[85] covering this field have been recently published we will exclusively focus our attention on light-driven transition-metal based molecular machines, one of the areas of study along this thesis.

Light-Driven Transition-Metal Based Molecular Machines

To make a machine work, energy inputs have to be supplied ("external stimuli" in the above mentioned definition). If chemical energy is used, need of addition of fresh reactants ("fuel") at any step of the working cycle, and formation of waste products will be unavoidable. However, nature shows in green plants that light can act as an efficient, clean, energy input. Thus, an increasing interest in the development of photon-powered molecular-level machines has grown in the scientific community and several examples have been reported.[86c,87] In this respect, the rotary motor proposed by Feringa and Harada[87(a-b)] is a remarkable example because the rotation motion is realized via a sequence of photochemical or thermal steps, without consuming any chemical reagent.

Transition-metal based light-driven molecular machines are particularly promising and ruthenium coordination compounds a first-class example among them. Therefore, for example, complexes of the $Ru(bpy)_3^{2+}$ family are interesting because, by introducing appropriate modifications in the bpy backbone, photochemical expulsion of a given ligand can be carried out specifically and quantitatively.[88] Furthermore, some examples of subsequent thermal re-coordination of the fotoexpelled ligand have been reported (Scheme 1.8(a)).[88a] A similar dissociation-binding behavior has been reported by Kojima et al. for other Ru(II)-polypyridylic complexes[89] (Scheme 1.8(b)).



Scheme 1.8

These systems, with two different well defined states accessible in a reversible way through non-chemical external stimulus, work in the same way that macroscopical switches do, changing from one state to another depending on external environmental influences. However, molecular switches are extremely tiny and their application in biomedicine, nanotechnology and computer chip design sets up completely new perspectives.

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Chapter 2

Objectives

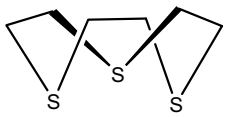
Science is a field that grows step by step. Accordingly, all the interesting properties and reports commented in *Chapter 1* have contributed to choose the starting goals of this thesis. The following points are the initial ideas where this work was initially supported. Of course, the research course has directed us, at times, towards slightly different places. This is, in my opinion, the most fascinating trait of research; you always know where you start but never where you will finish.

General

Understand how to design catalysts structures to control catalytic activity and selectivity is one of the main challenges that the scientific community is trying to solve nowadays. In this sense, our group has been working for years in the field of redox catalysis, where the thermodynamic and kinetic characterization of the different oxidation state species of a catalyst is of paramount importance. The presence of multiple redox states that need to be cycled through within the different transition metal complex species makes this characterization unavoidable if representative advances are persecuted. Within this field, ruthenium aqua-complexes have been extensively studied as they present rich redox chemistry derived from the acid-base properties of the aqua ligand. Therefore, the synthesis and thorough characterization of a set of new chiral and non-chiral ruthenium compounds and the evaluation of their catalytic behavior would enable us to establish important relationships between catalyst electronic and geometric parameters and its reactivity.

Project I. Non-chiral Complexes

In spite of intensive research by many groups in this field, no ruthenium aqua-complexes have been reported containing thioether ligands. Thus, the target of this initial project was the synthesis and characterization of a new family of this kind of complexes, being the 1,4,7-trithiacyclononane ([9]aneS_3) and 1,10-phenantroline (phen) the ligands of choice.

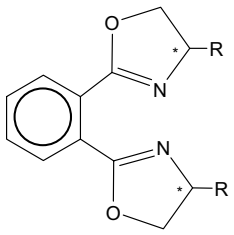


[9]aneS_3

The electronic and geometric properties transferred by the thioether ligand to the metal center would have significant influence over the catalytic performance of the Ru-aqua complex and, furthermore, over the substitution reactions between members of this family of compounds.

Project 2. Chiral Complexes

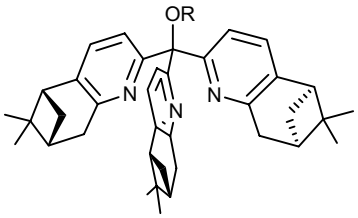
The generation, control, and induction of chirality is of current prominent interest in the scientific community. Therefore, the stereoselective synthesis and characterization of chiral ruthenium compounds and their use as asymmetric catalysts was chosen as second project for this thesis. Bis-oxazolines, were firstly selected for this purpose with trpy as ancillary ligand.



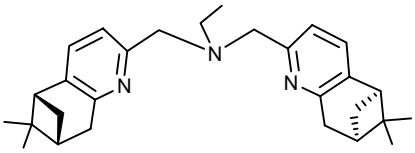
Phbox-R (R = Et, iPr)

The Phbox-R ligand exhibits free rotation around the C-C bonds that link the aromatic ring with the oxazolinic entities. We anticipated that, upon coordination to the $[Ru^{III}Cl_3(trpy)]$ precursor, the rotation would be restricted leading to two limiting orientations generating two interdependent chiral axes that should lead to atropisomerism. The understanding and control of this atropisomeric system jointly with the catalytic performance of the whole set of complexes were goals of this second project.

Chiral polypyridylic ligands were our next choice. In collaboration with prof. A. von Zelewsky`s group (Fribourg University, Switzerland), we decided to prepare a large family of compounds where the chirality originate from the monoterpen chiral pool.



R = H, Pinene[5,6]tpmOH
R = Me, Pinene[5,6]tpmOMe



Pinene[5,6]bpea

Therefore, the synthesis of new chiral tripodal ligands, their coordination chemistry jointly with N,N or P,P didentate ligands and their reactivity in asymmetric oxidations and reductions, were also targets of this second project.

The objectives of this thesis can be summarized as:

- Synthesis of new ruthenium complexes containing the [9]aneS_3 and phen ligands. Structure, redox properties, catalytic activity and substitution mechanisms.

- Synthesis of new ruthenium complexes containing chiral didentate oxazolinic ligands. Structural characterization, redox chemistry and atropisomeric control.

- Development of new chiral "pineno-fused" polypyridylic ligands. Coordination chemistry in combination with other N,N or P,P didentate ligands. Spectroscopic/electrochemical characterization and study of their applications as catalysts for asymmetric redox reactions.

Chapter 3

Synthesis, Structure, Redox Properties and Substitution Mechanism of new Ru(II) Complexes containing the 1,4 7–Trithiacyclononane and 1,10–Phenantroline ligands*

The synthesis, spectroscopic characterization and redox properties of a new Ru-H_2O complex containing 1,10-phenantroline and the soft [9]aneS_3 ligand are reported. Even though its higher oxidation states are not stable, they are sufficiently reactive to rapidly oxidize benzyl alcohol to benzaldehyde. Furthermore, the substitution pathways of a new Ru-py complex, $[Ru(phen)(py)([9]aneS_3)]^{2+}$, to form the corresponding Ru-NCMe complex, $[Ru(phen)(MeCN)([9]aneS_3)]^{2+}$, have been established through kinetic analysis with and without irradiation. Electronic effects exerted by the [9]aneS_3 macrocycle on the Ru center are responsible for the relatively high rates of substitution obtained, and have allowed the kinetic establishment of a reaction intermediate.

* The work presented in this chapter has been published: (a) Sala, X.; Poater, A.; Romero, I.; Rodríguez, M.; Llobet, A.; Solans, X.; Parella, T.; Santo, T. M. *Eur. J. Inorg. Chem.* **2004**, 612-618. (b) Sala, X.; Romero, I.; Rodríguez, M.; Llobet, A.; Gonzalez, G.; Martinez, M.; Benet-Buccholz, J. *Inog. Chem.* **2004**, 43, 5403-5409.

Chapter 4

New Ru(II) Complexes Containing a Chiral Didentate Oxazolinic Ligand. Synthesis, Redox Chemistry and Atropisomeric Discrimination[*]

A new family of Ru(II) complexes containing the C_2-symmetric didentate chiral phenyl-1,2-bisoxazolinic ligand is described and thoroughly characterized in the solid state by X-ray diffraction analysis, in solution by NMR and spectrophotometric techniques, and in the gas phase thanks to DFT calculations. Rotationally restricted isomers are produced upon coordination of the oxazoline to a ruthenium metal center. These isomers show significantly different energy values due to steric effects in the coordination sphere, thus allowing the direct synthesis of pure atropisomers.

[*] Part of the work presented in this chapter has been published: Sala, X.; Plantalech, E.; Rodríguez, M.; Romero, I.; Llobet, A.; Benet-Buchholz, J.; Jansat, S.; Gómez, M.; Parella, T.; Poater, A.; Solà, M.; Duran, M. *Chem. Eur. J.* **2006**, 12, 2798-2807.

Chapter 5

Ruthenium Catalysts for Asymmetric Oxidations and Reductions: Ligand Synthesis, Coordination Chemistry and Catalytic Performance*

New synthetic routes towards chiral "pineno-fused" N-donor ligands are described here. A wide set of Ru(II) complexes containing different combinations of this and other chiral/achiral N-/P-donor ligands is also reported and their catalytic ability to reduce and oxidize C=C double bounds is evaluated. The enantioselective hydrogenation of a challenging enamide (N-(3,4-dihydro-2-naphthalenyl)-acetamide, **1**) has been performed using *cis-fac*-Δ-[Ru^{II}Cl{(*R*)-(bpea)}{(*S*)-(BINAP)}]BF_4, *cis-fac*-Δ-(*R*)-(*S*)-**3**, as catalyst achieving good conversions and enantioselectivities up to 74%. Also, promising results in styrene asymmetric epoxidation has been achieved using [Ru^{II}Cl(tpmOMe)(*bpy*)](BF_4), **5**, with ee up to 36%.

* Part of the work presented in this chapter has been published: (a) Sala, X.; Rodríguez, A.; Rodríguez, M.; Romero, I.; Llobet, A.; von Zelewsky, A.; Benet-Buchholz, J.; Parella, T. J. Org. Chem. **2006**, *71*, 9283-9290. (b) Sala, X.; Serrano, I.; Rodríguez, M.; Romero, M.; Llobet, A.; van Leeuwen, P. W. N. M. Tetrahedron: Asymmetry (submitted).

Chapter 6

Results and Discussion

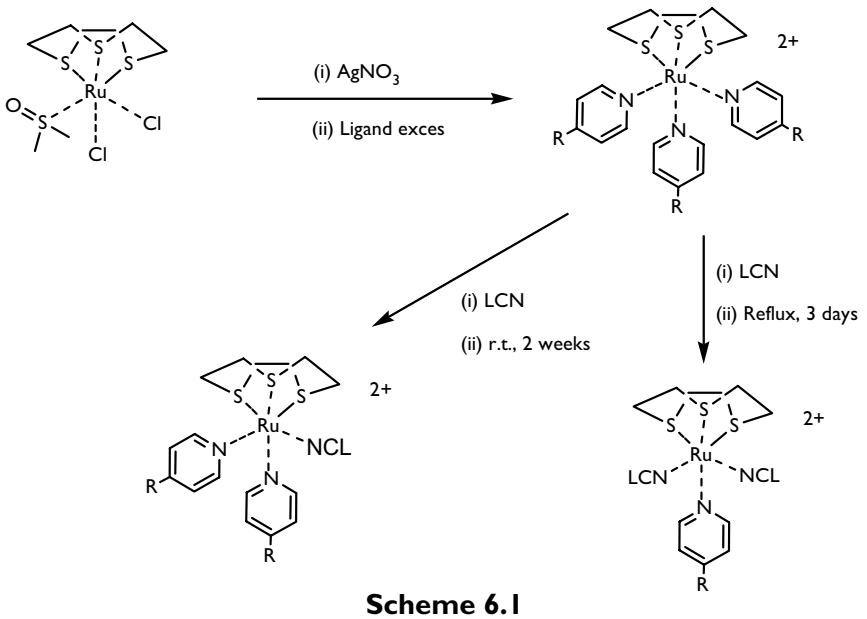
A general outlook of the work presented in Chapters 3-5 is provided here. Extra information not included in the papers but relevant for purposes of comparison is also added and discussed. As is intended, this chapter tries to provide linkage between the previously proposed objectives (Chapter 2) and the experimental results obtained, being an appropriate way to enter in the final chapter of this thesis, the general conclusions.

New Ruthenium Complexes Containing N, P and S-Donor Type of Ligands: Coordination Chemistry, Characterization and Application to Asymmetric and non-Asymmetric Catalysis

Two separated but closely related projects were defined as objectives of this thesis (Chapter 2) taking into account if chiral or non-chiral ligands were planned to be used in the synthesis of ruthenium complexes. Here on, the results obtained and previously presented as separate papers will be discussed, in a more compacted way, for each initial project.

Project 1. Non-chiral Complexes – Chapter 3

The fact that no Ru-OH_2 complexes had been described containing thioether ligands focused our attention on the *[9]aneS_3* tridentate one. In addition to the thorough study of the redox and catalytic properties of its complexes, the substitution mechanisms between [$Ru^{II}S_3$-N_3] structures seemed also to be attractive. Quite surprising substitution reactions containing the [Ru([9]aneS_3)] fragment, inverse to the general trend for this type of complexes, had been recently published. [1] In that contribution, nitrile complexes were formed from pyridylic synthetic intermediates (Scheme 6.1), and this unusual behavior was merely attributed to steric factors.

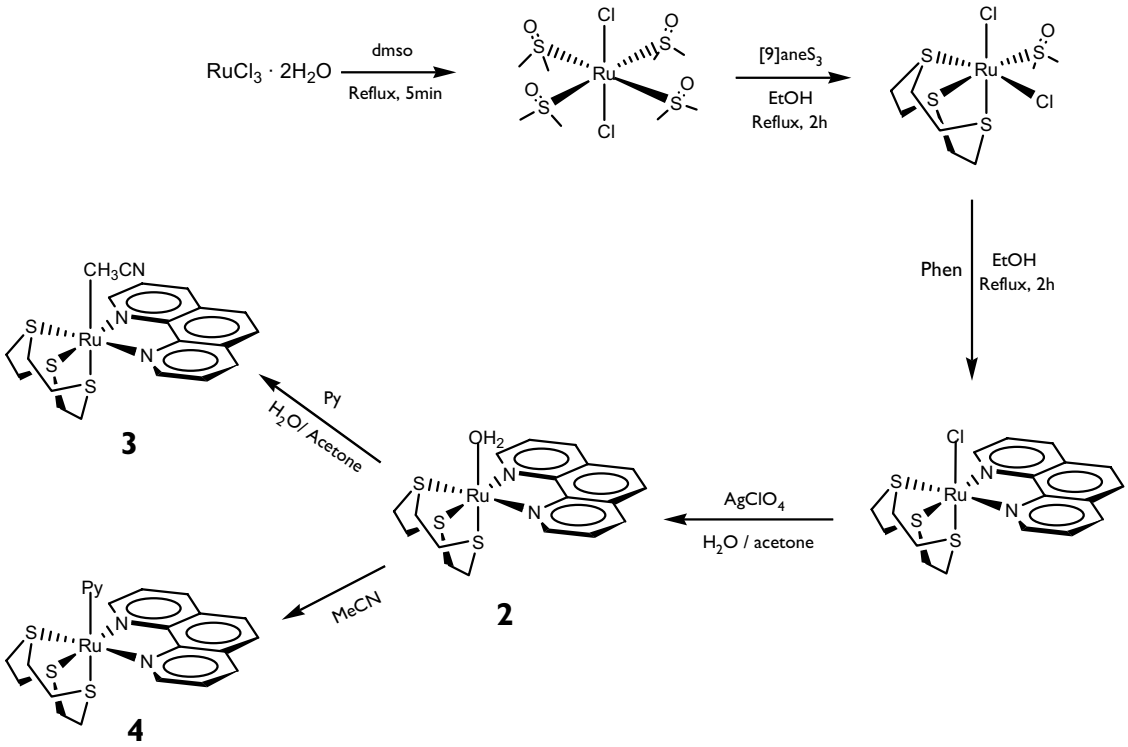


Scheme 6.1

The study of the role that other parameters such as electronic factors could play in this kind of reactions prompted us to synthesize a new family of Ru complexes of general formula $[Ru(Y)(phen)([9]aneS_3)]^{n+}$ (Y = H_2O, py or MeCN). The most prominent features we encountered for this group of compounds are next detailed:

A) Synthesis and Solid State Structure

Starting from $[Ru(dmso)_4Cl_2]$ as precursor, the introduction of *[9]ane*S_3 and subsequent coordination of the didentate phen ligand followed by chloride exchange by a water molecule, provided the desired Ru-OH_2 complex **2**. The substitution of this water molecule by pyridine or acetonitrile was carried out under mild conditions, affording the Ru-MeCN, **3**, and Ru-py, **4**, complexes in almost quantitative yields (Scheme 6.2).



Scheme 6.2 Synthetic strategy and reaction conditions for complexes **2**, **3**, and **4**.

Suitable crystals for X-ray diffraction analysis were obtained for **2**, **3**, and **4**. In all cases, the Ru metal presents a pseudo-octahedral structure with the *[9]ane*S_3 ligand coordinated in a facial manner and exerting strong steric interactions over the rest of the ligands. Two different conformomers (λ,λ,λ and δ, δ, δ) were identified for complex **3** depending on the disposition of the $–CH_2$-CH_2- groups around the metal center (Figure 6.1).

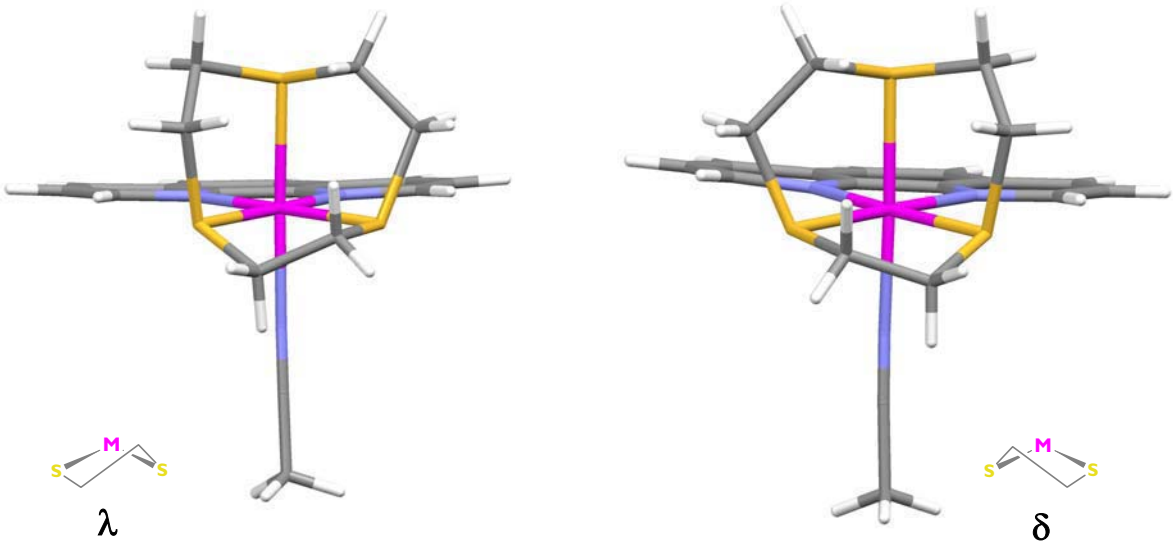


Figure 6.1 X-ray structures for the two conformomers of **3** and schematic representation of their conformation.

Comparison of the structural parameters of this family of complexes with the ones previously reported for similar compounds having N-donor instead of S-donor ligands (Table 6.1) has allowed us to find out important differences which can be attributable to the electronic influence of the *[9]ane*S_3 ligand.

Table 6.1 Selected bonding metric parameters for **3**, **4**, and related complexes.

entry	Complex	Ru-N(py) (Å)	Ru-N_{CH3CN} (Å)	ref
1	$[Ru(py)(phen)(\textit{[9]aneS}_3)]^{2+}$, **4**	2.1166		this work
2	$[Ru(py)_3(\textit{[9]aneS}_3)]^{2+}$	2.148*		1
3	$[Ru(tpm)(Py)_3]^{2+}$	2.083*		2
4	$[Ru(MeCN)(phen)(\textit{[9]aneS}_3)]^{2+}$, **3**		2,106	this work
5	$[Ru(MeCN)(trpy)(ph\text{-}box)]^{2+}$		2.018	3

*calculated mean value

A general enlargement of the Ru-$N_{(py\ or\ MeCN)}$ bonds *trans* to one of the S atoms can be observed in comparison to analogous bonds *trans* to N-atoms of geometrically similar ligands. Comparing, for instance, entry 3 with entries 1 and 2, one can see that there is an increase of 3.4 pm and 6.5 pm respectively in the Ru-py bond distance for the complexes having the S-donor ligand. A similar effect is manifested in entries 4 and 5, with a bond distance increase of 8.4 pm. Therefore, as we will confirm later in the redox chemistry section, not only steric factors are responsible for the lability of the pyridyl or nitrile ligands, but also the strong π-electron acceptor character of the *[9]aneS$_3$* ligand will contribute to weaken its *trans* bonds.

B) Redox Chemistry and Catalytic Activity

The redox chemistry of the Ru-OH_2 complex **2** was quite more complicated than expected a priori. A chemically irreversible wave ($E_{1/2}$ = 0.77 V, pH = 7) corresponding to the Ru^{III}/Ru^{II} couple was obtained from cyclic voltammetry experiments, showing the Ru^{III}-OH species as highly unstable compounds. Furthermore, the Ru^{IV}/Ru^{III} couple, commonly observed for Ru-OH_2 type of complexes, was not found all over the entire pH range. Mathematical simulations using the software DIGISIM 3.0 were then performed to help the mechanistic investigation of this decomposition process. A mechanism where the Ru^{III}-OH species was chemically decomposed (leading to an undetermined species C) after oxidation from the initial Ru^{II}-OH_2 precursor provided a quite exact simulation of the experimental behaviour found (Figure 6.2, right).

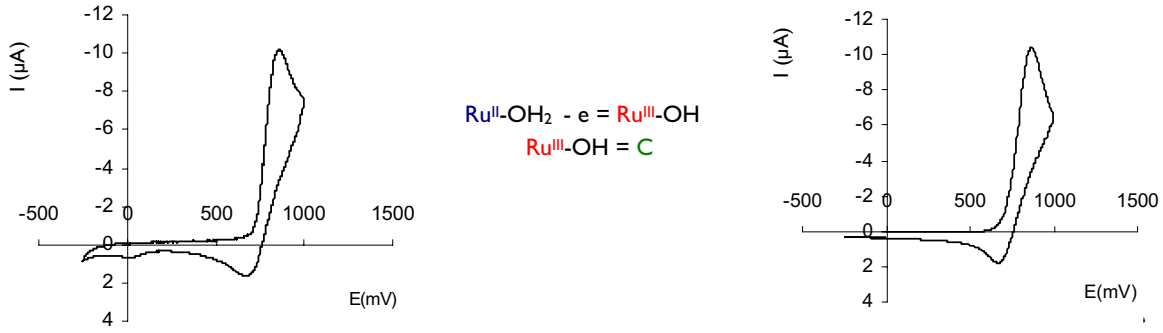


Figure 6.2 Experimental (left) and simulated (right) cyclic voltammetries for complex **2**.

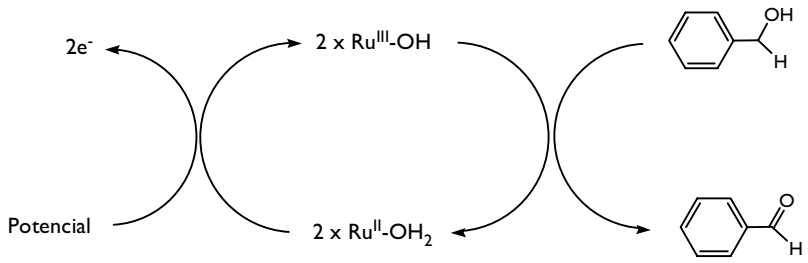
Decomposition product C was then investigated through chemical oxidation of **2** with NaOCl. As found electrochemically, decay was observed. Product C was isolated by precipitation and its structure was determined by ^{1}H-NMR. As can be inferred by the shift to lower fields observed for all the methylenic protons of the the *[9]ane*S_3 ligand, the species C corresponds to a new Ru^{II} compound where the thioether ligand has been oxidized to its corresponding sulfoxide.

This unexpected behaviour for a Ru-OH_2 complex type (high redox potentials and unstable high oxidation species) was only attributable to the electronic character of the tioeter ligand. Comparison with geometrically similar complexes previously reported[4] such as $[Ru(tpm)(phen)(H_2O)]^{2+}$ (Table 6.2) showed the strong π-electron acceptor nature of the *[9]ane*S_3 ligand, rising more than 0.3 V the average $E_{1/2}$ value for the Ru^{III}/Ru^{II} couple.

Table 6.2 Electrochemical data comparison at pH =7, in μ = 0.1 phosphate buffer solution for **2** and related Ru-OH_2 complexes

Complex	$E_{1/2}$ (IV/III)	$E_{1/2}$ (III/II)	
$[Ru^{II}(acac)(trpy)\ OH_2)]^{2+}$	0.56	0.19	← σ-donating ligands (acac) ⇒ high oxidation states stabilization ($E_{1/2}$ ↓)
$[Ru^{II}(bpea)(bpy)(OH_2)]^{2+}$	**0.46**	**0.34**	
$[Ru^{II}(trpy)(tmen)(OH_2)]^{2+}$	**0.59**	**0.36**	
$[Ru^{II}(tpm)(bpy)(OH_2)]^{2+}$	**0.71**	**0.40**	
$[Ru^{II}(tpm)(phen)(OH_2)]^{2+}$	0.71	0.41	← 0.36 V higher with *[9]aneS₃* ⇒ strong electro acceptor ligand
$[Ru^{II}(trpy)(bpy)(OH_2)]^{2+}$	0.62	0.49	
$[Ru^{II}([9]aneS_3)(phen)(OH_2)]^{2+}$, 2	-	0.77	←
$[Ru^{II}(trpy)(dppene)(OH_2)]^{2+}$	1.53	1.17	← π-acceptor ligands (dppene) ⇒ low oxidation states stabilization ($E_{1/2}$ ↑)

The catalytic activity of 2 was tested despite the relative chemical instability of the oxidized species. The electrochemical oxidations reaction of benzyl alcohol (BzOH) was tried as target reaction, and unexpected positive results were obtained. **2** and BzOH were mixed and cyclic voltammetry experiments were performed. An unambiguous enhancement of the anodic peak current was observed along the experiments (Figure 6.3), clearly demonstrating the entrance of complex **2** in a catalytic cycle (Scheme 6.3) where BzOH is electrocatalytically oxidized.



Scheme 6.3

As depicted in Scheme 6.3, Ru^{III}-OH species are proposed as the catalytically active ones. Accordingly, the oxidation of BzOH by the Ru^{III}-OH species should be faster than the previously commented decomposition process. The unusual high reactivity of these Ru^{III} species (generally Ru^{IV} species are the active ones) can be interpreted again as a consequence of the electronic perturbations exerted by the *[9]ane*S_3 ligand.

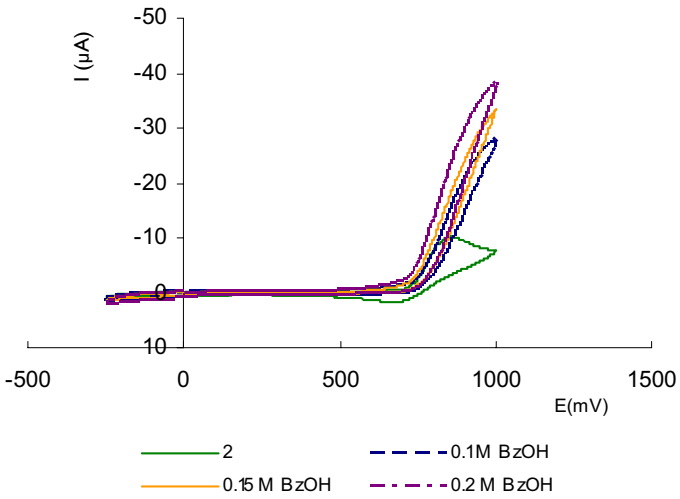
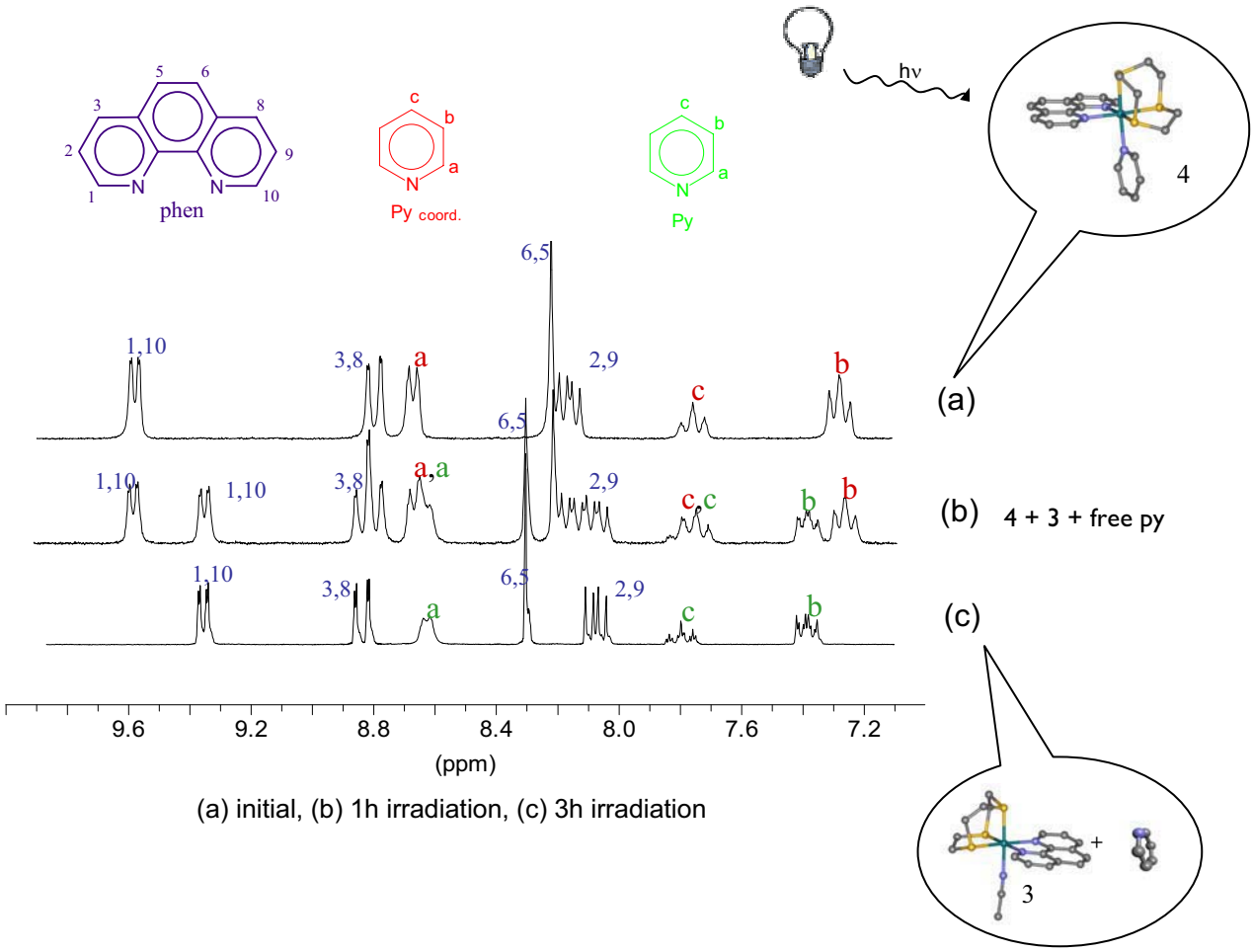


Figure 6.3 Cyclic voltammograms at a scan rate of 20 mV/s of complex **2** at pH = 7 in in absence and presence of different BzOH concentrations.

From catalytic experiments at variable BzOH concentrations (Figure 6.3) a second-order rate constant for this catalytic process was calculated, k_{cat} = 19.3 $M^{-1}S^{-1}$, that perfectly fits the calculated one via mathematical simulation (DIGISIM 3.0).

C) Substitution Reactions and Mechanistic studies

The above mentioned weakness of Ru-N bonds *trans* to S atoms of the *[9]ane*S_3 ligand, caused mainly by electronic factors, seemed to be a suitable starting point for our studies in this field. Therefore, a solution of the Ru-py complex **4** in acetonitrile-d_3 was exposed to UV-vis irradiation and ^{1}H-NMR monitoring of the potential changes was performed. Surprisingly, quite fast transformations were appreciated (Figure 6.4) corresponding to the photo-triggered substitution of pyridine by a solvent molecule (MeCN-d_3).



(a) initial, (b) 1h irradiation, (c) 3h irradiation

Figure 6.4 ^{1}H-NMR monitoring (aromatic region) of the substitution process upon irradiation of complex **4** in acetonitrile-d_3.

As can be appreciated (Figure 6.4 (c)), 3 hours irradiation assure the complete formation of Ru-MeCN complex **3**.

Experiments in the dark were carried out at different temperatures and also followed by NMR checking, showing no changes from the initial Ru-py complex **4**. In this manner, the stability of **4** without irradiation was established, confirming the substitution above mentioned as a photo-triggered process.

To gain deeper insight into this process, kinetic studies were then carried out and UV-vis spectroscopy was employed as monitoring system. Well-defined isosbestic points were found for this reaction. Observed rate constants (k_{obs}) were calculated at different temperatures and these values represented in the corresponding Eyring Plot (Figure 6.5).

T (C)	k_{obs}
21.6	5.94E-05
26.6	1.00E-04
30.0	1.43E-04
30.8	1.77E-04
40.0	2.70E-04
45.6	3.26E-04
48.5	3.33E-04
60.1	4.51E-04
70.2	4.01E-04
75.6	5.32E-04

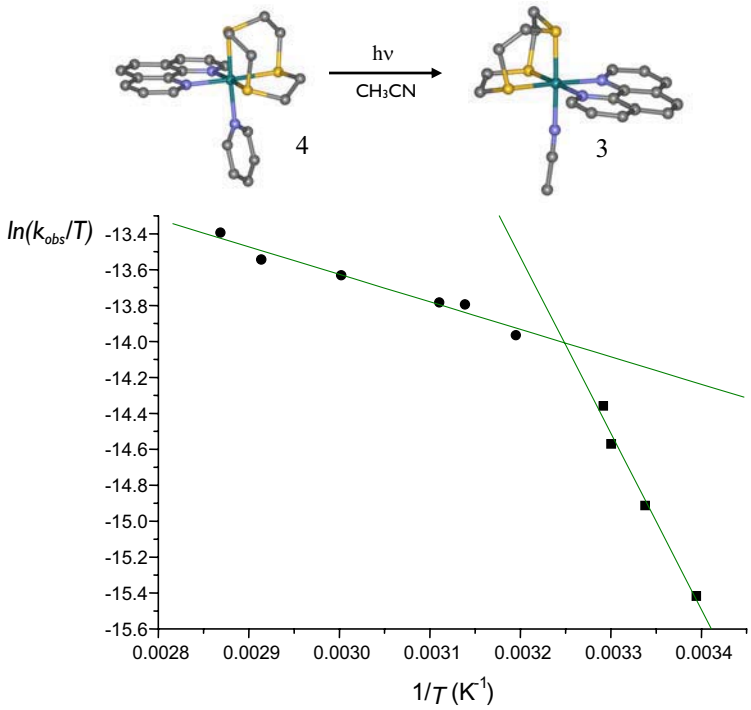


Figure 6.5 K_{obs} values and their corresponding Eyring plot after photochemical excitation of **4** in MeCN.

Unexpectedly, a non-linear diagram was obtained, highlighting the occurrence of two different reactions within the substitution process. As could be inferred from the slopes in the plot, higher temperatures seemed to slow down this reaction. This fact prompted us to check if the inverse substitution process (**3** → **4**) was taking place in these conditions. Experiments in the dark were performed at various temperatures and spectral changes attributable to pyridine re-coordination and MeCN expulsion were observed either by NMR and UV-vis analysis. This thermal inverse process (**3** → **4**) was then separately studied in absence of irradiation starting both from the Ru-py **4** complex (k_{-2}) and the Ru-MeCN complex **3** (k_2). Kinetic constants and thermal activation parameters were calculated for this reaction at various temperatures,* and a k_2/k_{-2} ratio always higher than 1 was obtained. Therefore, the higher thermodynamical stability of the Ru-py complex **4** was confirmed.

The photo-triggered process (**4** → **3**) was then investigated in a more detailed way. Experiments with different concentrations of the outgoing and incoming ligands (py and

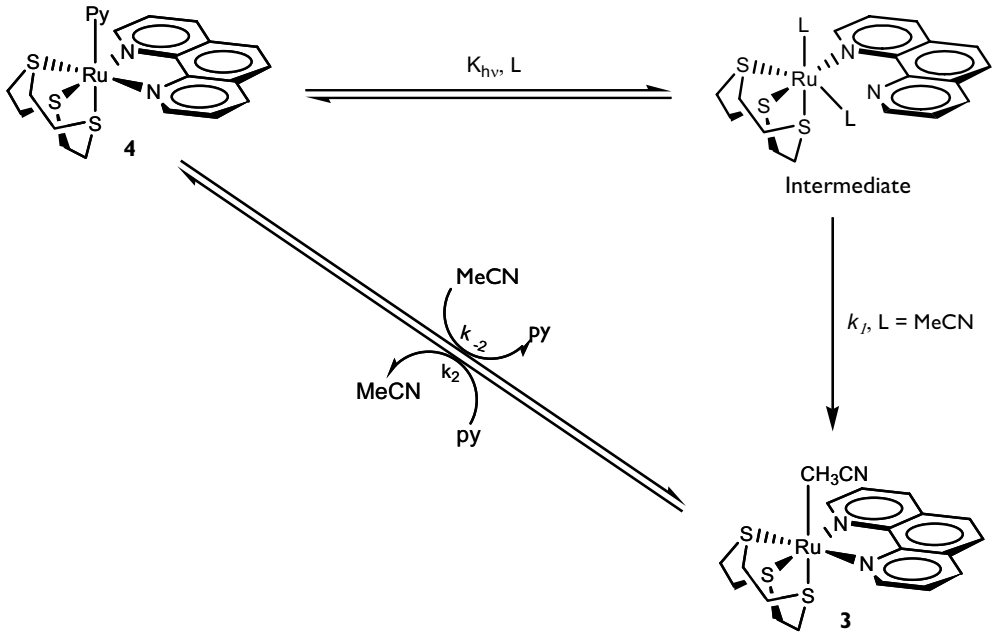
* See Chapter 3, page 62 for further details.

MeCN respectively) were performed and the corresponding k_{obs} calculated (see Table 6.2).

Table 6.2 Values of k_{obs} at different pyridine concentrations in MeCN, [Ru] = 1.3 x 10^{-4} M, T = 303.8 K

[py] /M	[MeCN] /M	$10^4 \cdot k_{obs}$ /s^{-1}	
0	19.0	1.67	
0.21	18.7	1.69	
0.42	18.4	1.63	
0.83	17.7	1.71	⇒ Constant value
1.04	17.4	1.72	
2.08	15.8	1.66	
3.12	14.2	1.71	
6.20	9.40	1.72	

The constant values obtained for k_{obs} even in experiments performed at high pyridine concentrations suggested us that this photo-triggered process (**4** → **3**) was not a so simple substitution reaction. If it were so, a rise in the outgoing ligand concentration should cause a clear drop in the k_{obs} value. Consequently, a two step process with the second one acting as rate limiting step was proposed for this transformation (Scheme 6.4).



Scheme 6.4 Global mechanism proposed for the ligand exchange process between complexes **3** and **4**

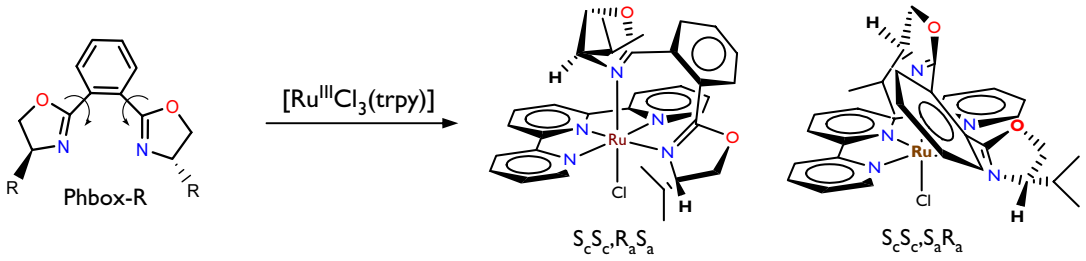
After photochemical activation of **4**, an intermediate compound is formed through pyridine dissociation and solvent coordination. The fact that increasing amounts of free pyridine didn't influence the observed rate constant (Table 6.2) suggest that this ligand is probably not bounded to the metal centre in the rate limiting step. Therefore, an intermediate compound with two bounded MeCN molecules and one of the polydentate ligands partially decoordinated has been proposed. Afterwards, a thermal chelation process conducts to the final product **3**. Therefore, we have generated a system with two stable positions (complexes **3** and **4**) that are connected in a reversible way through external environmentally friendly stimulus (light and temperature). For that reason, this work can also be defined as the generation of a molecular-level switch.[†]

As general conclusion for this first project and taking into account all the data reported, we can state that the electronic perturbations exerted by the thioether ligand over the metal centre are the main force that control and drive the substitution chemistry and reactivity of these complexes containing the [Ru([9]aneS$_3$)] fragment.

Project 2. Chiral Complexes – Chapters 4 and 5

The chiral Phenyl-1,2-bisoxazolinic ligand (ph-box-R, Scheme 6.5) was our first chronological choice for this project. Through this C_2-symmetric compound, two stimulating and challenging fields within coordination chemistry, stereoselective synthesis and asymmetric catalysis, could be treated together. Molecular modelling studies allowed us to infer that the coordination of this ligand to a [Ru^{III}Cl$_3$(trpy)] precursor could lead to a restricted rotation within its C-C bonds connecting the aromatic ring with the oxazolinic entities. Therefore, two possible limit orientations and, consequently, two independent chiral axes and atropisomeric forms could be generated, as detailed in Scheme 6.5):

[†] See Chapter 1 (General Introduction), pages 21-23, for further information about molecular-level machines.



Scheme 6.5

How to control the formation of one or the other atropisomer was then our main goal, since this control would allow us to prepare pure atropisomeric complexes potentially useful as asymmetric catalysts. We anticipated here, again by means of molecular models, that a plausible method to achieve a unique atropisomer was through the ligand chirality, linked to steric arguments. Thus, a simple change in the Phbox-R stereochemistry (form the S,S to the R,R form) for a given atropisomer seemed to produce strong changes in the steric hindrance of this complex. That prompted us to work towards the synthesis of a set of atropisomeric complexes containing the R,R-Phbox-Et, (R_cR_c)-**a**, and the S,S-Phbox-iPr, (S_cS_c)-**b**, ligands in order to check whether or not pure atropoisomers could be generated and applied as catalysts in asymmetric transformations.

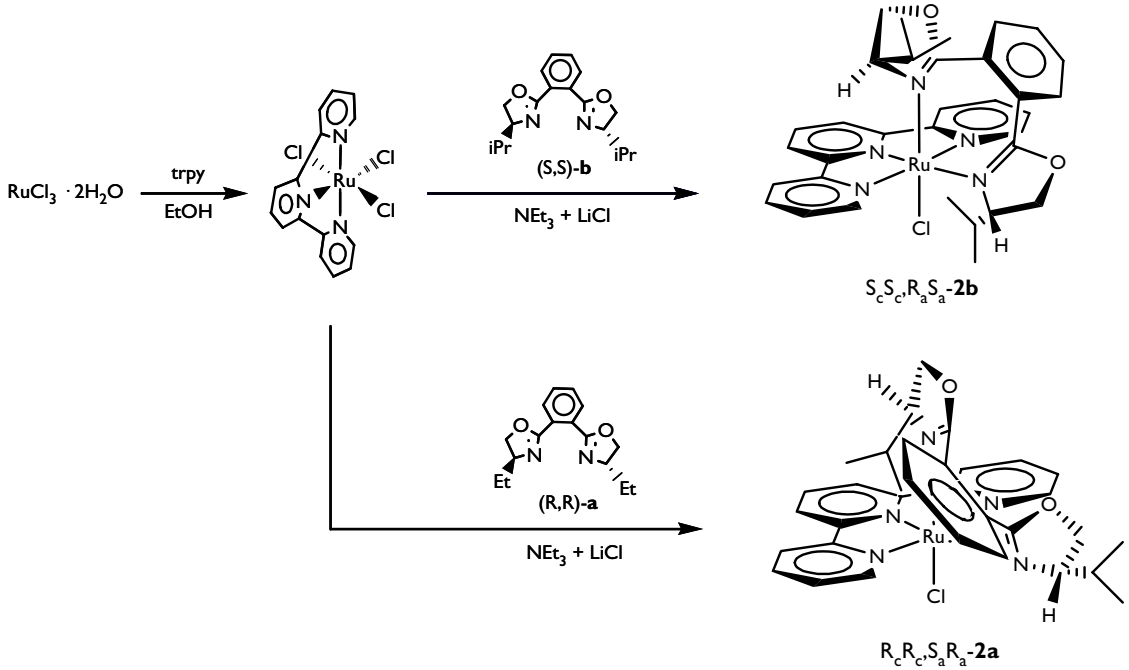
The most prominent features we encountered for this group of compounds with general formula $[Ru(Y)(trpy)(Phbox\text{-}R)]^{n+}$ (Y = Cl, H_2O, py, MeCN or 2-OH-py) are next detailed:

A) Stereoisomeric Analysis

According to the previously mentioned anticipations, we tested fist if the stereoselective synthesis of pure atropisomeric complexes could be achieved from trpy and the (R_cR_c)-**a** and (S_cS_c)-**b** ligands. Reactions with $[Ru^{III}Cl_3(trpy)]$ as precursor were carried out (Scheme 6.6) and the expected results were confirmed by NMR spectroscopy and X-ray diffraction analysis. Only one stereoisomer ((R_cR_c,S_aR_a)-**2a**[‡])

[‡] See Chapter 4, page 74, for specific information about ligands and complexes nomenclature.

was obtained when the (R_cR_c)-**a** ligand was used and its atropisomeric counterpart ((S_cS_c,R_aS_a)-**2b**) appeared, also as sole isomer, when employing the (S_cS_c)-**b** one. Furthermore, no atropisomeric interconversion was observed upon applying temperatures up to 120 °C.

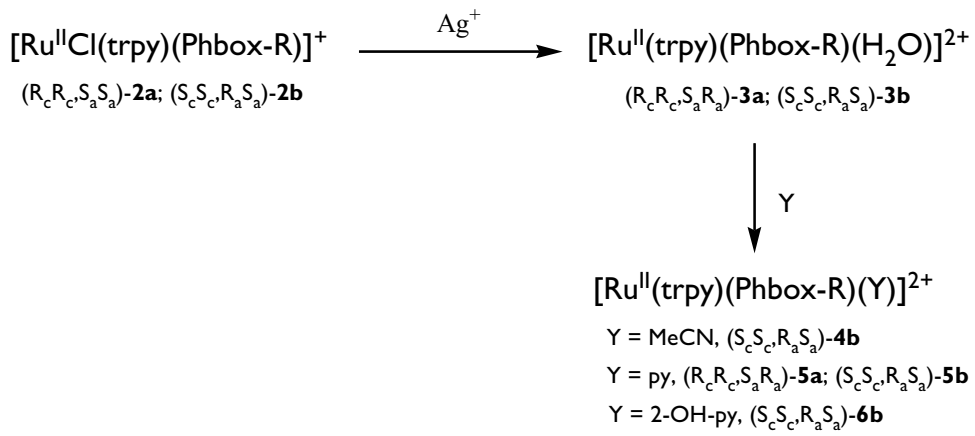


S_cS_c,R_aS_a-**2b**

R_cR_c,S_aR_a-**2a**

Scheme 6.6

Therefore, these Ru-Cl (**2a** and **2b**) complexes were used as starting products for the synthesis of the whole family of pure atropisomeric compounds described in Scheme 6.7.



Scheme 6.7

B) Solid State, Solution and Gas-phase (DFT-calculated) Structural Characterization

The structural characterization of these pure atropisomeric complexes was carried out exhaustively through X-ray diffraction analysis ((R_cR_c,S_aR_a)-**2a**, (S_cS_c,R_aS_a)-**2b** and (S_cS_c,R_aS_a)-**4b**) in the solid state, 1D and 2D NMR experiments in solution, and DFT calculations (for complexes containing the (S_cS_c)-**b** ligand) in the gas-phase.

Crystal structures showed, in all cases, the Ru metal centre in a pseudo-octahedral environment, with the trpy ligand coordinating in a meridional fashion and the Ph-box-R ligand in a chelate manner. As expected, confirmation that pure atropisomeric complexes had been synthesized with their chiral axes configuration discriminated through the ligand chirality was obtained with **2a** and **2b** diffractions (Figure 6.6).

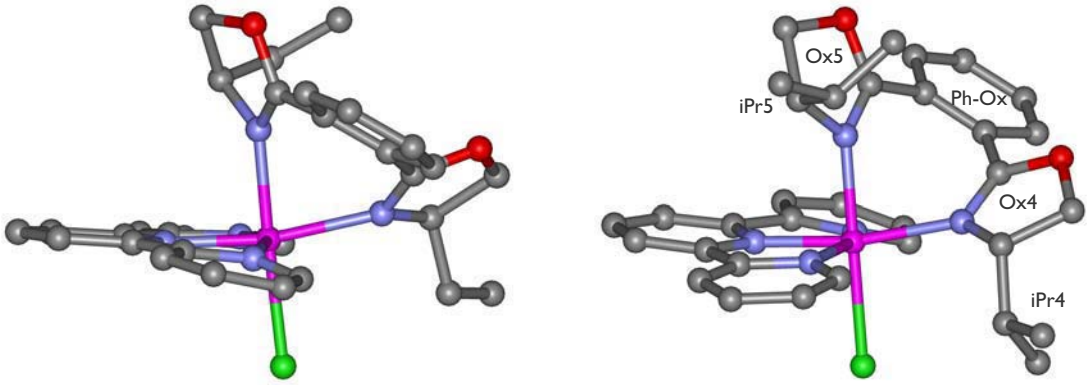


Figure 6.6 X-ray structures for (R_cR_c,S_aR_a)-**2a** (left) and (S_cS_c,R_a,S_a)-**2b** (right) and the labelling scheme of their plane.

Complexes **2a** and **2b** show similar three-dimensional networks over the crystal, with π-stacking and hydrogen bonding interactions between adjacent molecules (Figure 6.7). However, **4b** presents a different network where layers of two independent but very similar molecules are successively alternated (see the supplementary digital material of Chapter 4).

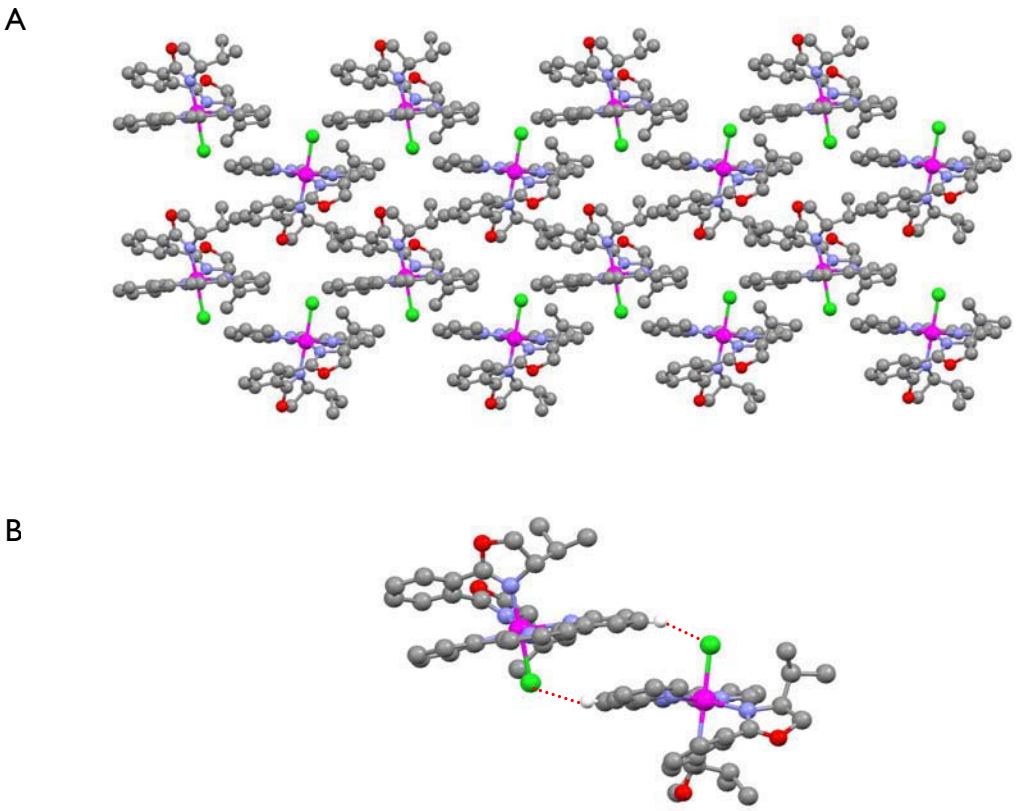


Figure 6.7. (A) 3D Network for (R_cR_c,S_aR_a)-**2a** (B) Interactions between neighboring molecules. Hydrogen atoms are partially omitted for clarity reasons.

DFT calculations for complexes containing the (S_cS_c)-**b** ligand were then performed showing good agreement with the solid state data. Thus, calculations for the two atropisomeric **4b** complexes showed the (S_cS_c,R_aS_a)-**4b** isomer (the one synthetically obtained) stabilized 5.7 kcal mol^{-1} regarding to the S_cS_c,S_aR_a-**4b** one. As can be inferred from the calculated structures (Figure 6.8), the position of the alkyl groups in the chiral oxazolinic centres is the factor that establishes discrimination between them, being exclusively formed the less hindered compound. In addition, a 26.0 kcal mol^{-1} energy barrier value was also obtained from the calculation of a possible transition state (TS) between these isomers, explaining why no atropisomeric interconversion was experimentally observed.

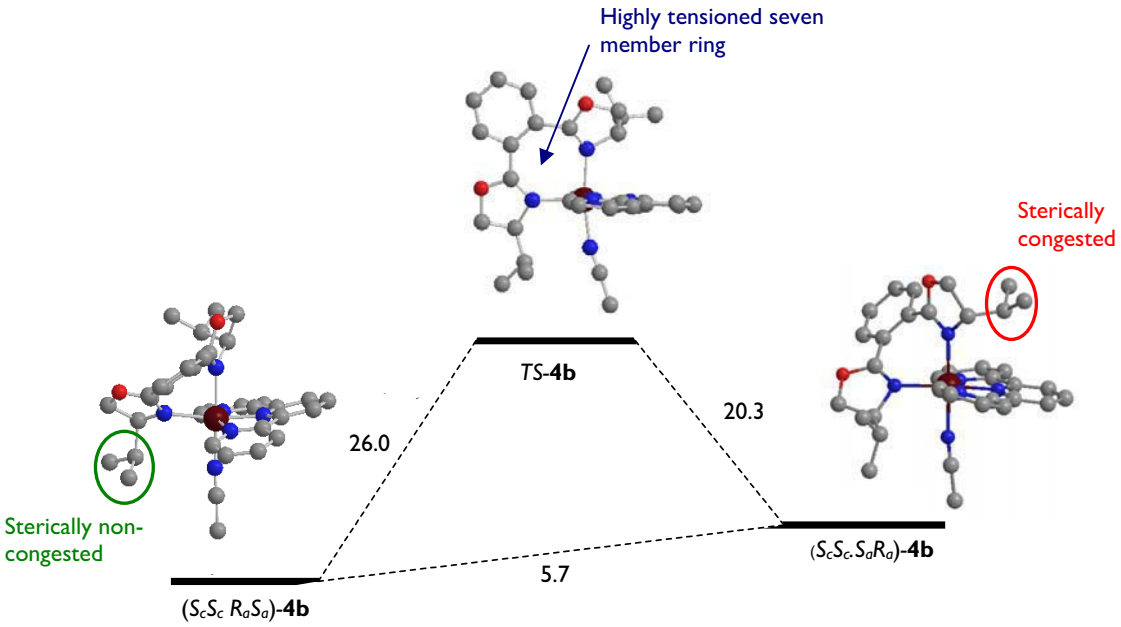


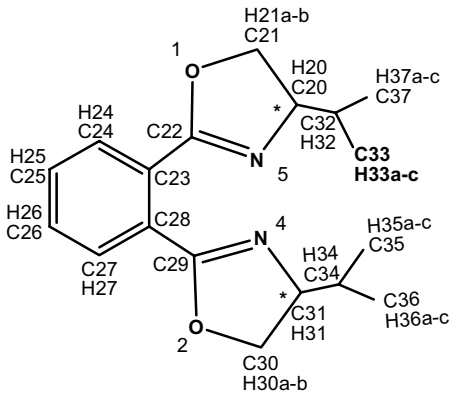
Figure 6.8. Relative energy diagram for the two possible atropisomers of **4b** and the transition state (TS-**4b**) connecting them. Energies in kcal mol^{-1}.

Extremely similar structures to the ones in the solid state were found in solution (NMR spectroscopy) as expected for this type of Ru d^6 complexes. However, interesting structural changes were appreciated in chemical shifts and the NOE map when varying the monodentate ligand, particularly in the case of the 2-OH-pyridine complex ($S_cS_cR_aS_a$)-**6b** (Table 6.3).

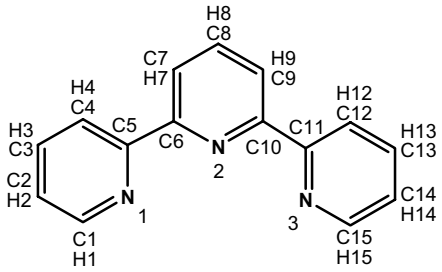
Table 6.3 Selected NMR data for **2b**, **3b**, **4b**, **5b**, and **6b** complexes, and labeling scheme.

		($S_cS_oR_aS_a$)-**2b**	($S_cS_oR_aS_a$)-**3b**	($S_cS_oR_aS_a$)-**4b**	($S_cS_oR_aS_a$)-**5b**	($S_cS_oR_aS_a$)-**6b**
trpy[a]	H1	7.95	7.97	7.92	8.10	8.97
	H15	9.41 (H31, H34, H32)	9.46 (H31, H34, H32)	9.35 (H31, H34, H32, H36)	9.32 (H31, H34, H36)	9.00 (H31)
Ph-Ox	H24	7.26	7.25	7.31	7.33	6.27
	H25	7.57	7.58	7.60	7.65	7.22
	H26	7.90	7.95	7.92	7.98	5.83
	H27	8.13	8.20	8.21	8.20	6.12
CH-Ox5	H20	2.97	2.91	3.15	3.14	3.58
CH_2-Ox5	H21a	4.31	4.29	4.43	4.39	3.91
CH_2-Ox5	H21b	3.82	3.84	3.99	3.92	4.35
CH-*i*Pr5	H32	1.11	1.06	1.18	1.03	1.50
Me-*i*Pr5	H33a-c	0.28	0.25	0.28	0.28	0.67
Me-*i*Pr5	H37a-c	0.53	0.57	0.58	0.55	0.70
CH-Ox4	H31	5.56	5.67	5.64	5.4	4.58
CH_2-Ox4	H30a	5.16	5.20	5.14	5.20	4.54
CH_2-Ox4	H30b	5.00	5.11	5.12	5.07	4.13
CH-*i*Pr4	H34	3.72	2.88	3.04	1.51	3.54
Me-*i*Pr4	H36a-c	1.13	1.18	1.30	1.02	0.85
Me-*i*Pr4	H35a-c	1.18	1.21	1.30	1.20	1.17

[a] The most significant NOE contacts are indicated in parentheses.



Phbox-iPr, SS-**b**



trpy

DFT calculations were then performed for complex **6b** to deepen our understanding about these structural alterations. Two possible isomers (*in*-($S_cS_oR_aS_a$)-**6b** and *out*-($S_cS_oR_aS_a$)-**6b**), depending on the relative orientation of the hydroxyl group versus the phenyl group of the oxazoline ligand, were calculated. Similar energy values were

obtained (0.6 kcal mol^{-1} energy difference), thus indicating the free rotation of the 2-OH-py ligand in solution. These gas-phase calculations perfectly fit the NMR data reported in Table 6.3 allowing us to explain the previously mentioned structural differences. Therefore, the strong steric hindrance exerted by the OH group of the 2-OH-py ligand against the iPr4 group produces a slight rotation of the chiral axes and an increment of the angle between the best adjusted planes that describes the two oxazolinic rings (from 73.4° in **5b** to 89.6° in *in*-**6b**), moving the phenyl oxazolinic group (Ph-Ox) closer to the trpy ligand.

C) Redox Chemistry and Catalytic Activity

The redox behavior of the whole family of complexes **2-6** was studied through cyclic voltammetry experiments. The chloro complexes **2a** and **2b** show a simple chemically and electrochemically reversible wave in acetonitrile, corresponding to the Ru^{III}/Ru^{II} couple, at $E_{1/2}$ values of 0.70 and 0.71 V respectively. The analogous pyridine complexes **5a** and **5b** undergo an equivalent redox process at higher potential values ($E_{1/2}$ = 1.15 and 1.18 V), that are consistent with both the lower electron-donating and the stronger electron-accepting capability of the py ligand with regard to the chloro ligand. This effect is manifested even more intensely in **4b**, having the even more π-accepting acetonitrile ligand, with a redox potential of 1.22 V.

The electrochemical properties of the aqua complexes **3a** and **3b** were tested both in dichloromethane and in phosphate buffer aqueous solution. In CH_2Cl_2 only one redox process is manifested at $E_{1/2}$ = 0.98 V for both compounds, corresponding to the Ru^{IV}/Ru^{III} redox couple. In aqueous solution (pH = 6) two reversible waves, corresponding to the Ru^{IV}/Ru^{III} and Ru^{III}/Ru^{II} redox couples can be observed, at 0.64 and 0.46 V respectively for complex **3a**, and at 0.65 and 0.46 V for **3b**.

The pH-dependence of the redox potential was investigated for complex **3b**, and the corresponding pourbaix diagram manifests the existence of two independent one-electron redox processes that take place with simultaneous proton-transfer at pH values between 2 and 11. The pKa for the equilibrium $Ru^{II}\text{-}OH_2 \leftrightarrows Ru^{II}\text{-}OH + H^+$ is

11.2, also consistent with the value determined from a spectrophotometric acid-base titration of the complex.

A redox spectrophotometric titration was also performed on complex **3b** through oxidation of **3b** with Ce^{IV}, and two sets of isosbestic points were observed for $Ru^{II} \rightarrow Ru^{III}$ and $Ru^{III} \rightarrow Ru^{IV}$ oxidations, confirming the net formation of the corresponding oxidized species in each case.

The redox catalytic properties of ($S_cS_\sigma R_aS_a$)-**3b** were tested in the electrochemical oxidation in aqueous neutral media of target substrates such as benzyl alcohol and methyl *p*-tolyl sulfide. The corresponding oxidized products (benzyl alcohol and methyl *p*-tolyl sulfoxide) were selectively obtained but in poor yields (up to 50 and 13 catalytic cycles respectively) and, in the case of the prochiral sulfide substrate, no ee's were observed for the sulfoxide.

The catalytic ability of ($S_cS_\sigma R_aS_a$)-**3b** was also tested with regard to its aptitude to epoxidize alkenes. Styrene and trans-stilbene were chosen as substrates with PhIO and $PhI(OAc)_2$ as oxidants in 1,2-dichloroethane, and the results are reported in Table 6.4.

Table 6.4. Alkene epoxidation catalyzed by ($S_cS_\sigma R_aS_a$)-**3b**

Substrate	Oxidant	Substrate:cat	Conversion (%)	Epoxide yield (%)	benzaldehyde yield (%)	catalytic cycles
styrene	$Ph(IOAc)_2$	200:1	67.3	36.1	6.1	71.3
trans-stilbene	$Ph(IOAc)_2$	150:1	71	37.4	4.1	57.9
styrene	PhIO	200:1	48.9	22.4	10.1	44.1
trans-stilbene	PhIO	200:1	74.3	44	29.6	87.6

A first glance at Table 6.4 shows that in all cases the main products formed are the corresponding epoxides (styrene oxide and trans-stilbene oxide) with minor amounts of benzaldehyde. However, despite good selectivity was achieved towards the desired products, the enantioselectivity values for these reactions were low, never upper than 10% ee. A potential explanation for this low enantioselectivity can be inferred from Figure 6.9, where a spacefill structure (($S_cS_\sigma R_aS_a$)-**2b**) representing the whole ($S_cS_\sigma R_aS_a$)-**b**-type of complexes is shown.

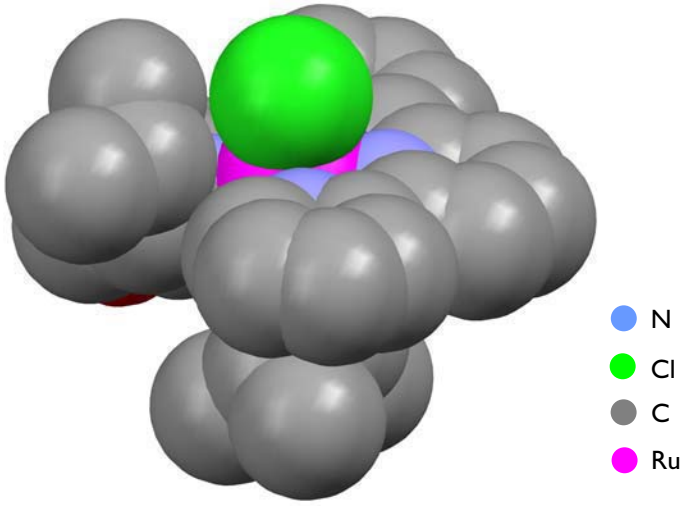


Figure 6.9

Considering the approach of a substrate to molecules like the one in Figure 6.9, once the coordination position liberated by the labile ligand (represented as a green sphere in the figure) becomes available, we can visualize how the catalyst-substrate interaction can occur through multiple orientations due to the non-hindered, planar nature of the trpy ligand. Thus, this contact will probably can take place without any influence of the chiral centres of the oxazolinic ligand, leading to racemic mixtures in the reaction products.

These disappointing catalytic results in terms of enantioselectivity prompted us to design new chiral ligands that could coordinate the Ru metal-centre in a more appropriate manner. C3-symmetric polypyridylic ligands seemed an interesting alternative owing to: a) they potential ability (upon coordination to an octahedral metal centre) to reduce the number of possible diastereomeric intermediates or transition states in a catalytic reaction[5] b) the 'chiral pocket' that they could generate upon coordination (see Figure 6.10) and c) the fact that they had been hardly ever studied in their chiral versions.[6] Therefore, in cooperation with Professor Alexander von Zelewsky's group (University of Friboug, Switzerland), we though that the introduction of enantiomerically pure monoterpenic moieties to pyridine nucleus could be an appropriate synthetic strategy for these ligands and C3-symmetric compounds with the basic structure shown in Figure 6.10 were designed.

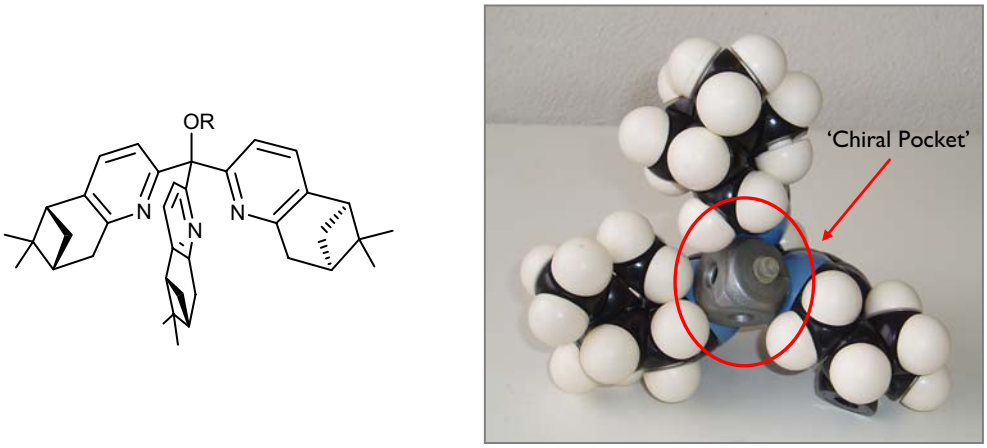
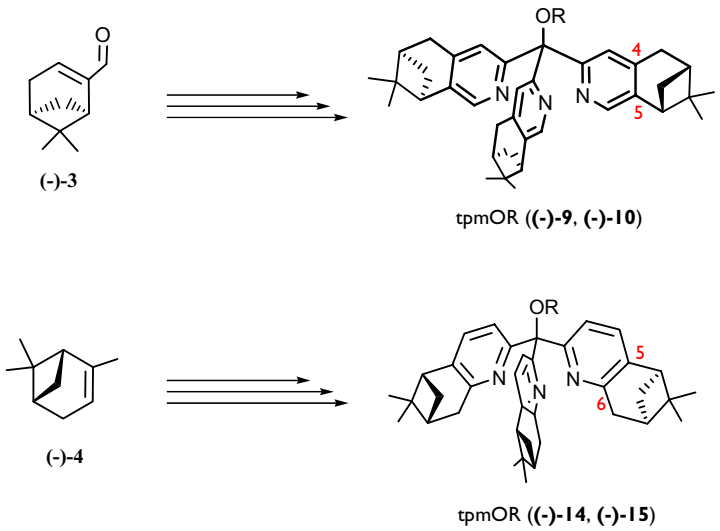


Figure 6.10 Basic structure for the C3-symmetric chiral ligands designed (left) and CPK molecular model of their facial coordination to an octahedral metal-centre (right).

The most prominent features we encountered within the synthesis, coordination chemistry and catalytic application of this new set of chiral ligands are next detailed:

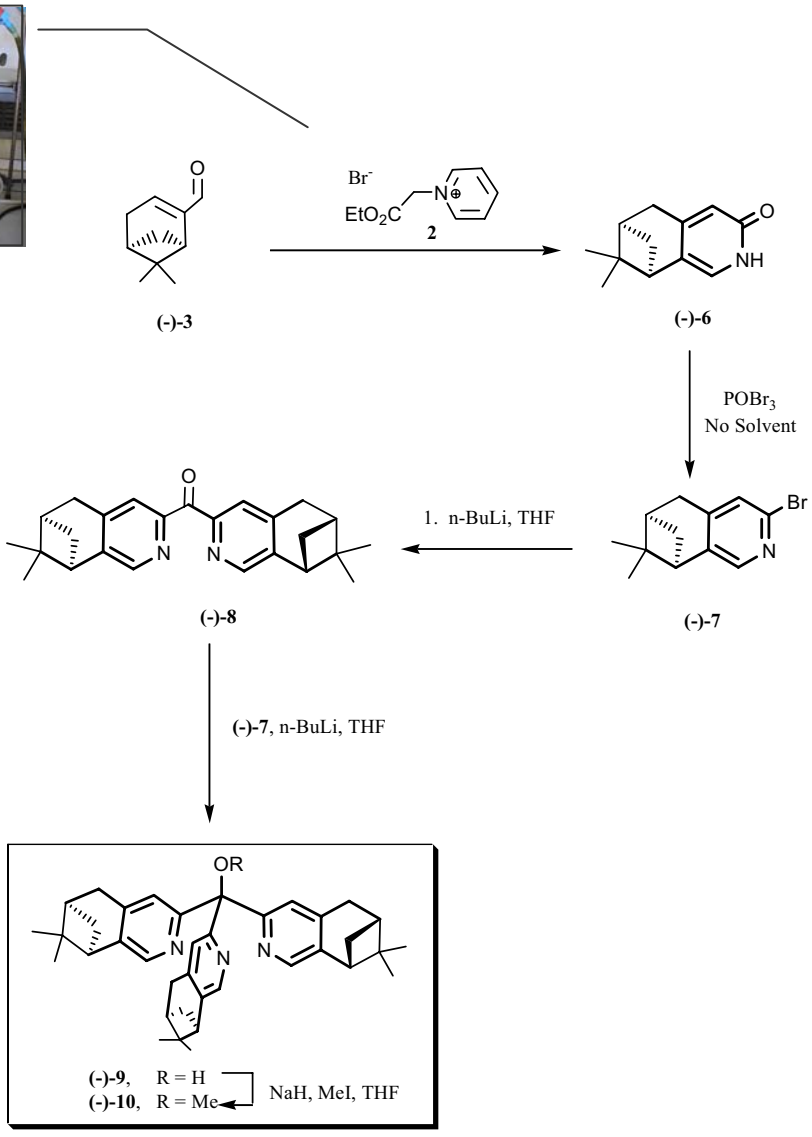
A) Ligand Synthesis

(-)-Myrtenal **(-)-3** and (-)-α-pinene **(+)-4** were the monoterpenic natural products chosen to introduce chirality into pyridilic units. Therefore, their annulation reactions through the methodology introduced by Krönke in the 70s[7] allowed us to synthesize C3-symmetric ligands with the chiral groups either in the 4,5 or 5,6-positions of the pyridine rings (Scheme 6.8).



Scheme 6.8

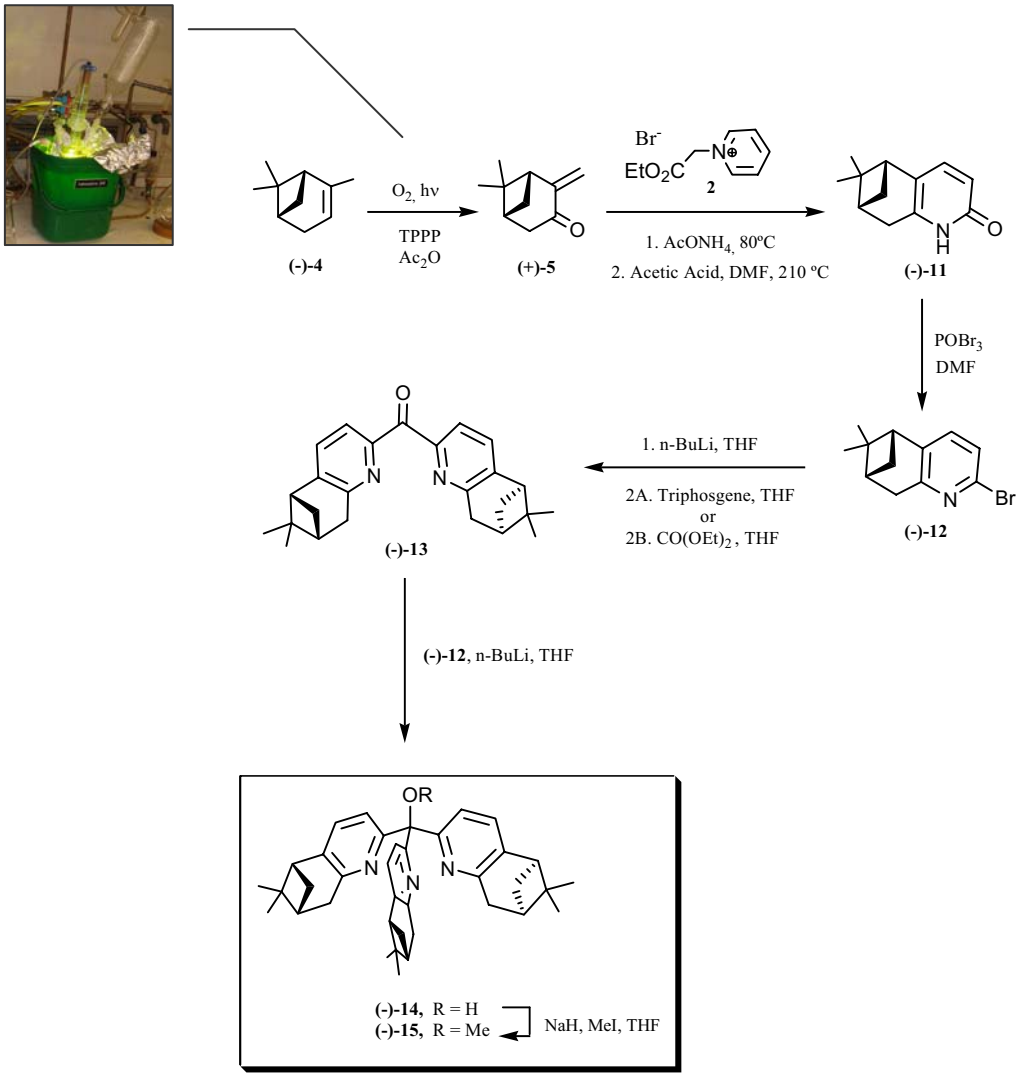
The synthetic procedures towards these 4,5 and 5,6-pinene ligands were similar in the number of steps and the nature of the reactions, but rather different in their experimental conditions due to the varied chemical reactivity of the formed intermediates.[§] Thus, the first disparity between the synthesis of 4,5-ligands (-)-9 or (-)-10 (Scheme 6.9), and those of 5,6-ligands **(-)-14** and **(-)-15** (Scheme 6.10), arises from the initial natural product available. While **(-)-3** can be directly annulated, **(-)-4** must be firstly oxidized by means of singlet dioxygen generated under photo-irradiation (picture in Scheme 6.10).



Scheme 6.9

[§] See Chapter 5 pages 122-125 (experimental part) for further experimental details.

In the annulation step (**(-)-3** → **(-)-6** and **(+)-5** → **(-)-11**) is where more differences can probably be found between these two synthetic schemes. The instability of aldehyde **(-)-3** at high temperatures made necessary longer reaction times, slowly increasing the reaction temperature, if acceptable yields wanted to be reached (picture in Scheme 6.9). The bromination of the annulated pyridones (**(-)-6** → **(-)-7** and **(-)-11** → **(-)-12**) was a difficult transformation as well. $POBr_3$ was in both cases efficient as brominating agent (other less expensive and toxic reactants were attempted unsuccessfully). However, while DMF can be used as solvent for the 5,6 compound, stronger no-solvent reaction conditions were required for the 4,5 one, thus indicating the change in reactivity imposed by the different position of the pinene group in the pyridyl ring.



Scheme 6.10

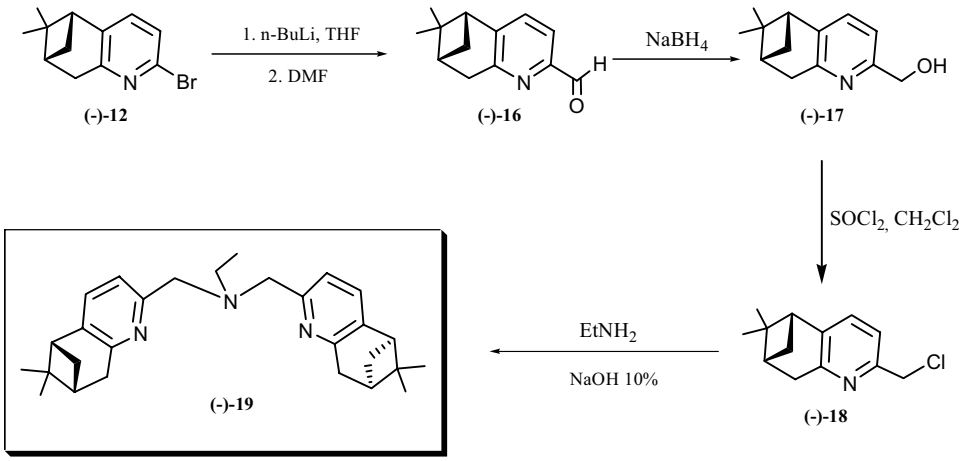
The synthesis of the trispyridyl ligands **(-)-14** and **(-)-15** was first assayed through a one-step approaches by means of the lithiation of bromopyridine **(-)-12** followed by slow addition of triphosgene or diethylcarbonate respectively. However, and as expected from similar procedures described in the literature,[8] higher yields were achieved with a two-step sequence via ketone **(-)-13**. Therefore, the same procedure was applied for the 4,5 case (Scheme 6.9), firstly synthesizing ketone **(-)-8** as intermediate. Subsequently, the slow addition of these bipyridylic ketones over lithiated solutions of bromopyridine **(-)-7** or **(-)-12** afforded the final tripodal ligands **(-)-9** and **(-)-14** in reasonable yields.** Finally, the o-alkylated derivatives **(-)-10** and **(-)-15** were synthesized in high yields through nucleophilic attack of the corresponding alkoxides to methyl iodide. Smoother conditions could be employed in the 5,6 case thanks to the less hindered nature of its R_3-O^- group that enhances its nucleophilicity. This final alkylation step was necessary when mixtures of isomeric complexes were obtained upon preliminary coordination attempts of the tpmOH ligands (**(-)-9** and **(-)-14**) to a Ru metal centre. Three coordination behaviours (N, N', N'' symmetric mode, N, N', O'' asymmetric mode and N, N', O-O, N'' bridging mode between two metal centres) had been previously reported for analogue achiral tris-pyridyl methanol ligands when they coordinated octahedral metal ions, while their corresponding o-alkylated versions had led only to the symmetric N,N',N" mode.[9] As we will see later on, the alkylated ligands **(-)-10** and **(-)-15** will coordinate only in this later mode.

The next step in this project was the synthesis of the chiral bpea ligand **(-)-19** (Scheme 6.11), that was prepared for purposes of comparison. A wide range of Ru complexes containing its achiral analogue in combination with other N,N or P,P ligands had been developed within our group along the last years, showing interesting structural, electrochemical and catalytic properties.[10] Therefore, comparison of these features with similar chiral complexes containing **(-)-19** seemed an interesting goal.

The synthetic procedure designed for ligand **(-)-19** was intended as an extension of the previously described synthesis of C3-symmetric compounds to other ligands with reduced symmetry. Therefore, aldehyde **(-)-16** was synthesized through **(-)-12**

** See Chapter 5 pages 122-125 for detailed yield values of each reaction step.

lithiation and reaction quench with DMF. This synthetic intermediate can be seen as an interesting building block for the introduction of chirality to a wide range of chiral polypyridylic ligands, as now proved by parallel research projects in our group.[††] Subsequent reduction and chlorination of **(-)-16** followed by the double attack of ethylamine over the formed hydrochloride compound **(-)-18**, afforded ligand **(-)-19** in moderate yields.



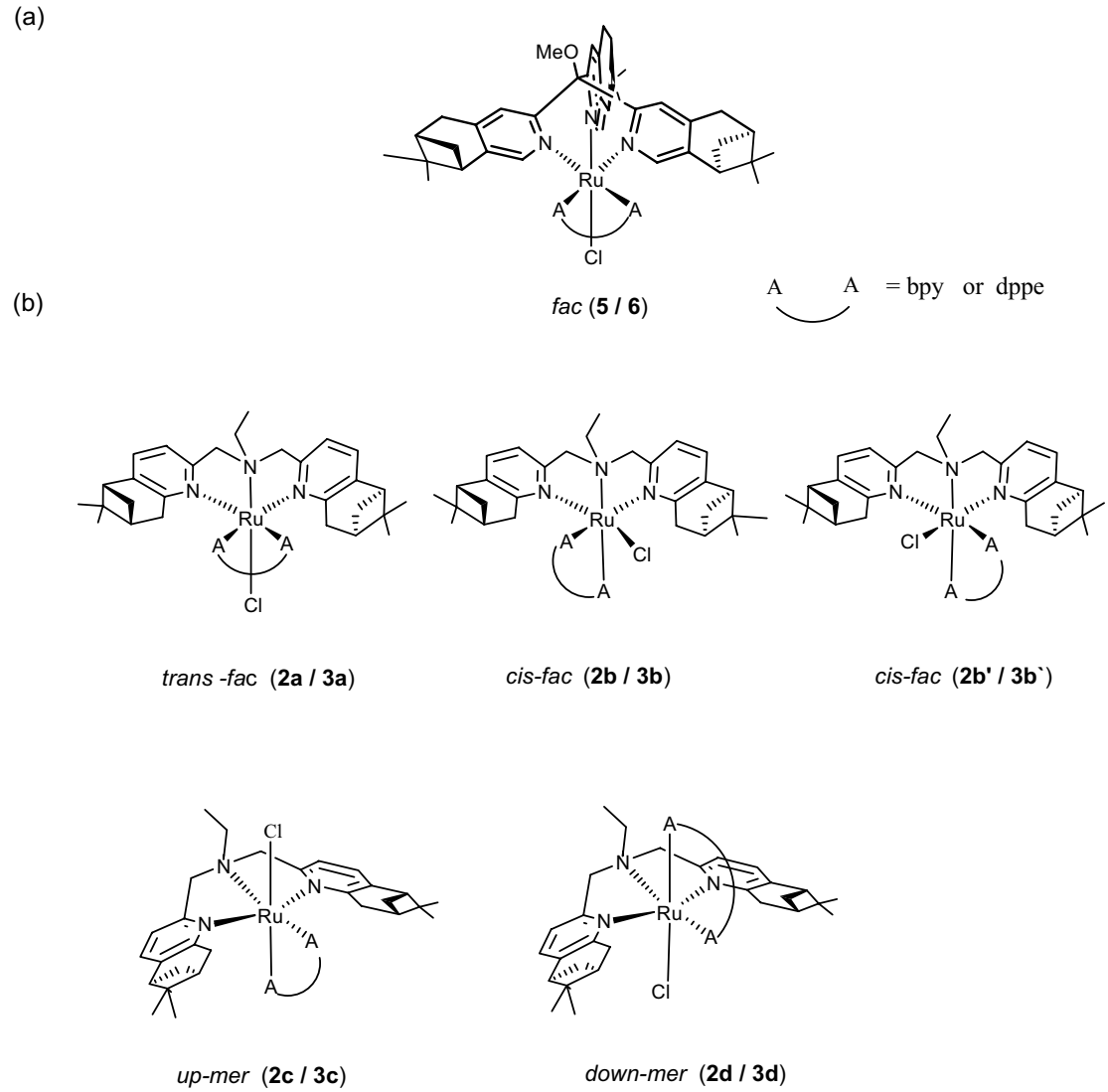
Scheme 6.11

B) Coordination Chemistry

Bpy and *dppe* were selected to accompany the chiral tridentate ligands *pinene[5,6]bpea* **(-)-19** (**L1**) and *pinene[4,5]tpmOMe* **(-)-10** (**L2**) in its coordination to a ruthenium ion. Despite their condition of symmetric didentate ligands, strong differences were expected in their respective coordination behaviour jointly to the new chiral compounds prepared. The set of distinct electronic and geometric characteristics shown by bpy and dppe should lead to different complex families, all of them potentially useful in a wide range of asymmetric catalytic transformations.

[††] Other ligands synthesized using this method: (a) Gómez, M.; Company, A.; Sala, X.; Costas, M.; Llobet, A.; Benet-Buchholz, J. unpublished results. (b) Franco, E.; Sala, X.; Romero, I.; Rodríguez, M.; Llobet, A.; Fontrodona, X. unpublished results.

Therefore, the synthesis of the [$Ru^{III}Cl_3$(**L**)] (**L** = **L1** or **L2**)] starting products, **1** and **4** respectively, was our first purpose. Similar reaction procedures to the ones applied for the coordination of other tripodal ligands to a $RuCl_3 \cdot nH_2O$ precursor[11] were applied and the desired trichloro complexes obtained in reasonable yields. However, significant differences between **1** and **4** must be considered when symmetric didentate ligands (*bpy* or *dppe*) are planed to be introduced in these complexes. While the C3-symmetric compound **4** can only lead to one stereoisomer with **L2** always coordinating in a facial fashion, the less symmetric **1** (where **L1** can coordinate in both facial and meridional modes) can potentially produce a mixture of five different isomers (Scheme 6.12).



Scheme 6.12. Possible stereoisomers generated upon coordination of a didentate ligand to (a) [Ru(L2)Cl_3], **4** and (b) [Ru(L1)Cl_3], **1**.

Among this collection of isomeric complexes, and as expected also from molecular modeling simulations, the coordination mode of the bulkier *dppe* ligand will be strongly determined by steric factors, whereas the smaller and flat *bpy* ligand will easily accommodate itself in almost any of the coordination modes described. Accordingly, while *bpy* leads experimentally to four of the five potential isomers when it coordinates to complex **I** (*trans-fac* **2a**, *cis-fac* **2b**/**2b'** and *mer* **2c**), the more voluminous *dppe* rends only the less hindered compound *trans-fac* **3a**, displaying lower steric interactions between its *pyridyl-pinene* moieties and the *phenyl-dppe* groups. The **2b**/**2b'** diastereomeric mixture has been isolated by $CHCl_3/Et_2O$ recrystallization.

Interesting discrepancies were found between this steric rationalization and the results previously reported[10] for the coordination of *bpy* or *dppe* to the non chiral [$Ru^{III}Cl_3$(*bpea*)] precursor. Surprisingly, in the *bpy* case, only pure *trans-fac* complexes were obtained (instead of isomeric mixtures as above mentioned for its chiral counterpart). For *dppe,* a combination of trans-fac, *cis-fac* and *mer* complexes were determined. To shed light on these apparently contradictory experimental facts, DFT theoretical calculations were performed for the whole set of chiral and non-chiral complexes. As expected, the relative energies found for these complexes were consistent with the relative yields synthetically obtained[‡‡] clearly indicating that, sometimes, steric factors are not enough to accurately predict the thermodynamic stability of these compounds. For the non-chiral compounds, the strong hydrogen bonding interactions (Figure 6.11) between the X atom (Cl or O) and both pyridylic-*bpea* hydrogen atoms in α-N-positions are proposed as the key features, strongly stabilizing the *trans-fac* **9b**/**10b** complexes and allowing their production as sole isomers. However, this electronic interaction cannot take place by using the chiral precursor **I** because pinene entities, instead of H atoms, are found in the α-N-positions (Figure 6.11). Then, only steric factors are responsible for the ratio of isomers formed.

[‡‡] See Chapter 5 Pages 169-170 for specific energy values and metric parameters of the calculated structures.

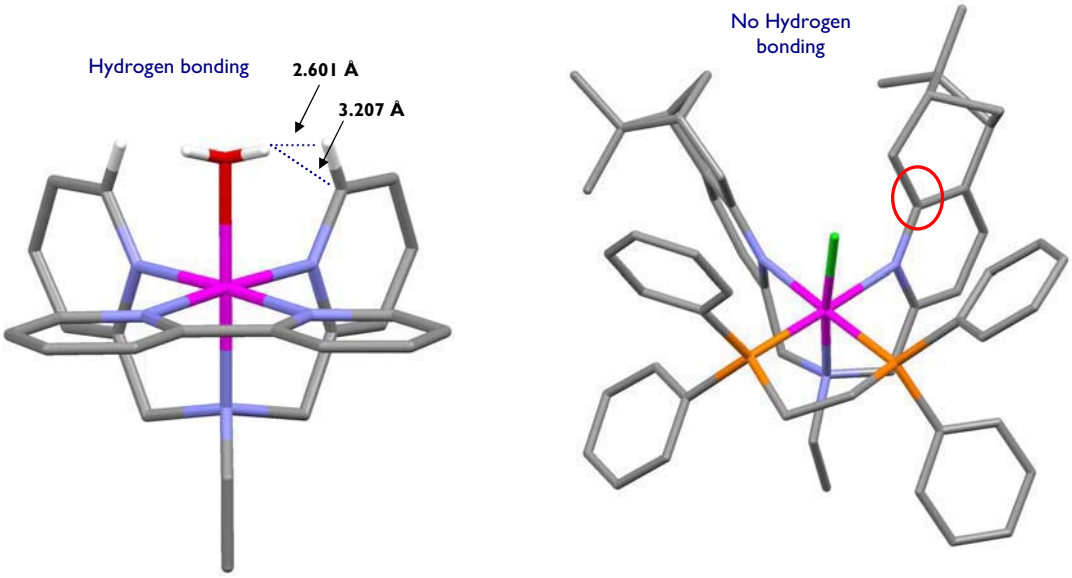


Figure 6.11 X-ray structures of $[Ru(bpea)(bpy)H_2O]^{2+}$ **10a** and $[RuCl(bpea[5,6]pinene)(dppe)]^{+}$ **3a**. Hydrogen atoms are partially omitted for clarity reasons.

The introduction of these didentate ligands taking the C3-symmetric complex **4** as starting material was easier. Complexes **5** and **6** (with *bpy* and *dppe* respectively) were obtained in high yields and purities, thus exemplifying the advantages that C3-symmetry offers in the synthesis of octahedral coordination compounds.

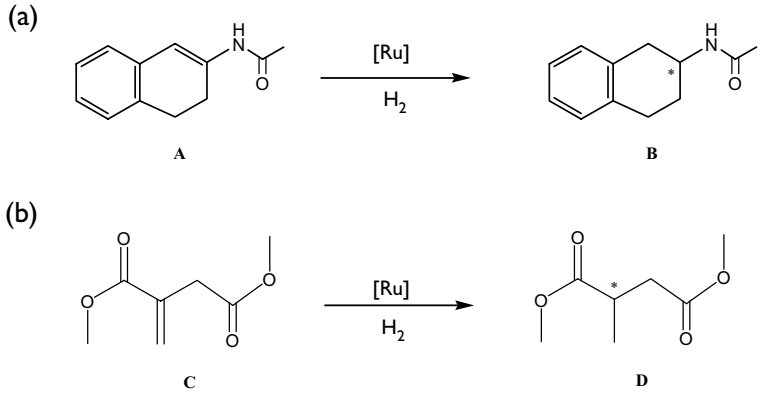
C) Catalytic activity

The catalytic performance of Ru-phosphine complexes **3a** and **6** (see scheme 6.12) was tested with regard to its aptitude to carry out asymmetric reduction reactions while the Ru-N_{donor} complex **5** was employed as catalyst for asymmetric oxidations.

• *Asymmetric hydrogenation*

As commented in Chapter 1 (General Introduction), asymmetric hydrogenation is one of the best studied and more successful examples of how chiral metal-catalysts can be employed in asymmetric synthesis. A wide range of compounds can be reduced with this method reaching high yields and enantioselectivities but, however, there are still some challenging substrates that justify the ongoing intensive research efforts in this

area. Therefore, cyclic enamide **A** (Scheme 6.13 (a)) was chosen as one of these difficult compounds since only few rhodium and ruthenium catalysts have been successful in its enantioselective reduction. However, the much more studied dimethyl itaconate **C** was also tested (Scheme 6.13 (b)).



Scheme 6.13

At this point, and in view of the outstanding ee values recently reported by our group by employing the *cis-fac*-Δ-[$Ru^{II}Cl\{(R)$-(bpea)$\}\{(S)$-(BINAP)$\}]BF_4$, cis-fac-Δ-(R)-(S)-**3** complex in substrate **C** hydrogenation (ee > 99 %),[10b] comparison between this complex and the new ones synthesized seemed attractive. **3a** and *cis-fac*-Δ-(R)-(S)-**3** are both RuN_3P_2Cl complexes, only differing in the situation of the chiral center (at the N-donor ligand or at the P-donor one respectively). Therefore, complex **3a**, together with compound **6**, were tested first in the dimethyl itaconate reduction (Scheme 6.13 (b)) and the results are gathered in Table 6.4.

Table 6.4 Hydrogenation of **C** in protic solvents.

Entry	Catalyst	Solvent	T(°C)	P_{H2}	t (h)	Conversion (%)
1	3a	MeOH	70	9	17	<1
2	3a	MeOH	70	30	17	1
3	3a	MeOH	70	50	17	23
4	3a	iPrOH	100	62	17	100
5	3a	Toluene	100	62	17	100
6	6	MeOH	70	9	17	<1
7	6	MeOH	70	50	17	23
8	6	iPrOH	100	62	17	11.5
9	6	Toluene	100	62	17	18.5

High pressures and temperatures were needed to completely hydrogenate **C** with **3a** (62 bar, 100 °C, entries 4 and 5) while 8 bar and 80 °C had been enough using the Ru-*Binap cis-fac*-Δ-(R)-(S)-**3** complex. Complex **6**, probably owing to its more constrained nature having three 'pineno-fused' pyridines, was the less effective one, reaching only poor conversions (18.5 %, entry 9) at high P and T values. Furthermore, no enantioselectivity was observed in any of these reduction reactions.

The hydrogenation of the challenging enamide **A** was then assayed with catalysts **3a** and *cis-fac*-Δ-(R)-(S)-**3**. Again, outstanding results with good conversions and ee's up to 74 % were achieved with this later catalyst (Table 6.5, entries 6-8 and 11-12) but **3a** showed poorer results (Table 6.5, entries 13-16). It is worth mentioning here that the ee values reached with the *cis-fac*-Δ-(R)-(S)-**3** complex are between the best three results achieved so far for this difficult substrate.

Table 6.5 Enantioselective hydrogenation of enamide **A** in protic solvents.

Entry	Catalyst	Solvent	Temp. (°C)	P_{H2} (bar)	Time (h)	Conversion (%)	Ee (%)
1	3	MeOH	75	8	13	<1	63 (+)
2	3	MeOH	75	56	13	1	80 (+)
3	3	MeOH	100	62	13	30	n.d.
4	3	MeOH	120	56	13	60	71 (+)
5	3	iPrOH	75	56	13	1	77 (+)
6	3	iPrOH	100	62	13	82	74 (+)
7	3	iPrOH	120	56	13	>99	70 (+)
8	3	iPrOH	120	30	13	86	72 (+)
9	3	THF	75	56	60	<1	75 (+)
10	3	Toluene	75	56	60	23	70 (+)
11	3	Toluene	100	62	13	97	72 (+)
12	3	Toluene	120	30	13	94	70 (+)
13	3a	MeOH	100	56	13	1	9 (+)
14	3a	iPrOH	120	56	13	12	7 (+)
15	3a	Toluene	100	30	13	2	8 (+)
16	3a	Toluene	120	56	13	19	5 (+)

Thoroughly studying the X-ray structure of **3a** (Figure 6.11), we can infer that the chiral centers in the pinene moieties could be quite too far from the active centre of the catalyst to produce significant discrimination between the prochiral sides of the entering substrate.

• *Asymmetric epoxidation*

Preliminary results with regard to the aptitude of complex [RuCl(pinene[4,5]tpmOMe)(bpy)]BF_4 **5** to catalyze styrene epoxidation employing $PhI(OAc)_2$ as cooxidant showed promising ee values up to 36 %.[§§]

[§§] See Chapter 5 page 126 for detailed reaction conditions.

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Chapter 7

Conclusions and Future Work

Specific points for each project developed along this thesis as well as general conclusions are presented in this chapter. Furthermore, proposals for the extension of the work reported here are also included.

- A new family of Ru(II) complexes containing the tridentate facial [9]aneS$_3$ ligand, of general formula [Ru(Y)(phen)([9]aneS$_3$)]$^{n+}$ (Y = H_2O, py or MeCN), have been prepared and structurally, spectroscopically and electrochemically characterized.

- The bonding of the thioether ligand to the metal centre causes important anodic shifts in the corresponding Ru^{III}/Ru^{II} redox couples if they are compared with the reported ones for geometrically related complexes. Therefore, the weak σ- and strong π-bonding capacities exerted by the macrocyclic ligand over the Ru metal centre strongly influence the electronic properties of these complexes.

- The electronic effect that the ligand exerts over the metal centre is also responsible for the manifested instability showed by the Ru^{III}-OH species, in the aqua-complex **2** case. However, this oxidation state +III is able to catalyze the oxidation of BzOH with a second-order rate constant of 19.3 $M^{-1}s^{-1}$ before its decomposition.

- Constant irradiation of complex [Ru(phen)(py)([9]aneS$_3$)](ClO$_4$)$_2$, **4**, in MeCN provokes the labilization of the Ru-py bond, favouring the substitution of py by MeCN and forming the [Ru(phen)(MeCN)([9]aneS$_3$)](ClO$_4$)$_2$, **3**, complex. This reaction has been monitored by means of UV-vis spectroscopy showing well-defined isosbestic points and corresponding to a first-order shape.

- The representation of k_{obs} vs T for the substitution reaction indicates the presence of two different processes in a temperature-dependence competition: a photoinduced process (**4** → **3**) and the inverse thermal reaction (**3** → **4**) manifested only at high temperatures, then being the Ru-py complex **4** the thermodynamically favoured compound. The corresponding activation parameters has been determined.

- The study of the photoinduced process **4** → **3** (*path 1*) in presence of additional concentrations of pyridine (outgoing ligand) points to the presence of an equilibrium previous to the rate limiting step, involving **4** and a photochemically induced species. A possible structure for this species has been proposed, containing two MeCN

molecules and the phen ligand coordinated to the metal centre through only one of its N atoms.

- A new family of pure atropisomeric Ru(II) complexes containing the didentate phenyl-1,2-bisoxazolinic ligand (Phbox-R), of general formula $[Ru(Y)(trpy)(Phbox\text{-}R)]^{n+}$ (Y = Cl, H_2O, py, MeCN or 2-OH-py), have been prepared and structurally characterized in the solid state (X-ray), in solution (NMR) and in the gas-phase (DFT calculations).

- Atropisomeric discrimination has been achieved through control of the chiral axes configuration in the complexes formed, from ligand chirality. Steric interactions favour R_aS_a axes when the S_cS_c ligand is used and the opposite configuration (S_aR_a) when employing the R_cR_c one.

- DFT calculations have demonstrated the major thermodynamic stability of the atropisomers synthetically formed. A high energy-barrier value has been found for the interconversion of the two possible isomers, thus preventing it at room temperature.

- Subtle but important changes in the general structure of these complexes when varying the monodentate ligand have been identified by a thorough NOESY NMR study and confirmed by their DFT calculated structures.

- The catalytic properties of the Ru-aqua complex $S_cS_\sigma R_aS_a$-**3b** have been tested with regard to its aptitude to epoxidize styrene and trans-stilbene, affording moderate conversions with low enantioselectivities (up to 10 % ee). The planar nature of the *trpy* ligand, allowing multiple ways of substrate-catalyst interaction, is proposed as the cause of this lack of chiral induction.

- A new family of C_3-symmetric chiral polypyridylic ligands have been designed and synthesized with pyridine and the monoterpenic natural products (-)-α-pinene and (-)-Myrtenal as starting materials. Extension of the asymmetric synthesis procedure

proposed to other commonly used polypyridines has been achieved trough a new aldehyde building block (**(-)-16**).

- The coordination behavior of ligands *pinene[5,6]bpea* (**L1**) and *pinene[4,5]tpmOMe* (**L2**) has been tested, and their corresponding trichloro Ru(III) complexes (**1** and **4** respectively) initially synthesized. Their combination with the non-chiral didentate ligands *bpy* and *dppe* affords a collection of [Ru(**L1** or **L2**)(B)Cl]$^{n+}$ chiral chloro-complexes. As expected, a unique isomer was obtained when the C3-symmetric precursor **4** was employed ([Ru^{II}Cl(L2)(*bpy*)](BF$_4$), **5** and [Ru^{II}Cl(L2)(*dppe*)](BF$_4$), **6**). However, when starting from the less symmetric precursor 1, isomeric mixtures were achieved (a mixture of *trans,fac*-**2a**; *cis,fac*-**2b/2b'** and *mer*-**2c** when bpy is coordinated; a sole isomer, *trans-fac*-**3a**, when *dppe* is used).

- DFT calculations for the whole set of chloro-complexes formed, jointly with their achiral analogues (with the *bpea* ligand) have been performed. From both experimental and theoretical results, we can state that the number of isomers formed from **1** (or its achiral counterpart) through coordination of a didentate symmetric ligand has proved to be function of: a) the steric encumbrance of each coordination environment and b) the intramolecular electronic interactions through hydrogen bonding in each isomer.

- Complexes **3a** and **6** have been tested as catalysts for dimethyl itaconate asymmetric hydrogenation to establish comparison with the previously reported cis-fac-Δ-[Ru^{II}Cl{(R)-(bpea)}{(S)-(BINAP)}]BF$_4$, *cis-fac*-Δ-(R)-(S)-**3** (were the chirality is situated in the P-donor ligand instead of in the N-donor one). Higher P and T values were needed for the formers and no enantioselectivity (contrasting with the outstanding values for the Δ-(R)-(S)-**3**) was observed.

- Complexes **3a** and Δ-(R)-(S)-**3** have also been tested in the hydrogenation of the challenging N-(3,4-dihydro-2-naphthalenyl)-acetamide substrate. Good conversions and excellent ee's (up to 74%) were reached with the Ru-Binap catalyst **3** while rather poor results were achieved employing **3a**.

- Complex [$Ru^{II}Cl(L2)(bpy)](BF_4)$, **5**, has proven to be a promising olefin epoxidation catalyst. High selectivity and ee's up to 36 % have been obtained, as preliminary results, being styrene the substrate of choice.

Future Work

- The chiral induction of complexes containing the **L1** ligand could be potentially improved by slightly modifying this ligand, through addition of new chiral centers by alkylation reactions (Figure 7.1). A particularity of these '5,6-pineno-fused' ligands is that the protons on the β-N-positions can be stereospecifically deprotonated by a sterically demanding base and then alkylated with various halides, leading to a large variety of enantiopure derivatives.

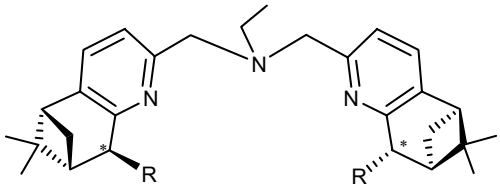

Figure 7.1

Upon facial coordination to an octahedral metal-ion, these new chiral centers will be placed close to the active site of the catalyst, hopefully producing better enantioselection in the reaction products.

- Bearing in mind the preliminary results obtained in styrene epoxidation reactions employing the *pinene[4,5]tpmOMe* (**L2**) (ee's up to 36%) the synthesis of analogue complexes with the *pinene[5,6]tpmOMe* **(-)-15** ligand seems interesting. The presence of the pinene moieties closer to the metal centre upon coordination should improve the 'chiral pocket' formed and would potentially allow affording higher ee's. Also the diastereoselective alkylation of this 5,6 ligand could be an interesting option to improve the enantioselectivity of the reaction. However, difficulties to achieve coordination of the ligand can arise due to its bulky nature. Small first-row transition metals could overcome this problem.