UNIVERSITY OF UDINE

FACULTY OF AGRICULTURE

Doctoral course in Food Science
Department of Food Science
(Course XXIV)

DOCTORAL DISSERTATION

Synthesis of Products of Biological Relevance Assisted by Metal Catalysts

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Contents

Results & Discussion

Chapter 2: Reduction of carbonyl compounds to alcohols via transfer hydrogenation (TH) and hydrogenation (HY) reactions

Chapter 3: Asymmetric reduction of ketones to chiral alcohols

Chapter 4: Racemization and deuteration of alcohols

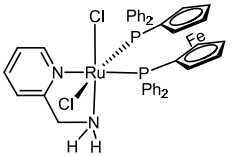
Chapter 5: Dehydrogenation of alcohols and sterols

Abbreviations

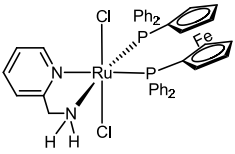
Ac = acetyl
Acac = acetylacetonato; 2,4-pentanedionato
Ampy = 2-aminomethylpyridine
ATP = adenosine triphosphate
BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BMTP = (*R*)-3,5-bis-trifluoromethylphenyl ethanol
CAL-B = *Candida antarctica* lipase B
Cy = cyclohexyl
de (diastereoisomeric excess) = $|\% D_1 - \% D_2|$
DHY = dehydrogenation
DKR = dymanic kinetic resolution
DPEN = 1,2-diphenyl-1,2-diaminoethane
dppb = 1,4-bis(diphenylphosphino)butane
dppf = 1,1'-bis(diphenylphosphino)ferrocene
dppp = 1,3-bis(diphenylphosphino)propane
ee (enantiomeric excess) = |% R - % S|
en = ethylenediamine
FDA = food and drug administration
FID = flame ionization detector
GRAS = generally recognized as safe
HY = hydrogenation
KO*t*Bu = potassium *tert*-butoxide
Me = methyl
NADH = nicotinamide adenine dinucleotide hydride
NADPH = nicotinamide adenine dinucleotide phosphate hydride
NaOEt = sodium ethoxide
NaO*i*Pr = sodium isopropoxide
NK-1 = Neurokinin 1
Novozyme® 435 = lipase from *Candida antarctica* immobilized on macroporous acrylic resin
OMe = methoxy
OTf = triflate
Ph = phenyl

(*R*, *S*)-Josiphos = (*R*)-1-[(*S*)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
(*R*, *S*)-Josiphos* = (*R*)-1-{(*S*)-2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]ferrocenyl} ethyldicyclohexylphosphine
(*S*)-MA20565 = (*S*)-2-(methoxyimino)-N-methyl-2-[2-1{-(3-trifluoromethylphenyl)ethoxy-imino}methyl]phenyl]acetamide
(*S*, *R*)-Josiphos = (*S*)-1-[(*R*)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
(*S*, *R*)-Josiphos* = (*S*)-1-{(*R*)-2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]ferrocenyl} ethyldicyclohexylphosphine
TH = transfer hydrogenation
TLC = thin layer chromatography
TMS = tetramethylsilane
TOF (turnover frequency) = moles of ketone converted to alcohol per mole of catalyst per hour at 50 % conversion
TON (turnover number) = moles of ketone converted to alcohol per mole of catalyst
Tsdpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine

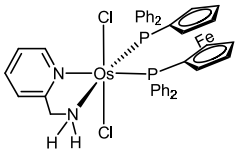
List of catalysts used



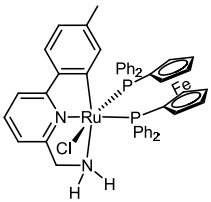
***cis*-1**



***trans*-1**



***trans*-2**



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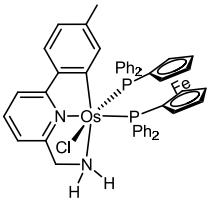

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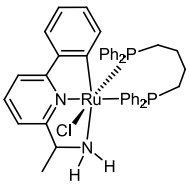

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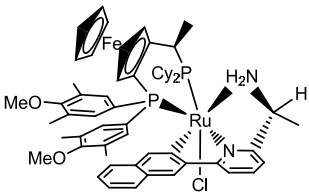

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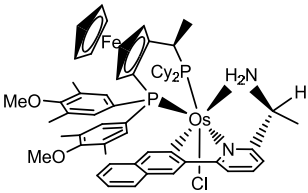

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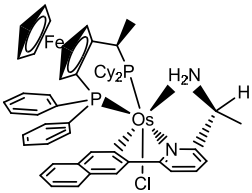

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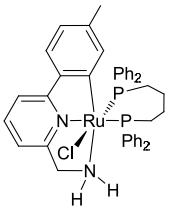

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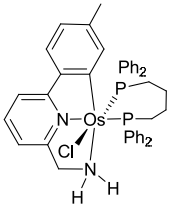

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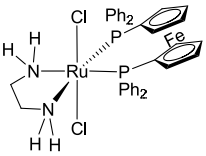

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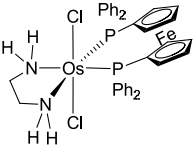

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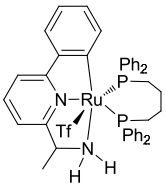

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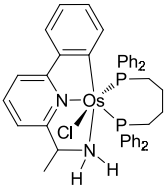

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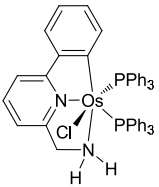

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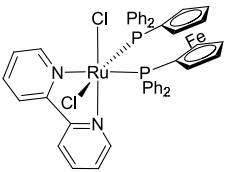

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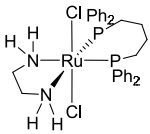

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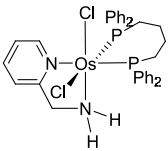

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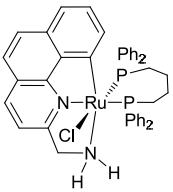

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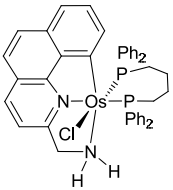

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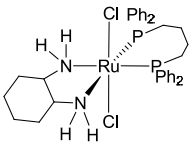

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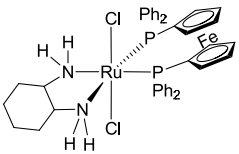

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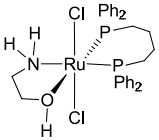

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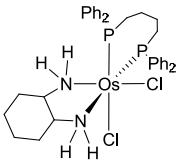

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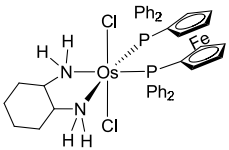

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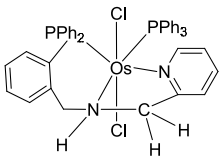

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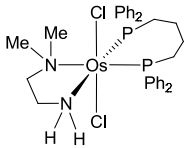


27

Aim of the PhD thesis

In contemporary organic chemistry there is a continuous search for simple, efficient and innovative methods to obtain valuable organic products. The development of synthetic procedures involving the use of non-toxic reagents and solvents that produce by-products in small quantities and with low environmental impact is a current issue and a final target. The catalysis in homogeneous phase, allowing the activation of substrates under mild reaction conditions and with high control of chemo- regio- and stereo-selectivity of the transformations, may play a crucial role in this context. The growing demand for enantiomerically pure products in the pharmaceutical field, in agriculture and in the chemistry of natural products has led to the enantioselective synthesis using catalysts based on transition metals. Moreover, there is also a great interest for multitasking catalysts able to efficiently promote different organic transformations by a careful switching of the reaction parameters, namely temperature, solvent and co-catalyst concentration. In this context ruthenium has become one of the preferred metals because of its high performance and versatility for a variety of organic catalyzed reactions.
Homogeneous catalytic systems consist on a central metal core, often of noble metals such as palladium, rhodium and ruthenium, that binds achiral or chiral organic ligands that in this last case could be very expensive. Their use for cost-effective production of high value added "*fine chemicals*" is explained since these systems have high activity and can be used with high substrate / catalyst ratio maintaining a very high enantioselectivity. It is noteworthy that as turnover in fine chemical industry, the production of flavors and fragrances is second only to that of pharmaceutical products.
This PhD thesis has been focused on the study of the catalytic activity of a number of homogeneous ruthenium(II) and osmium(II) complexes in a range of important reactions entailing carbonyl compounds and alcohols in order to obtain molecules of biochemical interest with applications in food, pharmaceutical and agrochemical industry.

Summary

In this PhD thesis the catalytic activity of several ruthenium(II) and osmium(II) complexes has been studied in: stereoselective transfer hydrogenation, non stereoselective transfer hydrogenation and hydrogenation at low H_2 pressure of aldehydes and ketones, racemization and deuteration of alcohols, acceptorless dehydrogenation of alcohols, α-alkylation of ketones with primary alcohols, isomerization of allylic alcohols.

The catalytic systems here described have been synthesized and characterized by the group of inorganic and organometallic chemistry of the University of Udine and some of them have been isolated for the first time.
In the first part of this work, transfer hydrogenation (TH) and hydrogenation (HY) of a number of aldehydes and ketones to primary and secondary alcohols were investigated using the ampy and pincer ferrocenyl complexes ***cis***- / ***trans*-1**, ***trans*-2**, **3**, **4** and the pincer complex **5** (Cap. 2, figure 33), containig the dppb alkyl backbone, in basic 2-propanol at reflux temperature. These derivatives catalyze the selective reduction via TH of aldehydes and ketones to alcohols using low catalyst loading (0.1 - 0.0005 mol %) showing high rate (TOF values up to 3.0×10^5 h^{-1} with the ampy complexes and 4.5×10^6 with the pincer ones). The pincer complexes displayed a faster conversion with respect to the ampy systems in the reduction of unsaturated and of aromatic aldehydes expecially with osmium while much the same activity was reached in the reduction of ketones with the exception of acetophenone, reduced in only 3 min (TOF = 3.4×10^5) with the pincer complex **5** (0.005 mol %) and (-)-menthone, reduced faster (10 min) with the ampy systems (0.05 mol %). The easily accessible complexes MCl_2(dppf)(ampy) (M = Ru ***cis*-1**, Os ***trans*-2**) have been found active also in the HY of aldehydes and ketones in an alcoholic medium (EtOH with ***cis*-1** at 50 °C or MeOH / EtOH mixture with ***trans*-2** at 90 °C) under 5 atm H_2 achieving TOF values up to 7.5×10^4 h^{-1}.
Data showed that osmium has proven to be a valid complement to ruthenium for both HY and TH reactions, even if it generally requires a higher temperature with respect to ruthenium, and remains active at high temperature.
Through TH and HY reactions a series of primary alcohols of biological relevance and of interest in food industry, have been isolated in good to high yield (78 - 92 % yield) starting from aldehydes: *p*-anisyl alcohol, 2-methyl-1-butanol, hexyl alcohol, (±)-citronellol, (*S*)-citronellol, 2-phenylethanol.
In addition, some acetates and propionates of these alcohols have also been synthesized: anisyl acetate, hexyl acetate, citronellyl propionate, phenethyl propionate. In order to quantify the metal concentration in the isolated product, the amount (ppm) of Ru was measured after filtration of anisyl acetate over a short chromatography column filled, following the first method with 2 cm and then with 10 cm of SiO_2. Interestingly, using the second procedure, 1.7 ppm of Ru (< 5 ppm, the common limit of oral intake for Ru and Os) was checked in the product by ICP analysis (Cap. 2, table 6).
Particular attention was also devoted to the asymmetric reduction of ketones to alcohols. By this way optically active alcohols of practical interest such as linear alcohols (food aromas, pheromones), cyclic alcohols (natural flavors) and benzhydrols (pharmaceutical intermediates) have been obtained on a small and medium scale using low catalyst loading and mild, clean reaction conditions.
In this context, some complexes MCl(CNN)(PP) (M = Ru, Os; PP = chiral Josiphos diphosphine) prepared *in situ* with a series of chiral pincer ligands (*S*)-**1a** - **1g** (Cap. 3, figure 36), of general formula (*S*)-2-(1-aminoethyl)-6-(aryl)pyridine

(HCNN) (aryl = substituted phenyl, naphthyl), obtained by lipase-catalyzed dynamic kinetic resolution, have been initially tested in TH of acetophenone at 60 °C. The immobilized form of lipase B from *Candida antarctica* (Novozyme® 435) has been employed for the enantioselective acylation of secondary alcohols in the process to obtain the final (*S*)-ligands.

The ligand containing the 2-naphthyl group, (*S*)-**1g**, in combination with the (*R*,*S*)-Josiphos* gave the best results for both ruthenium and osmium catalysts *in situ* generated. By using the corresponding isolated complexes (**6 - 8**, Cap. 3, eq. 8) several alkyl aryl ketones have efficiently been reduced via asymmetric transfer hydrogenation to (*R*)-chiral alcohols in 2-propanol at 60 °C, in the presence of NaO*i*Pr. Using 0.005 mol % of complex, TOF of 10^4 - 10^6 h^{-1} and up to 99 % *ee* were achieved. Valuable alcohols, such as (*R*)-1-phenylpropan-1-ol, (*R*)-3,5-bistrifluoromethyl-phenyl-ethanol (BTMP) have been obtained with catalysts **6** and **8**. Interestingly, the osmium **8** displayed for many substrates higher catalytic activity and enantioselectivity than the ruthenium **6** (Cap. 3, table 10 and 11) proving to be a valid complement to ruthenium, particularly at high temperature where deactivation is retarded.

Moreover, in order to find the ideal conditions for the stereoselective TH of (-)-menthone to (-)-menthol, preventing the formation of the other isomers, some catalytic systems have been prepared and studied in this reaction. Initially, a number of *in situ* catalysts have been prepared from the precursors $RuCl_2(PPh_3)_3$ and $OsCl_2(PPh_3)_3$ with the tridentate CNN ligand **L-1** (Cap. 3, figure 41) and the chiral / achiral diphosphines (**P1 - 13,** Cap. 3, figure 42) or from $RuCl_2(PPh_3)_3$ with the pincer ligands (*S*)**-1b - 1f**. The employment of $RuCl_2(PPh_3)_3$ with the ligand (*S*)**-1b**, gave the best results in terms of activity and stereoselectivity leading to 80 % of (-)-menthol and 20 % of (+)-neomenthol in 2 h from the reduction of (-)-menthone. The purification of the menthols mixture over a SiO_2 column led to the only diastereoisomer (-)-menthol of 90 % purity (73 % yield).

The study of this PhD thesis was then focused on other transformation appealing for applications in fine chemistry and industry. Interestingly a number of catalysts bearing bidentate and tridentate amino ligands, including the ampy systems ***cis*-1**, ***trans*-2**, found effective in TH and HY reactions, were proven to be active for organic transformations entailing the activation of the C-H bond close to the hydroxyl group of alcohols, thus enhancing the alcohol reactivity.

Some of these systems have been found active for both the racemization of optically active secondary alcohols in basic 2-propanol (***cis*-1**, ***trans*-2**, **3 - 5**, **9 – 18**, Cap. 4, figure 46) and for the deuteration of primary and secondary alcohols in basic 2-propanol-d_8 (**3 - 5**, **9 - 10**, **17 - 18**). Much the same activity has been observed for the ruthenium and osmium pincer complexes, which are superior with respect to the complexes $MCl_2(NN)(PP)$ (NN = bidentate amine or pyridine ligand) while derivatives bearing the ferrocenyl diphosphine are active at a slightly higher temperature with respect to the analogous complexes which show an alkyl backbone (dppb). Racemization of alcohols is particularly relevant in combination

with the dynamic kinetic resolution (DKR) for the preparation of chiral alcohols achieving the desired enantiomer, while deuteration is of interest for obtaining deuterium-labeled compounds for pharmaceutical and analytical chemistry.
Continuing with the catalytic studies, the systems ***cis***- / ***trans***-**1**, ***trans***-**2**, **9 - 12**, **19 - 25** (Cap. 5, figure 50, 51), containing the N-H moiety, have been investigated in dehydrogenation reactions (DHY). Catalytic alcohol dehydrogenation, through the direct formation of hydrogen and without the need of oxidizing agents, is a straightforward route to achieve carbonyl compounds, such as ketones, aldehydes, and esters. These systems have been found to catalyze the acceptorless DHY of alcohols. In particular the compounds *trans*-[MCl_2(dppf)(en)] (M = Ru **11**, Os, **12**) displayed very high activity and different substrates, including cyclic and linear alcohols and 5-en-3β-hydroxy steroids, have been efficiently oxidized to ketones by using 0.8 - 0.04 mol % of catalyst at 130 - 145 °C in *t*BuOH or *t*BuOH / toluene (2 : 1, v / v). The ruthenium **11** generally led to a faster conversion into ketones with respect to the osmium **12** which instead displayed better activity in the dehydrogenation of 5-en-3β-hydroxy steroids (e.g. *trans*-dehydroandrosterone to androstenedione, pregnenolone to progesterone).
In order to show the potential of the catalytic dehydrogenation for synthetic applications, some compounds of interest in food, pharmaceutical and agrochemical industry have been prepared. Thus, 1-indanone, α-tetralone, 4′-methoxyacetophenone, 2-heptanone and cholest-4-en-3-one were isolated in high yield (77 - 90 % yield). Interestingly, androstenedione and progesterone and have also been obtained by this way.
Another notable topic related to dehydrogenation that has been described in this thesis is the hydrogen generation from alcohols as a potential method for energy generation from biomass products. A preliminary study showed that hydrogen can be prepared from 2-propanol or 2-butanol with several Ru and Os complexes (Cap. 5, table 26 and 27). Using the isolated catalysts **9**, **12**, **19**, **26** and **27** (Cap. 5, figure 59) at reflux temperature, the hydrogen production showed to be generally more favored from 2-butanol than from 2-propanol, complex **12** being the most active with an average TOF value up to 933 h^{-1}. As regards the employment of the *in situ* prepared system $RuCl_2$(dppb)(PPh_3) / **L-2 - 10** ligand (table 27), 1,2-diaminocyclohexane (**L-5**) led to the best results affording average TOF values of 483 h^{-1} and 680 h^{-1} in 2-propanol and 2-butanol, respectively.
In the final part of this PhD thesis, to further extend the application of the ampy, ferrocenyl complexes ***cis***-**1**, ***trans***-**2**, versatile catalysts for a range of organic transformations such as TH and HY of carbonyl compounds, racemization of chiral alcohols, DHY of alcohols, were also found active in the alkylation of α-tetralone with primary alcohols and in the isomerization of allylic alcohols.
The α-alkylation of ketones with primary alcohols is an important way to achieve valuable chemical intermediates with industrial applications. Promising results were achieved with both catalysts, expecially with ***trans***-**2**, in the alkylation of α-tetralone with EtOH, *n*PrOH and *n*BuOH, in *tert*-butanol / toluene (1 : 2, v / v) at

120 °C, achieving TOF up to 2800 h^{-1}. In this reaction also the Ru complex **11** containing ethylenediamine was tested giving good results although displaying lower activity. In the isomerization of allylic alcohols, ***cis*-1** and ***trans*-2** showed good conversion rate too, achieving 62 - 94 % conversion to ketones in basic *t*BuOH at 70 - 120 °C, ruthenium showing better performances and requiring lower reaction temperature. This reaction is a useful way for the preparation of carbonyl compounds such as 2-butanone, 2-heptanone, propiophenone and its derivatives.

Publications in journals

The work of this PhD thesis resulted in the following publications in journals:

- ✓ W. Baratta, F. Benedetti, A. Del Zotto, L. Fanfoni, F. Felluga, S. Magnolia, E. Putignano, P. Rigo, **Chiral Pincer Ruthenium and Osmium Complexes for the Fast and Efficient Hydrogen Transfer Reduction of Ketones**, *Organometallics* **2010**, *29*, 3563.

- ✓ W. Baratta, G. Bossi, E. Putignano, P. Rigo, **Pincer and Diamine Ru and Os Diphosphane Complexes as Efficient Catalysts for the Dehydrogenation of Alcohols to Ketones**, *Chem. Eur. J.* **2011**, *17*, 3474.

- ✓ G. Bossi, E. Putignano, P. Rigo, W. Baratta, **Pincer Ru and Os complexes as efficient catalysts for racemization and deuteration of alcohols**, *J. Chem. Soc.*, *Dalton Trans.* **2011**, *40*, 8986.

- ✓ W. Baratta, G. Bossi, E. Putignano, **Ru and Os catalysts for alcohol C-H activation reactions**, *Focus on Milestones in Chemistry - supplement to chimica oggi / Chemistry Today, n. 5 September / October* **2011**, 20; *Chimica oggi / Chemistry Today - vol. 30 n. 1 January / February* **2012**.

- ✓ E. Putignano, G. Bossi, P. Rigo, W. Baratta, **MCl_2(ampy)(dppf) (M = Ru, Os): Practical and Multi-Task Catalysts for Carbonyl Compounds / Alcohols Interconversion Reactions**, *Organometallics* **2012** in press (online publication, DOI: 10.1021/om201189r).

Introduction

Chapter 1

1.1 Catalysis

The use of catalysts in chemical and refining processes has increased rapidly since 1945, when oil began to replace coal as the most important industrial raw material. More than 90 % of today's chemical and refining processes use catalysts. The world is dependent on catalysts for food, fuel, plastics, synthetic fibers, pharmaceutical intermediates and many other everyday commodities. The use of catalytic processes simply increased with the demand for new products and gradual improvements in engineering technology. New construction materials have made plant operation more efficient and led to the development of better processes and catalysts.[1]

1.1.1 Historical notes on catalysis

By far the oldest homogeneous catalysts are metallo-enzymes, such as iron porphyrin complexes active for oxidation, zinc complexes for the alcohol dehydrogenase, nickel complexes in hydrogenase enzymes for hydrogen activation, cobalt corrin (methylcobalamin) complexes for carbon-carbon bond formation, copper imidazole histidine-complexes in hemocyanin, etc. One of the oldest in vitro uses of whole-cells (in contrast with isolated enzymes) is probably yeast for the fermentation of sugars to alcohol.
A very old catalytic process is the making of sulfuric acid (H_2SO_4) via the so-called "lead chamber process" (~ 1750) in which NO_2 oxidise SO_2 to the SO_3 and NO is re-oxidised by air to NO_2. From 1870 onwards a number of heterogeneous catalytic processes has been found and applied industrially.
The studies of F. Haber and C. Bosch in the early twentieth century led to the synthesis of ammonia directly from nitrogen and hydrogen, catalyzed by iron oxides (1910).[2] This research conducted in the laboratories of BASF led to the creation of a big industrial process for the synthesis of ammonia, opened the way for the production of fertilizers, explosives and a wide range of nitrogen products. In the same period, in the laboratories of BASF the synthesis of methanol from syn-gas was developed, *i.e.* from a mixture of CO and H_2 obtained directly from carbon and water, using ZnO as a catalyst. Starting from syn-gas through a catalyst based on iron and cobalt were also prepared a range of organic products, including alcohols, aldehydes, ketones, fatty acids, ethers and hydrocarbons, which are used as feedstock for the chemical industry and as fuels for internal combustion engines (F. Fischer - H. Tropsch, 1925).[3]
The first industrially applied catalyst working in solution involving organometallic intermediates is, most likely, mercury sulfate ($HgSO_4$) which was used in the nineteen twenties for the conversion of acetylene to acetaldehyde and involves the addition of water to acetylene. Industrially it is the predecessor of the Wacker chemistry, which uses ethylene for an oxidative conversion to acetaldehyde. This

change came about when the coal based economy (coal to acetylene using electric arcs) changed to oil in the 1950's.[4]
In the fifties, the great interest in the catalysts was focused on the chemistry of polymers and plastics in general and the work of the Natta's group carried to obtaining isotactic polypropylene from propylene using titanium catalysts.[5]
Another valuable process that came on stream in the fifties, involving homogeneous catalysts, is the oligomerization of ethylene using cobalt complexes, but the number of homogeneously catalyzed processes remained low. In the sixties four more processes came on stream, namely the nickel catalyzed hydrocyanation (Dupont), the cobalt catalyzed carbonylation of methanol to acetic acid (BASF), cobalt catalyzed hydroformylation (Shell) (discovered already in 1938 Ruhrchemie), and the molybdenum catalyzed epoxidation of propene (Halcon Corporation). Since the seventies the proportion of homogeneous catalysts has been increasing with success stories such as that of rhodium catalyzed carbonylation of methanol (Monsanto), rhodium catalyzed hydroformylation (Union Carbide Corporation using Wilkinson's findings), Shell's higher olefins process, asymmetric hydrogenation to *l*-dopa (Monsanto), and ring-opening polymerization of cyclooctene using tungsten metathesis catalysts (Huels).
The majority of the homogeneous processes were developed for bulk chemicals as only products having a sufficiently large volume could justify the expenditure needed for the development of totally new catalysts and the engineering involved. It was only in the nineties that studies for the synthesis of fine chemicals, products with high added value which have applications also in food industry, took off, utilising the research results of the bulk chemicals area and the large academic effort that had been set up in the meantime. Some of these interesting molecules are vitamins (K_1, E), pharmaceutical ingredients (*l*-dopa, chloramphenicol, (*R*)-carnitine, taxol, (*S*)-propranolol, (*S*)-tetramisolo, (*S*, *S*)-diltiazem, naproxen, ibuprofen, morphine), fragrances (nerol, citronellol, geraniol, damascone, (-)-menthol), herbicide (*S*-metolachlor) (figure 1).[6]

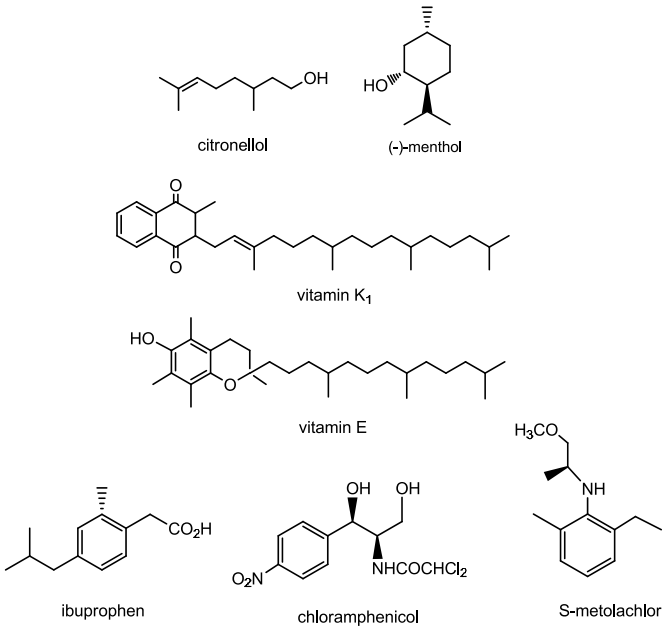


Figure 1

1.1.2 What is a catalyst?

The term catalysis was coined by Berzelius over 150 years ago when he had noticed that some substances undergo transformations when they were brought in contact with small amounts of certain species called "ferments". The definition used today reads as follows: *A catalyst is a substance which increases the rate at which a chemical reaction approaches equilibrium without becoming itself permanently involved.*

The catalyst may be added to the reactants in a different form, the catalyst precursor, which has to be brought into an active form ("activated"). During the catalytic cycle the catalyst may be present in several intermediate forms when we look more closely at the molecular level. An active catalyst will pass a number of times through this cycle of states; in this sense the catalyst remains unaltered. Many chemical reactions, allowed by a thermodynamic point of view, are kinetically disadvantaged, thus increasing the speed of a reaction is crucial for obtaining the desired products. As a matter of fact, a temperature increase, which leads to an increase in the reaction rate is not always feasible (e.g. exothermic reactions). The general method to increase the speed of a reaction is to choose the pathway involving a lower activation energy by means of a catalyst. In the reaction

a catalyst takes part in the formation of intermediate species that do not appear at the beginning and at the end of the reaction, lowering the activation energy (E_a), resulting in increased speed and decreased reaction time (figure 2).

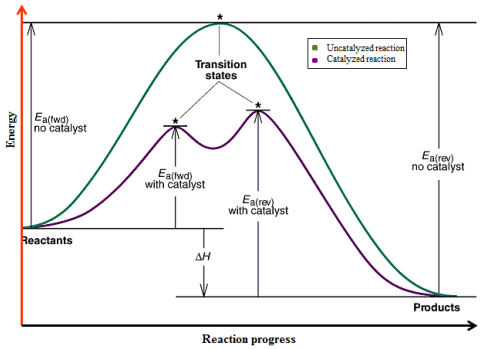


Figure 2. Different trend of a reaction with or without a catalyst

Two important parameters for studying a catalyst are its productivity and its activity. The first is defined as turnover number (TON), *i.e.* the number of moles of product produced with one mole of catalyst. This number determines the catalyst costs. If a catalyst can be re-used, its productivity is increased.
The second factor, defined as turnover frequency (TOF), *i.e.* how many moles of product one mole of the catalyst produces per time unit, determines the production capacity of a given apparatus.
Substrates are present in larger amounts than the catalyst, when we report on catalytic reactions the ratio of substrate to catalyst is an important aspect.
An inhibitor is a substance that retards a reaction, it is also present in catalytic or sub-stoichiometric amounts. In a metal catalyzed reaction an inhibitor could be a substance that adsorbs onto the metal making it less active or blocking the site for substrate co-ordination.
Organometallic catalysts consist of a central metal surrounded by organic (and inorganic) ligands. Both the metal and the large variety of ligands determine the properties of the catalyst.
The set of ligands forming the coordination sphere of the complex and the number of ligands is called coordination number (CN) which usually ranges from 3 to 6.
Parameters affecting the coordination number is the oxidation number and the electronic configuration of the central ion, the type of ligands (big and bulky ligands reduce the CN) and the interactions within the complex. Examples of transition metal complexes, their geometry and preferred reactions are reported in figure 3.

Metal, oxidation state	Example	Geometry	Preferred reactions
Ni^0	$Ni(CO)_4$	Tetrahedral	Ligand dissociation
Pd^0	$Pd(PR_3)_2$	Linear	Oxidative adition
Rh^I, Ir^I, Ru^{II}	$[Rh(PR_3)_2(\mu\text{-}Cl)]_2$	Square planar	Oxidative addition
Ru^{II}	$Ru(PR_3)_3X_2$	Trigonal pyramid	Ligand dissociation, oxidative addition
Ru^{II}, Rh^{III}, Ir^{III}	$Rh(PR_3)_3XH_2$	Octahedral	Reductive elimination

Figure 3

The ligands can form one or more links with the central atom and, in the second case are said chelating agents. Depending on the number of the bonds with the central atom, a ligand could be monodentate, bidentate, tridentate, or, in general, polydentate (figure 4).

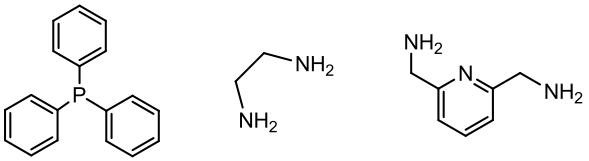


Figure 4

The presence of chiral ligands allows to obtain catalysts able to induce stereoselective reactions. The high efficiency of these catalysts is reaching a level comparable to that of the enzymes with the advantage of being able to use a wider range of substrates.

One of the most important criteria for judging a catalyst is its selectivity, defined as the ratio of the desired product to the sum of all products. A high selectivity is essential for an economical as well as an ecological process.

The following types of selectivity can be distinguished in a chemical reaction:

✓ *Chemoselectivity*. The preferential reaction of one of the several potentially reactive functional groups.

✓*Regioselectivity*. The preferential reaction at one of the several potentially reactive centers of a conjugated system.

✓*Stereoselectivity*. The preferential formation of one of the several possible stereoisomers.
✓*Enantioselectivity*. The preferential formation of one enantiomer. The selectivity can be defined as enantiomeric excess (*ee* %), as the difference between the amount (%) of the desired and the amount (%) of the undesired enantiomer).
In addition, other aspects such as availability and cost of ligands and metal precursors, catalyst stability and sensitivity, handling problems, catalyst separation, space time yield, poisoning of the catalytic system, process sensitivity, toxicity, safety, special equipment, etc. can be of importance when applying homogeneous catalysts.[4,6]

1.1.3 Homogeneous, heterogeneous and enzymatic catalysis

Heterogeneous catalysts, which act in a different phase respect to that of the reactants, are wider used in industry than homogeneous catalysts, because the former shows a wider scope, higher thermal stability and can be easily separated from the products and reused. Heterogeneous catalysts are employed in several processes such as cracking, and reforming hydrocarbons, ammonia synthesis, hydrogenation of fatty acids for the production of margarine, etc.
Nevertheless, many important value-added products are manufactured by homogeneous catalytic processes to obtain fine chemicals, pharmaceutical intermediates, polymers, etc.
The commercial success of many homogeneous-catalyst based industrial processes is due to several reasons.
First, by a choice of the optimal catalyst and process conditions, it is possible to achieve a selectivity similar to that of enzymes, but with a higher stability and durability than enzymes. Indeed, an interesting application of homogeneous catalysis is the enantioselective (asymmetric) catalysis. It deals with the synthesis of enantiopure intermediates for pharmatheuticals, agricultural products, flavors, fragrances and some advanced materials.
Furthermore, the activity of a homogeneous catalyst can be fine-tuned by optimal selection of the ligand environment and process conditions.[7]

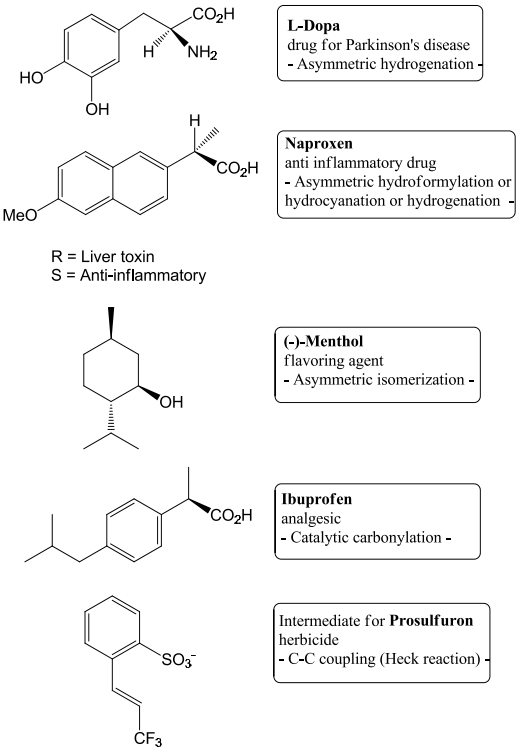


Figure 5. Some products of homogeneous catalytic reactions and their uses

In addition to homogeneous and heterogeneous systems, enzymatic catalysis deserves special attention.

The metallo-enzymes, such as hydrolytic enzymes (carboxy peptidase), the monooxygenase (cytochrome P-450, ribonucleotide reductase), oxidoreductase (alcohol dehydrogenase), show a strong analogy with the catalysts used for the synthesis of fine chemicals. The metal which plays a key role in the catalytic process is generally coordinated by polydentate ligands.[8]

Tetradentate ligands are present in chlorophyll, in the cytochrome P-450 and cytochrome c (Fe), in the heme system of the oxygen carriers myoglobin and hemoglobin (Fe) and in the vitamin B_{12} (Co), giving extreme stability to the complex. This is particularly important, as the stability of the enzyme system is crucial to achieve high catalytic efficiency. Therefore, in the design of highly active catalysts for the synthesis of organic products, enzyme systems are subject of inspiration (figure 3).[9]

1.2 Chirality

The term “chiral” in general is used to describe an object that is non-superimposable on its mirror image. On the contrary achiral objects are identical to their mirror image. Human hands are perhaps the most universally recognized example of chirality.
Nature has provided a wide variety of chiral materials in great abundance, ranging from amino acids to carbohydrates to terpenes.

1.2.1 Chirality in chemistry

The concept of "chirality" has been known in chemistry since the 1870's although it would be nearly a hundred years before chemists began using this term. The term “chiral” is derived from the greek name *kheir* meaning "hand" and, apparently, was coined by Lord Kelvin in 1904, in his Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light in which he stated ..."I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."
A chiral molecule is a type of molecule that lacks an internal plane of symmetry and thus has a non-superimposable mirror image. The feature that is most often the cause of chirality in molecules is the presence of one or more asymmetric carbon atoms.[10]
Such molecules exhibit optical activity and therefore have the ability to rotate the plane-polarised light. Two stereoisomers which are mirror images of each other are said to be enantiomers.
If two enantiomers exist in equal proportions, then the mixture is called racemic. Enantiomers can be laevorotatory (*l*, -), meaning rotating the plane of the polarised light to the left; or dextrorotatory (*d*, +), that is, rotating the plane of the polarised light to the right. Racemic mixtures show zero rotation. In addition, as regards the geometrical disposition of the functional groups that bind the central carbon atom, the UPAC nomenclature assigns prefixes (*R*) (from the latin *rectus*, right) and (*S*) (from the latin *sinister*, left) to the isomers according to the Cahn-Ingold-Prelog (CIP) rule.[11]

1.2.2 Chiral compounds

Many molecules are chiral, *i.e*. they exist in two forms that have the same composition and connectivity, but are not superimposable. Because the two enantiomers very often have different biological properties, the preferential synthesis of one enantiomer, called enantioselective synthesis, is highly desirable for obtaining pharmaceuticals, agrochemicals and flavors or fragrances.

Although enantioselective catalysis, which involves chiral catalysts is still a young discipline, several catalytic processes are already applied on an industrial scale: the *l*-dopa process of Monsanto, (*S*)-metolachlor process of Ciba-Geigy/Novartis, glycidol process of Arco (Sipsy), (-)-menthol process of Takasago, Suzuki coupling for the production of 4'-methyl-2-cyano-biphenyl (Clariant) and others.[6]
In the world of aroma compounds, the enantiomers may have different organoleptic characters. For example, (*R*)-(-)-carvone smells like spearmint, while (*S*)-(+)-carvone, smells like caraway. Moreover, as shown in figure 6, the enantiomers of limonene and menthol are perceived as smelling differently. The *R*-enantiomer of limonene has an orange smell, while the *S*-enantiomer has a tipical lemon-turpentine one.

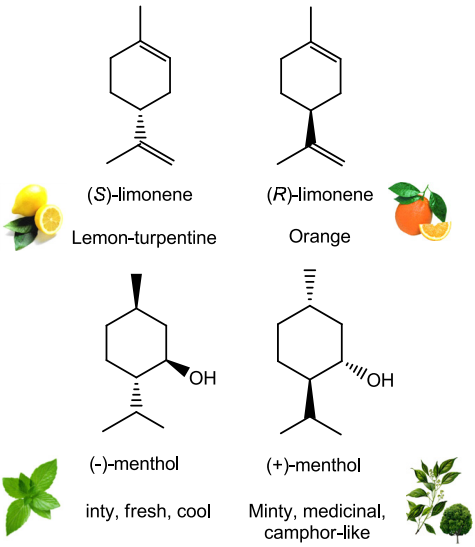


Figure 6

In this PhD thesis special attention has been given to (-)-menthol, an important flavoring agent with a world production exceeding 15000 ton per year, widely used in many consumer products, such as toothpaste, chewing gum, cigarettes, in food and pharmaceutical industry, and is classified by the US Food and Drug Administration as a topical analgesic.
Menthol is the main component of peppermint and cornmint oils obtained from the *Mentha piperita* and *Mentha arvensis* species. It is a cyclic terpene alcohol with three asymmetric carbon atoms, therefore, it occurs as four pairs of optical isomers named (+)-menthol and (-)-menthol, (+)-neomenthol and (-)-neomenthol, (+)-isomenthol and (-)-isomenthol, and (+)-neoisomenthol and (-)-neoisomenthol. The

four menthols derived from the reduction of (-)-menthone and its epimer (+)-isomenthone are given in figure 7.

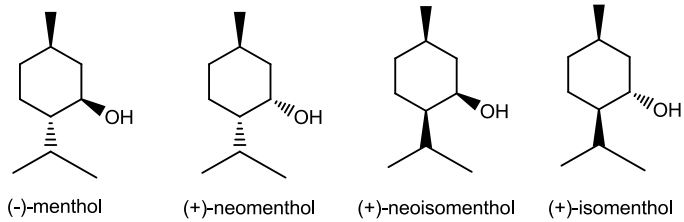


Figure 7. Menthol isomers

(-)-Menthol and its stereoisomers exhibit conformational isomerism. (-)-Menthol and (+)-Neomenthol are epimers differing in configuration only at the carbon bearing the OH group. For (-)-menthol, the chair configurations with the three substituents attached to the cyclohexane framework equatorially oriented, are thermodynamically the most stable.
In neomenthol, the hydroxyl group is supposed to take an axial orientation in the chair structure (figure 8).

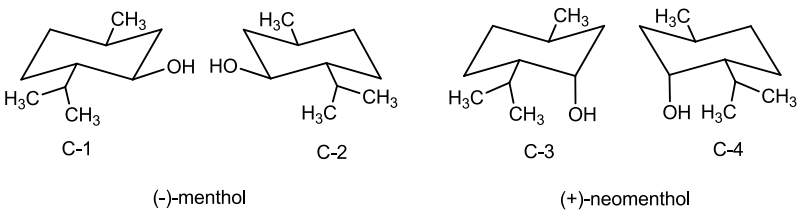


Figure 8

Among the optical isomers, (-)-menthol occurs most widely in nature. The (-)-menthol differs from the (+)-menthol for the characteristic peppermint odor and its characteristic cooling effect while (+)-menthol has a camphor-like, medicinal fragrance (figure 6). In general the other isomers do not possess the cooling effect typical of (-)-menthol and are, therefore, not considered to be "refreshing".[12]
In addition, it has been described that (-)-menthol is able to increase the pain threshold, whereas (+)-menthol is completely devoid of any analgesic effect, but they are able to induce an equiactive anesthetic effect.[11]
Nowadays several processes exist for the industrial production of (-)-menthol, but only the routes starting from myrcene or thymol are of commercial importance. The major portion of the world-wide annual demand is obtained from *Mentha arvensis* oil.[13]

The Takasago menthol synthesis as single enantiomer (> 95 % of purity) starting from myrcene, involves an asymmetric synthesis developed by Noyori's group (Takasago menthol synthesis). This first Takasago process is shown below in figura 9.

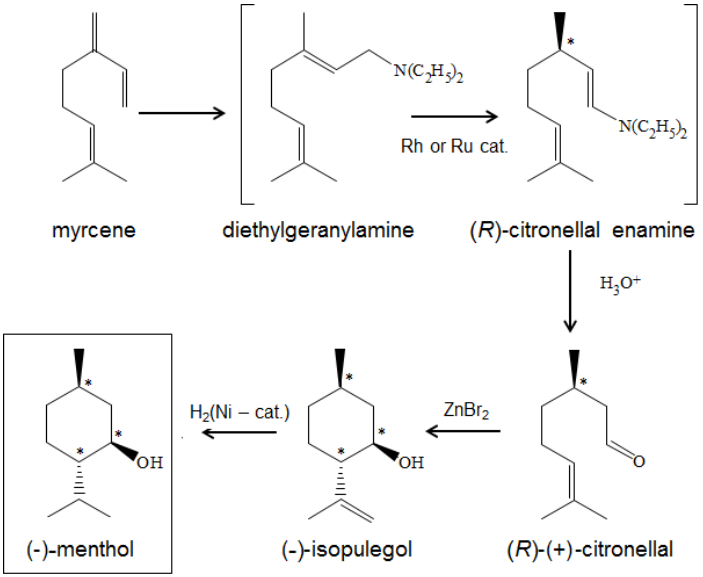


Figure 9

The process begins by forming an allylic amine from myrcene, which undergoes asymmetric isomerization in the presence of a rhodium complex containing (*S*)-BINAP, to give after hydrolysis, enantiomerically pure *R*-citronellal. The cyclization of this aldehyde to isopulegol is then followed by the isopulegol hydrogenation to give pure (1*R*, 2*S*, 5*R*)-(-)-menthol.
Now with this asymmetric synthesis technology the Takasago company selectively produces optically active compounds using BINAP rhodium catalysts or BINAP ruthenium catalysts for the production of antibiotics and antibacterial agents.
Takasago has also patented (2002) a second synthesis of (-)-menthol, starting from piperitone (figure 10).[14]

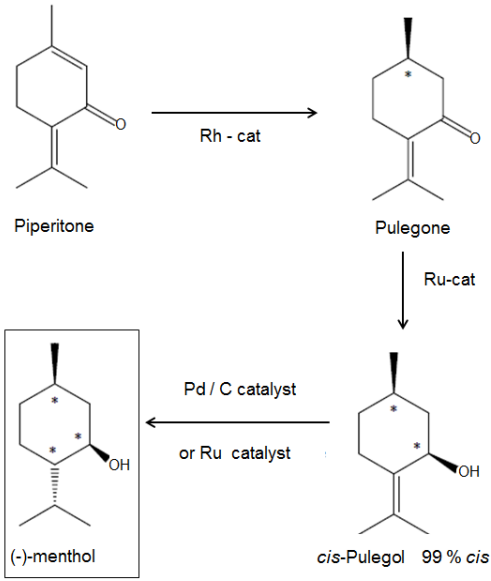


Figure 10

As with the commercial process via myrcene, this synthesis utilizes chiral hydrogenation catalysts at several stages. In this case piperitone is hydrogenated with a chiral rhodium catalyst achieving pulegone (> 95% *ee*). Then the *cis* diastereoselective reduction of pulegone is obtained with an achiral or with a chiral Noyori hydrogenation catalyst.[15] The final step is the diastereoselective hydrogenation of the allylic alcohol *cis*-pulegol, reaching (-)-menthol, by using Pd / C catalysts, or with $Ru(OAc)_2$biphosphine catalysts.
Another interesting example of chiral molecule with wide industrial application especially in perfumery and in the production of vitamin E, is linalool whose enantiomers differ slightly in odor. (*R*)-(-)-Linalool has a floral, woody lavender odor and the (*S*)-enantiomer has a sweet, floral odor reminiscent of petitgrain and lavender (figure 11).

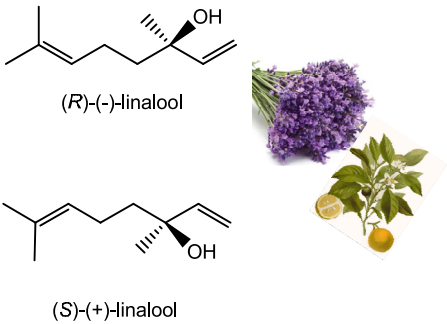


Figure 11

Chiral molecules may have also different taste like (*R*)-citronellol and (*S*)-citronellol. Interestingly, (*S*)-(-)-β-citronellol has a sweet, peach-like flavor and floral, rose-like, odor (it is a component of rose and geranium oil) whereas (*R*)-(+)-β-citronellol, has a bitter taste and it is a typical component of citronella oil (figure 12).[16] In addition FDA considers citronellol as generally recognized as safe (GRAS) for food use.

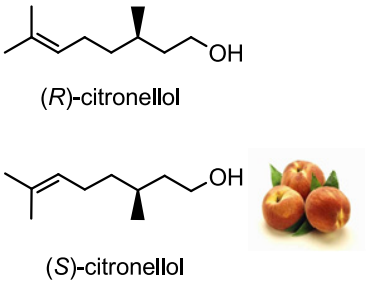


Figure 12

As regards other chiral molecules whose enantiomers have different properties, vitamin C or ascorbic acid, for example, comes in four stereoisomers but only the natural identical form (+) ascorbic acid has pharmacological activity and is active in the treatment of scurvy (figure 13).[17]

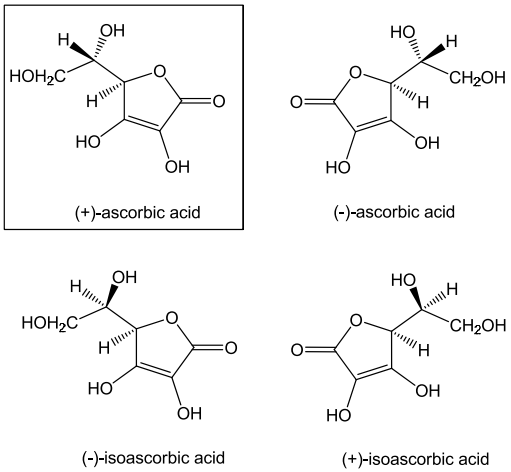


Figure 13

Another example is Thalidomide, introduced as a sedative drug in the late 1950s and typically used to cure morning sickness in pregnant women.
The drug was commercialized in the form of racemic and studies have revealed that the *R*-enantiomer has sedative properties, while the *S*-enantiomer has a markedly teratogenic activity by inhibiting angiogenesis and causing severe birth defects.[18]
Another group of compounds whose activity is influenced by the chirality, is that of pheromones which play important roles in chemical communication among organisms and the surrounding environment. Many derivatives have only one of the two enantiomers with transmission properties.
In the case of olean, 1,7-dioxaspiro(5.5)undecane, the olive fruit fly (*Bactrocera oleae*) pheromone, its (*R*)-isomer is active for the males, and the (*S*)-isomer is active for the females.
The pheromone (*R*)-japolinure, (5*R*)-5-(1Z)-1-decenyldihydro-2(3H)furanone, is a coleopteran attractant first isolated from *Popillia japonica* Newman, while the (*S*)-enantiomer is inactive (figure 14).

Popillia japonica

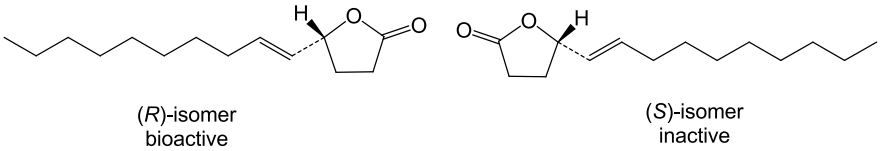


Figure 14

Other examples of chiral pheromones are (*S*)-(+)-2-pentyl-(2E)-2-methyl-2-pentanoate, an aggregation pheromone of the beetle bostrichide *Rhyzopertha dominica*, and (3*S*, 4*R*)-faranal a tracer pheromone of the pharaonic ant (*Monomorium pharaonis*). Interestingly, neither the (*R*)- nor (*S*)-enantiomer of sulcatol, the aggregation pheromone of an ambrosia beetle *Gnathotrichus sulcatus*, is behaviorally active for this species, while their mixture [65 % of (*S*)-(+) and 35 % of (*R*)-(-)] is bioactive for it. Another species, *Gnathotrichus retusus*, is sensitive only to the (*S*)-enantiomer, and its response seems to be inhibited by the (*R*)-enantiomer.[19,20]

The main techniques to obtain economically enantio-pure or enantio-enriched compounds are:

1. Resolution of the racemic mixture via chromatography, polymer supported liquid membrane, crystallization.

Crystallization technique is used for the production of about more than 50 % of enantio-enriched. Currently, new technologies such as HPLC separation "simulated bed technology" are being explored even if this technique, applied in the early stages of the process studies, is not applicable on an industrial scale. In both cases, large amounts of solvents are used, and at least 50 % of the wrong configuration material, must be recycled or disposed of.

2. The use of "chiral pool", chiral precursors, derived from natural products, to construct the final molecule. It is a widely used method in the early stages of a compound's production that can be applied to large-scale productions.

3. Biological synthesis through microbial or enzymatic transformations.

These techniques require a biological system suitable for the desired process and this could be a limiting factor.

4. Enantioselective synthesis by chiral systems.

This technique involves the use of chemical enantioselective catalysts, in which the chiral system, which is the most expensive component, is used in catalytic

amounts, with considerable economic advantage especially if it is readily recyclable.
Finally, asymmetric transformations obtaining enantiomeric products can be achieved combining efficiently enzyme and metal catalysis, e.g. via dynamic kinetic resolution (DKR).

1.2.3 Biocatalysis

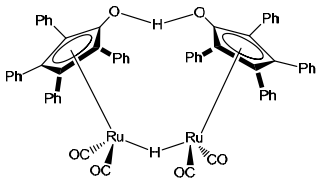
Biocatalysis concerns catalysis by bacteria, fungi, yeast, or their true catalytic components: enzymes. Enzymes are proteins that are able to accelerate organic transformations under mild reaction conditions. The available enzymes are traditionally divided into six classes according to the specific type of reaction catalyzed: oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases.
The enzymes action mechanism consist on a lock-and-key model: the active site has the right shape and functional groups to bind, activate and draw up the reacting molecules forming of enzyme-substrate intermediate. After reaction the products are released and the enzyme is ready for a new cycle. The hallmark of enzymes is their remarkable ability to catalyze very specific chemical reactions, some enzymes are so well designed for this purpose that they can accelerate the rate of a chemical reaction by as much as 10^{12} fold over the rate of spontaneous reaction. This remarkable enhancement results from the juxtaposition of chemical reactive groups within the binding pocket of enzyme (the enzyme active site) and other groups from the target molecule (substrate), in a way that facilities the reaction steps required to convert the substrate into the product.
Some enzymes require the association with additional chemicals to facilitate rapid reaction and regeneration. Thus, enzymes incorporate non-protein molecules called cofactors through non-covalent interactions such as H-bonding and hydrophobic interactions. Cofactors can be either inorganic (e.g., metal ions and iron-sulfur clusters) or organic compounds (e.g., flavin). Organic cofactors can be either prosthetic groups, which are tightly bound to an enzyme, or coenzymes, which are released from the enzyme's active site during the reaction Coenzymes include NADH, NADPH and ATP, these molecules transfer chemical groups between enzymes. Using enzymes as whole cells it is possible to avoid the addition of cofactors to regenerate the enzyme during the reaction.
The interest in biocatalysts is mainly due to the need to synthesize enantiopure compounds as chiral building blocks for drugs and agrochemicals and as flavor molecules for food and pharmaceutical industry, with a system which minimizes problems of undesired side-reactions, such as decomposition, isomerization, racemization and rearrangement, which often plague traditional methodology. Biocatalysts could be used both in full cells and as isolated enzymes, the latter could be either native or immobilized on an inert support.

Enzymatic catalysis in organic solvents significantly broadens conventional aqueous based biocatalysis. Water is a poor solvent for nearly all applications in industrial chemistry since most organic compounds of commercial interest are very sparingly soluble and are sometimes unstable in aqueous solutions. Furthermore, the removal of water is more tedious and expensive than when organic solvents are used due to their lower boiling point. The use of organic solvents presents several advantages, such as: (a) easy recovery of the substrate and product with high yield; (b) the possibility to use non-polar substrates; (c) avoids side reactions; (d) in many cases enzymes are thermodynamically more active; (e) shifting thermodynamic equilibrium to favour synthesis over hydrolysis.
Biocatalysis in non-aqueous media has been widely used for the resolution of alcohols, acids or lactones through enzymatic transesterificacion reactions using different lipases. The use of biocatalysis to obtain enantiopure compounds can be divided in two main different methods: kinetic resolution of a racemic mixture (KR) and biocatalyzed asymmetric synthesis.[21]
Biocatalytic procedures employing isolated enzymes have emerged as a reliable alternative to chemical methods[22,23,24]for the synthesis of a variety of chiral building blocks with a high degree of selectivity, under mild reaction conditions.[25]

1.2.4 Dynamic kinetic resolution (DKR)

Kinetic Resolution (KR) occurs when the reaction, between a chiral agent and a racemate, leads to a kinetic preference for one enantiomer over the other and therefore, leads to a resolution. Dynamic Kinetic Resolution (DKR) is an improvement of kinetic resolution. In DKR, a racemization reaction takes place concurrently to the enantiomer formation, leading to the desired compound in 100 % yield.
Kinetic resolution of racemates with enzymes to obtain enantiomerically pure compounds for fine chemicals is a commonly used technique in industrial applications. A limitation with this approach is that only 50% of the racemate is used, since the enzyme only converts one of the enantiomers. In 1997 the Bäckvall group reported the first efficient process for transformation of all of the racemate of an alcohol into enantiomerically pure product. In this process enzyme catalysis is combined with transition metal catalysis and this leads to the so called dynamic kinetic resolution. The alcohol is exposed to a ruthenium catalyst that racemizes the alcohol during the enzymatic resolution. The enzyme recognizes only one of the enantiomeric alcohols and transforms it to the enantiomerically pure product in high yield (> 99.5 % *ee*).
The reaction was extended to a variety of different alcohols and these studies have attracted a lot of interest on the international level. A number of groups have used this new technique in combination with a ruthenium catalyst and an enzyme for the deracemization of alcohols. In 2002 DSM Fine Chemicals developed a large scale

industrial process based on this method for production of enantiomerically pure alcohols in ton scale.
For the racemization of secondary alcohols transition metal complexes have been proved to be very useful, in combination with the lipase mediated transesterification in organic solvents.[26] In particular, Bäckwall and coworkers developed an efficient system via hydrogen transfer based on the use of a redox Ruthenium catalyst (Shvo's catalyst, figure 15), in combination with the *Candida Antarctica* B (CAL-B) mediated transesterification, with *p*-chlorophenyl acetate as acyl donor.



Shvo's catalyst

Figure 15

A wide range of substrates including substituted aromatic and aliphatic secondary alcohols and secondary diols[27] have been converted into the corresponding ester with a very high chemical and optical yield.[28,29]
In summary, the combination of enzyme catalysis (for the resolution of a racemate) and chemo catalysis (for the racemization of the slow-reacting enantiomer) has successfully applied in DKR processes. The high efficiency of these processes makes them an attractive alternative to the asymmetric catalysis.[28c]
In this PhD thesis the chemoenzymatic DKR of *sec*-alcohols have been employed for the synthesis of the HCNN (*S*)-ligands used for the synthesis of chiral catalysts for the asymmetric reduction of a number of ketones to chiral alcohols (Cap. 3).

1.2.5 Lipases

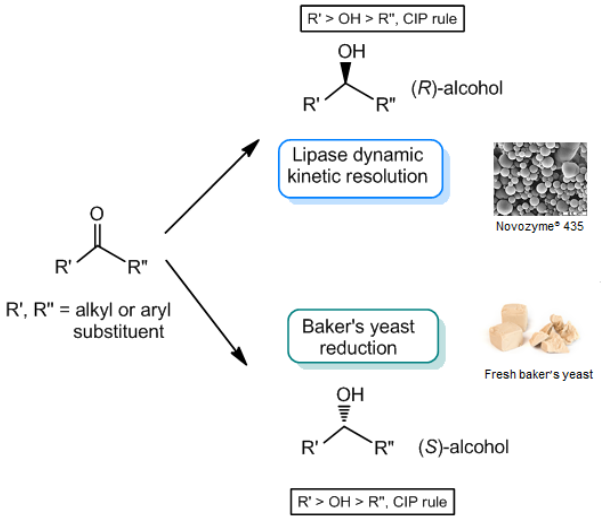
Lipases are ubiquitous enzymes widely distributed in nature, being synthesized by plants, animals and microorganisms. Lipases from microorganisms, mainly bacterial and fungal, are the most used as biocatalysts in biotechnological applications and organic chemistry. Fungal lipases from *Candida rugosa*, *Candida antarctica*, *Thermomyces lanuginosus* and *Rhizomucor miehei* and bacterial lipases from *Burkholderia cepacia*, *Pseudomonas alcaligenes*, *Pseudomonas mendocina* and *Chromobacterium viscosum* are examples of commercially available lipases widely used in biotechnology. Depending on their sources (bacterial, fungal, plant or animal), lipases have a wide range of properties like positional specificity,

enantioselectivity, temperature tolerance and pH dependence. Most microbial lipases show maximum activity at pH 7 - 9 and temperatures of 30 - 40 °C.[30] They catalyze not only the hydrolysis but also the synthesis of long-chain acylglycerols. Important uses in biotechnology include their addition to detergents, the manufacture of food ingredients, pitch control in the pulp and paper industry, and biocatalysis of stereoselective transformations.
This makes them the most widely used class of enzymes in organic chemistry. The reasons for the enormous biotechnological potential of microbial lipases include the facts that they are (1) stable in organic solvents, (2) do not require cofactors, (3) possess a broad substrate specificity and (4) exhibit a high enantioselectivity.[21]
Lipases are employed by organic chemists for a long time to catalyze a wide variety of chemo-, region and stereoselective transformations.[31] The majority of the lipases used as catalysts in organic chemistry are of microbial origin. There are two basic types of enantioselective organic transformations amenable to lipase catalysis: the reaction of prochiral substrates and kinetic resolution of racemates.[29c,32] Traditionally, chiral alcohols and carboxylic-acid esters are the two main classes of substrates with which lipases are used but the range of compounds includes also diols, α- and β-hydroxy acids, cyanohydrins, chlorohydrins, diesters, lactones, amines, diamines, amino-alcohols, and α- and β-amino-acid derivatives.[33] The use of immobilized lipases in organic solvents has many advantages compared to their use in the native form: a higher thermal stability, adsorbing the enzymes onto solid matrices leads to higher surface area to volume ratio which promotes enzyme-substrate interaction, an increase in activity and selectivity, easier recovery of the enzymes.
Candida antarctica lipase B (CAL-B) is one of the most frequently employed lipase in organic solvents for transesterification reactions. It is commercialized also in an immobilized form on polyacrylamide (Novozyme® 435). This enzyme shows a very high and general specificity for the (*R*)-enantiomer in the acylation of chiral secondary alcohols[34] which has fully been explained at the molecular level.[35]

1.2.6 Baker's yeast

Baker's yeast is the common name for the strains of yeast commonly used as a leavening agent in baking bread and bakery products where it converts the fermentable sugars present in the dough into carbon dioxide and ethanol. Baker's yeast, also called brewer's yeast, belongs to the species *Saccharomyces cerevisiae*, which is commonly used in alcoholic fermentation and in the production of dairy products. Baker's yeast (*Saccharomyces cerevisiae*) is commercially available as fresh or dry form and as immobilized yeast too.
Besides using lipases, it represents another way to obtain enantiomerically pure secondary alcohols through asymmetric reduction of prochiral ketones (scheme 1).[36] Thank to the regioselectivity of lipases and baker's yeast, ketones can be reduced by fermenting yeast, according to Cahn-Ingold-Prelog priority rule, to give

mainly the corresponding (*S*)-alcohols, while lipase dynamic kinetic resolution generally leads to (*R*)-alcohols. Only few examples of product predominantly *R*-configured have been observed using baker's yeast.



Scheme 1. Regioselectivity of lipases and baker's yeast

Baker's yeast is by far the most widely employed microorganism for the asymmetric reduction of ketones. It is ideal for non-microbiologists as it is readily available at a very low price, does not reqire sterile fermenters and can be therefore be handled using standard laboratory equipments. It is a very complex enzymatic system in which a number of different dehydrogenanses are present, possessing opposite stereochemical preferences. As a consequence, the stereochemical direction of the reduction may be controlled by careful design of the substrate.
Thanks to its versatility and selectivity different non-natural substrates were reduced by *Saccharomyces cerevisiae,* such as: cycloalkanones, aliphatic alkanones, sulphur containing molecules, nitrocarbonyl compounds, cyclic and acyclic dicarbonyl compounds (diketones, α,β-ketoesters), fluorine-containing compounds and organometallic compounds.
Baker's yeast has been successful used also in some C-C bond formation reaction and cyclization which require high stereoselectivity.[36b]

1.3 Compounds of biological interest

As was previously explained catalysis plays an important role in the chemical industry and homogeneous catalysts, thanks to their high selectivity are becoming

increasingly important for the manufacture of tailor-made plastics, fine chemicals, pharmaceutical intermediates, and others. The sector of fine chemicals including pharmaceuticals, agrochemicals, dyes and pigments, fragrances and flavors, intermediates and performance chemicals, is growing fast. The fine chemical industry invests strong effort in the development of sustainable technologies, based on environmental acceptability.
Nowadays, the chemical synthesis is industrially appealing if it can be considered a "green" technology, e.g. reducing the amount of waste produced in a process and choosing the optimized procedure, comparing it to other procedures, according to safety, atom efficiency, energy conservation, recyclability.
In this PhD thesis, a number of compounds of biological interest, namely achiral and chiral alcohols, esters and ketones, that can be obtained by homogeneous catalysis in mild and environmentally friendly conditions have been described. The increasing demand for flavors, pharmaceuticals, agrochemicals led to the development of the chemical synthesis of natural compounds with a lower cost with rispect to that of the naturally extracted products.
In several cases the synthesis of molecules is economically favored because the process can be easily controlled and high yields and purity of the product can be achieved in few reaction steps. An interesting alternative to chemical synthesis is the existing technology using microorganisms or enzymatic synthesis.[37,38]

1.3.1 Alcohols and aldehydes

Alcohols are very fundamental organic molecules through which a variety of compounds such as alkenes, aldehydes, ketones, carboxylic acids, esters, amines can be obtained.
Alcohols contain a hydroxy group (OH group) bonded to a sp^3 hybridized carbon atom and are classified as primary, secondary or tertiary. They are widespread in nature and have many industrial applications as reagents or solvents. Besides, alcohols are employed as preservatives for samples, hand sanitizers and some alcohols, mainly ethanol and methanol, can be used as fuel. Among alcohols ethanol is used as solvent in medical drugs, perfumes, and vegetable essences such as vanilla, because of its low toxicity and ability to dissolve non-polar substances. It is often used also in alcoholic beverages, as antiseptic and in the formulation of soaps.[10]
As flavoring material, free and esterified, saturated primary alcohols occur widely in nature, e.g. in fruit. Since their odor is relatively weak, their use as components in fragrance compositions is limited. Their use in aroma compositions, especially for fruit flavors, is by far more important (e.g. straight-chain C_4 - C_{10} alcohols, isoamyl alcohol). Isoamyl alcohol is used in pharmaceutical products, photographic chemicals and as solvent for the preparation of synthetic apricot, banana, cherry, greengage, malt, orange, plum, and whisky flavors. Unsaturated alcohols are most important (e.g. leaf alcohol with its intensely green odor) and

may impart characteristic notes to compositions. Naturally occurring fatty alcohols used in the fragrance industry are produced principally by reduction of the methyl esters of the corresponding carboxylic acids, which are obtained by transesterification of natural fats and oils with methanol. Industrial reduction processes include catalytic hydrogenation in the presence of Cu - Cr oxide catalysts (Adkins catalysts) and reduction with sodium (Bouveault - Blanc reduction). Unsaturated alcohols can also be prepared by the latter method.
Many alcohols are components of essential oils extracted from flowers (e.g. lavender, orange), leaves (e.g. mint, sage), cortex (e.g. cinnamon), wood (e.g. cedar, sandalwood), roots (e.g. angelica), rhizomes (e.g. calamus), fruits (e.g. lemon, bergamot, fennel). Among these there are many terpene and sesquiterpene alcohols such as menthol, (+)-borneol, citronellol, linalool, geraniol, nerol, myrcenol, farnesol, and linear alcohols. As already described, (-)-menthol because of its cooling and refreshing effect, is a characteristic ingredient in cigarettes, cosmetics, toothpastes, chewing gum, sweets, and medicines. (±)-Menthol can be used in medicines and liniments. Except for menthol, the acyclic terpene alcohols geraniol (figure 16), linalool, and citronellol are the most important terpene alcohols used as fragrance and flavor substances. Geraniol finds application in fruity flavors as well as in scents.

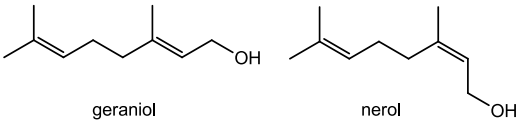


Figure 16

Monoterpenes with hydroxy groups, such as linalool, geraniol and nerol (figure 16), are present in fruit juice at least in part as glycosides. It is important to remember that linalool is an important intermediate in the manufacture of vitamin E and is also used by pest professionals as a flea and cockroach insecticide.
Citronellol is one of the most widely used fragrance materials employed in perfumes and as food flavor. It is also used in insect repellents and as a mite attractant.
Among other interesting linear alcohols for applications as fragrance and flavor components there are for example 2-methyl-1-butanol, hexyl alcohol, 2-heptanol, 1-octen-3-ol.
2-Methyl-1-butanol has a cooked, roasted aroma with fruity or alcoholic undernotes and can be employed as a flavor and fragrance agent.
Hexyl alcohol which has an herbaceous, mild, fruity odor and an aromatic flavor, can be used as an intermediate for food flavoring agents and in the perfume industry. Besides, hexyl alcohol is a component of alarm pheromones emitted by the Koschevnikov gland of honey bees. Hexyl alcohol is reported found among the

constituents of several essential oils and aromas: apple, strawberry, tea, violet (leaves and flowers), Java citronella, Bourbon geranium, lavender, lavandin, spike and others.
2-Heptanol finds some use in perfumes and in flavors for herbaceous-green top note themes. It has fruity, somewhat green, but also bitter taste and an herbaceous reminiscent of lemon odor. The (*S*)-enantiomer has a smell of mold and mushrooms, while the (*R*)-isomer has very intense fruity notes.
1-Octen-3-ol, also known as mushroom alcohol, is a chemical that attracts biting insects such as mosquitos. It is found, for example, in lavender oil and is a steam-volatile component of mushrooms used in lavender compositions and in mushroom aromas as food additive. Several alcohols containing an aromatic group display industrial interest (figure 17).

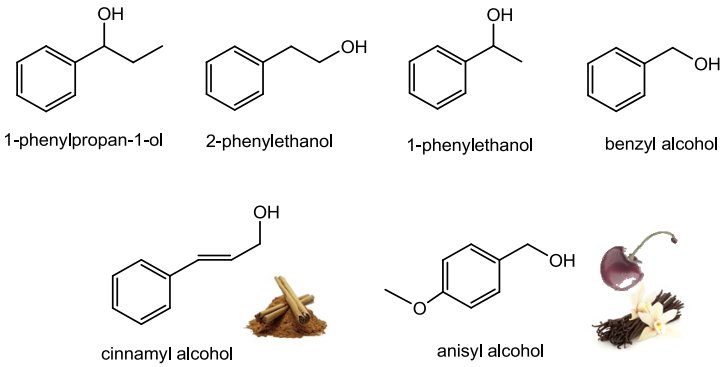


Figure 17

1-Phenylpropan-1-ol which has a sweet, honey-like taste and a floral odor, is listed by FDA as a flavoring agent. 2-Phenylethanol (phenethyl alcohol) is used in large amounts in perfumery, cosmetics and as flavoring agent for soft drinks (orange juice), candy, cookies, wine and beer, for its characteristic rose-like odor and sweet, reminiscent of peach taste. In addition 2-phenylethanol has been identified as the most important aromatic component of the roasty note of wheat bread. This alcohol is qualitatively and quantitatively one of the most important fragrance substances that belongs to the class of aromatic alcohols.
The alcohol 1-phenylethanol is a component of food, tea and mushroom aroma. It is widely used in the production of esters among which the corresponding acetate which has fruity odor.
Benzyl and cinnamyl alcohols are valuable fragrance and flavors materials. Benzyl alcohol has a weak sweet odor and it is used in fragrance and flavor compositions mainly as a solvent and for dilution. It is the starting material for a large number of benzyl esters, which are important fragrance and flavor substances.

Cinnamyl alcohol is extremely important, it occurs naturally in *cis* and *trans* forms, the latter is best represented. This compound is widely used in perfumery, as aroma of cinnamon, hyacinth and fruit flavors. It is also a starting material for various cinnamic esters, widely used as aromas. The cinnamyl alcohol is also an intermediate for the synthesis of the antibiotic Chloromycetin.
Finally, *p*-Anisyl alcohol has a sweet, floral fragrance with notes of lilac, rose, hyacinth, appreciated by the cosmetics and perfumery industry and has a sweet taste of vanilla, cherry, cocoa. Also *p*-anisyl alcohol is listed as a food additive for human consumption by FDA.[11,12,13a,39,40]
The alcohols mentioned above are nearly always prepared synthetically for use in compositions. For example, 2-phenylethanol can be industrially synthesized following the Friedel - Crafts reaction of benzene and ethylene oxide or by hydrogenation of Styrene Oxide. 1-Phenylethanol can be easily prepared by catalytic hydrogenation of acetophenone or by oxidation of ethylbenzene. Benzyl alcohol is typically obtained synthetically from benzyl chloride by the action of sodium or potassium carbonate. Cinnamyl alcohol is usually produced by reduction of cinnamaldehyde with sodium or potassium hydroxide but also by selective hydrogenation of cinnamaldehyde with, for example, an osmium-carbon catalyst.[12,39] In the category of phenolic alcohols can be mentioned BHA (E320) and BHT (E321) used as antioxidants and preservatives in foods, polymers and cosmetics industry, where act also as preservatives. Among the substances used by insects as messengers (pheromones), there are several straight chain alcohols with low molecular weight and high volatility. These substances can be synthesized and employed as crop protection systems and for the disinfection of premises, without the use of toxic substances. Within this class, there are different pheromones where only one of the two enantiomers is active. For example, (*R*)-2-heptanol is a sex pheromone of *Eriocrania cicatricella* (lepidoptera) (figure 18) and (*R*)-2-decanol is a defense pheromone of *Trinervitermes bettorianus* (termites).[41]

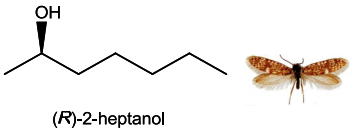
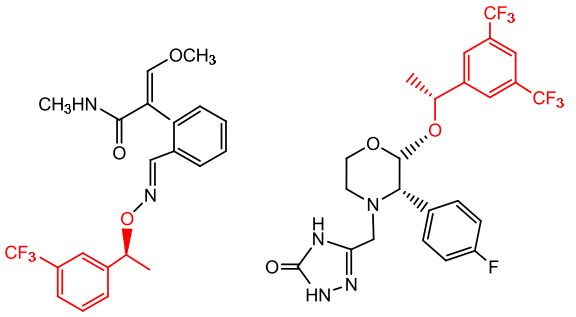


Figure 18

Several alcohols are also used as pharmaceuticals and agrochemical intermediates as well.
For istance, (*S*)-1-[3-(trifluoromethyl)phenyl]ethanol is a key intermediate for the synthesis of a the wide spectrum agricultural fungicide, (*S*)-MA20565, while (*R*)-3,5-bistrifluoromethyl phenyl ethanol (BTMP), is a interesting building block for a number of pharmaceutically interesting targets, such as an NK-1 receptor antagonist used for chemotherapy (figure 19).[42,43]



(*S*)-MA20565 Aprepitant, NK-1 receptor antagonist

Figure 19

Another group of alcohols of great industrially interest is that of benzhydrols which have two aryl groups linked to the carbon atom of the hydroxyl group. These compounds are intermediates for the synthesis of valuable pharmaceutical products such as antihistamines, antifungals, anti-inflammatory, antihypertensive and calcium antagonists (figure 20).[44] The current industrial processes of producing benzhydrols rely on stoichiomeric reduction using $NaBH_4$. Alternatively, benzophenone can be hydrogenated using a carbon-supported palladium catalyst (Pd / C, heterogeneous catalyst), in hexane or a 1 : 1 mixture of ethanol and acetic acid with formation of large amounts of diphenylmethane, an over-reduction product. In addition, another standard method to prepare benzydrols consists on the addition of arylmetals to benzaldehydes.[45] Recently, Noyori and co-workers have developed a process for the hydrogenation of benzophenone derivatives to benzhydrols which involves the use of ruthenium complexes with phosphine and amine ligands, in basic 2-propanol under H_2 (8 atm), without production of diphenylmethane (substrate / catalyst = 2000 - 20000). At 35 °C complete conversion of benzophenone to benzhydrol was achieved in 48 h, while 4-chlorobenzophenone was reduced to 4-chlorobenzhydrol in 8 h.[45]

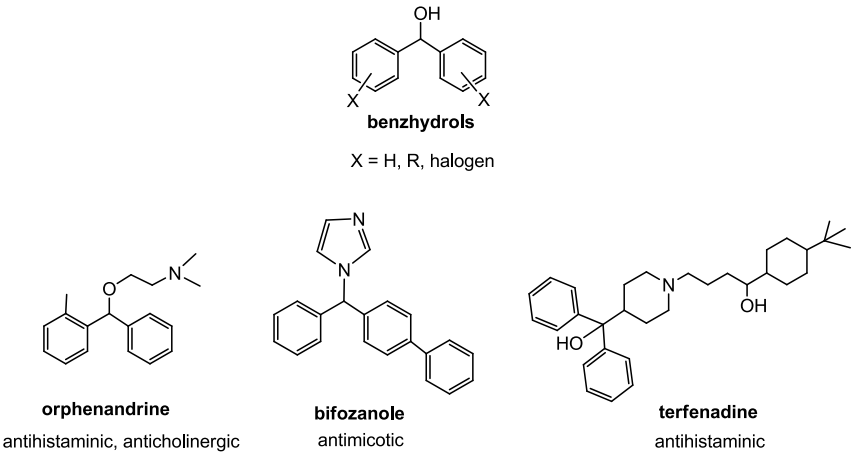


Figure 20

In addition to alcohols, many aldehydes have often employed in perfumes, cosmetics and food as flavorings. Among the aldehydes best known and used in the food industry, benzaldehyde is used in aroma compositions for its bitter almond odor. It is the starting material for a large number of fragrance and flavor materials. The natural production of benzaldehyde is by extraction from fruits, such as apricots, but the extraction process leads to the formation of highly toxic hydrogen cyanide. The global consumption of benzaldehyde amounted, approximately, around 7000 ton per year.[46]
Cinnamaldehyde is is the main component of artificial cinnamon oil and has a strong spicy, cinnamon odor and taste.
Vanillin (4-hydroxy-3-methoxybenzaldehyde) is the most universally accepted aroma chemical used in processed foods, pharmaceuticals and perfumeries.The chemical synthesis of vanillin today covers 99 % of the total market while the direct extraction from the seeds of *Vanilla planifolia* is expensive and limited by the availability of the plant. The synthesis of vanillin can also be obtained by microbiological or enzymatic way. In addition, other aldehydes find commercial applications as precursors to alcohols.[11]

1.3.2 Esters

Esters are alkyl derivatives of carboxylic acids and ubiquitous compounds. Most naturally occurring oils and fats are fatty acid esters of glycerol. Phosphodiesters are the backbone of the helical strands in DNA, nitro esters, like nitroglycerin, are known for their inherent explosive properties. Polyesters, polymers which contain the ester functional group in their main chain, are the material of various plastics,

widely used in many fileds such as the packaging industry as PET (polyethylene terephthalate).
Esters with a low molecular weight commonly have a use as fragrances, generally found in pheromones and essential oils.
Aliphatic esters are preferred for artificial fruit aromas and in nature acetates and ethyl esters prevail. Most esters are derived from alcohols and acids with an even number of carbon atoms. In addition to straight-chain saturated compounds, branched-chain compounds such as isoamyl esters, and unsaturated compounds such as hexenyl esters are important. Although the odor of aliphatic esters with a small number of carbon atoms is strictly fruity, it changes to fatty-soapy and even metallic as the number of carbon atoms increases.
Some of these esters commonly used in food industry as flavors are: isoamyl acetate (banana odor, bittersweet, pear taste), ethyl propionate (pinapple, rum-like odor and taste), ethyl butyrate (sweet, fruity, pineapple odor and taste), methyl-2-methylbutyrate (fruity, apple-like odor and taste), hexyl acetate (fruity odor, bittersweet, pear taste), *trans*-3-hexenyl acetate (fruity odor and taste) (figure 21).
The low molecular weight acid esters (particularly the acetates) of the terpene alcohols geraniol, linalool, citronellol and (-)-menthol are extremely important both as fragrance in perfumery and as flavor substances. Citronellyl acetate and propionate for example have fresh-fruity, roselike odor with citrus flavors and can be employed to round off fruit flavors. (-)-Menthyl acetate is used mainly in peppermint flavors but also to a small extent in perfumery.
Among the esters of aromatic alcohols and aliphatic acids there are several fragrant compounds with a pleasant fruity taste such as benzyl esters, cinnamic esters, anisyl acetate, phenethyl acetate and propionate (figure 21).

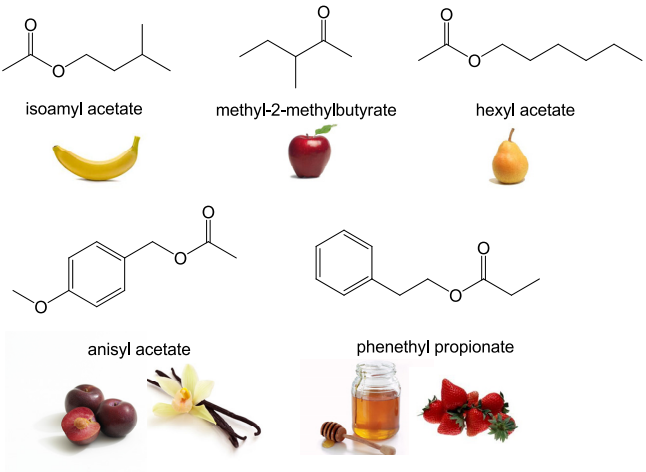


Figure 21

Finally some esters of aromatic acid and aliphatic alcohols are of interest such as methyl anthranilate, with an orange-flower odor and a bitter taste, that acts as well as a bird repellent. Moreover, methyl salicylate is not used only in small quantities as cosmetic, flavor and fragrance agent, as an alternative to the more common peppermint and spearmint oils for its minty-spicy, sweet aroma, but also as an attrack and bait substance for male orchid bees, in medicine (analgesic and antiseptic), in photography and other fields.
Interestingly, lactones are also of interest for commercial aromatization of food, because of their pleasant creamy-coconut or fruity aroma such as sotolone, β-methyl-γ-octalactone (wiskey lactone) γ-valerolactone, γ-decalactone, δ-decalattone. They are constituents of many essential oils and plant volatiles, such as coumarin.[10,11,12,37]

1.3.3 Ketones

Ketones are carbonyl organic compounds, produced on massive scales in industry as solvents, polymer precursors, and pharmaceuticals. Some ketones are interesting molecules for perfumery and food aromas.
Aliphatic ketones such as methyl ketones C_7, C_9, C_{11} possess a characteristic nutty note, thus they are used, e.g., in cheese flavor compositions and the diketone butanedione is added mainly in aromas for butter and roast notes as well as for flavoring margarine like also acetoin (3-hydroxy-2-butanone).
The linear ketone 2-heptanone acts as an alarm pheromone produced by a number of families of insects as cockroaches (*Platyzosteria* spp.), beetles (*Dyschrus* spp.) and honeybees,[47] and is also discussed as an alarm pheromone in the urine of rats.[48] It has a banana-like, fruity odor, occurs naturally in certain foods (such as beer, white bread, butter, various cheeses and potato chips) and is listed as a food additive.
2-Undecanone, with a characteristic rue odor and sweet-peach flavor, is used in the perfumery and flavoring industries, but because of its strong odor it is primarily used as an insect repellent (against mosquito) or animal repellent.
In addition 2-pentanone can be added in small amounts in foods as flavoring additive for example in baked goods and soft candies because of its sweet, fruity, banana-like taste and fruity odor.[39]
A few of the cyclic terpene ketones are commercially important as fragrance and flavor substances, for example, menthone and carvone, which have the *p*-menthane skeleton, and the ionones. Some cyclic terpene ketones are the main components of essential oils (e.g. camphor in camphor oil). In addition nootkatone is known for its grapefruit, citrus taste and is used in beverages (figura 22).
Menthone exists with its stereoisomer isomenthone. Both stereoisomers occur in many essential oils, often as a single enantiomer species. Menthone is a constituent of the essential oils of pennyroyal, peppermint, *Pelargonium* geraniums, and others. In most essential oils, it is a minor compound. Menthone and isomenthone

are used for synthetic peppermint oils and bases for foods, cosmetics and perfumes. The ionones and their methyl-substituted homologues, components of blossom and rose perfume compositions, are some of the most valuable fragrance materials and are used in aroma compositions as well. Notably β-ionone is converted into intermediates for vitamin A synthesis.
Cycloaliphatic ketones such as cyclopentanone derivatives and others are characterized by floral odor and then added in cosmetics and perfumes. The aromatic ketones that occur or are used as fragrance and flavor materials are predominantly aryl methyl ketones, which include acetophenones and β-naphthyl methyl ketone with their floreal smell, widely used in soap perfumes and detergents. 4′-Methylacetophenone has a strawberry-like flavor so can add as flavoring agent in foods, similarly 4′-methoxyacetophenone finds application in vanilla, nut, tobacco and butter flavors but it is also an intermediate in the manufacture of pharmaceuticals and resins. Finally, *p*-hydroxybenzyl acetone (raspberry ketone), a higher mass phenol ketone, has a characteristic raspberry aroma (figura 22).[11,12,39]

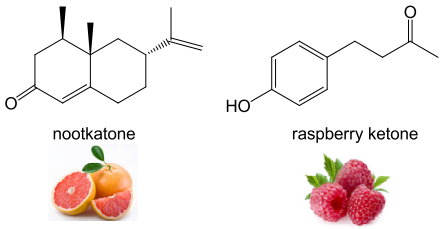


Figure 22

Other applications of some ketones concern chemical, pharmaceutical and agrochemical industry. Propiophenone, as well as being a constituent of synthetic floral perfumes, food additives and of paints to stabilize other ingredients, finds interesting application especially in the pharmaceutical industry in the preparation of drug derivatives such as psychoactive stimulants (figure 23). Bupropion is an example which has propiophenone moiety. Bupropion is an aminoketone class antidepressant.[49] Propiophenone is also used in the synthesis of ketoamphetamines such as cathinone and methcathinone. Some propiophenone derivatives such as paroxypropione (4'-hydroxypropiophenone) is a drug called adrenergic β-antagonist which bind to but do not activate β-adrenergic receptors thereby blocking the actions of β-adrenergic agonists. Adrenergic β-antagonists are used for treatment of hypertension, cardiac arrhythmias, angina pectoris, glaucoma, migraine headaches, and anxiety. In addition propiophenone is important in the synthesis of ephedrine an alkaloid derived from various plants (family

Ephedraceae) commonly used as a stimulant, appetite suppressant, concentration aid, decongestant, and to treat hypotension associated with anaesthesia.[39,50]

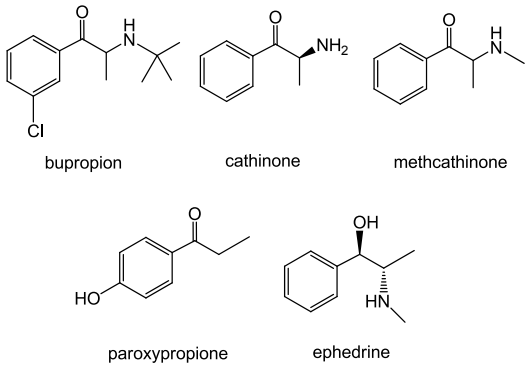


Figure 23

Benzophenone is used as a constituent of synthetic perfumes and as a starting material for the manufacture of dyes, pesticides and drugs (especially anxiolytic and hypnotic drugs). This organic compound is employed as a photoinitiator of UV-curing applications in inks, adhesive and coatings, optical fiber as well as in printed circuit boards and prevents UV light from damaging scents and colors in products, such as perfumes and soaps. It can also be added to the plastic packaging as a UV blocker. In biology benzophenones find application as photo-physical probes to identify peptide-protein interactions.[51]

Indane class compounds can be employed in the formulation of perfumes, aroma chemicals or fragrance enhancers as well. 1-Indanone, derived from indane, is known as an important drug intermediate for serotonin reuptake inhibitors and others, having analgesic and antibiotic properties. Tetralone derivatives find extensive applications in color industry, plastics, in preparing pesticides or agrochemicals and as intermediates for dyes, drugs (contraceptives) and in medicine in general especially α-tetralone.[52,53] Another valuable class of compounds of high biological interest is that of steroid hormones which contain a carbonyl along with other functional groups. Steroid hormones are biological regulators of the lives of mammals. These molecules control a variety of body functions, also as intermediates, such as reproduction (male and female sexual hormones), carbohydrate metabolism (glucocorticoids), ion transport (mineralocorticoids), etc. Thus steroid hormones and their analogues are widely used in human, veterinary medicine and in pharmaceutical industry. For example, cortisone and prednisone are two antinflammatory steroids with closely related structures. Cortisone is secreted by the body's adrenal gland, whereas prednisone is

a synthetic analogue used in thetreatment of inflammatory diseases such as arthritis and asthma (figure 24).[10]

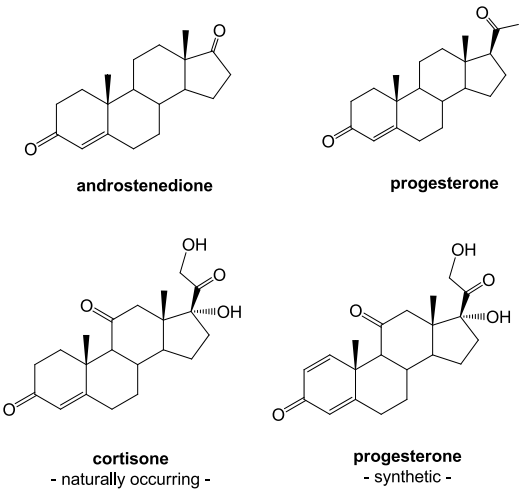


Figure 24. Some important steroid hormones

1.4 Synthesis of alcohols

Alcohols can be prepared from different sources and the principal methods are shown below, in figure 25.

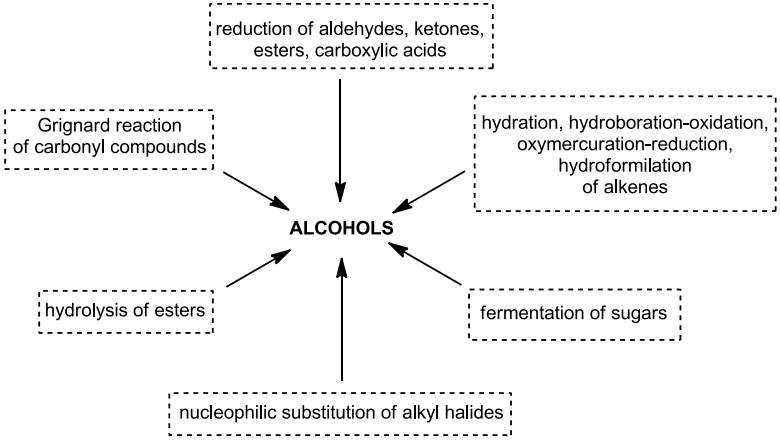
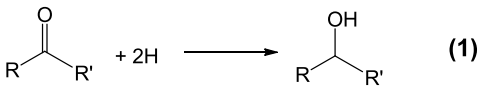


Figure 25

In industry, alcohols are produced substantially by hydration and hydroformylation of alkenes and fermentation of sugars by yeasts.[54] Among the methods to prepare alcohols in laboratory, the reduction of carbonyl compounds (aldehydes and ketones) using metal catalysts has exstensively been investigated and represents a key way to achieve optical active alcohols and fine chemicals in general.
In this PhD thesis the reduction of aldheydes and ketones with both chiral and achiral ruthenium(II) and osmium(II) homogeneous catalysts has been investigated, in order to obtain compounds of biological and industrial interest, particularly for food, agrochemical and pharmaceutical industry. Special attention has been devoted to the catalytic transfer hydrogenation and hydrogenation reactions. The catalytic racemization and deuteration of alcohols have also been decribed.

1.4.1 Reduction of aldehydes and ketones

The reduction of an aldehyde or a ketone leads to the formation of a primary or secondary alcohol, respectively, through a formal hydrogen addition (eq.1).



(1)

R, R' = alkyl, aryl

This reaction may occur through stoichiometric or catalytic procedures. The first method involves the use of reducing agents such as $LiAlH_4$ or $NaBH_4$, while in the

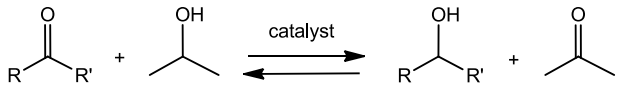
second case gaseous hydrogen (H_2) or hydrogen donor molecules (2-propanol, formic acid) are used in the presence of transition metal complexes. Regarding ketones, if the carbonyl has two different substituents (R, R') the use of achiral reducing agents leads to a racemic mixture of the secondary alcohol.

1.4.2 Stoichiometric and catalytic reduction

Fine chemicals and specialities manufacture is rampant with classical "stoichiometric" technologies, many of which date from the 19th century. In the enantioselective reduction of ketones to chiral alcohols, noteworthy studies were led by Brown[55] and Midland[56] who used chiral boron DIP chloride and Alpine-Borane as reducing agents. Another important route of synthesis is that developed by Corey, which involves the use of oxazaborolidine and BH_3 as a reducing agent. With this procedure it was possible to obtain enantioselective reduction of a large number of substrates, and this method is followed today for the industrial preparation of a number of pharmaceutical products. Widely used stoichiometric reactions require in particular the employment of reducing metals (Na, Mg, Zn, Fe) or metal hydrides ($LiA1H_4$, $NaBH_4$, etc.) and oxidizing agents such as permanganate or dichromate.
Nevertheless, the replacement of old stoichiometric methodologies with cleaner catalytic alternatives, such as catalytic transfer hydrogenation (TH) and hydrogenation (HY), represents a valuable choice for waste minimization. Thus, the catalytic reduction of carbonyl substrates, using finely divided metals or transition metal complexes to achieve alcohols has been exstensively studied and used. In this case, the reducing sources are H_2 or hydrogen donor molecules, such as 2-propanol or formic acid.
Hence, catalysis will play a pivotal role in the development of clean, environmentally benign processes that generate minimum amounts of wastes.[57]

1.4.3 Catalytic transfer hydrogenation (TH) with 2-propanol

The reduction of polarized unsaturated compounds via transfer hydrogenation is a topic that has extensively been investigated in the last decade. A large number of homogeneous transition metal complexes have been found to catalyze the reduction of ketones, aldehydes and imines using 2-propanol (eq. 2) or formic acid as hydrogen donor.



(2)

R = alkyl, aryl
R' = H, alkyl, aryl

The equilibrium of the reaction can be easily shifted toward the product using an excess of 2-propanol, used as a solvent, or eliminating acetone by distillation.
It is worth noting that, because of the higher redox potentials of aldehydes compared to ketones, the equilibrium of the transfer hydrogenation reaction of aldehydes with 2-propanol is more shifted toward the products. By contrast, reduction of aldehydes to primary alcohols via transfer hydrogenation as well as the control of the chemoselectivity of this reaction are considered rather difficult processes because of the production of side reactions that may occur during the catalytic reaction, usually performed in basic media. As a matter of fact, the hydrogens of the α-CH group are susceptible to deprotonation and can lead to aldol condensation. Furthermore, during catalysis aldehydes may also undergo decarbonylation reactions, which may result in deactivation of the catalysts through coordination of carbon monoxide. Therefore, in order to suppress these side reactions, weak basic conditions and very short reaction time are prerequisites to achieve efficient aldehyde reduction.
Since the 20*s* it was known that 2-propanol, in the presence of aluminum isopropoxide, was able to reduce carbonyl compounds, according to the Meerwein-Ponndorf-Verley reaction. Through this reaction ketones and aldehydes can be reduced selectively and under mild conditions. It is noteworthy that using alkoxides it is also possible to obtain ketones from alcohols using as oxidizing agent a ketone, such as acetone (Oppenauer oxidation).[58,59]
The use of 2-propanol as reducing agent has a number of advantages: it is stable, can be stored for a long time, is not toxic, is a good solvent and is inexpensive. In addition, the only byproduct of the reaction is acetone. These mild, simple, clean reaction conditions are suitable for the preparation of alcohols of small and medium scale in complete safety.
Among the different metal complexes, important results have been obtained with rhodium and ruthenium based catalysts. The lowest cost of ruthenium compared to that of rhodium and palladium allows a cost-effective use in the industrial field.
The complex $RuCl_2(PPh_3)_3$ isolated by Wilkinson in the 60*s*, is one of the most important precursors of the chemistry of ruthenium,[60] through a number of complexes containing phosphine ligands and the nitrogen ligands in different combinations can be obtained.[61] A significant breakthrough came in the early 90*s* with the discovery by Chowdhury and Bäckvall that the catalytic activity of $RuCl_2(PPh_3)_3$ could be increased by addition of a strong base (NaOH) to 2-propanol, reaching values of turnover frequency (TOF) of 1000 h^{-1} (figure 26).

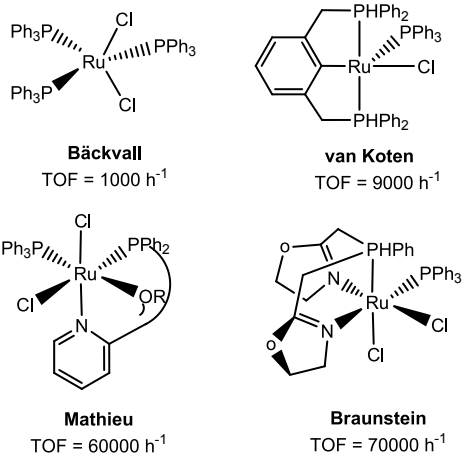


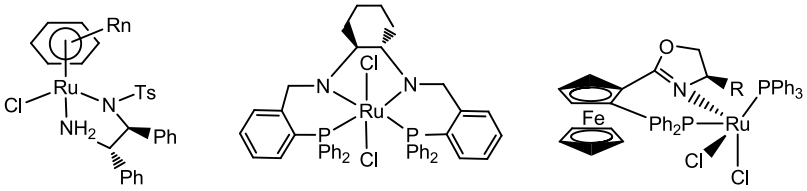
Figure 26

In the following years Mathieu reported that, by the reaction of $RuCl_2(PPh_3)_3$ with tridentate pyridine-phosphine ligands, a catalytically active complex in the reduction of acetophenone to 1-phenylethanol was obtained, with TOF values of 60000 h^{-1}.[62] Subsequently, van Koten and co-workers isolated cyclometalled phosphine complexes containing a robust ruthenium-carbon bond which gave TOF values of 9000 h^{-1} in the reduction of acetophenone, using low catalyst loading (0.01 mol %).[74b] In 1999 Braunstein described a new ruthenium complex, containing oxazoline ligands, highly active in the reduction of ketones (TOF up to 70000 h^{-1}).[63]

It is noteworthy that the described systems were the most active catalysts reported in literature in transfer hydrogenation reactions, but they are not very active in asymmetric catalysis.

A fundamental contribution to the development of new enantioselective transfer hydrogenation catalysts was given by Noyori and co-workers in the late 90*s*, who observed that the activity of ruthenium arene complexes can be enhanced using N–O and N–N bidentate ligands where one N is a primary amine achieving enantiomerically pure alcohols (99 % *ee*) in 2-propanol.[64,65] The presence of a primary or secondary amino group is crucial for catalytic activity, in fact the analogous complexes with tertiary amine ligands are completely inactive. Evidence has been provided that during catalysis the *cis*-RuH/-NH_2 motif plays a fundamental role for the high activity.

High stereoselectivity was also observed with arene[64a,66] and terdenatate (P_2N_2) systems,[67] and with the chiral bidentate oxazolinic complexes prepared Sammakia and Uemura (figure 27).[68]



Noyori
TOF = 10^2 - 10^3 h^{-1}

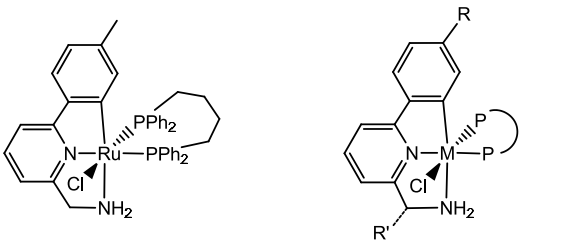
Sammakia - Uemura
TOF = 10^2 h^{-1}

Figure 27

The reseach group of inorganic chemistry of the University of Udine has been studing for some years the synthesis and the application of a number of ruthenium(II) and osmium(II) catalysts in both TH and HY reactions, achieving interesting results.

Our group found that the complexes *cis*-[$RuCl_2$(PP)(ampy)], containing a diphosphine (PP) and the mixed bidentate nitrogen ligand 2-aminomethylpyridine (ampy), display high catalytic activity for the TH of ketones in basic 2-propanol.[69] Fast enantioselective reduction of ketones has been achieved with the system $RuCl_2$(diphosphine)(ampy) when chiral diphosphines are employed.[69a]

A more efficient catalyst is the pincer complex RuCl(CNN)(dppb), [dppb = 1,4-bis(diphenylphosphino)butane], obtained by *ortho*-metalation of the ampy-type ligand 2-(1-aminomethyl)-6-(4-metylphenyl)pyridine (HCNN), which displayed extremely high activity for the transfer hydrogenation of ketones, affording TOF numbers up to 2.5 × 10^6 h^{-1} (figure 28) [70]



RuCl(CNN)($Ph_2P(CH_2)_4PPh_2$) Chiral Ru and Os pincer complexes

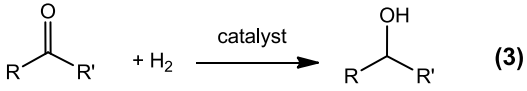
Figure 28

The chiral pincer complexes RuCl(CNN)(PP), prepared from chiral Josiphos diphosphines and racemic HCNN ligands, have proven to catalyze the ketone TH with both high enantioselectivity and productivity.[71]

Interestingly, the analogous osmium complexes $OsCl_2(PP)(ampy)$ and OsCl(CNN)(PP) display very high catalytic activity in the enantioselective ketone TH.[72,71a-b]
These osmium compounds are among the most active systems reported in literature for the reduction of ketones to alcohols via transfer hydrogenation and in some cases gave better results compared to ruthenium. Osmium is thought to give more stable complexes and less active catalysts compared to ruthenium, as a consequence of the stronger bonding. On account of the high performance of the pincer complexes,[73] this class of compounds appears attractive for obtaining robust catalysts,[74] relevant for industrial applications. The high stability and productivity of MCl(CNN)(PP) complexes arise from tridentate CNN ligand which has a strong chelating effect due to two nitrogen atoms and the peculiarity of coordinating the metal through the formation of a strong σ-metal-carbon bond. The presence of the *ortho*-metalated CNN and the bidentate phosphine, prevents ligand dissociation, retarding catalyst deactivation.
Finally, since transfer hydrogenation is an equilibrium reaction, the catalysts active in this reaction can also be used for the chiral resolution of racemic mixtures (KR) via a selective oxidation of one enantiomer using acetone as a hydrogen acceptor.[75]

1.4.4. Catalytic hydrogenation (HY) with H_2

Homogeneous hydrogenation is a fundamental synthetic procedure and is one of the most extensively studied reactions of the homogeneous catalysis. The hydrogenation of organic unsaturated substrates is usually performed with molecular hydrogen under pressure (eq. 3).



(3)

R = alkyl, aryl
R' = H, alkyl, aryl

Until the early 80*s* only a limited number of transition metal complexes were found active in the hydrogenation of ketones. During the early years of the catalyst development (1960 - 1980), rhodium chemistry dominated the scene, led by the investigations, for example, of Wilkinson, Kagan, Osborn, and Knowles. The more complex catalytic chemistry of ruthenium was slower to develop, starting with the studies by Halpern and Wilkinson during the 1960s. This continued with an exploration of the types of ruthenium complexes that were active hydrogenation catalysts in the 1970*s*, as reviewed by James. The anionic complex

$K_2[Ru_2H_4(PPh_2)(PPh_3)_3]\cdot 2O(CH_2CH_2OCH_3)_2$ was one of the first catalyst able to reduce acetophenone in toluene at low H_2 pressure.[76]
During the 1980*s* the search for new chemistry for the syn-gas (CO, H_2) and coal utilization to combat petroleum shortages (the "energy crisis") shifted attention to Ru and Os complexes, and promising activity was found for the hydrogenation of difficult substrates such as arenes, simple ketones, nitriles, and esters.
For both economic and scientific reasons, attention then shifted to enantioselective hydrogenations using rhodium and ruthenium complexes. For this application, ruthenium complexes containing phosphine and chiral nitrogen ligands were particularly interesting.[77,78]
A crucial contribution in the catalytic HY and TH has been given by Noyori and Ikariya, leading to the systems *trans*-[$RuCl_2$(diphosphine)(1,2-diamine)][79] and (η^6-arene)RuCl(Tsdpen) (figure 29).[65] Expecially the hexacoordinated complexes $RuCl_2$(diphosphine)(diamine), containing chiral diamine and diphosphine ligands, developed by the group of Noyori, reached high chemo stereo and enantioselectivity in HY of carbonyl compounds in the presence of a base.[15a,80]
The development of this series of catalysts containing chiral phosphines and amines opened the way to the enantioselective reduction of many polyfunctional ketone compounds.
The high selectivity of these catalysts, with which chiral alcohols with high enantiomeric purity (*ee* > 95 %) can be obtained, and their efficiency (ratio substrate / catalyst = 10^5), make these catalytic systems high appealing for a large number of industrial applications particularly for the synthesis of natural products such as perfumes, pheromones and pharmaceutical products.
It should be noted that hydrogenation reactions are "clean" with no formation of byproducts so they are ideal in terms of atomic economy and environmental impact.[81] Nevertheless hydrogenation reactions could be dangerous for the employment of H_2 under pressure, thus milder reducing methods may be preferred such as catalytic transfer hydrogenation.[82]
Other complexes (η^6-arene)Ru(OTf)(Tsdpen),[83] MCl_2(PP)(ampy) (M = Ru,[69] Os;[72] ampy = 2-aminomethylpyridine) and the related pincer MCl(CNN)(PP)[71,84] (HCNN = 1-(6-arylpyridin-2-yl)methanamine) (figure 29), containing the ampy motif, were demonstrated to be efficient catalysts for both transfer hydrogenation (TH) and hydrogenation (HY) reactions, by a careful switching of the reaction parameters, namely temperature, solvent and base concentration.

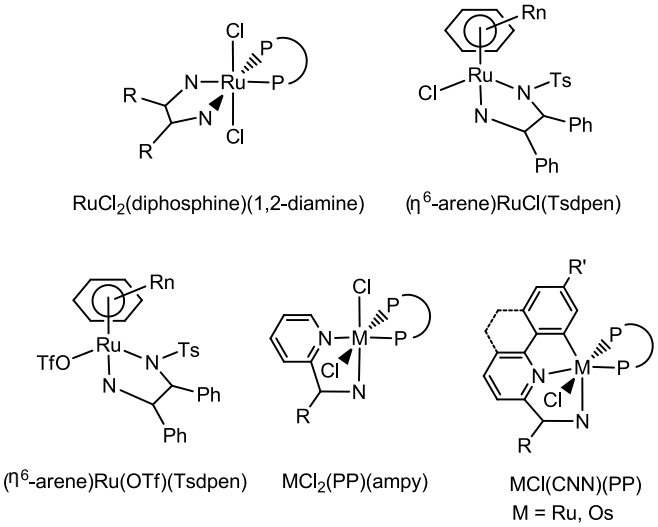


Figure 29

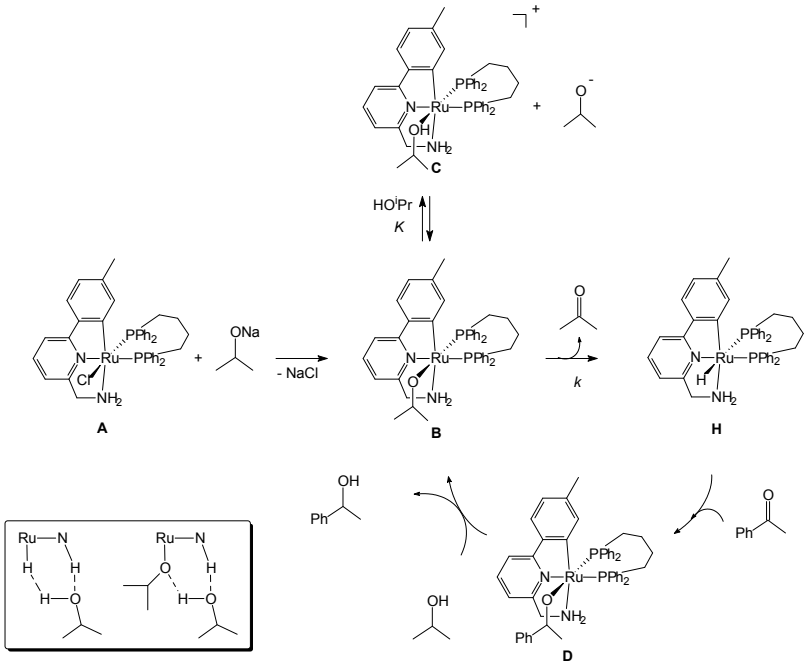
It is worth noting that the ampy ligand, containing the NH_2 function and the pyridine ring, has unique properties for the catalysis, leading to acceleration of both TH and HY reactions and allowing the reduction of bulky substrates (*tert*-alkyl ketones), on account of the flat pyridine ring that facilitates the approaching of the ketone.

1.4.5 Catalytic cycle of transfer hydrogenation and hydrogenation reactions

In recent studies our group found that the catalytic activity of the chloride terdentate complex RuCl(CNN)(dppb) (**A**) in the TH of acetophenone in 2-propanol is strongly affected by the base / Ru ratio and that the activity of the ruthenium system increases at higher base concentration (NaO*i*Pr). The limit rate has been observed when NaO*i*Pr is used in high excess (catalyst / base molar ratio > 10).[85]

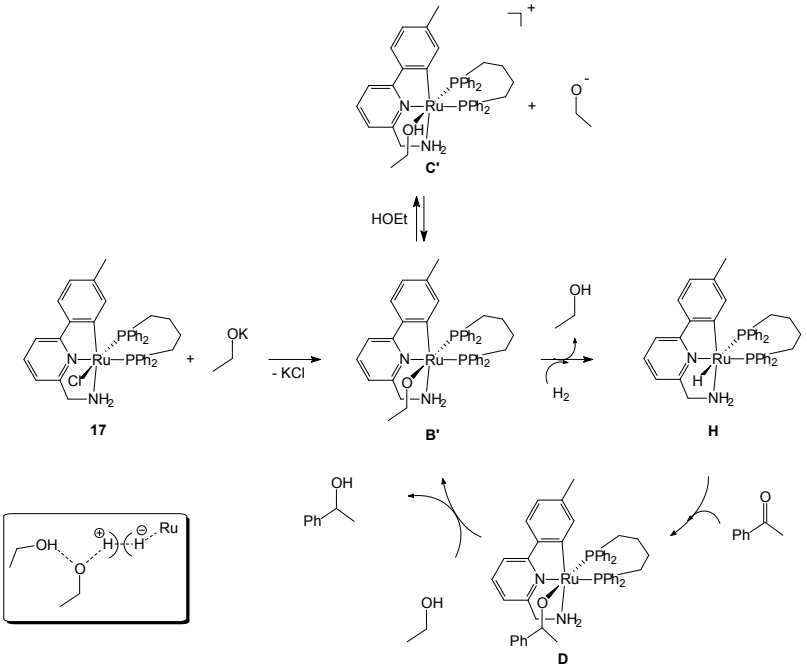
The scheme 2 below describe the catalytic cycle proposed for the transfer hydrogenation of acetophenone with **A**. The derivative **A**, reacts with the base (NaO*i*Pr) leading to the formation of the alkoxide species **B**. This system in 2-propanol is in pre-equilibrium with the cationic species **C** through the constant K. Complex **B** undergoes β-hydrogen elimination process affording the ruthenium hydride **H** which subsequently reacts with acetophenone leading to the ruthenium alkoxide **D**. In the final step of the catalytic cycle the ruthenium alkoxide reacts

fast with 2-propanol, which is in large excess, affording 1-phenylethanol and the isopropoxide **B** that closes the cycle. The formation of **H** from **B** is likely to be rate determining step of the catalytic transfer hydrogenation in which most of ruthenium is present as **B** and **C** species, according to the base concentration. The results of the kinetic study showed that the isopropoxide **B** and the hydride **H** are the catalytically active species and that the activity of the hydride is affected by the base concentration.



Scheme 2

Further studies performed on the influence of the base on the activity of the system RuCl(CNN)(dppb) in the hydrogenation of acetophenone (acetophenone / Ru / KO*t*Bu = 10000 / 1 / 200), pointed out a bell-shaped trend in the catalytic activity which is strongly influenced by base concentration.[85] At high base loading (> 2 mol %), the formation of the Ru-H bond and thus of the catalytically active hydride species is prevented. This probably determines a rapid decrease of the catalytic activity. In agreement with the kinetic studies on the transfer hydrogenation, a catalytic cycle for the hydrogenation reaction promoted by complex **A** was proposed (scheme 3).



Scheme 3

By reacting catalyst **A** with the base (KOEt), **B′** species in equilibrium with **C′** species is formed. The ethoxide **B′** reacts with H_2 affording ethanol and hydride **H**. Then system **H** reacts with acetophenone leading to the ruthenium alkoxide **D** which reacts with ethanol affording 1-phenylethanol and **B′** that closes the cycle. In this cycle the formation of hydrogen bonds between the ethoxide ligand and ethanol is crucial for the formation of the Ru-H bond and consequently for the hydrogen activation. It represents the slower step of the catalytic cycle.
Another important parameter which controls the rate of a catalytic reaction is temperature. It is known that an increase of 10 °C leads to about double the rate of a reaction. In the hydrogenation reactions an additional parameter to consider is the solubility of molecular hydrogen in the solvent in which catalysis is carried out and which decreases increasing temperature.[85]

1.4.6 Racemization and deuteration of alcohols

Activation of the C-H bond close to the hydroxyl group is a fundamental step for broadening the alcohol reactivity for C-C and C-N coupling reactions which occur through borrowing hydrogen.[86c] Most of these catalytic reactions entail the

reversible alcohol dehydrogenation with formation of the more reactive carbonyl compound (aldehyde, ketone).
In this context, the racemization of alcohols mediated by transition metal complexes is an important transformation that in association with the kinetic resolution can allow the preparation of optically active alcohols widely used in fine chemicals (*i.e.* agrochemicals, pharmaceuticals, food aromas) and material science (*i.e*. liquid crystals and polymers) as described in the paragraph 1.2.4. To date, the kinetic resolution of a racemate is still one of the major methods for the production of enantiomers on an industrial scale.[26,28,87]
The C-H bond activation at the α position is also a crucial process in the catalytic H / D exchange at the carbon centers of alcohols for obtaining deuterium-labeled compounds for the pharmaceutical and analytical chemistry. A period of intensive research in the 1960*s* and 1970*s* was followed by a much quieter time in the field of H / D-exchange reactions. It was not until the mid-1990*s* that the area experienced a renaissance as a result of the growing interest in catalytic C-H bond activation and the increasing demand for isotopically labeled compounds as reference materials in mass spectrometry. The use of isotopically labeled internal standards is of particular advantage in the investigation of environmental, animal, and human samples in which matrix effects can interfere with the quantification of toxins. This is because these effects can be almost totally excluded by the physical and chemical similarity of the substance under investigation and the standard.[88]
Chiral alcohols can be converted to racemate by several transition metal complexes and several systems, including $RuCl_2(PPh_3)_3$, supported Ru and Pd, have been found as efficient catalysts for the deuteration of alcohols using D_2O. Among the different metals used for these processes, ruthenium has widely been investigated and the search for new catalysts able to activate alcohols under mild conditions remains a challenge.[89]

1.5 Synthesis of ketones

Many methods exist for the preparation of ketones in academic laboratories and on industrial scale. Some of the most common preparation methods of ketones are shown in figure 30.

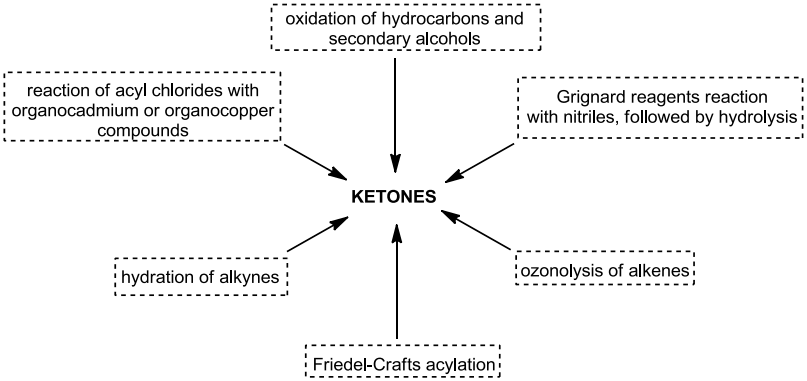


Figure 30

In industry, the most important method probably involves oxidation of hydrocarbons, often with air. For specialized or small scale organic synthetic applications, ketones are often prepared by oxidation of secondary alcohols.[54] Other interesting ways to achieve ketones involving alcohols, are the isomerization of allylic alcohols and the α-alkylation of ketones with primary alcohols. In particular these two reactions and the dehydrogenation of secondary alcohols using ruthenium(II) and osmium(II) homogeneous catalysts has been studied in this work.

1.5.1 Dehydrogenation (DHY) of alcohols and hydrogen production

The oxidation of alcohols into the corresponding carbonyl compounds plays a central role in organic synthesis and has been extensively investigated. The development of catalytic oxidations of alcohols under mild reaction conditions is highly appealing because of its industrial significance. The importance of environmental acceptability of processes has led to much effort in the development of sustainable technologies. Important criteria include high atom efficiency, formation of little (in)organic waste, use of acceptable solvents, and selective synthesis of the desired products. Traditional methods for performing oxidations of alcohols generally involve the use of stoichiometric quantities of inorganic oxidants, notably chromium(VI) reagents. However, from both an economic and environmental viewpoint, atom efficient, catalytic methods that employ clean oxidants such as O_2 and H_2O_2 or low loading of catalysts are more desirable. The highest possible atom efficiency is achieved in the catalytic acceptorless dehydrogenation of secondary alcohols to yield ketones along with H_2 as the sole byproduct, without using oxidizing agents.[38,94g] Interestingly, this reaction represents a key step for broadening the alcohol reactivity through a hydrogen

borrowing process as well as a promising method to produce H_2, an attractive feedstock for energy generation due to the progressive depletion of fossil fuel reserves and the continuously increasing energy demands.[86] An obvious advantage of a hydrogen economy is the significant reduction of the emission of green house gases.

Apart from the ultimate solution, which is water cleavage, renewable resources such as biomass or its fermentation products, e.g. alcohols are a promising basis for the on-time production of hydrogen for stationary devices. However, efficient hydrogen production from renewable resources remains difficult and improved chemical and engineering technologies for generating hydrogen at higher reaction rates and under milder conditions are required. In this respect the development of more efficient catalysts and their understanding will be a key issue. Many metal catalysts, both homogeneous and heterogeneous, can be applied in the dehydrogenation of alcohols. In the past, improvements have been made mainly in the field of heterogeneous catalysis.[90b] For example Davda *et al.* reported on the generation of hydrogen from sugars and alcohols using a Pt / Al_2O_3 catalyst at 227 °C.[91]

As regards homogeneous catalysis, a number of transition-metal complexes have been shown to display good to high catalytic activity for both H_2 generation and the preparation of carbonyl compounds from alcohols, ruthenium being the metal of choice. It is worth noting that because of the higher redox potentials of aldehydes / primary alcohols relative to those of ketones / secondary alcohols, the dehydrogenation of secondary alcohols is thermodynamically favored.[92] Dobson and Robinson,[93] Morton and Cole-Hamilton[94] and Beller[90] found active ruthenium systems for the generation of H_2 from alcohols. The research group of Milstein,[94c-d,95] Adair and Williams,[94e] Hulshof [96],Williams[94e] and Park[97] reported the preparation of carbonyl compounds via DHY of secondary or primary alcohols using ruthenium complexes. Zhao and Hartwig described also the application of several Ru derivatives, including hydrido-phosphane, diphosphane-diamine, and Shvo complexes in the dehydrogenation of 1,4-butanediol to γ-butyrolactone.[94f] A few iridium catalysts were also shown to be active in the alcohol dehydrogenation (figure 31).[98]

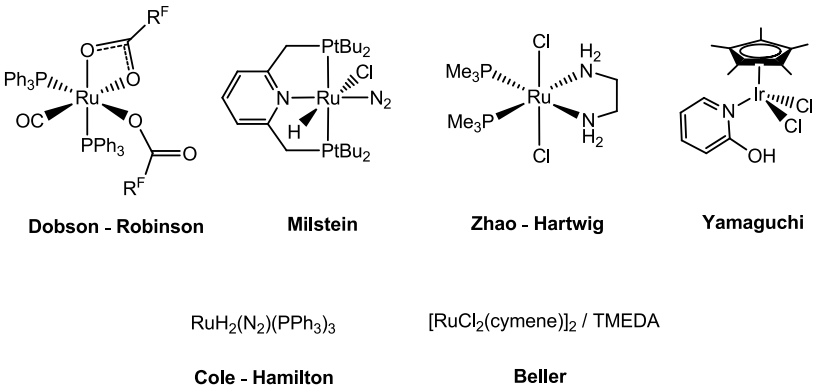


Figure 31. Some interesting ruthenium and iridium complexes that promote alcohol dehydrogenation

As regards the dehydrogenation of steroid alcohols, different routes, including the use of Cr(VI),[99a,b] MnO_2[99c] and the Oppenauer oxidation with ketones mediated by $Al(OiPr)_3$ have been described for the oxidation of 5-en-3β-hydroxy steroids with concomitant C=C double-bond isomerization.[100] In the middle of the 90' Bäckvall *et al.* reported the oxidation of sterols using acetone as oxidant agent via a hydrogen transfer reaction, catalyzed by $[RuCl_2(PPh_3)_3]$ and $[Ru_2(CO)_4(\mu\text{-}H)][(\eta^5\text{-}C_4Ph_4CO)_2H]$ complexes.[101] It is also important to consider that catalysts such as *trans*-$[RuCl_2(PP)(diamine)]$ described by Noyori *et al.*,[79,102c] *trans*-$[OsCl_2(PP)(diamine)]$[103] and *cis*-$[MCl_2(PP)(ampy)]$ (M = Ru,[69a-c] Os,[71]), which are highly active for the (asymmetric) transfer hydrogenation and hydrogenation of ketones, are expected to promote DHY and several related reactions[101].

1.5.2 α-Alkylation of ketones with primary alcohols

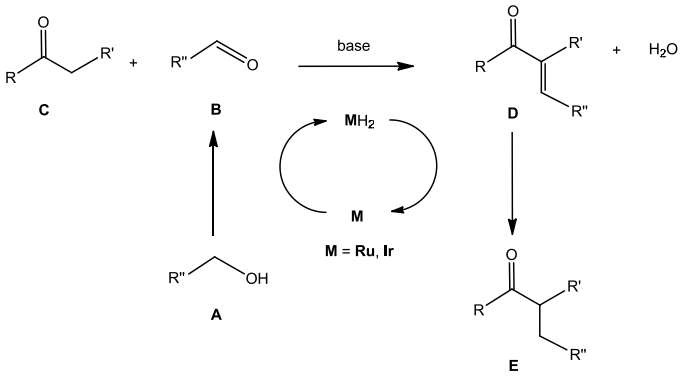
Transition metal-catalyzed carbon-carbon and carbon-heteroatom bond forming reactions have been extensively explored and used as an easy synthetic access tool for compounds which play an important role as an intermediate for the synthesis of pharmaceuticals and organic materials.[104] In general, alcohols display a limited reactivity which can be enhanced by addition of a base, forming a nucleophilic alkoxide, or an acid to provide an electrophilic species. However, there is an alternative pathway, which involves the temporary oxidation of an alcohol into the corresponding aldehyde or ketone. As a matter of fact, carbonyl compounds usually have a much wider range of reactivity than alcohols and are amenable to nucleophilic addition reactions, as well as acting as nucleophiles themselves (such as enol or enolate). Using the oxidation as an activation step for alcohols, catalytic

process will entail the subsequent reduction of the carbonyl compound, or its derivative, under the reaction conditions.[86c]

The α-alkylation of ketones with alcohols has been widely investigated with a number of homogeneous and heterogeneous catalysts.

Cho, Shim and co-workers have used $RuCl_2(PPh_3)_3$, with KOH to effect a range of ketone alkylations, including the alkylation of acetophenone and tetralone with benzyl alcohol and butanol.[105] Related chemistry has been reported by the group of Yus using $Ru(DMSO)_4Cl_2$ as an alternative catalyst.[106] The iridium system $[Ir(COD)Cl]_2$ / PPh_3 was also found to be an effective catalyst for the alkylation of ketones with primary alcohols.[107] In addition, there are several examples of heterogeneous palladium catalysts used in related processes.[104,108]

A general possible pathway for the the α-alkylation of ketones is proposed in scheme 4 on the basis of the work of Bäckwall.[109] The initial removal of hydrogen from alcohol (**A**) generates the corresponding aldehyde (**B**), which can then undergo an aldol condensation reaction with ketone (**C**) giving the α,β-unsaturated ketone (**D**). Subsequent hydrogenation leads to the saturated ketone (**E**). It has not been established whether this latter reduction process occurs *via* direct reduction of the C=C bond or *via* reduction of the ketone to give an allylic alcohol followed by isomerization to the more stable ketone (**E**).

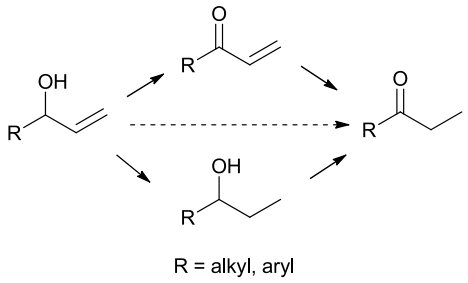


Scheme 4. α-Alkylation of ketones using primary alcohols

Finally, several groups have reported a related process where α-alkylation of ketones leads to an alcohol as the final product, where the ketone (**E**) has been reduced in the last step.[110]

1.5.3 Isomerization of allylic alcohols

The catalytic redox isomerization of allylic alcohols into the corresponding saturated carbonyl compounds represents an atom-economic and elegant shortcut to valuable carbonyl compounds.



Scheme 5. Isomerization of allylic alcohols

Conventionally, the transformation involves a two-step sequential oxidation and reduction process.[111f] The simple and effective one-step isomerization of allylic alcohols has been used in smart routes to some natural products improving overall yields considerably.

Primary allylic alcohols are substrates difficult to be isomerized with respect to secondary allylic alcohols, due to the side reactions that may occur during the process, in particular in a basic medium. As a matter of fact, the C-H group close to the carbonyl of the aldehyde is susceptible to deprotonation, which may degenerate into aldol condensation products. Furthermore, the aldehydes may also undergo decarbonylation reactions, which cause catalyst deactivation.[110]

In the last few decades, various transition metal complexes, including Rh, Co, Ni, Mo, Ir, Fe, Os, Pd and Pt, have been explored as catalysts for this isomerization and, in particular, ruthenium complexes have been described as the most efficient catalysts.[111, 112] Different ruthenium complexes are involved in the isomerization reaction of alcohols and/or alkenes, ethers, esters: ruthenium chloride complexes (e.g. $HRuCl(PPh_3)_3$), $Ru(acac)_3$ complexes (acac = acetylacetonato), $[Ru(H_2O)_6](OTs)_2$, ruthenium(II)-cyclopentadienyl (Cp) complexes and others.

Expecially this last class of catalysts has been found to be very efficient for the redox isomerization of allylic alcohols, in particular for secondary alcohols. A substituted Cp has been used as ligand by Bäckvall in a dinuclear ruthenium complex (Svho catalyst). This complex isomerizes allylic alcohols at 65 °C in THF.[112a,113,114] Recently, bis(allyl)-ruthenium(IV) complexes have been disclosed by Gimeno *et al.* as the most efficient catalysts for the redox isomerization of allylic alcohols. Moreover, the dicationic ruthenium complex *cis*-$[Ru(6,6'\text{-}Cl_2bipy)_2(H_2O)_2]\cdot(OTf)_2$ has been found highly efficient for this reaction by Lau

and co-workers.[111f] Interestingly, also some osmium complexes were found active in this reaction, namely $H_2Os_3(CO)_{10}$ and the system shown in figure 32.[112]

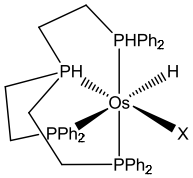


Figure 32

Results & Discussion

Chapter 2

Reduction of carbonyl compounds to alcohols via transfer hydrogenation (TH) and hydrogenation (HY) reactions

Despite the high interest for the asymmetric reduction of ketones,[115,116a] the design of highly productive and easily accessible non chiral catalysts is a current issue of industrial relevance for the synthesis of valuable organic compounds, such as the preparation of primary and rac-secondary alcohols from carbonyl compounds.
Alcohols are extremely important organic compounds which can be used as intermediates for the preparation of alkenes, carboxylic acids, esters, amines. These derivatives exhibit broad applications with particular regard to the food and pharmaceutical industry, as well as for the preparation of perfumes and cosmetics. In the Introduction it was described the synthesis of alcohols by reduction of carbonyl substrates using transition metal complexes in homogeneous phase. In this case, the reducing agents used were molecular hydrogen (H_2), via hydrogenation, and 2-propanol or formic acid, via transfer hydrogenation. A number of homogeneous catalytic systems based on Ru, Rh, Ir, and more recently Os complexes have been developed for the ketone hydrogenation (HY)[15a,116,102] and transfer hydrogenation reactions (TH).[117,118] Among the transition metals used, ruthenium is one of the most studied for the high efficency of its systems in the transfer of hydrogen from 2-propanol to ketones. In addition, the low cost of ruthenium compared to that of rhodium and palladium, allows a wider use in industry. Hydrogen transfer reactions are operatively simple and safe using a hydrogen source such as 2-propanol which is cheap, no toxic and environmentally friendly. Despite the broad use of Ru in TH of ketones, only few catalytic systems with this metal have been described for the transfer hydrogenation of aldehydes, namely some ruthenium phosphane complexes,[102a,119a,120] and chiral arene-amino derivatives.[102a,121] As explained in Chapter 1, the reduction of aldehydes to primary alcohols via TH and the control of the chemoselectivity of this reaction are considered rather difficult processes although the higher redox potentials of aldehydes compared to ketones facilitates the reduction of the RCHO compounds. The difficulty of the catalytic reduction of aldehydes arises from the side reactions that may occur during the catalytic reaction usually performed in basic media.[115]

2.1 Reduction of aldehydes and ketones via transfer hydrogenation (TH) and hydrogenation (HY) reactions

The Ru (II) and Os (II) complexes ***cis***- / ***trans***-**1**[122], ***trans***-**2**, **3** - **5** [89] reported in figure 33 were prepared for the first time in the laboratories of organometallic chemistry of the University of Udine and were found active in the transfer hydrogenation and the hydrogenation of aldehydes and ketones to alcohols. In particular complex ***cis***-**1** was prepared starting from $RuCl_2(PPh_3)_3$, adding 1,1'-bis(diphenylphosphino)ferrocene (dppf) and ampy in toluene at 50 °C to give the derivate of *trans* configuration (***trans***-**1**), isolated in 92 % yield. This complex was then treated with toluene and stirred for 24 h at 120 °C to give ***cis***-**1** (92 % yield) (eq.4).

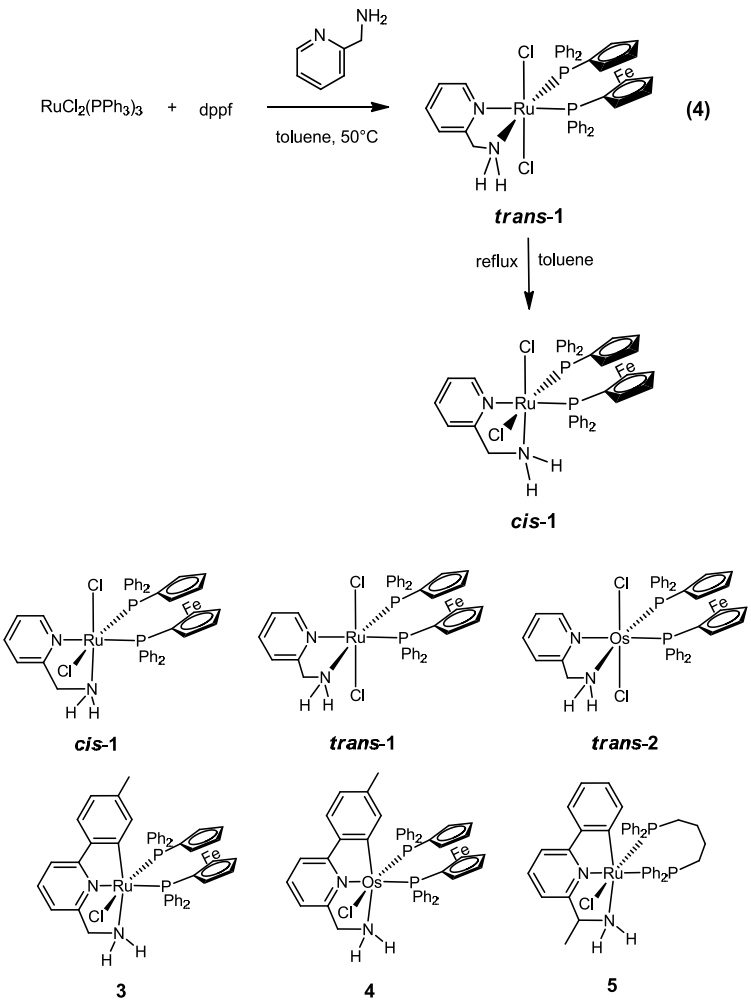


Figure 33

2.1.1 Transfer hydrogenation (TH) of aldehydes and ketones

From previous studies performed in our group it was shown that the activity of the complex RuCl(CNN)[$PPh_2(CH_2)_4PPh_2$] in transfer hydrogenation and hydrogenation reactions is strongly influenced by the base concentration.[85] To optimize the catalytic conditions for transfer hydrogenation of aldehydes to

primary alcohols, the role of the base was investigated using complex ***cis*-1**. It is interesting that the aromatic aldehyde *p*-anisaldehyde has been reduced with NaO*i*Pr without Ru (96 % in 20 h) whereas with the weaker base K_2CO_3 incomplete conversion has been achieved (47 %) (table 1).

Table 1. Influence of the base on the TH of aldehydes (0.1 M) with Ru ***cis*-1** in 2-propanol at reflux temperature

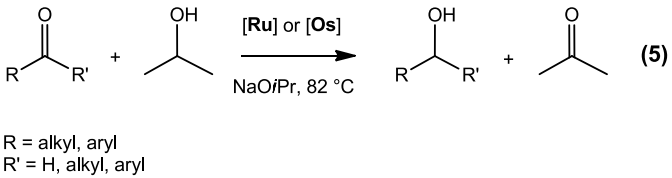
Substrate	***cis*-1** [mol %]	Base	Base conc. [mol %]	Conv. [%][a]	Time [h]
AD-2[b]	-	NaO*i*Pr	2	96	20
	-	K_2CO_3	2	47	20
	0.005	NaO*i*Pr	2	93	1
AD-4[b]	-	NaO*i*Pr	1	3	20
	0.005	NaO*i*Pr	0.5	12	20
	0.005	NaO*i*Pr	1	81	20
	0.005	K_2CO_3	1	9	20
AD-5[b]	0.005	NaO*i*Pr	1	99	10 min
	0.005	K_2CO_3	2	92	20

[a] Conversion into alcohol was determined by GC analysis. [b] For substrate numeration see **figure 34**.

Addition of ***cis*-1** (0.005 mol %), in presence of NaO*i*Pr, efficiently increases the rate of the TH with production of *p*-anisol in 1 h. As regards the aliphatic aldehydes, hexanal in the presence of NaO*i*Pr and without ***cis*-1** is poorly converted to alcohol (3 %) in 20 h. In the presence of ***cis*-1** (0.005 mol %) the conversion was 12 and 81 % (20 h) with 0.5 and 1 mol % of NaO*i*Pr, respectively. The use of K_2CO_3, which is partially soluble, instead of NaO*i*Pr, leads to a lower conversion of alcohol (9 %). With ***cis*-1**, 2-methylbutyraldehyde is rapidly reduced to alcohol in the presence of NaO*i*Pr (99 %) in 10 min, whereas with K_2CO_3 92 % conversion has been attained in 20 h.

These results indicate that while aromatic aldehydes can be reduced in basic 2-propanol, the addition of ***cis*-1** dramatically increases the rate of conversion. By contrast aliphatic aldehydes necessitate the presence of ***cis*-1**, which is activated by NaO*i*Pr, whereas with K_2CO_3 the rate is significantly lower.

On the basis of these considerations and the previous studies, the activity of the complexes **1-5** was studied in TH of aldehydes and ketones in basic 2-propanol (eq. 5).



Quantitative conversion of several carbonyl compounds (figure 34) has been achieved using a catalyst loading of 0.1 - 0.0005 mol % and in the presence of NaO*i*Pr (1 - 2 mol %) at 82 °C (reflux temperature). The results of the TH of aldehydes and ketones with **1** - **5** are shown in table 2, 3 and 4 respectively.

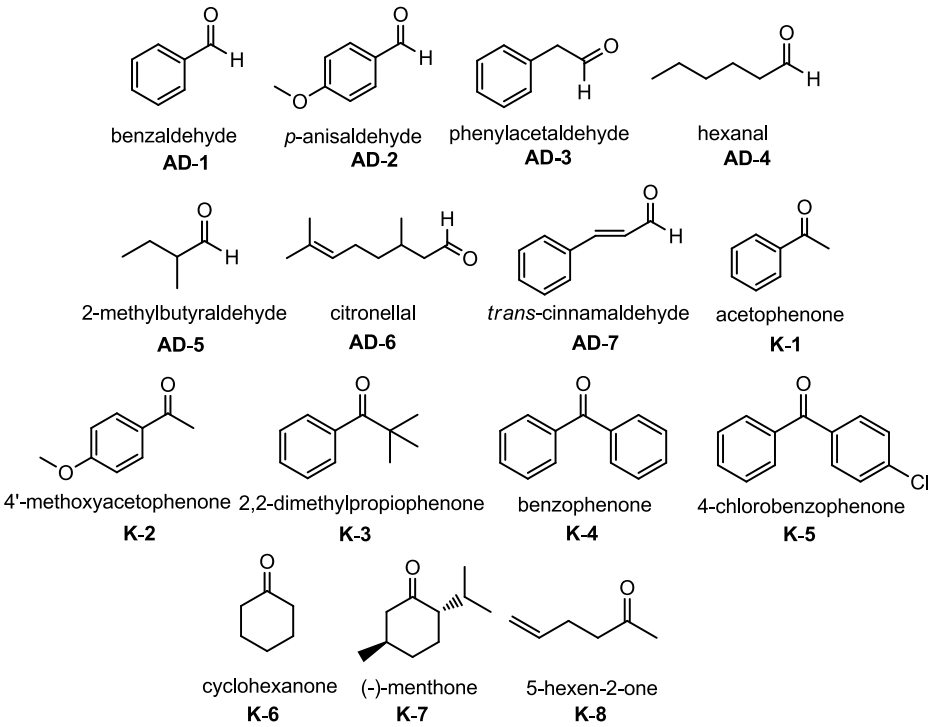


Figure 34

Table 2. TH of aldehydes and ketones (0.1 M) with Ru ***cis*-1** and Os ***trans*-2**, NaO*i*Pr (2.0 mol %) in 2-propanol at reflux temperature

		Catalyst			
		***cis*-1**		***trans*-2**	
Substrate	Catalyst [% mol]	Conv. [%][a] (min)	TOF [h^{-1}][a]	Conv. [%][a] (min)	TOF [h^{-1}][a]
AD-1	0.005	96 (2 h)	2.8×10^4	98 (5)	3.0×10^5
AD-2	0.005	96 (1 h)	5.4×10^4	98 (5)	1.8×10^5
	0.002	92 (4 h)	2.1×10^4		
	0.0005	91 (6 h)	1.8×10^5		
AD-4	0.05[b]	94 (5)	2.6×10^4	98 (30)	6.0×10^3
	0.005[b]	81 (20 h)	9.3×10^3		
AD-5	0.005[b]	99 (10)	1.0×10^5	99 (30)	1.5×10^5
AD-6	0.05[b]	87 (2 h)	2.4×10^3	98 (2 h)	2.6×10^3
AD-7	0.05	95 (30)	1.5×10^4	90 (2 h)	8.9×10^4
	0.005	75 (20 h)	1.8×10^4		
K-1	0.005	93 (30)	8.6×10^4	98 (10)	1.9×10^5
	0.002	92 (20 h)	2.5×10^4		
	0.002	43 (20 h)[c]	-		
K-2	0.1	85 (30)	5.0×10^3	87 (5)	1.0×10^4
K-3	0.05	90 (1 h)	2.2×10^3	91 (1 h)	4.7×10^3
K-4	0.005	96 (2 h)	7.2×10^4	98 (1 h)	7.8×10^4
K-7	0.05	96 (10)[d]	4.6×10^4	96 (10)[e]	4.6×10^4
	0.05	93 (1 h)[c, f]	1.3×10^4		
K-8	0.05	90 (30)	1.8×10^4	98 (5)	4.3×10^4

[a] The conversion and TOF (moles of aldehyde or ketone converted into alcohol per mole of catalyst per hour at 50 % conversion) were determined by GC and NMR analyses. [b] NaO*i*Pr 1.0 mol %. [c] With ***trans*-1**. [d] (+)-neomenthol = 74 %, (-)-menthol = 23 %. [e] (+)-neomenthol = 64 %, (-)-menthol = 32 %. [f] (+)-neomenthol = 59.5 %, (-)-menthol = 33.5 %.

Table 3. TH of aldehydes and ketones (0.1 M) with Ru **3** and Os **4**, NaO*i*Pr (2.0 mol %) in 2-propanol at reflux temperature

		Catalyst			
		3		**4**	
Substrate	Catalyst [% mol]	Conv. [%][a] (min)	TOF [h^{-1}][a]	Conv. [%][a] (min)	TOF [h^{-1}][a]
AD-1	0.005	97 (5)	8.0×10^5	99 (5)	7.8×10^5
AD-2	0.005	95 (2)	1.0×10^6	96 (30 s)	3.6×10^6
	0.002	96 (5)	7.5×10^5	99 (1)	4.5×10^6
	0.0005	98 (20 h)	5.7×10^4		
AD-4	0.05	99 (20 h)	95	99 (20 h)	4.0×10^2
AD-5	0.005	99 (10)	1.0×10^5	99 (30)	9.2×10^4
AD-6	0.05	99 (5)	3.0×10^4	97 (5)	1.0×10^5
AD-7	0.005	98 (3)	6.0×10^5	98 (2)	6.0×10^5
K-1	0.005	98 (10)	3.0×10^5	97 (30)	1.7×10^5
K-2	0.1	86 (30)	5.0×10^3	88 (10)	9.5×10^3
K-3	0.05	98 (2 h)	1.5×10^3	98 (1 h)	9.0×10^3
K-4	0.005	95 (1 h)	3.2×10^4	94 (2 h)	2.1×10^4
K-7	0.05	89 (20 h)[b]	1.2×10^3	87 (20 h)[c]	5.0×10^2
K-8	0.05	99 (5)	4.3×10^4	90 (10)	2.3×10^4

[a] The conversion and TOF (moles of aldehyde or ketone converted into alcohol per mole of catalyst per hour at 50 % conversion) were determined by GC and NMR analyses. [b] (+)-neomenthol 36.5 %, (-)-menthol 52.5 %. [c] (+)-neomenthol = 28 %, (-)-menthol = 59 %.

Table 4. TH of aldehydes and ketones (0.1 M) with Ru **5** and NaO*i*Pr (2.0 mol %) in 2-propanol at reflux temperature

		Catalyst	
		5	
Substrate	Catalyst [% mol]	Conv. [%][a] (min)	TOF [h^{-1}][a]
AD-1	0.005	96 (2)	1.0×10^6
AD-2	0.005	98 (5)	6.8×10^5
AD-4	0.005	72 (48 h)	5.0×10^2
AD-7	0.005	99 (2)	2.4×10^5
K-1	0.005	92 (3)	3.4×10^5
K-4	0.005	91 (1 h)	6.2×10^4
K-7	0.05	99 (1 h)	8.6×10^3[b]

[a] The conversion and TOF (moles of aldehyde or ketone converted into alcohol per mole of catalyst per hour at 50 % conversion) were determined by GC and NMR analyses. [b] (+)-neomenthol = 39.7 %, (-)-menthol = 59.3 %.

With 0.005 mol % of ***cis*-1**, benzaldehyde is efficiently reduced to benzyl alcohol in 2 h, whereas with the pincer systems **3** and **5** the almost quantitative conversion is achieved in only 5 min and 2 min, respectively, with the same catalyst loading. When using 0.005 mol % of catalyst, substrate **AD-2**, *p*-anisaldehyde is reduced in 1 h with ***cis*-1** and in a few minutes with **3** (2 min, TOF = 1.0×10^6 h^{-1}) and **5** (5 min, TOF = 6.8×10^5 h^{-1}). *p*-Anisyl alcohol is also formed using a significantly lower amount (0.0005 mol %) of ***cis*-1** (91 %, 6 h) and **3** (98 %, 20 h).
Interestingly, the osmium ***trans*-2** and **4** (0.005 mol %) displays higher activity for these aromatic aldehydes, leading to quantitative conversion in 5 min with TOF up to 3.0×10^5 h^{-1} in the first case and in 30 s in the second case with TOF up to 3.6×10^6 h^{-1}. In addition, employing 0.002 mol % of **4**, leads to the reduction of the aldehyde in 1 min, affording an impressive high TOF value (4.5×10^6 h^{-1}).
Aliphatic aldehydes, such as hexanal, 2-methylbutyraldehyde are also promptly converted into alcohols using ***cis*-1** and ***trans*-2** (5 - 30 min), while with **3** and **4** complete reduction of hexanal is achieved in 20 h and of 2-methylbutyraldehyde in 10 - 30 min (0.05 - 0.005 mol %, TOF up to 1.5×10^5 h^{-1}). The ruthenium complex **5** displays a lower activity with hexanal, leading to 72 % conversion in 48 h. Under these catalytic conditions, the unsaturated aldehydes (±)-citronellal and *trans*-cinnamaldehyde have selectively been reduced at the C=O bond using ***cis*-1**, ***trans*-2**, **3**, **4**, without hydrogenation or isomerization of the C=C bond, pincer

complexes **3** and **4** (0.05 - 0.005 mol %, TOF up to 6.0×10^5 h^{-1}) being faster compared to the ampy systems ***cis*-1** and ***trans*-2** (0.05 mol %, TOF up to 8.9×10^4 h^{-1}). Also pincer **5** (0.005 mol %) showed high activity in the TH of cinnamaldehyde giving complete conversion in 2 min (TOF = 2.4×10^5 h^{-1}).

These results indicate that ampy and pincer complexes efficiently catalyze the reduction of aldehydes, the pincer complexes displaying a higher rate with respect to the ampy systems in the reduction of aromatic aldehydes, especially with osmium. Moreover the pincer systems **3**, **4**, **5**, display higher activity than the ampy ***cis*-1**, ***trans*-2**, in the reduction of unsaturated aldehydes, while for hexanal the ampy ***cis*-1** and ***trans*-2** gave better results**.**

As regards alkyl aryl ketones, acetophenone, 4'-methoxyacetophenone and the bulkier 2-2-dimethylpropiophenone have also been reduced to secondary alcohols with ***cis*-1** and ***trans*-2** at 0.1 - 0.002 mol %, affording TOF = 10^3 - 10^5 h^{-1}. These ketones have been converted even with the pincer **3** and **4** at the catalytic conditions described above, reaching TOF up to 3.0×10^5 h^{-1}. Interestingly, 2-2-dimethylpropiophenone, having a *tert*-butyl group close to the carbonyl group, has efficiently reduced with ***cis*-1**, ***trans*-2**, **3** and **4**. As a matter of fact, only few systems have been described for the TH of this bulky ketone.

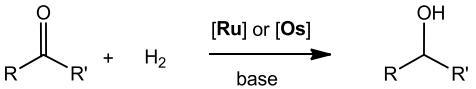
With **5** (0.005 mol %) complete formation of 1-phenylethanol from acetophenone was observed in 3 min, affording TOF = 3.4×10^5 h^{-1}. It is worth noting that the ***cis*-1** and ***trans*-1** isomers display different catalytic activity. As a matter of fact, employment of ***trans*-1** (0.002 mol %) leads to TH of acetophenone with only 43 % conversion after 20 h, whereas ***cis*-1** gives 92 %, indicating that the *cis* diastereoisomer is more active than the *trans* analogue.[69] The diaryl ketone benzophenone has also quantitatively reduced to benzhydrol with ***cis*-1**, ***trans*-2**, **3**, **4**, **5** (0.005 mol %), osmium ***trans*-2** and ruthenium **3** being the most efficient leading to complete conversion in 1 h. Benzhydrol was formed (91 %) also with **5** (0.005 mol %) achieving TOF = 6.2×10^4 h^{-1}.

Interestingly, the cyclic derivative (-)-menthone has rapidly been reduced with the Ru ***cis*-1** (0.05 mol %) in 10 min affording (+)-neomenthol 74 % and (-)-menthol 23 %, while with Os ***trans*-2** formation of (+)-neomenthol 64 % and (-)-menthol 32 % was observed. With the less active ***trans*-1** (0.05 mol %), 93 % of conversion was achieved in 1 h obtaining 60 % of (+)-neomenthol and 34 % of (-)-menthol.

Finally the selective TH of the unsaturated ketone 5-hexen-2-one with the production of 5-hexen-2-ol was performed. No reduction at the C=C was observed as inferred from GC and NMR analyses, ***trans*-2** and **3** displaying higher rate with respect to the corresponding ***cis*-1** and **4**. The ketone 5-hexen-2-one was also reduced with **5** with lower rate compared to the other systems (99 % conversion in 1 h). In summary, the systems **1** - **5** efficiently promote the TH of aldehydes and ketones to alcohols in 2-propanol at 82 °C with high activity and in short time, using a low amount of catalyst (0.1 - 0.005 mol %) and achieving TOF up to 4.5×10^6 h^{-1}.

2.1.2 Hydrogenation (HY) of aldehydes and ketones

The catalysts ***cis*-1** and ***trans*-2** which were found highly efficient in TH of carbonyl compounds, have been tested in HY of aldehydes and ketones at low hydrogen pressure (5 atm) (eq. 6).



(6)

Table 5. HY of carbonylic compounds (0.5 M) with the Ru ***cis*-1** and Os ***trans*-2** (0.1 mol %) under 5 atm H_2

	***cis*-1**[a]			***trans*-2**[b]		
Substrate	T °C	Conv. [%][c] (min)	TOF [h^{-1}][c]	T °C	Conv. [%][c] (min)	TOF [h^{-1}][c]
AD-1	50	99 (10)[d]	7.5×10^4	90	97 (10)	1.0×10^4
AD-2	50	95 (5)[d]	5.0×10^4	90	97 (30)	4.7×10^3
AD-3	50	98 (10)	9.1×10^3	90	91 (8 h)	1.0×10^3
AD-7	50	98 (1 h)[d]	2.8×10^4	90	90 (30)	4.6×10^3
K-1	30	93 (1 h) 94 (20 h)[e]	5.4×10^3 4.5×10^2	90	98 (10)	9.0×10^3
K-2	50	98 (1 h)	7.0×10^3	90	95 (30)	3.7×10^3
K-5	30	95 (5 h)	2.7×10^3	90	97 (30)	4.6×10^3
K-6	50	94 (1 h)	2.5×10^4	90	99 (15)	6.8×10^3
K-7	50	35 (3 h)	-	90	90 (2 h)[f]	3.7×10^3

[a] NaOEt (2 mol %) in ethanol. [b] KO*t*Bu (2 mol %) in methanol / ethanol (3 : 1, v / v). [c] The conversion and TOF (moles of aldehyde or ketone converted into alcohol per mole of catalyst per hour at 50 % conversion) were determined by GC and NMR analyses. [d] Catalyst = 0.02 mol %. [e] Reaction with ***trans*-1**. [f] (+)-neomenthol = 60 %, (-)-menthol = 30 %.

On the basis of the studies of the Ru and Os complexes MCl(CNN)(PP) on the catalytic HY reactions [71,84] it was found that ***cis*-1** (0.1 - 0.02 mol %) rapidly hydrogenates a number of aliphatic and aromatic carbonyl compounds at 30 - 50 °C and in the presence of NaOEt (2 mol %) using ethanol as solvent.

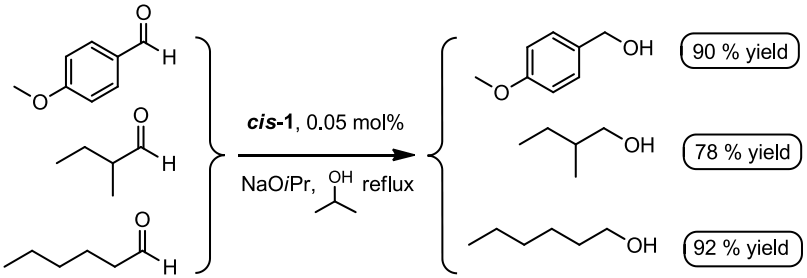
For the osmium ***trans*-2**, the best performances have been achieved at 90 °C with KO*t*Bu (2 mol %) in a methanol / ethanol mixture (3 : 1, v / v).
As shown in table 5, the aromatic aldehydes benzaldehyde and *p*-anisaldehyde are quickly reduced to benzyl alcohol and *p*-anisyl alcohol at 50 °C using 0.02 mol % of ***cis*-1** in 10 and 5 min (TOF = 7.5×10^4 and 5.0×10^4 h^{-1}, respectively). With the osmium ***trans*-2** (0.1 mol %) quantitative conversion to alcohols has been achieved at 90 °C in 10 and 30 min (TOF up to 1.0×10^4 h^{-1}). Phenylacetaldehyde is efficiently converted into 2-phenylethanol (98 % in 10 min) using ***cis*-1** (0.1 mol %), whereas with the osmium ***trans*-2** at 90 °C, 91 % conversion is achieved after 8 h (85 %). Interestingly, the aromatic unsaturated aldehyde *trans*-cinnamaldehyde, is reduced with ***cis*-1** (0.02 mol %) at 50 °C in 60 min (TOF = 2.8×10^4 h^{-1}) and with **2** (0.1 mol %) at 90 °C, with no hydrogenation at the C=C bond.
In the HY of ketones, the ruthenium ***cis*-1** efficiently catalyzes the reduction of acetophenone, 4'-methoxyacetophenone and 4-chlorobenzophenone in 1 - 5 h (93 - 98 %). It is worth nothing that ***cis*-1** leads to 1-phenylethanol (93 %) in 1 h, whereas analogous *trans*-[$RuCl_2$(dppf)(ampy)] (***trans*-1**), displays a lower activity, with 94 % conversion in 20 h, under the same catalytic conditions. With osmium ***trans*-2** quantitative HY of these ketones has been achieved in 10 - 30 min at 90 °C (TOF up to 9.0×10^3 h^{-1}). As regards cyclic ketones, cyclohexanone was reduced to cyclohexanol with ***cis*-1** at 50 °C in 1 h, whereas with ***trans*-2** the reaction was completed after only 15 min at 90 °C. Because of the interest for (-)-menthol, the ketone (-)-menthone has also been reduced via HY. With ***cis*-1** at 50 °C poor conversion is attained (35 % in 3 h), whereas the osmium ***trans*-2** leads to 90 % conversion in 2 h at 90 °C, giving (+)-neomenthol / (-)-menthol = 2.
These data agree with those found for the TH and suggest that osmium is a valid complement to ruthenium for both HY and TH reactions, osmium generally requires a higher temperature with respect to Ru and it remains active at high temperature on account of the stronger bonding.

2.2 Application of TH and HY in food, chemical and pharmaceutical industry

2.2.1 Preparation and isolation of alcohols and esters of interest

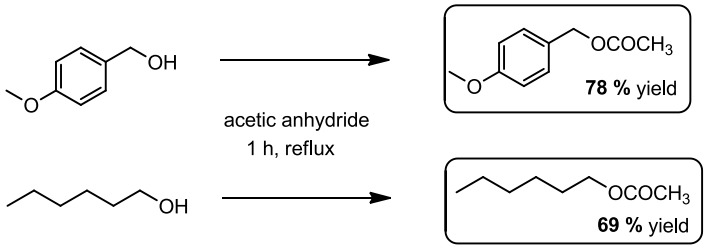
The employment of Ru and Os catalysts ***cis*-1**, ***trans*-2**, **4** in TH and HY reactions, allowed the synthesis and isolation in good yield of a series of primary alcohols and esters of biological relevance and of interest in food industry, starting from aldehydes. The simplicity of this approach, as described below, makes TH and HY useful alternative methods to the use of reducing agents such as $NaBH_4$, $LiAlH_4$ and $Al(OC_3H_7)_3$ (Meerwein-Ponndorf-Verley reaction) widely used in industry. By employment of *p*-anisaldehyde, 2-methylbutanal and hexanal with ***cis*-1**, *p*-anisyl alcohol, 2-methyl-1-butanol and hexyl alcohol were obtained via TH in good yield

on a gram scale. The procedure for the reduction of these aldehydes to the corresponding alcohols via TH consists in refluxing a solution containing the aldehyde (0.28 M), ***cis*-1**, and NaO*i*Pr, in 2-propanol (substrate / catalyst = 2000 / 1). Starting from and 1.70 mL of *p*-anisaldehyde, 1.50 mL of 2-methylbutyraldehyde and 1.72 mL of hexanal, using 5.8 mg of ***cis*-1**, complete conversion to alcohol was observed in 30 minutes achieving after filtration and evaporation of the solvent, 90 % yield of *p*-anisyl alcohol (1.74 g), 78 % yield of 2-methyl-1-butanol (0.96 g), 92 % yield of 1-hexanol (1.31 g) (scheme 6).



Scheme 6

By employment of the isolated *p*-anisyl and hexyl alcohols, the corresponding acetates were synthesized by esterification with acetic anhydride at reflux temperature for 1 h (scheme 7). Anisyl acetate (1.77 g) and hexyl acetate (1.28 g) were obtained with this procedure with 78 % and 69 % yield respectively after elimination of the acetic anhydride via distillation.



Scheme 7

The high purity of anisyl acetate has been inferred from NMR analysis. The ^{1}H and ^{13}C NMR spectra of the isolated ester are shown in figure 35.

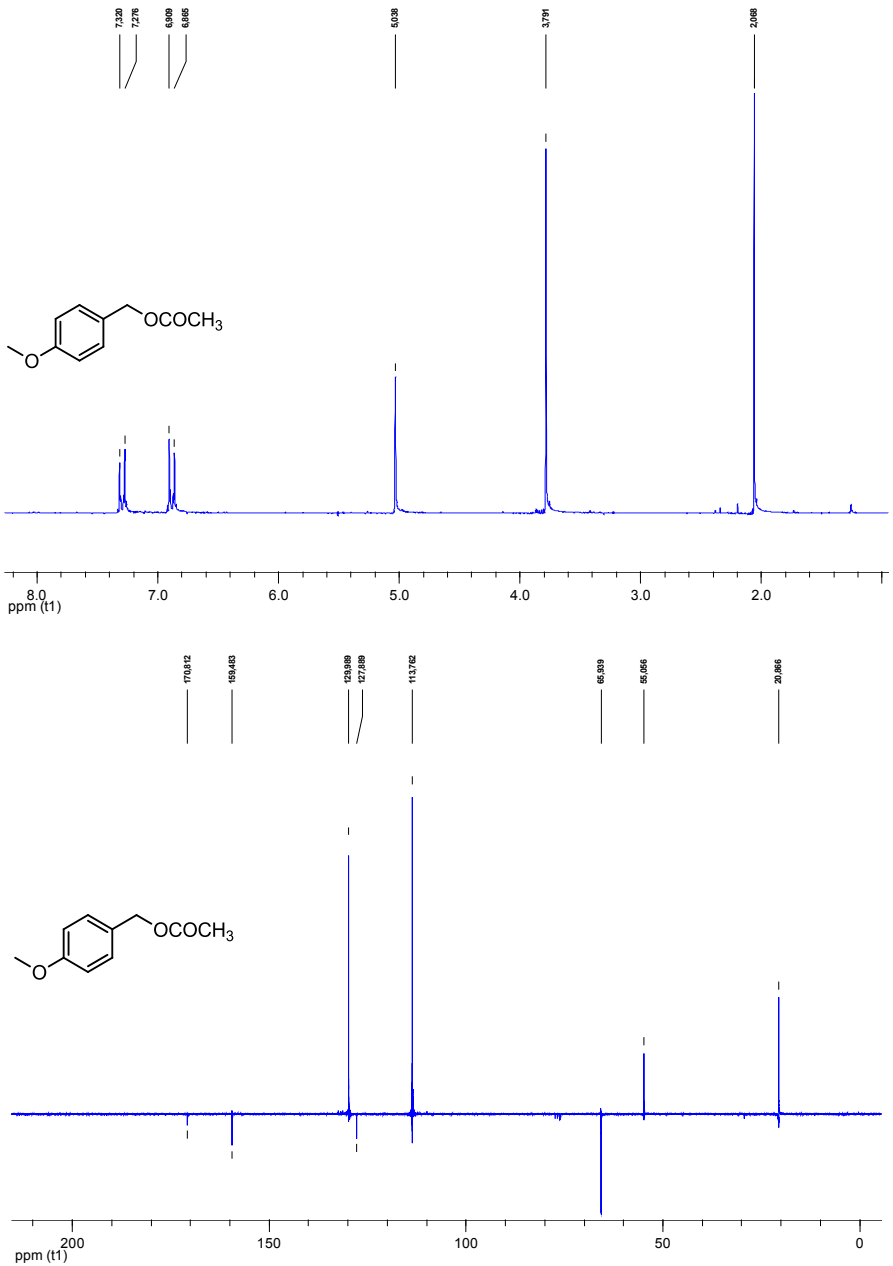


Figure 35. ^{1}H and ^{13}C NMR spectrum of the isolated anisyl acetate in $CDCl_3$

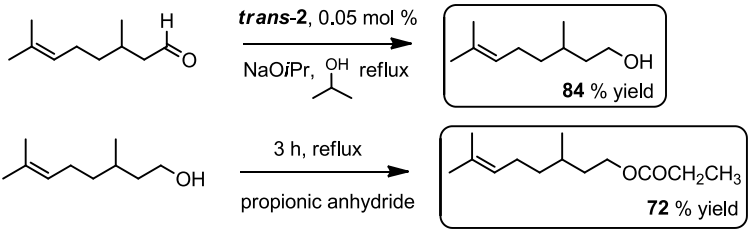
Anisyl acetate has a floral, fruit-like pleasant odor (vanilla, plum) and a slight pungent, sweet fruity taste. It is also a cosmetic perfuming agent while hexyl acetate is widely employed as a solvent for resins, polymers, fats, oils, and as a paint additive. Hexyl acetate has a pleasant fruity, apple, cherry, pear, floral odor and a bittersweet taste suggestive of pear. Both esters, naturally presents in fruits, can be used in fruit aroma compositions for confectionery and beverages.[12,39]
In order to measure the metal concentration in the final esters, the isolated anisyl acetate has been analyzed through ICP measurements.
The starting *p*-anisyl alcohol obtained with ***cis*-1** (5.8 mg), has been filtered following two different procedures. According to the first method, the alcohol has been filtered over a short column filled with 2 cm of silica and the Ru concentration value checked in the final sample of anisyl acetate was 152 ppm. In the second procedure, a short column filled with 10 cm of silica was employed for filtration achieving 1.7 ppm of Ru in the final sample (table 6). This last data represents an interesting result because the limit of oral intake for Ru and Os is generally about 5 ppm. Thanks to the good result achieved, this filtration procedure has been used for isolation of the alcohols described in this PhD thesis.

Table 6. Measurements of the Ru concentration (ppm) in the isolated anisyl acetate

Method	Average[a] Ru [ppm]	σ[a]	S. E.[a]
1	152	0.005	0.003
2	1.7	0.002	0.001

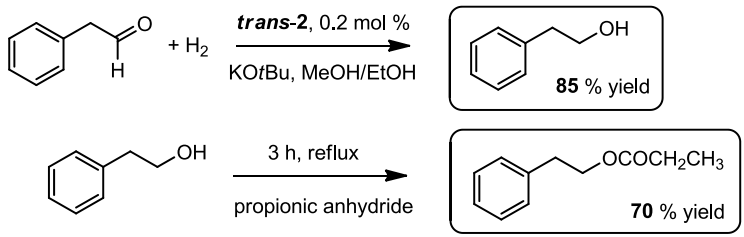
[a]Average concentration value (ppm), standard deviation (σ) and standard error (S. E.) were calculated on three measurements on the mineralized sample by ICP analysis

Following the procedure described for the preparation of alcohols with ***cis*-1** via TH, using ***trans*-2** (6.5 mg), which showed high activity in the TH of (±)-citronellal, 1.84 g of (±)-β-citronellol (84 % yield) has been obtained after 2 h starting from 2.52 mL of (±)-citronellal (substrate / catalyst = 2000 / 1). Similarly, 1.92 g of (*S*)-(-)-β-citronellol (88 % yield) has been prepared from 2.54 mL of (*S*)-(-)-citronellal with **4** (6.8 mg).
By reacting the isolated (±)-citronellol with propionic anhydride at reflux temperature, citronellyl propionate (1.10 g) has been synthesized in 3 h and isolated in 72 % yield (scheme 8). This ester, with a rose-like odor and a bitter-sweet, plum-like taste, can be used as flavoring agent in baked goods, beverages, candies and ice creams.



Scheme 8

These procedures showed that catalytic transfer hydrogenation is a valid method for the small and medium scale synthesis of alcohols and esters of wide interest for the food, agrochemical and pharmaceutical industry under mild reaction conditions, without employment of hazardous reducing agents.
Finally, in order to show the potential of the catalytic hydrogenation for synthetic applications, 1.04 g of 2-phenylethanol (85 % yield) has been prepared with 18.5 mg of ***trans*-2**, from 1.16 mL of phenylacetaldehyde (substrate / catalyst = 500 / 1) The reaction has been carried out in a MeOH / EtOH (3 : 1 in volume) with KO*t*Bu as co-catalyst in a thermostated reactor at 90 °C for 8 h, under 5 atm H_2. After isolation, 2-phenylethanol has been refluxed with propionic anhydride affording phenethyl propionate (1.06 g, 70 % yield) in 3 h according to the procedure previously described (scheme 9).



Scheme 9

2.2.2 Synthesis of other relevant alcohols

As regards other interesting alcohols quantitatively and quickly obtained via catalytic TH and HY reactions that can be easily isolated by the procedure described above, benzyl alcohol is used in fragrance and flavor compositions mainly as a solvent and for dilution. It is the staring material for a large number of benzyl esters which are important fragrance and fruity flavor substances. *trans*-

Cinnamyl alcohol is an aromatic component of many flowers (lilac, hyacinth, lily) and a widely used flavoring for its cinnamon notes and rounding off fruit aromas. Moreover several cinnalyl esters, such as cinnamyl acetate, are valuable fragrance materials employed in food industry.[12,39]

It also known that 1-phenylethanol is used in perfumery for its rose notes and mainly for the production of its esters some of which are food additives such as α-methylbenzyl acetate with a floral and fruity aroma. Finally, benzhydrols are widely used as intermediates for the synthesis of valuable pharmaceutical products.[44]

In conclusion, (-)-menthone has been quantitatively converted with high activity to menthols, alcohols of great importance for their applications in food, pharmaceutical industry and cosmetics, by catalysts **1** - **5** via TH and HY. Menthol has eight possible stereoisomers, but the main form occurring in nature is (-)-menthol which has the typical cooling / refreshing effect, thus the separation of (-)-menthol from the other isomers is high appealing.

Chapter 3

Asymmetric reduction of ketones to chiral alcohols

The synthesis of chiral substances in the enantiomerically pure form has been extensively studied in the last years, since these compounds are widely used in food, pharmaceutical and agrochemical industry. Asymmetric reduction of prochiral ketones for the synthesis of optical active alcohols is one of the most researched areas in homogeneous catalysis.
Among the catalytic methods available for the accomplishment of this transformation, enantioselective hydrogenation with molecular H_2 (HY) and transfer hydrogenation (TH) are continuously being developed and represent a current subject of industrial and academic research.
In this section the activity of new ruthenium(II) and osmium(II) catalysts prepared with new chiral pincer HCNN ligands and chiral Josiphos diphosphines has been investigated.
These compounds were used to prepare the *in situ* systems of general formula MCl(CNN)(Josiphos) for the TH of acetophenone in basic 2-propanol. On account of the high performance of the HCNN ligand containing the 2-naphthyl moiety, the corresponding Ru and Os complexes, showing the correctly matched chiral ligands, were isolated.
These catalysts have proven to catalyze the enantioselective TH of alkyl aryl ketones to obtain alcohols of interest with low loading (0.005 mol %), high rate (TOF $\approx 10^5$ - 10^6 h^{-1}), and up to 99 % *ee*.

3.1 Chiral HCNN ligands

Recently, excellent results were obtained in the asymmetric reduction of prochiral ketones catalyzed by Ru(II) and Os(II) complexes using achiral CNN-pincer and chiral diphosphines, via hydrogenation and transfer hydrogenation reactions, with excellent productivity (TOF up to 10^5 h^{-1}) and enantioselectivity (*ee* up to 99 %). Based on the high activity of the MCl(CNN)(PP) complexes, the design of new chiral pincer ligands of the HCNN type (figure 36) was performed by the group of F. Benedetti and F. Felluga of the Department of Chemistry of the University of Trieste, displaying different steric and electronic properties in order to investigate their effect on the formation of the MCl(CNN)(PP) complexes (M = Ru / Os) and in the catalytic activity. The new pincer CNN ligands show different aryl substituents at the position 6 of the pyridine groups namely functionalized ranged from 1-phenyl (**1b - 1e**) and 2-naphtyl (**1f**, **1g**) groups. In the laboratories of organometallic chemistry of the University of Udine we prepared new Ru(II) and Os(II) catalysts with these ligands and commercially available chiral diphosphines, by matching the correct combination of the disphosphines and of the pincer ligands to achieve highly efficient catalytic systems.

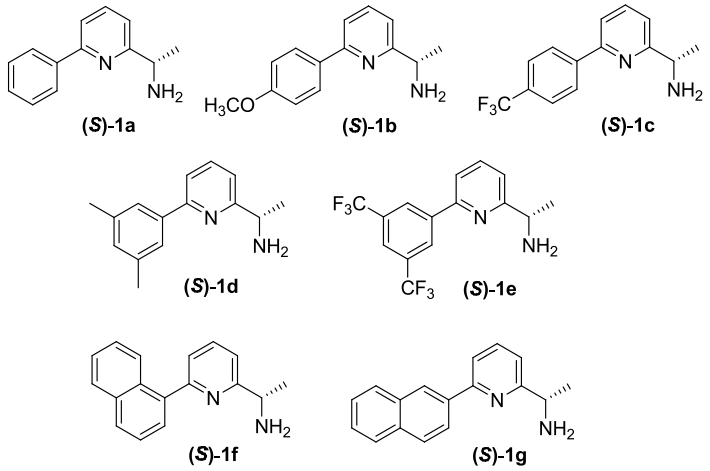
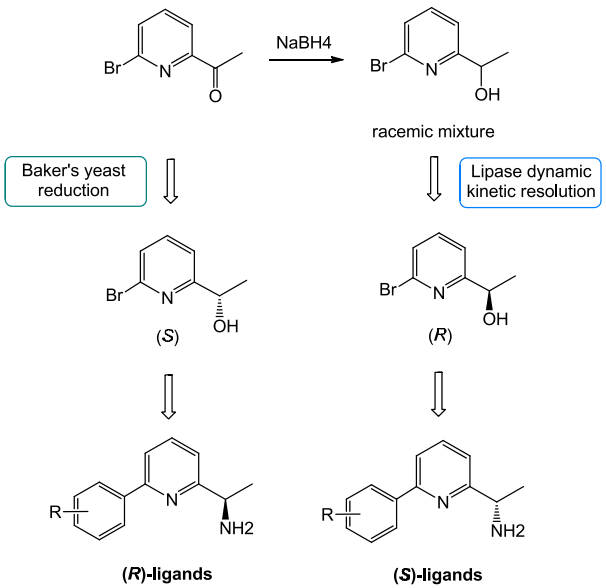


Figure 36. Chiral HCNN ligands (*S*)-**1a - 1g**

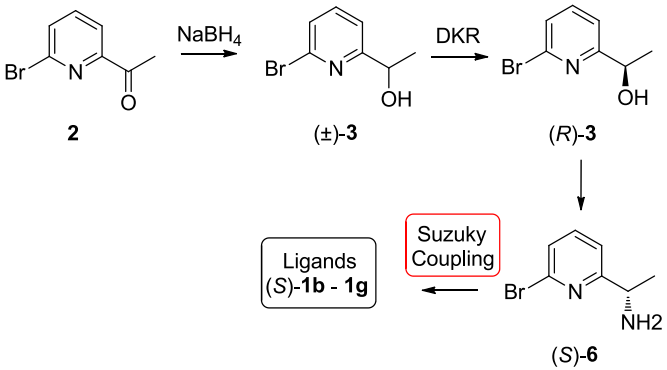
The synthesis of pyridyl ligands with a chiral center directly attached to the heterocyclic ring is fundamental to achieve high enantioselectivity and is a challenging topic that has widely been explored.[123]
In the Indroduction has been described that enantiomerically pure secondary alcohols can be efficiently obtained by lipase-catalyzed resolution of the corresponding racemic mixtures[34c,32] and by the asymmetric reduction of prochiral ketones with isolated dehydrogenases[124] or with baker's yeast (*Saccharomyces cerevisiae*) (scheme 10).[36]



Scheme 10. General strategy for the synthesis of chiral not racemic pincer ligands

Lipases are very flexible enzymes for their wide acceptance of structurally different substrates and their ability to retain their activity and selectivity also in no conventional media, such as organic solvents,[125a] and ionic liquids.[125b] Specifically, lipase B from *Candida antarctica* (CAL-B) has shown a quite general enantioselectivity toward linear and benzylic secondary alcohols,[126] and the origin of this behavior has been fully explained from the knowledge of the protein structure.[35]

As outlined in scheme 11, the HCNN ligands **1b** - **1g** of *S* configuration were obtained in excellent enantiomeric excess, starting from the commercial 2-acetyl-6-bromopyridine. It is worth noting that the phenyl derivative (*S*)-**1a** was prepared via DKR, starting from 2-(1-hydroxyethyl)-6-phenylpyridine and amination of the chiral alcohol.[127]

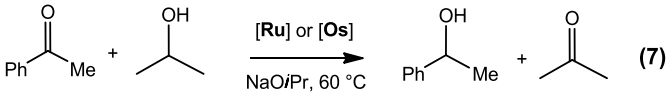


Scheme 11. Synthesis of optically active HCNN pincer ligands (*S*)-**1b** - **1g**

The (*R*)-2-(1-hydroxyethyl)-6-bromopyridine [(*R*)-**3**] was first obtained in the enantiodifferentiating step by the lipase mediated dynamic kinetic resolution (DKR) of *rac*-**3**. As a matter of fact, *Candida antarctica* lipase B (CAL-B) dispays high enantioselectivity in the acetylation of 2-pyridyl alcohols.[128] Based on the wide literature reported on this topic,[28,29] the dynamic kinetic resolution of racemic 6-bromo-1-(2-pyridyl)ethanol (±)-**3**, obtained by $NaBH_4$ reduction of 2-acetyl-6-bromopyridine (**2**), was run combining CAL-B mediated enzymatic acetylation with the *in situ* racemization of the slow reacting enantiomer catalyzed by the Ru redox catalyst $[Ru_2(CO)_4(\mu\text{-}H)(C_4Ph_4\text{-}COHOCC_4Ph_4)]$ (Shvo's catalyst). In this application CAL-B was used immobilized on Polyacrylamide (Novozyme® 435) in order to obtain best performance.
The enantiomerically pure alcohol (*R*)-**3** was then transformed into the amine (*S*)-**6** with inversion of configuration. Amine (*S*)-**6** was the common intermediate for the synthesis of all ligands (*S*)-**1b** - **1g**, which were obtained in good overall yield and enantiomeric excess by the Suzuki coupling of **6** with the appropriate arylboronic acid.

3.2 Asymmetric transfer hydrogenation (TH) of ketones

In order to investigate the stereoelectronic effects of the substituents of the pincer ligand in the asymmetric TH we have prepared *in situ* ruthenium and osmium catalysts with the ligands (*S*)-**1b** - **1g**, containing one or two electron donating *vs* electron withdrawing groups on the aryl moiety. These systems of general formula MCl(CNN)(PP) (M = Ru, Os; PP = Josiphos diphosphine), have been employed in the transfer hydrogenation (TH) of acetophenone in basic 2-propanol at 60 °C with 0.005 mol % of catalyst (eq. 7).



(7)

The *in situ* generated pincer complexes were obtained by refluxing a 2-propanol solution of $MCl_2(PPh_3)_3$ (M = Ru, Os) with a Josiphos diphosphine (1 h) and a (*S*) pincer ligand (1 h). To study the matched / mismatched ligand effect, the *in situ* prepared catalytic system generated from $RuCl_2(PPh_3)_3$, (*S,R*)-Josiphos* and (*S*)-**1a**, was employed in the asymmetric transfer hydrogenation of acetophenone, affording quantitatively (*S*)-1-phenylethanol with 75 % *ee*. By contrast the use of the other diphosphine enantiomer (*R*,*S*)-Josiphos* led to the *R* alcohol in 30 min with a higher rate and enantioselectivity (TOF = 1.6×10^5 h^{-1}, 92 % *ee*) (table 7), indicating that (*R*,*S*)-Josiphos* and (*S*)-**1a** is the correctly matched combination of the chiral ligands, in agreement with the results obtained with the related *cis*-$[RuCl_2$(Josiphos)(R-ampy)$]$[69c] complexes.

Table 7. Catalytic TH of acetophenone (0.1 M) with the system $RuCl_2(PPh_3)_3$ / (*R*,*S*)-Josiphos* / HCNN ligand (Ru = 0.005 mol %) and NaO*i*Pr (2 mol %) in 2-propanol at 60 °C

HCNN ligand	Conv. [%][a]	Time [min]	TOF [h^{-1}][b]	*ee* [%][a]
(*S*)-**1a**	98	30	1.6×10^5	92 *R*
(*S*)-**1b**	97	30	1.3×10^5	86 *R*
(*S*)-**1c**	95	30	6.5×10^4	85 *R*
(*S*)-**1d**	27	120	-	84 *R*
(*S*)-**1e**	4	60	-	-
(*S*)-**1f**	95	60	6.5×10^4	85 *R*
(*S*)-**1g**	98	30	1.5×10^5	92 *R*

[a] The conversion and *ee* were determined by GC analysis. [b] Turnover frequency (moles of ketone converted to alcohol per mole of catalyst per hour) at 50 % conversion.

It is worth noting that (*R*,*S*)-Josiphos*, containing 4-OMe was used in all experiments since it leads to a better enantioselectivity with respect to the less bulky (*R*,*S*)-Josiphos bearing the Ph substituents (figure 37).

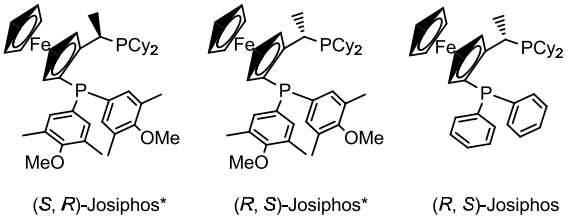


Figure 37. The chiral Josiphos diphosphine employed

The *in situ* ruthenium catalysts formed with (*S*)-**1b** and (*S*)-**1c** with OMe and CF_3 in the *para* position respectively, gave complete reduction of acetophenone (30 min) with TOF = 1.3×10^5 and 6.5×10^4 h^{-1} with 86 and 85 % *ee* respectively, suggesting that the presence of a group in the *para* position decreases slightly the enantioselectivity, whereas the electron-withdrawing CF_3 group results in a decrease of the activity of the catalyst.
Employment of the 3,5-disubstituted Me and CF_3 ligands (*S*)-**1d** and (*S*)-**1e**, gave 27 and 4 % conversion, indicating that the presence of two groups in the 3 and 5 positions affords less active systems, possibly inhibiting the *ortho*-metalation, thus affecting the productivity. Interesting results were obtained with the ligands (*S*)-**1f** and (*S*)-**1g**, containing the 1-naphthyl and 2-naphthyl moieties bound to the pyridine ring, resulting in the quantitative conversion of acetophenone with TOF = 6.5×10^4 and 1.5×10^5 h^{-1} and 85 and 92 % *ee*. These data suggest that in both cases *ortho*-metalation occurs, the 2-substituted ligand affording the best performance in terms of rate and enantioselectivity.
The effect of the substituents on the ligands (*S*)-**1a** - **1g** was explored also with the osmium precursor $OsCl_2(PPh_3)_3$ and we observed a trend similar to that found for ruthenium. The *in situ* generated complexes, prepared by refluxing a 2-propanol solution of $OsCl_2(PPh_3)_3$ with (*R*,*S*)-Josiphos* (1.5 h) in combination with the pincer ligands (1 h), namely the phenyl (*S*)-**1a**, the *para* methoxyphenyl (*S*)-**1b** and the 1-naphthyl (*S*)-**1f** ligands gave good values of rate (6.6×10^4 to 1.5×10^5 h^{-1}) and enantioselectivity (81 and 83 % *ee* respectively) in the TH of acetophenone (table 8).

Table 8. Catalytic TH of acetophenone (0.1 M) with the system $OsCl_2(PPh_3)_3$ / (*R*,*S*)-Josiphos* / HCNN ligand (Os = 0.005 mol %) and NaO*i*Pr (2 mol %) in 2-propanol at 60 °C

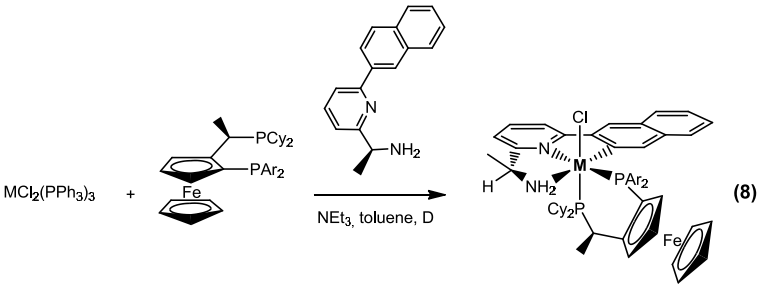
HCNN ligand	Conv. [%][a]	Time [min]	TOF [h^{-1}][b]	*ee* [%][a]
(*S*)-**1a**	96	30	1.5×10^5	83 *R*
(*S*)-**1b**	96	30	1.2×10^5	85 *R*
(*S*)-**1c**	76	120	6.0×10^4	83 *R*
(*S*)-**1d**	39	120	-	75 *R*
(*S*)-**1e**	8	60	-	-
(*S*)-**1f**	70	120	6.6×10^4	81 *R*
(*S*)-**1g**	96	30	1.5×10^5	87 *R*

[a] The conversion and *ee* were determined by GC analysis. [b] Turnover frequency (moles of ketone converted to alcohol per mole of catalyst per hour) at 50 % conversion.

As for ruthenium, the 2-naphthyl ketone (*S*)-**1g** shows the best performance with TOF = 1.5×10^5 h^{-1} and 87 % *ee*. Comparing the ligands **1f** and **1g** which have similar electronic properties but a different orientation of the naphthylic substituent, **1g** gave the most productive and selective Ru and Os complexes, which displayed the highest TOF (1.5×10^5 h^{-1} in each cases) and gave the products with the highest enantiomeric excesses (92 % *ee* for Ru, 87 % *ee* for Os). Moreover, the variation of the geometric requirements going from **1f** to **1g** had a stronger effect on the Os complexes. The ligand (*S*)-**1c**, containing the electron withdrawing group CF_3, led to lower rate and conversion (76 %) in 2 h, whereas the disubstituted methyl and CF_3 ligands (*S*)-**1d** and (*S*)-**1e** gave incomplete conversion of acetophenone (39 and 8 %, respectively) as observed for ruthenium, suggesting that also in this case the presence of two substituents in the 3,5 positions may hinder the *ortho*-metalated reaction. Both Ru(II) and Os(II) complexes with ligand **1b**, bearing the strong electron releasing methoxy group, afforded the reduction of acetophenone with a significantly higher rate with respect to the analogous complexes with the ligand **1c** showing the electron-withdrawing CF_3 group.

On the basis of the good results achieved with the *in situ* prepared metal catalysts obtained from (*R*,*S*)-Josiphos* in combination with the 2-naphthyl ligand (*S*)-**1g**, the corresponding ruthenium and osmium complexes were isolated (eq. 8) and

investigated in the transfer hydrogenation reaction of different prochiral ketones (figure 38). Catalysts **6** - **8** have been prepared for the first time by the group of organometallic chemistry of the University of Udine, by treatment of $MCl_2(PPh_2)$ with Josiphos* and (*S*)-**1g** in toluene and in the presence of NEt_3.[71e]



(8)

	M	Ar
6	Ru	4-OMe-3,5-$Me_2C_6H_2$
7	Os	Ph
8	Os	4-OMe-3,5-$Me_2C_6H_2$

The model substrate acetophenone is rapidly and quantitatively converted into (*R*)-1-phenylethanol in 2-propanol at 60 °C using **6**, **7** and **8** (0.005 mol %) and in the presence of NaO*i*Pr (2 mol %), achieving *ee* = 92, 89, 91 % and TOF = 1.2×10^5 - 3.2×10^5 h^{-1} (table 9).

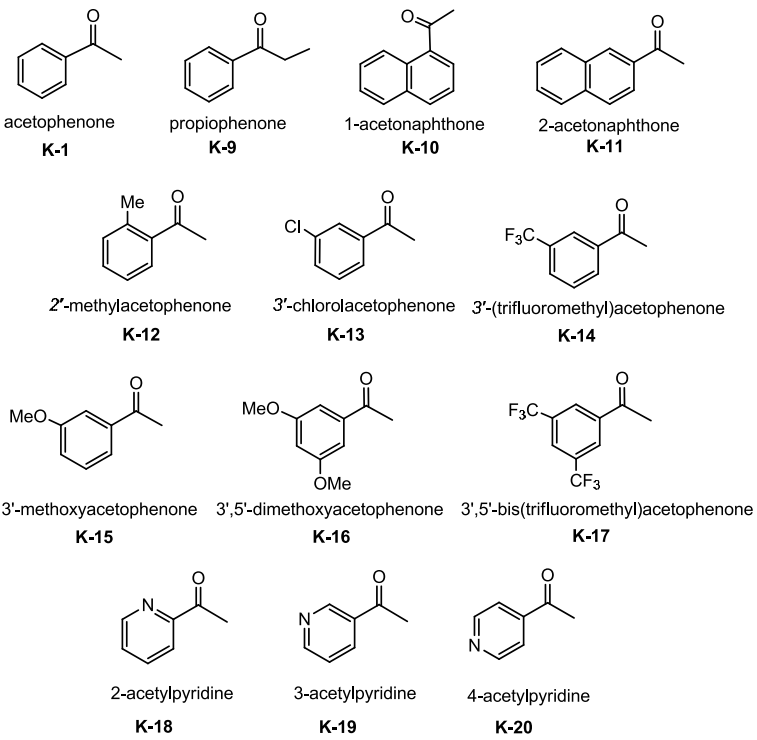


Figure 38

Table 9. Catalytic TH of acetophenone, **K-1**, (0.1 M) with the complexes **6** - **8** (0.005 mol %) NaO*i*Pr (2 mol %) in 2-propanol at 60 °C

Complex	Conv. [%][a]	Time [min]	TOF [h^{-1}][b]	*ee* [%][a]
6	95	30	1.2×10^5	92 *R*
7	96	30	2.5×10^5	89 *R*
8	97	30	3.2×10^5	91 *R*

[a] The conversion and *ee* were determined by GC analysis. [b] Turnover frequency (moles of ketone converted to alcohol per mole of catalyst per hour) at 50 % conversion.

These data show that the osmium complexes **7** and **8** are faster compared to the ruthenium **6**, indicating that the formation of the catalytically active osmium species is a rapid process. In addition, the complex **8** with the bulkier (*R*,*S*)-Josiphos* respect to the complex **7**, shows both higher *ee* and rate. On account of the good results obtained using (*R*,*S*)-Josiphos*, the systems **6** and **8** were employed in the reduction of a range of alkyl aryl ketones using 0.005 mol % of catalyst and their activity has been compared (table 10).

Table 10. Catalytic TH of ketones (0.1 M) with the system **6** (0.005 mol %), NaO*i*Pr (2 mol %) in 2-propanol

Ketones	Conv. [%][a]	T [°C]	Time [min]	TOF [h^{-1}][b]	*ee* [%][a]
K-9	90	60	120	7.7×10^4	99 *R*
K-10	98[c]	60	30	4.7×10^4	96 *R*
K-11	96	60	30	1.6×10^5	93 *R*
K-12	80[c]	60	60	2.5×10^4	96 *R*
K-13	99	60	30	1.3×10^5	99 *R*
K-13	99	82	5	8.4×10^5	99 *R*
K-14	99	60	30	2.6×10^5	96 *R*
K-15	96	60	60	9.0×10^4	94 *R*
K-16	97	60	30	2.1×10^5	95 *R*
K-16	97	82	2	1.8×10^6	91 *R*
K-17	99[c,d]	60	60	1.9×10^4	98 *R*
K-18	93	60	60	3.9×10^4	86 *R*
K-19	99[d]	60	30	6.6×10^4	92 *R*
K-20	99[c,d]	60	10	1.2×10^5	97 *R*

[a] The conversion and *ee* were determined by GC analysis. [b] Turnover frequency (moles of ketone converted to alcohol per mole of catalyst per hour) at 50 % conversion. [c] Substrate / **6** / NaO*i*Pr = 10000 / 1 / 200. [d] *In situ* reaction.

Propiophenone **K-9** has been reduced to (*R*)-1-phenylpropan-1-ol with 99 % *ee* and TOF = 7.7×10^4 h^{-1}, whereas the 1-acetonaphthone **K-10** and 2-acetonaphthone **K-11** are converted into the corresponding (*R*)-alcohols with 96 and 93 % *ee* and TOF = 4.7×10^4 and 1.6×10^5 h^{-1}, respectively. The *ortho* methyl acetophenone **K-12** and the *meta* substituted Cl, CF_3 and OMe derivatives **K-13**, **K-14** and **K-15** are promptly reduced to (*R*)-alcohols with both high TOF (2.5×10^4 to 2.6×10^5 h^{-1}) and enantioselectivity (94 - 99 % *ee*). Only 5 min occurs for the reduction of the ketone **K-20** at 82 °C with remarkably high rate (TOF = 8.4×10^5 h^{-1}) and without erosion of *ee* (99 %). At 60 °C, also the 3,5-disubstituted ketones **K-16** and **K-17** have quickly been converted into (*R*)-alcohols with TOF up to 2.1×10^5 h^{-1} and 95 and 98 % *ee*. At 82 °C the derivative **K-16** undergoes a rapid reduction (2 min) with very high TOF (1.8×10^6 h^{-1}) and a lower enantioselectivity (91 % *ee*). Heterocyclic ketones, such as 2, 3 and 4-pyridylmethylketones **K-18** - **20**, have been converted quantitatively at 60 °C into the (*R*)-pyridyl alcohols with TOF in the range 3.9×10^4 to 1.2×10^5 h^{-1} and 86, 92 and 97 % *ee*, respectively. Attempts to reduce more sterically demanding ketones such as 2-methyl-1-phenylpropan-1-one, or dialkyl ketones, such as 2-decanone or 1-esen-2-one, resulted in low alcohol conversion (< 10 %). In the same catalytic conditions, the osmium derivative **8** promotes asymmetric TH of **K-9** with the same enantioselectivity (99 % *ee*) observed for ruthenium and a higher rate (TOF = 1.4×10^5 h^{-1}) (table 11).

Table 11. Catalytic TH of ketones (0.1 M) with the system **8** (0.005 mol %), NaO*i*Pr (2 mol %) in 2-propanol

Ketones	Conv. [%][a]	T [°C]	Time [min]	TOF [h^{-1}][b]	*ee* [%][a]
K-9	93	60	30	1.4×10^5	99 *R*
K-10	98[c]	60	30	5.9×10^4	96 *R*
K-11	97	60	10	3.4×10^5	99 *R*
K-12	93[c]	60	60	5.9×10^4	94 *R*
K-13	97	82	5	4.8×10^5	99 *R*
K-14	99	60	20	1.8×10^5	94 *R*
K-15	97	60	30	2.0×10^5	99 *R*
K-16	97[d]	82	10	9.0×10^5	97 *R*
K-17	99[c,e]	60	30	5.1×10^4	98 *R*
K-18	99	60	30	1.2×10^5	91 *R*
K-19	99[e]	60	30	7.6×10^4	90 *R*
K-20	99[c,e]	60	10	8.3×10^4	97 *R*

[a] The conversion and *ee* were determined by GC analysis. [b] Turnover frequency (moles of ketone converted to alcohol per mole of catalyst per hour) at 50 % conversion. [c] Substrate / **8** / NaO*i*Pr = 10000 / 1 / 200. [d] Substrate / **8** / NaO*i*Pr = 50000 / 1 / 1000. [e] *In situ* reaction.

The naphthyl substrates **K-10** and **K-11** were efficiently converted with **8** into the (*R*)-alcohols with higher rate (TOF up to 3.4×10^5 h^{-1}) respect to **6** and up to 99 % *ee*. The mono-substituted acetophenone substrates **K-12** - **15** were reduced with TOF = 5.9×10^4 - 4.8×10^5 h^{-1} and 94 - 99 % *ee*.

It is worth noting that **K-13** is reduced with 99 % *ee* at 82 °C, without erosion of enantioselectivity. While the disubstituted ketone **K-17** is converted with the same *ee* but with higher rate with respect to ruthenium **6**, the substrate **K-16** is reduced with higher *ee* (97 %, figure 39) even at 82 °C and with a lower catalyst loading (0.002 mol %), compared to **6**. These data agree with those found for other Os catalysts for asymmetric TH[71a-b,72] and hydrogenation[103,71d] of ketones and confirm that osmium is a valid complement to ruthenium for asymmetric synthesis, especially at high temperature on account of the stronger bonding. Finally, the

pyridyl ketones **K-18** - **20** are efficiently reduced with the osmium complex with much the same performance of ruthenium, with TOF values being up to 1.2×10^5 h^{-1} and enantioselectivity up to 97 %. As the results show, different alkyl-aryl ketones have been converted into alcohol using 0.005 mol % of complex **6** and **8** with TOF 10^4 - 10^5 h^{-1} and up to 99 % *ee*. Interestingly, the osmium complex displays much the same catalytic activity of ruthenium, leading to a better performance for some substrates. Similar enantioselectivity is also observed for the two metals, osmium being a valid complement to ruthenium, particularly at high temperature where deactivation is retarded.

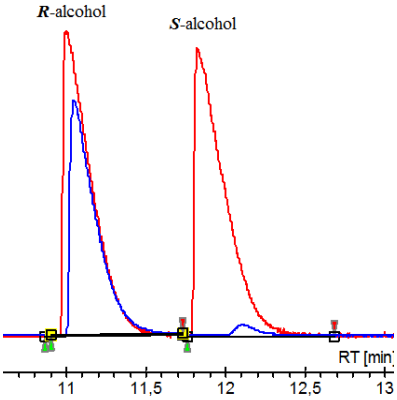


Figure 39. Enantioselective reduction of the ketone **K-16** to the corresponding (*R*)-alcohol with system **8**

3.3 Applications of the asymmetric TH in food, chemical and pharmaceutical industry

3.3.1 High purity chiral alcohols

As described in the Introduction, asymmetric transfer hydrogenation catalyzed by chiral complexes of transition metals is a convenient approach for the synthesis of chiral alcohols with high enantiomeric purity that can be used as components or intermediates of interest in food, chemical and pharmaceutical industry. This reaction offers several advantages such as the possibility to prepare the opposite stereoisomers by simply changing the configuration of the chiral ligand, the formation of very low amounts of byproducts and waste materials, mild reaction conditions and the possibility to recycle solvent and catalyst.

Through the asymmetric reduction of ketones, optically active alcohols of practical interest such as linear alcohols (food aromas, pheromones), cyclic alcohols (natural flavors) and benzhydrols (pharmaceutical intermediates) can be obtained on a small and medium scale using low catalyst loading. This procedure represents a valid alternative to the use of stoichiometric reducing agents or molecular hydrogen. With Ru **6** and Os **8**, (*R*)-1-phenylpropan-1-ol and (*R*)-3,5-bistrifluoromethyl-phenyl-ethanol (BTMP) have been obtained with high enantioselectivity. (*R*)-1-Phenylpropan-1-ol is used as a flavor and fragrance agent and 1-phenylpropan-1-ol is a food additive with a sweet-floral odor and a honey-balsamic taste. BMTP is a building block for a number of pharmaceuticals such as NK-1 receptor antagonist.[43]
It is noteworthy that with the ligand (*S*)-**1g**, the enantioselective reduction of 3'-trifluoromethylacetophenone **K-14** in the same reaction conditions was obtained, affording (*R*)-1-[3-(trifluoromethyl)phenyl]ethanol in 96 % *ee* and 94 % *ee* with **6** and **8** respectively (table 10 and 11). Since with the baker yeast reduction it is possible to synthesize the analogue (*R*)-**1g** ligand, this protocol would lead to the (*S*)-alcohol enantiomer which is a key agrochemical intermediate to achieve the fungicide (*S*)-MA20565.[42]

3.3.2 Diastereoselective reduction of (-)-menthone to (-)-menthol

Menthol is a high value alcohol with a peppermint-like odor and refreshing properties used in large quantities in cosmetics, pharmaceuticals, perfumes and as mint flavoring agent in foods. As described in Chapter 1, menthol has three asymmetric carbon atoms in its cyclohexane ring resulting in four pairs of optical isomers, (-)-menthol being one that occurs most widely in nature. The stereoselective reduction of (-)-menthone to (-)-menthol, which is the isomer responsible for the characteristic cooling effect, it is a very interesting reaction of industrial importance. The reduction of this ketone is particularly difficult because of the presence of the bulky isopropyl group bound to the carbon in position 2 which is an unstable chiral center. This leads to an equilibrium reaction in which (-)-menthone epimerizes to (+)-isomenthone (figure 40).

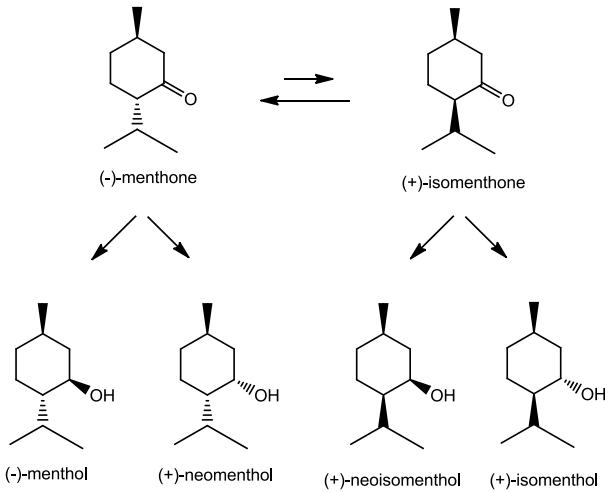
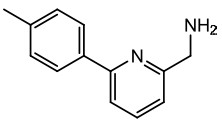


Figure 40. Menthol's isomers derived from the reduction of the mixture (-)-menthone and (+)-isomenthone

The aim of this study was to find the ideal conditions for the selective catalytic TH of (-)-menthone to (-)-menthol preventing the formation of (+)-neomenthol in addition to (+)-isomenthol and (+)-neoisomenthol which may form from the (+)-isomenthone. Noyori and co-workers found that the hydrogenation of (-)-menthone with the chiral system (*R*)-BINAP / (*S*,*S*)-DPEN system led exclusively to (+)-neomenthol (> 99 %).[15a] The isolation of (-)-menthol from mixtures of menthol isomers can be performed via crystallization, fractional distillation, freeze-drying or column chromatography affording (-)-menthol with high purity. Herein it is reported the preparation of a series of *in situ* Ru(II) and Os(II) catalysts employed in the reduction of (-)-menthone to (-)-menthol as main stereoisomer. The catalysts were prepared by refluxing a 2-propanol solution of $RuCl_2(PPh_3)_3$ or $OsCl_2(PPh_3)_3$ with diphosphine (1.5 h), followed by addition of the CNN-pincer ligand (**L-1**, figure 41), (1 h at reflux temperature). A series of chiral and achiral diphosphines of interest have been used (figure 42).



L-1

Figure 41. CNN-pincer ligand

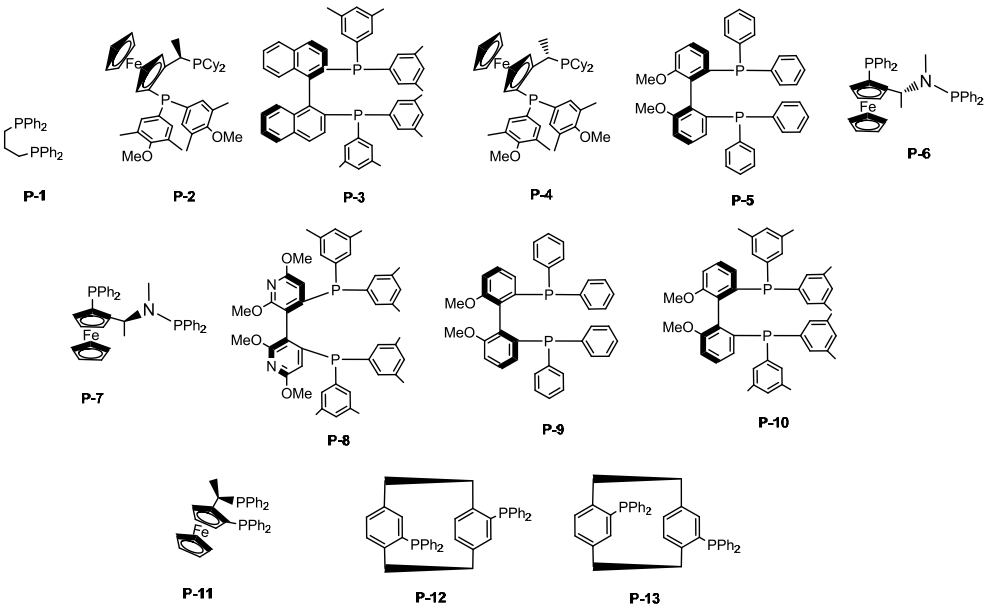


Figure 42. Diphosphines used for the catalytic TH of (-)-menthone

These systems were employed in TH of (-)-menthone using a catalyst loading of 0.05 mol % and in the presence of NaO*i*Pr (2 mol %) in 2-propanol at reflux temperature. The reduction of (-)-menthone, monitored by GC analyses using a β-cyclodextrins chiral column, resulted in the formation of two stereoisomers, namely (-)-menthol and (+)-neomenthol, as also established by NMR measurements.
Total conversion (%) of (-)-menthone and the amounts (%) of (-)-menthol and (+)-neomenthol formed are shown in table 12.

Table 12. Asymmetric TH of (-)-menthone (0.1 M) with the *in situ* systems $MCl_2(PPh_3)_3$, [M = Ru, Os] / **P-n** (**n** = **1** - **13**) / **L-1** (Ru or Os = 0.05 mol %), NaO*i*Pr (2 mol %) in 2-propanol at refluxed temperature

Phosphine	(-)-Menthol [%][a]	(+)-Neomenthol [%][a]	Conv. Tot. [%][a] (min)
P-1	18	82	99 (30 min)
P-2	67	30	96 (1 h)
P-2	47[b]	19[b]	66 (20 h)[b]
P-2	73[c]	25[c]	97.5 (2 h)[c]
P-3	48	47	95 (1 h)
P-4	60	33	92 (2 h)
P-5	64	29	93 (20 h)
P-6	65	35	99 (20 h)
P-7	67	32	99 (20 h)
P-8	68	32	99 (4 h)
P-9	68	31	99 (2 h)
P-10	71	28	99 (4 h)
P-11	72	28	99 (20 h)
P-12	73	25	98.5 (2 h)
P-13	73	26	99 (2 h)

[a] The conversions were determined by GC and NMR analyses.
[b] Reaction at 60 °C. [c] With $OsCl_2(PPh_3)_3$.

The choice of the suitable diphosphine with different steric and electronic properties, allowed to have catalysts with different stereoselectivity in the reduction of (-)-menthone. The CNN-pincer ligand **L-1** was chosen on account of its flatness which lets the easy approaching of the bulky (-)-menthone. The aryl substituent in the 6 position of the pyridyl ring gives *ortho*-metalation, leading to high stability and durability to the pincer MCl(CNN)(PP) by virtue also of the strong chelating effect of the N atoms. In table 12 it is shown that with all diphosphines complete conversion was attained in 2-propanol at refluxed temperature. With dppp (**P-1**), the *in situ* system resulted the fastest, 99 %

conversion was observed after 30 minutes but only 18 % of (-)-menthol and 82 % of (+)-neomenthol were produced. This combination of ligand and phosphine has been found the most suitable to reach the maximum conversion into (+)-neomenthol. As described in table 12, the employment of **P-10 - 13** and **P-2** with $OsCl_2(PPh_3)_3$, gave up to 70 % of (-)-menthol and with (*R*)-Panephos (**P-13**) 73 % of (-)-menthol was achieved. These data suggest that the bulkyness of the diphosphine affects the stereoselectivity of the catalytic reduction of (-)-menthol. In particular, diphosphines showing bulky substituents, such as 3,5-xylyl *vs* phenyl, lead to a better diastereoselectivity. It is noteworthy that with **P-11** an increase of (-)-menthol (72 %) was obtained compared to the results achieved with **P-6** and **P-7** (65, 67 % respectively). Evaluating the activity of the *in situ* catalysts formed with (*S*,*R*)-Josiphos* (**P-2**), with this phosphine higher selectivity for (-)-menthol (67 % *de*) with respect to the (*R*,*S*)-Josiphos* (**P-4**) (60 % *de*) was achieved. Lowering the reaction temperature to 60 °C, with **P-2** a little decrease of diastereoselectivity for (-)-menthol (47 % *de*) was afforded. Interesting result was observed employing (*S*)-(+)-MeO-BIPHEP (**P-9**) which gave 68 % of (-)-menthol in 2 h. Interestingly, with $OsCl_2(PPh_3)_3$ and **P-2**, high selectivity of (-)-menthol (73 % *de*) was achieved showing that osmium is a valid complement to ruthenium for TH reactions as described for catalyst **8** in the paragraph 3.2. Since by changing the diphoshine with **L-1** only slightly differences were evidenced in the selectivity, the effect of the pincer ligands (*S*)**-1b - 1f** was studied preparing *in situ* systems from $RuCl_2(PPh_3)_3$, without addition of diphosphines. *In situ* catalysts, prepared refluxing a 2-propanol solution of $RuCl_2(PPh_3)_3$ and the ligands (*S*)-**1b - 1f** (1 h) (figure 36), promote the asymmetric TH of (-)-menthone at refluxed temperature (catalyst 0.05 mol%). The catalytic results are shown in table 13.

Table 13. Asymmetric TH of (-)-menthone (0.1 M) with the *in situ* systems $RuCl_2(PPh_3)_3$ / (*S*)-**1b - 1f** (Ru = 0.05 mol %), NaO*i*Pr (2 mol %) in 2-propanol at refluxed temperature

Ligand	(-)-Menthol [%][a]	(+)-Neomenthol [%][a]	Conv. Tot. [%][a] (min)
(*S*)-**1b**	80	20	> 99 (2 h)
(*S*)-**1c**	69	30	99 (3 h)
(*S*)-**1d**	55	38	93 (3 h)
(*S*)-**1e**	51	39	90 (20 h)
(*S*)-**1f**	46	36	82 (4 h)

[a] The conversions were determined by GC and NMR analyses.

These results indicate that the pincer ligands affect greatly the stereo-selectivity of the reduction of (-)-menthone with respect to the diphoshines. Also using these systems the asymmetric TH of (-)-menthone leads to two stereoisomers: (-)-menthol and (+)-neomenthol. With (*S*)-**1b** and (*S*)-**1c** with OMe and CF_3 in the *para* position, respectively, 99 % of conversion was observed, attaining 80 % and 69 % of the desired (-)-menthol using (*S*)-**1b** and (*S*)-**1c,** respectively. Employment of the 3,5-disubstituted Me and CF_3 ligands (*S*)-**1d** and (*S*)-**1e**, gave 93 and 90 % conversion in 3 and 20 h, respectively, with 55 and 51 % *de* of (-)-menthol. From these data it is clear that the presence of two groups in the 3 and 5 positions, which inhibits the *ortho*-metalation, leads to less active systems. With the ligand (*S*)-**1f**, containing the 1-naphthyl moiety, only 82 % conversion was detected affording 46 % of (-)-menthol. On account of the high activity and stereoselectivity achieved with $RuCl_2(PPh_3)_3$ in combination with the ligand (*S*)-**1b**, the isolation of (-)-menthol was carried out through this procedure. A 2-propanol solution containing (-)-menthone (0.35 M) and the *in situ* catalyst $RuCl_2(PPh_3)_3$ / (*S*)-**1b** with NaO*i*Pr (substrate / catalyst = 2000 / 1), was refluxed for 4 h (99 % conversion), affording 80 % of (-)-menthol and 20 % of (+)-neomenthol. Starting from 2.42 mL of (-)-menthone, 1.99 g of menthols (91 % yield) were obtained after filtration and evaporation of the final solution. The resulting products have been analyzed through GC (figure 43) and NMR measurements.

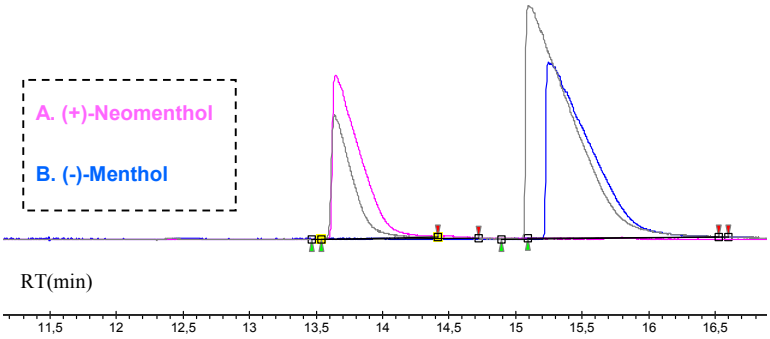


Figure 43. GC analysis of the menthols' mixture containing 80 % of (-)-menthol and 20 % of (+)-neomenthol

To separate the desired (-)-menthol from the diastereomer (+)-neomenthol, the resulting mixture of menthols, was dissolved in ethyl acetate and purified on a SiO_2 column using heptane / ethyl acetate (9 / 1 in volume) as eluent solution. Through separation, in which (+)-neomenthol displays a higher rate, (-)-menthol of 90 % purity (1.16 g, 73 % yield) was obtained as inferred from GC and NMR analyses (figures 44 and 45).

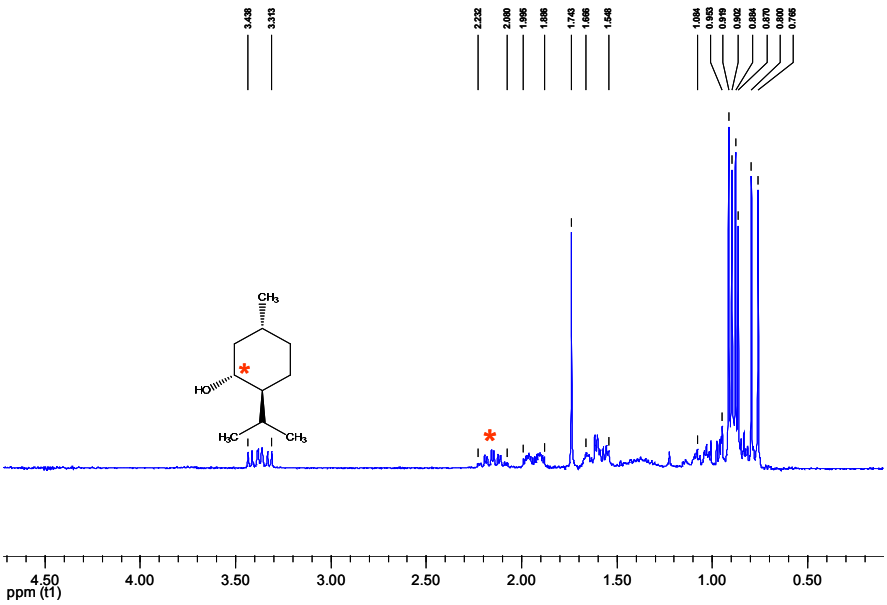


Figure 44. ^{1}H NMR spectrum of the purified (-)-menthol after separation by column chromatography

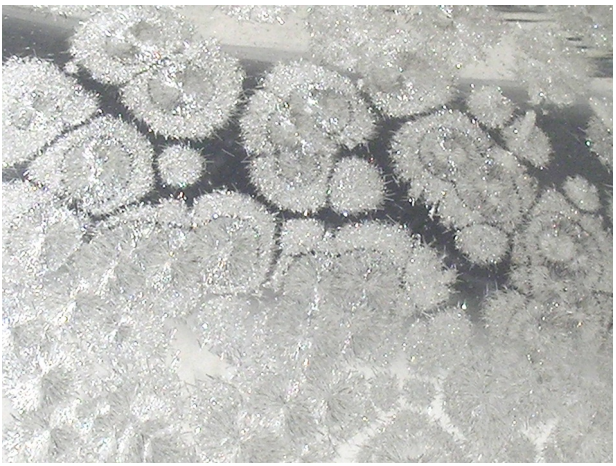


Figure 45. Crystals of the isolated menthol

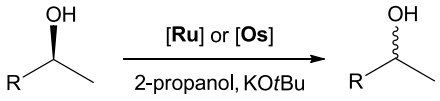
Chapter 4

Racemization and deuteration of alcohols

Racemization and deuteration of alcohols involving the activation of the C–H bond vicinal to the hydroxyl group are reactions of interest for broadening the reactivity of alcohols (Cap. 1, Par. 1.4.6.).
In addition racemization of alcohols is particularly relevant for the dynamic kinetic resolution (DKR) in which a lipase is combined with a ruthenium catalyst for the preparation of chiral alcohols achieving only the desired enantiomer.[26,28,87] Instead, the catalytic H / D exchange at the carbon centers of alcohols are of interest for obtaining deuterium-labeled compounds for pharmaceutical and analytical chemistry.[88]
This part of the PhD thesis is focused on the application of a number of ruthenium and osmium catalysts in these valuable reactions. Expecially in racemization reactions have been employed ***cis*-1** and ***trans*-2**, found already active in TH and HY (5 atm of H_2) of aldehydes and ketones, as described in the previous chapters.

4.1 Racemization of chiral alcohols

The complexes ***cis*-1** and ***trans*-2** **3**, **4**, **5** and those reported in (figure 46) have been studied in the racemization of optically active secondary alcohols (eq. 9, figure 47) in 2-propanol at 30 - 90 °C and in the presence of a base (NaO*i*Pr or KO*t*Bu). The complexes **13** and **14**[89] has been isolated for the first time.



(9)

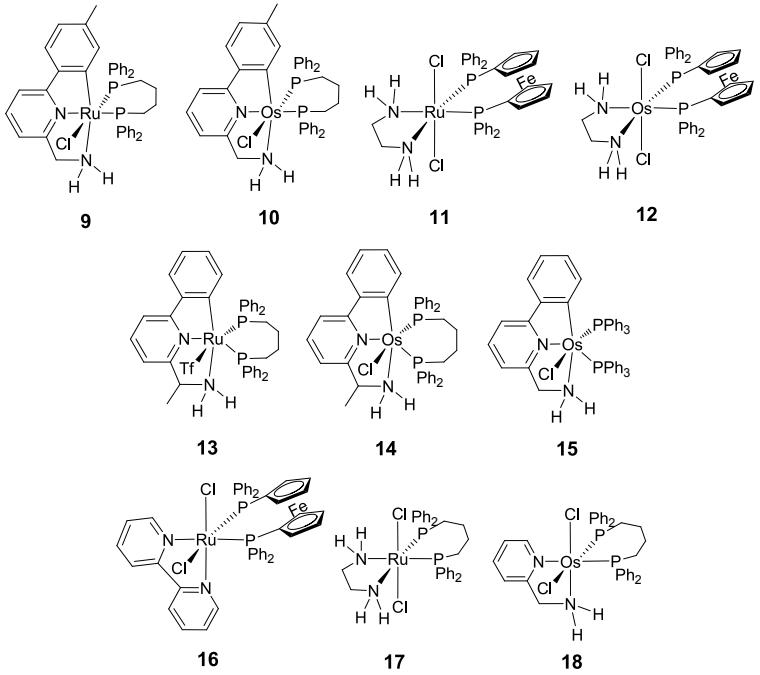


Figure 46

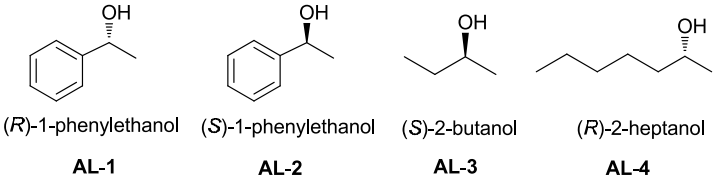


Figure 47. Chiral alcohols employed in the racemization reaction

In particular the synthesis of complex **9** (yield: 78 %) was carried out according to the literature procedure[70b] refluxing for 2 h a suspension of $RuCl_2(PPh_3)(dppb)$, the CNN-pincer ligand (**L-1**, figure 41) and triethylamine in 2-propanol. In figure 48 the molecular structure of **9** confirm by X-ray analysis is shown.

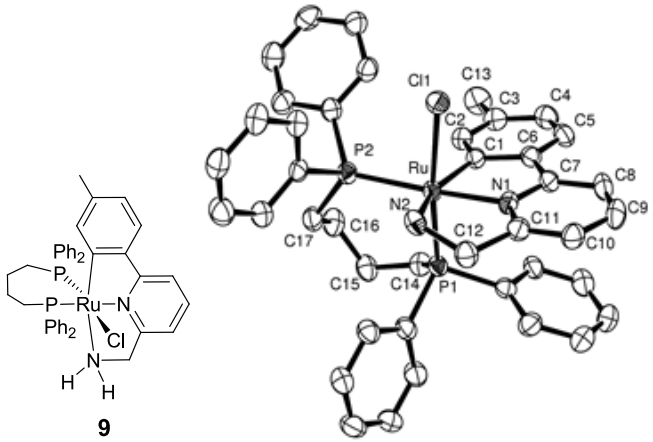


Figure 48. Complex **9** and its ORTEP structure

The complexes Ru ***cis*-1** and Os ***trans*-2** (0.5 mol %) were found active in the racemization of (*R*)-1-phenylethanol (**AL-1**) and (*S*)-2-butanol (**AL-3**) (0.33 M) in 2-propanol at 70 °C, in the presence of NaO*i*Pr (2.0 mol %) (table 14).

Table 14. Racemization of **AL-1** and **AL-3** (0.33 M) with the ***cis*-1** and ***trans*-2** (0.5 mol %) and NaO*i*Pr (2.0 mol %) in 2-propanol at 70 °C

		***cis*-1**	***trans*-2**
Substrate	Time [min]	*ee* [%][a]	*ee* [%][a]
AL-1	5	18	99
	10	0	54
	30		0
AL-3	5	46	64
	10	22	21
	30	0	0
	60		

[a] The conversion was determined by chiral GC analysis

With ***cis*-1**, reaction of (*R*)-1-phenylethanol leads to 18 % *ee* in 5 min, whereas complete racemization is achieved after 10 min. Complex ***trans*-2** is also catalytically active, affording 54 % *ee* in 10 min and 0 % *ee* in 30 min. The aliphatic alcohol (*S*)-2-butanol with ***cis*-1** gives 46 and 22 % *ee* in 5 and 10 min, respectively, and complete racemization in 30 min. With ***trans*-2** the reaction is slower (64 and 21 % *ee* in 10 and 30 min), leading to the racemate in 1 h. It is

worth noting that the analogous chiral derivatives *cis*-[$RuCl_2$(Josiphos)(R-ampy)][69c] were found extremely active catalysts for the asymmetric TH of methyl-aryl ketones, achieving alcohols with up to 99 % *ee*. These data suggest that both the enantioselective ketone reduction and the alcohol racemization, catalyzed by Ru and Os ampy complexes, occur through a reversible hydrogen transfer process.
With ***cis*-1** interesting results in the racemization of (*S*)-1-phenylethanol were also obtained (table 15, entry 1 - 2). This catalyst is almost not active at 30 °C and affords racemization in 45 min at 90 °C. In addition, the chiral (*S*)-1-phenylethanol was used as a model substrate in racemization reaction with catalysts **3** - **5**, **9** - **18** (table 15).

Table 15. Racemization of **AL-2** catalyzed by Ru and Os complexes (1.0 mol %) with KO*t*Bu (5.0 mol %) in 2-propanol

Entry	Catalyst	T °C	*ee* [%][a] (h)
1	***cis*-1**	30	96 (2)
2	***cis*-1**	90	0 (45 min)
3	**3**	30	26 (2)
4	**3**	50	0 (1)
5	**4**	30	40 (2)
			0 (4)
6	**4**	50	0 (2)
7	**5**	30	0 (1)
8	**9**	30	0 (2)
9[b]	**9**	30	0 (2)
10[c]	**9**	30	99 (2)
11	**10**	30	0 (1)
12	**10**	50	0 (40 min)
13[d]	**10**	30	0 (1)
14[e]	**10**	30	99 (2)
15	**11**	30	99 (2)
16	**12**	30	99 (2)
17	**13**	30	18 (2)
18	**14**	30	0 (2)
19	**16**	30	99 (2)
20	**16**	90	99 (2)
21	**17**	90	10 (4)
22	**18**	30	38 (2)

[a] The conversion and *ee* were determined by GC analysis. [b] The reaction was carried out in 2-propanol / toluene (1 / 1 in volume). [c] Without base. [d] Base: NaO*i*Pr (5.0 mol%). [e] Base: DBU (5.0 mol %).

The complex **3**, containing the ferrocenyl diphosphine, displays a low activity at 30 °C (26 % *ee* in 2h), whereas at 50 °C complete racemization is attained in 1 h (entries 3 and 4). The ferrocenyl osmium complex **4** affords complete racemization in 4 h at 30 °C, whereas at 50 °C the reaction occurs in 2 h (entries 5 and 6). Complex **5**, bearing a methyl group adjacent to the NH_2 function, catalyzed the complete racemization in 1 h at 30 °C (entry 7) and the analogous osmium **14** in 2 h (entry 18), indicating that the methyl substituent does not inhibit the catalysis. By contrast, the ruthenium triflate **13** gave only 18 % *ee* in 2 h (entry 17).
With **9**, **AL-2** is promptly racemized at 30 °C in 2 h, and the same result (0 % *ee*) is obtained using a 2-propanol / toluene mixture (1 / 1 in volume) (entry 9). Under these catalytic conditions, no racemization occurs with **9** without base, indicating that KO*t*Bu is crucial for the generation of the catalytically active ruthenium hydride species (entry 10). Under these experimental conditions, no formation of acetophenone, *i.e*. the product of dehydrogenation, was observed via GC analysis. Interestingly, the osmium pincer **10** is found extremely active, leading to complete racemization in 1 h at 30 °C and within 40 min at 50 °C (entries 11 and 12), while the ampy derivative **18** afforded 38 % *ee* in 2 h at 30 °C (entry 22). The comparison of these data with the corresponding ruthenium complex, indicates that the osmium is more active respect to ruthenium for which the reaction is complete in 2 h. With NaO*i*Pr, **10** displays much the same rate as with KO*t*Bu (entry 13), while no reaction occurs in the presence of the DBU base (entry 14).
The higher temperature requested for the dppf Ru and Os derivatives **3** and **4,** respect to complexes **9** and **10** respectively, may be related to the lower basicity of dppf, with respect to dppb, which may hinder the chloride dissociation and the formation of the catalytically active M-H species. The comparison of the catalytic activity of the Noyori type complexes MCl_2(NN)(PP), bearing bidentate amine or pyridine ligands, shows that these systems are less active with respect to the pincer complexes.
Regarding the *trans* diamine complexes, the ferrocenyl ruthenium **11** is not active at 30 °C (entry 15), similarly to the corresponding osmium complex **12** (entry 16), while **17** bearing dppb leads to 10 % *ee* after 4 h at 90 °C (entry 21).
Finally, it is worth noting that the *cis* dipyridine compound **16** displays no catalytic activity even at 90 °C (entry 19 - 20).
These results show that pincer ruthenium and osmium complexes display much the same activity in the racemization reaction. In addition, these compounds are more active with respect to the derivatives MCl_2(NN)(PP), where the order of activity is ampy > diamine > dipyridine.
The racemization of **AL-2** was also carried out in non protic solvents, such as toluene in the presence of a weak base (table 16). This point is of particular importance for applications in DKR in which the enzymatic reaction is generally not compatible with strong bases.

Table 16. Racemization of **AL-2** catalyzed by Ru and Os catalysts (1.0 mol %) in the presence of base (5 mol %) in toluene

Entry	Catalyst	Base	T °C	*ee* [%][a] (h)	Ketone
1	***cis*-1**	DBU	70	99 (6)	0
2	**3**	DBU	70	99 (4)	0
3	**4**	DBU	70	86 (24)	8
4	**4**	DBU[b]	90	0 (6)	8
5	**10**	KO*t*Bu	30	10 (2)	0
6	**10**	DBU	70	99 (4)	0
7	**10**	K_2CO_3	30	99 (2)	0
8	**13**	NEt_3	50	99 (2)	0
9	**13**	DBU	50	78 (2)	16
				2 (5)	33
10	**13**	DBU[b]	70	2 (6)	18
11	**17**	DBU	70	99 (6)	0

[a] The conversion and *ee* were determined by GC analysis.[b] Base 10 mol %.

The $MCl_2(NN)(PP)$ complexes ***cis*-1** and **17** in the presence of DBU were found not active at 70 °C (entries 1, 11) and ferrocenyl complex **3** with DBU is not active even at 70 °C (entry 2).
Derivative **4** with the same base (5 mol %) leads to 86 % *ee* at 70 °C in 24 h (entry 3). By increasing the amount of base (10 mol %), complete racemization is achieved at 90 °C after 6 h (entry 4). The osmium **10** with KO*t*Bu gives 10 % *ee* in 2 h at 30 °C without dehydrogenation (entry 5), while no reaction occurs with DBU at 70 °C (entry 6) or K_2CO_3 at 30 °C (4 h, entry 7). Finally, by using the labile triflate **13** (1 mol %) and NEt_3, in place of KO*t*Bu, no racemization was observed at 50 °C in 2 h (entry 8), whereas with DBU (5 mol %) the *ee* were 78 and 2 % after 2 and 5 h, respectively (entry 9).
It is worth noting that using toluene instead of *i*PrOH leads to concomitant formation of acetophenone (33 % in 5 h) via a dehydrogenation reaction. By increasing the amount of base (DBU 10 mol %) racemization occurs within 6 h at 70 °C and with lower formation of acetophenone (18 %, entry 10), indicating that both the base and the solvent affect the selectivity of the racemization reaction.
The comparison of the activity of the pincer complexes in toluene *vs* 2-propanol shows that high racemization rate is achieved in the protic media and in the presence of a strong base. Chiral aliphatic alcohols have also been racemized by the pincer complexes in 2-propanol (table 17).

Table 17. Racemization of **AL-3** and **AL-4** catalyzed by pincer Ru and Os complexes (1.0 mol %) with KO*t*Bu (5.0 mol %) in 2-propanol at 50 °C

Entry	Substrate	Catalyst	*ee* [%][a] (h)
1	**AL-3**	**3**	4 (2)
2	**AL-3**	**4**	64 (2)
3	**AL-3**	**5**	0 (2)
4	**AL-3**	**9**	0 (2)
5	**AL-3**	**10**	0 (4)
6	**AL-3**	**14**	0 (2)
7	**AL-4**	**3**	0 (2)
8	**AL-4**	**4**	48 (2)
9	**AL-4**	**5**	0 (2)
10	**AL-4**	**9**	0 (2)
11	**AL-4**	**10**	0 (2)
12	**AL-4**	**14**	0 (2)

[a] The conversion and *ee* were determined by GC analysis.

The ferrocenyl **3** (1 mol %) with (*S*)-2-butanol (**AL-3**) and KO*t*Bu (5 mol %), affords 4 % *ee* in 2 h (entry 1), a similar activity has been observed with the ruthenium **5** and **9** which led completely to the racemic 2-butanol in 2 h at 50 °C (entry 3, 4).
Complex **4** shows poor catalytic activity (64 % *ee* in 2 h) (entry 2) whereas the osmium derivatives **10** and **14** give the racemization in 4 and 2 h respectively (entries 5, 6).
Finally, the substrate (*R*)-heptanol (**AL-4**) is racemized at 50 °C with the ruthenium complexes **3**, **5** and **9** in 2 h (entries 7, 9, 10). Also the osmium complexes **10** and **14** lead to complete racemization in 2 h (entries 11 and 12), whereas **4** shows moderate activity (48 % *ee*, 2 h, entry 8).

4.2 Deuteration of alcohols

The Ru and Os complexes **3**, **4**, **5**, **9**, **10**, **17** and **18**, in the presence of KO*t*Bu have also been investigated in the deuteration of alcohols (figure 49) in 2-propanol-d_8 (eq. 10).

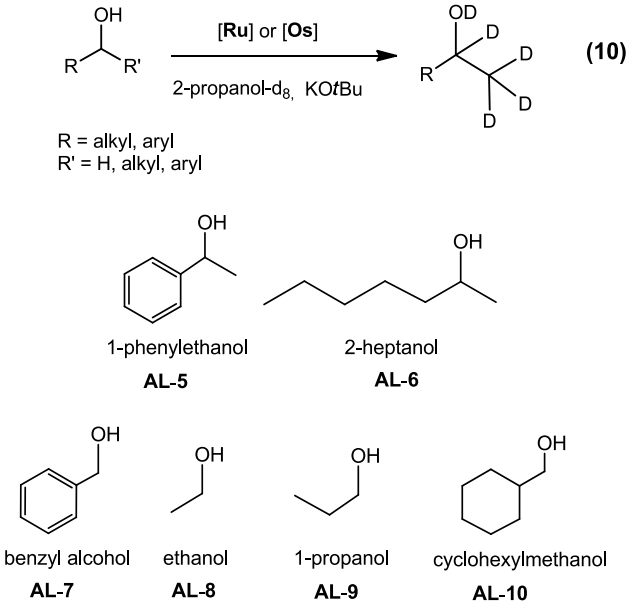


Figure 49

For secondary alcohols fast deuterium incorporation at the α and β positions to the hydroxyl group is easily achieved at 30 - 60 °C within a few hours using 1 mol % of catalyst in 2-propanol-d_8, as established by NMR measurements (table 18).

Table 18. Deuteration of secondary alcohols catalyzed by Ru and Os complexes (1 mol %) in the presence of KO*t*Bu (5 mol %) in 2-propanol-d_8

Entry	Substrate	Catalyst	T °C	Time [h]	D content in α [%][a]	D content in β [%][a,b]
1	**AL-5**	**3**	30	4	87	77
2	**AL-5**	**4**	30	4	92	84
3	**AL-5**	**5**	30	2	91	60
4	**AL-5**	**9**	30	2	96	80
5	**AL-5**	-	30	2	4	0
6[c]	**AL-5**	**9**	50	24	54	94
7	**AL-5**	**10**	30	2	96	90
8	**AL-5**	**17**	30	2	11	0
9	**AL-5**	**17**	60	2	93	89
10	**AL-5**	**18**	30	2	40	41
11	**AL-6**	**9**	30	24	50	40
12	**AL-6**	**9**	70	4	99	96[d]

[a] D content in α and β positions were determined by NMR analyses. [b] For the methyl group. [c] The reaction was carried out in D_2O. [d] Complete methylene deuteration was inferred from ^{13}C NMR.

High deuterium incorporation into the substrate is accomplished using 2-propanol-d_8 in large excess (2-propanol-d_8 / substrate = 40), which takes H in the α and β positions. As a matter of fact, nearly quantitative hydrogen exchange at the α position of the substrate and 2-propanol-d_8 has been inferred from ^1H NMR measurements.

The substrate 1-phenylethanol (**AL-5**) with complex **3** undergoes at 30 °C D incorporation of the α and β positions (87 and 77 % respectively) in 4 h. The ruthenium **5** and **9** catalyze the deuteration of (**AL-5**) leading to 91 and 60 % of incorporation at the α and β positions.

Without catalyst (entry 5) negligible deuteration at the α position (< 4 %) is observed with no β incorporation, indicating that the H-D exchange is catalyzed by Ru.

Using D_2O in place of 2-propanol-d_8 at 50 °C the deuteration is much slower and leads unexpectedly to a higher D content at the β position (94 % in 24 h) with respect to the α position (54 %) (entry 6). Although D_2O is the cheapest source for obtaining deuterium-labeled compounds, the use of 2-propanol-d_8 in combination with pincer complexes is a straightforward procedure for the deuteration of alcohols.

Also the pincer osmium derivatives **4** and **10** have been found highly active in the catalytic H - D exchange at 30 °C, leading to 92 % (4 h) and 96 (2 h) of α deuteration, while the values for the β incorporation are 84 and 90 %, respectively (entries 2, 7), the activity of **10** being comparable with that of **9**.
The ampy derivative **18** gives 40 and 41 % of α and β exchange at 30 °C (entry 10), whereas the diamine **17** is less active (entries 8). Conversely, at 60 °C **17** catalyzes the H – D exchange affording 93 (α) and 89 % (β) of D content in 2 h (entry 9). With **9** at 30 °C, 2-heptanol (**AL-6**) undergoes deuteration at the α position (50 % in 24 h) with a lower rate with respect to **AL-5** (entry 11). At 70 °C almost quantitative D incorporation has been attained for the α hydrogen (99 %), as well as the CH_3 and CH_2 β hydrogens in 4 h, as established by ^1H and ^{13}C NMR experiments (entry 12).
The comparison of the catalytic activity of the pincer complexes with the derivatives **17** and **18** shows that the latter are less active as for the racemization reaction.
Interestingly also primary alcohols (figure 49) are efficiently deuterated at the α position using the pincer complexes **9** and **10** in 2-propanol-d_8 at 50 °C with low or negligible D β incorporation (table 19).

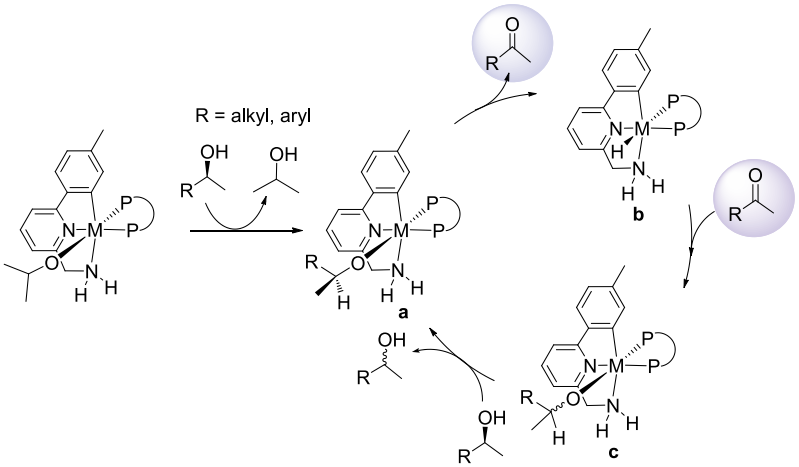
Table 19. Deuteration of primary alcohols catalyzed by **9** and **10** (1 mol %) with KO*t*Bu (5 mol %) in 2-propanol-d_8 at 50 °C

Entry	Substrate	Catalyst	Time [h]	D content in α [%][a]	D content in β [%][a]
1	**AL-7**	**9**	1	94	–
			3	95	–
2	**AL-8**	**9**	1	98	0
3[b]	**AL-8**	**9**	24	0	0
4	**AL-9**	**9**	1	94	0
			3	99	7
			5	99	14
5	**AL-9**	**10**	0.5	90	0
			1	95	0
6	**AL-10**	**9**	1	94	0
			2	95	0
			4	95	0

[a] D content in α and β positions were determined by NMR analyses. [b] The reaction was carried out in D_2O.

No deuteration of ethanol (**AL-8**) has been observed with **9** using D_2O, in place of 2-propanol-d_8, after 1 day (entry 3). Interestingly, 1-propanol (**AL-9**) undergoes moderate incorporation of D at the β position, as it was shown by the ^{1}H NMR measurements carried out after 3 and 5 h (7 and 14 %). %). High catalytic activity has also been observed with the osmium **10** (95 % of α incorporation of D after 1 h).

For both racemization and deuteration reactions, much the same activity has been observed with the Ru and Os complexes. The pincer complexes display a superior activity with respect to the related compounds $MCl_2(NN)(PP)$ (NN = bidentate amine or pyridine ligand). In addition it was observed that in 2-propanol-d_8 the pincer complexes catalyze the simultaneous deuteration and racemization of (*S*)-1-phenylethanol, the two processes being strictly correlated. To the best of our knowledge, no examples of osmium catalysts for racemization and deuteration of alcohols have previously been described. The results of this study on the racemization and deuteration of alcohols with the pincer Ru and Os complexes are in agreement with a mechanism involving the reversible formation of ketone (aldehyde) through a hydrogen transfer reaction. In the proposed catalytic cycle for the alcohol racemization, the isopropoxide M(O*i*Pr)(CNN)(PP), which is formed from MX(CNN)(PP) in basic 2-propanol, is protonated by the chiral substrate leading to the alkoxide M(OC*HRMe)(CNN)(PP) (**a**) (scheme 12).[89]



Scheme 12. Proposed catalytic cycle for the racemization of alcohols catalyzed by Ru and Os pincer complexes in 2-propanol

This species affords the hydride MH(CNN)(PP) (**b**) with extrusion of the ketone through a β hydrogen elimination reaction, assisted by the NH_2 function and the 2-propanol media.[129]
The non enantioselective reduction of the ketone affords M(OCHRMe)(CNN)(PP) (**c**) which is protonated by the chiral alcohol, affording the racemic alcohol and closing the cycle.
This mechanism resembles that proposed by Bäckvall for cyclopentadienyl Ru systems,[130] although at this stage it is not clear whether in protic media the formed ketone remains close to the Ru hydride or it is free, leading to reduction not at the same Ru-H center.

Chapter 5

Dehydrogenation of alcohols and sterols

The oxidation of alcohols to carbonyl compounds, such as ketones, aldehydes, and esters, is one of the most fundamental and important reactions in synthetic organic chemistry and it is important to develop a mild and less toxic oxidation system. Moreover this process is of great current interest as a potential method for hydrogen production from biomass products.[86,97]

Recently, much effort has been devoted to the transition-metal-catalyzed oxidation of alcohols using environmentally friendly oxidants such as oxygen, hydrogen peroxide, or acetone. However, from the viewpoint of atom efficiency and safety of the reaction, an oxidant-free reaction to give carbonyl products should be ideal.[98]

It is known that many transition-metal complexes have been shown to display good to high catalytic activity for both hydrogen generation and the preparation of carbonyl compounds from alcohols, ruthenium being the metal of choice (Cap. 1, Par. 1.5.1).

A number of ruthenium(II) and osmium(II) complexes easily obtained in one pot reactions from commercially available compounds, have been tested in the dehydrogenation of alcohols to obtain products of interest. The activity of the complexes MCl_2(dppf)(ampy) (M = Ru ***cis*-1**, Os ***trans*-2**) found active for a range of organic transformations, TH and HY of aldehydes and ketones, racemization and deuteration of alcohols is also described. These catalysts, promoting the activation of the C-H bond vicinal to the hydroxyl group, can enhance the alcohol reactivity giving access to new reactions, for example via hydrogen borrowing.[110]

Indeed, on the basis of the microscopic reversibility, it is expected that highly active catalysts for transfer hydrogenation (TH)[118a-b,117b-e] of carbonyl compounds can also induce the activation of alcohols. The fast rate observed in the transfer hydrogenation of aldehydes and ketones (TOF $\approx 10^5$ h^{-1}) (Cap. 2, table 2) indicates that the complexes ***cis*-1** and ***trans*-2** can efficiently promote the cleavage of the C-H bond vicinal to the hydroxyl group of 2-propanol. This suggests that alcohols can be easily converted into carbonyl compounds, giving access to a number of organic transformations by increasing the alcohol reactivity.

5.1 Catalytic dehydrogenation of alcohols and sterols to ketones

The activity of the complexes ***cis*- / *trans*-1**, ***trans*-2**, **9**, **10**, **11**, **12** and of a number of pincer and bidentate ruthenium and osmium catalysts (figures 50 and 51) has been studied in the acceptorless dehydrogenation of alcohols to ketones in a open system. Several alcohols, including 3-hydroxy sterols, have been efficiently oxidized with 0.8 - 0.04 mol % of catalyst at 130 - 145 °C (eq. 11). In this work, the first example of the use of osmium complexes in the alcohol dehydrogenation has been reported.

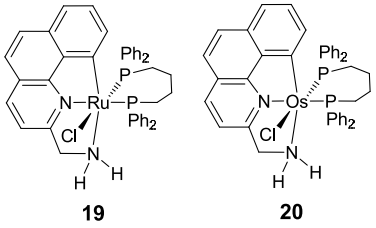


Figure 50. Pincer ruthenium and osmium complexes

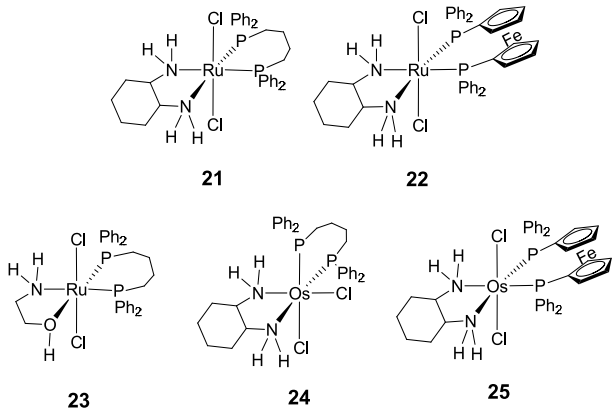
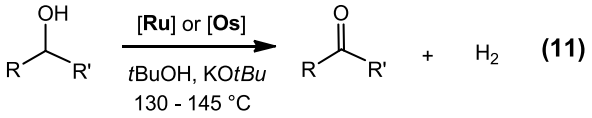


Figure 51. Ruthenium and osmium complexes bearing bidentate amino ligands



The pincer Ru and Os complexes **9**, **10**, **19**, **20** catalyze the dehydrogenation of 1,2,3,4-tetrahydro-1-naphthol (α-tetralol), which was taken as model compound for this study, on account of its low redox potential (E° = 0.080 V).[92]
High conversion of α-tetralol into α -tetralone (93 and 90%) was observed with the Ru derivatives **9** and **19** (0.4 mol %) and KO*t*Bu (2 mol %) in *t*BuOH at 130 °C (bath temperature) within 24 h (table 20). Under these experimental conditions, the yield of α-tetralone was equal to the conversion of the alcohol, as established by GC and ^{1}H NMR analyses, thus indicating a high selectivity.

Table 20. Dehydrogenation of α-tetralol with catalysts ***cis***- / ***trans*-1**, ***trans*-2**, **9** - **12**, **19** - **25** (0.4 mol %), in the presence of KO*t*Bu (2 mol %) in *t*BuOH at 130 °C

Catalyst	Conv. [%][a] after 1 h	Conv. [%][a] after 2 h	Conv. [%][a] (h)
9	13	27	93 (24)
19	10	19	90 (24)
10	4	6	44 (24)
20	4	5	36 (24)
21	21	40	97 (22)
22	74	94	97 (3)
11	80	93	98 (3)
12	31	65	98 (6)
23	6	8	86 (45)
24	20	38	93 (22)
25	14	28	96 (24)
***cis*-1**	73	82	92 (3)
***trans*-1**	82	90	97 (4)
***trans*-2**	36	55	87 (20)

[a] The conversion was determined by GC analysis.

To shift the reaction toward the ketone, the reaction was carried out in an open system. Tertiary butanol was chosen as a suitable protic solvent, which by contrast with primary or secondary alcohols is not involved in dehydrogenation reactions.
The corresponding pincer osmium complexes **10** and **20** display lower activity, thus leading to incomplete formation of α-tetralone (44 and 36 %). The ruthenium derivatives $RuCl_2$(PP)(diamine) **21**, **22** and **11** show higher activity with respect to the pincer complexes, affording fast and quantitative dehydrogenation of α-tetralol (97 - 98% conversion) in a shorter time. Interestingly, the diamine derivatives **22** and **11**, which display the dppf diphosphane, exhibit the highest rate, with up to 80 % conversion after 1 h.
The ruthenium complex **23** containing the 2-aminoethanol ligand is also active, although with lower efficiency (86 % conv. in 45 h). As regards osmium, the complexes **24**, **25** and **12** catalyze the DHY of α-tetralol and their activity was compared with that of the related ruthenium derivatives **21**, **22** and **11**. The osmium **24** (*trans* and *cis* isomers), displaying the same set of ligands of **21**, shows much the same activity (93 % conv. in 22 h), respect to **21** (table 20). The

compounds **25** and **12**, containing the dppf diphosphane, led also to complete conversion (96 - 98 %), even though with a rate lower compared to **22** and **11**. In particular **12** gave 65 % conversion after 2 h and 98 % in 6 h, indicating that osmium can efficiently be employed in alcohol dehydrogenation.
It is noteworthy that ***cis*-1** shows a slightly lower activity, with respect to ***trans*-1**, achieving 92 % conversion after 3 h while ***trans*-1** gave 97 % conversion after 4 h, thus differing from the activity of $RuCl_2$(dppb)(ampy) in the TH of ketones, for which the *cis* isomers gave the highest rate.[69a] This points out that systems ***cis*-1** and ***trans*-2** efficiently catalyze the reduction of aldehydes and ketones via transfer hydrogenation and hydrogenation reactions (Cap. 2, Par. 2.1.).
The dppf derivative ***trans*-1** with the ampy ligand shows activity similar to that of **11**, thus indicating that both the diamine and the ampy complexes, which are catalysts for hydrogenation and transfer hydrogenation, are highly efficient catalysts for the dehydrogenation reaction. Finally, the osmium ***trans*-2** shows a lower activity with respect to both ***cis*-1** and ***trans*-1** and, leading to 87 % conversion in 20 h.
These data show that $RuCl_2$(dppf)(ampy) ***cis*-1**, ***trans*-1** and *trans*-[MCl_2(dppf)(en)] (M = Ru **11**, Os **12**) are among the most active Ru and Os catalysts.
In order to study the effect of the metal in catalysis, the activity of **11** and **12** has been compared. The structure of the complex **12** is shown below in figure 52.
To investigate the role of the base on the activity of the ruthenium **11** and osmium **12** complexes the catalytic DHY was carried using KO*t*Bu in the range 0 to 40 mol %. Under the same experimental conditions previously described, in absence of base complexes **11** and **12** (0.4 mol %) were found not active in the dehydrogenation of α-tetralol (≤ 1 %, 2 h) (table 21).

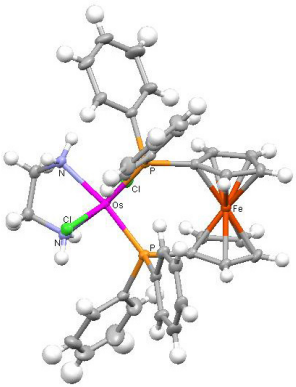


Figure 52

Table 21. Influence of the base (KO*t*Bu) on the dehydrogenation of α-tetralol with catalysts **11** and **12** (0.4 mol%) in *t*BuOH at 130 °C

	Catalyst **11**		Catalyst **12**	
KO*t*Bu [mol%]	Conv. [%][a] (2 h)	Conv. [%][a] (h)	Conv. [%][a] (2 h)	Conv. [%][a] (h)
0	0	–	1	–
0.5	1	–	8	–
1	43	91 (21)	45	91 (21)
2	97	98 (3)	65	98 (6)
3	97	98 (3)	60	94 (6)
6	96	98 (3)	58	92 (6)
40	66	96 (24)	47	95 (24)

[a] The conversion was determined by GC analysis.

With 0.5 mol % of base the ruthenium complex is catalytically not active, while osmium led to 8 % conversion after 2 h. Using 1 mol % of KO*t*Bu the two complexes show apparently the same behavior with 43 - 45 % conversion after 2 h and 91 % after 21 h. At higher base loading, namely 2 - 6 mol %, the Ru catalysts afforded almost quantitative conversion after 2 h, while the Os complex gave 58 - 65 % of α-tetralone in 2 h and up to 98 % in 6 h.

It is worth noting that in a closed system (25 ml schlenk) compounds **11** and **12** give incomplete conversion of α-tetralol in 4 h (65 and 56 %). At higher loading of KO*t*Bu (40 %) the Ru and Os systems are less active and complete conversion is reached after 24 h. In addition, without catalyst, no dehydrogenation of α-tetralol was observed in basic *t*BuOH at 130 °C after 2 h.

These data show that the activity of the catalysts depending on the base concentration seems to have a bell-shaped trend. Catalysis occurs efficiently when the base / complex > 2 and the base / complex < 40, suggesting that in dehydrogenation, similarly to hydrogenation, the dihydrido system MH_2(dppf)(en) (M = Ru, Os), formed by reaction of MCl_2(dppf)(en) with potassium α-tetralol alkoxide, is involved in catalysis (Cap.1, Par. 1.4.5.). Moreover in the presence of high loading of base (40 %), the reduction of the catalytic activity was pointed out probably due to the non-formation of the Ru-H bond which prevents the hydrogen activation.

To investigate the potential of **11** for the synthetic purposes, the dehydrogenation of α-tetralol was carried out at different catalyst loading, with a Ru / KO*t*Bu = 5. While at 0.4 mol % of Ru quantitative formation of ketone is attained in 3 h,

employment of 0.08 and 0.04 mol % of **11** gives 96 and 93 % conversion after 21 h (table 22).

Table 22. Catalytic dehydrogenation of α-tetralol at different loading of **11** (KO*t*Bu / **11** = 5) in *t*BuOH at 130 °C

Complex **11** [mol %]	Conv. [%][a]	Time [h]
0.4	98	3
0.08	96	21
0.04	93	21
0.02	80	46

[a] The conversion was determined by GC analysis.

Finally, at 0.02 mol % of **11** α-tetralone (80 %) is formed after 46 h, affording a TON (turnover number: moles of ketone converted to alcohol per mole of catalyst) = 4000 and suggesting that **7** can be used for the preparation of ketones. It is worth noting that complete dehydrogenation of α-tetralol (95 % conv. in 2 h) was also achieved using **11** (0.4 mol %), obtained *in situ* by treatment of $RuCl_2(PPh_3)_3$ with dppf (1 h at 110 °C) and ethylenediamine (1 h at 110 °C) in *t*BuOH. By contrast, no conversion (< 1 %) was observed under the same experimental conditions using the ligand $Me_2NCH_2CH_2NMe_2$ instead of $H_2NCH_2CH_2NH_2$, indicating that the N-H functionality is crucial for the fast catalytic dehydrogenation.
These results differs from those obtained for the $RuCl_2$(*p*-cymene) / amine system for which tertiary amines display higher activity, compared to primary ones.[90]
Based on the good results achieved in the DHY of α-tetralol with the ruthenium **11** and the analogous osmium **12**, the DHY of a number of interesting alcohol substrates (figure 53) was studied using these complexes (0.4 mol %) in basic *t*BuOH at 130 °C (table 23).

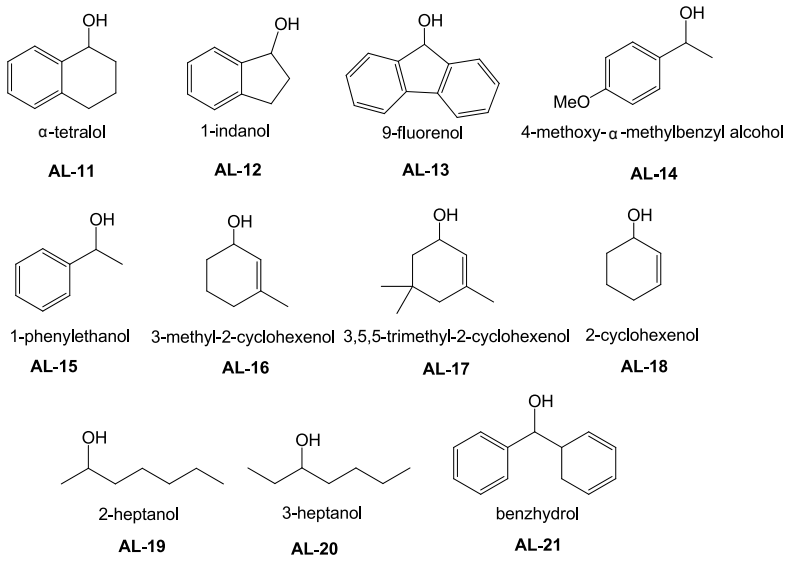


Figure 53

Table 23. Dehydrogenation of alcohols with catalysts **11** and **12** (0.4 mol %) in the presence of KO*t*Bu (2 mol %) in *t*BuOH at 130 °C

	Complex **11**			Complex **12**		
Alcohol	Conv. [%][a]	Time [h]	TOF [h^{-1}][a]	Conv. [%][a]	Time [h]	TOF [h^{-1}][a]
AL-11	98	3	200	98	6	80
AL-12	95	7	100	98	6	50
AL-13	99[b]	5	95	88[b]	20	20
AL-14	97	4	130	96	20	40
AL-15	58	20	-	68	20	-
AL-16	92	2	300	82	20	30
AL-17	95	2	120	97	20	70
AL-18	86[c]	5	100	91[c]	2	220
AL-19	72[d]	45	-	91[d]	20	15
AL-20	73	20	-	40	30	-
AL-21	5	20	-	41	30	-

[a] The conversion and TOF (moles of alcohol converted into ketone per mole of catalyst per hour

at 50 % conversion) were determined by GC analysis. [b] substrate / catalyst / KO*t*Bu = 125 / 1 / 5. [c] isomerization to cyclohexanone. [d] substrate / catalyst / KO*t*Bu = 50 / 1 / 5.

Quantitative conversion of **AL-11**, α-tetralol (1,2,3,4-tetrahydro-1-naphthol) into α-tetralone is achieved with **11** and **12** in 3 and 6 h with TOF = 200 and 80 h^{-1}, respectively. It was observed that with ***cis*-1**, 92 % conversion to α-tetralone was obtained in 3 h (table 20) with TOF = 600 h^{-1}, three times higher than the TOF observed using **11**, indicating a partial deactivation of the ampy complex after reaching 50 % conversion.
The cyclic 1-indanol (**AL-12**) and fluorenol (**AL-13**) were also dehydrogenated with 88 - 99 % conversion, ruthenium being faster compared to osmium. The ketone 4′-methoxy-acetophenone was formed quantitatively (up to 97 %) with **11** in 4 h and with **12** in 20 h, starting from the corresponding alcohol (**AL-14**). Comparing the activity of the ampy systems ***cis*-1** and ***trans*-2** with that of the diamine complexes **11** and **12**, 4-methoxy-α-methylbenzyl alcohol (**AL-14**) is oxidized to 4'-methoxyacetophenone (90 % conversion) with ***cis*-1** in 4 h, whereas with ***trans*-2** a longer reaction time is required (90 % conversion in 20 h).
It is clear from results that in the DHY of 4-methoxy-α-methylbenzyl alcohol and of α-tetralol, the diamine compounds **11** and **12** were found more active than the ampy ***cis*-1** and ***trans*-2**.
The alcohol 1-phenylethanol (**AL-15**) which exhibits a higher redox potential than 4-methoxy-α-methylbenzyl alcohol, led to 58 and 68 % of ketone with **11** and **12** after 20 h, respectively. Also the cyclic 3-methyl-2-cyclohexenol (**AL-16**) was rapidly converted to ketone (92 % in 2 h) with TOF = 300 h^{-1} using **11**, while with **12** the reaction is considerably slower. Complete dehydrogenation has been observed also with 3,5,5-trimethyl-2-cyclohexenol (**AL-17**), achieving 95 and 97 % conversion with **11** and **12** in 2 and 20 h, respectively. It is to point out that, the unfunctionalized alcohol 2-cyclohexenol (**AL-18**) isomerizes to cyclohexanone (86 %) in 5 h with **11**, whereas the osmium **12** gave 91 % conversion in 2 h. In addition, the substrate, 2-heptanol (**AL-19**) was converted (72 %) into 2-heptanone with **11** in 45 h, whereas **12** led to 91 % conversion in 20 h. On the other hand, 3-heptanone was obtained from 3-heptanol (**AL-20**), 73 % conv. in 20 h) with **11**, whereas with **12** poor conversion was observed (40 % in 30 h). Finally, **11** was found almost inactive in the dehydrogenation of benzhydrol (**AL-21**), whereas **12** led to poor conversion (41 % in 30 h).
Thanks to the interesting results obtained using systems **11** and **12** in the dehydrogenation of several alcohols, their activity was investigated also in the dehydrogenation of some sterols (figure 54) achieving steroidal compounds containing the 4-en-3-one functionality, such as of steroidal hormones, with concomitant C-C double bond isomerization (figure 55).

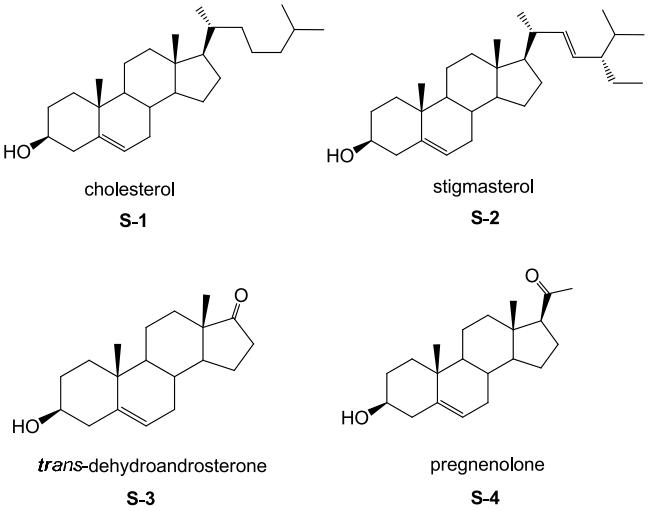


Figure 54

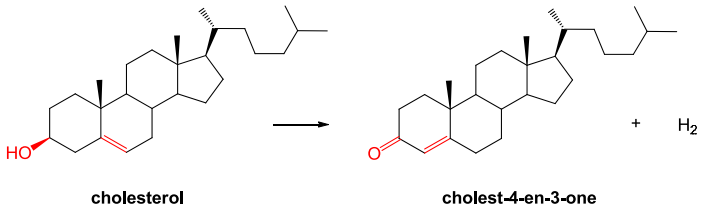


Figure 55. Dehydrogenation of cholesterol with C-C double bond isomerization

The ruthenium and osmium derivatives **11** and **12** in the presence of KO*t*Bu were employed in the dehydrogenation of sterols in *t*BuOH / toluene mixture at 145 °C (bath temperature). The results are shown in table 24.

Table 24. Catalytic dehydrogenation of sterols with complexes **11** and **12** (0.8 mol %) in the presence of KO*t*Bu (4 mol %) in *t*BuOH / toluene = 2 / 1 (in volume) at 145 °C

	Complex **11**			Complex **12**		
Sterol	Conv. [%][a]	Time [h]	TOF [h^{-1}][a]	Conv. [%][a]	Time [h]	TOF [h^{-1}][a]
S-1	> 98[b]	20	15	> 98[b]	20	15
S-2	80	36	5	> 98[b]	20	8
S-3	45	46	-	86	20	6
S-4	87	20	11	95	20	25

[a] The conversion and TOF (moles of alcohol converted into ketone per mole of catalyst per hour at 50 % conversion) were determined by ^{1}H and ^{13}C NMR analyses. [b] No side products were observed.

The compound cholest-4-en-3-one is formed quantitatively in 20 h by heating cholest-5-en-3β-ol (**S-1**) using **11** at 0.8 mol % and KO*t*Bu 4 mol %. Complete conversion of this 3-hydroxy sterol, which displays a very low redox potential (0.063 V),[15a] is also obtained with the osmium derivative **12**. In the same reaction conditions the acceptorless dehydrogenation of cholest-5-en-3β-ol with ***cis*-1** leads to cholest-4-en-3-one quantitatively (98 % conversion, TOF = 180 h^{-1}) in 3 h. A faster reaction has been observed with the osmium ***trans*-2** for which the formation of the steroid compound (97 % conversion) has been achieved in 1 h, affording a TOF = 210 h^{-1}, in agreement with the studies with Ru and Os diamine complexes.[122]

These data indicate that the ampy derivative ***cis*-1** and ***trans*-2** have a higher activity with respect to the related diamine compounds in the DHY of cholesterol, the osmium ***trans*-2** displaying fast conversion and high TOF value.

In addition, cholest-4-en-3-one is also formed (90 % conv. in 20 h), using complex **11** in polyethylene glycol (PEG 3400 MW) as reaction media. Stigmasterol (**S-2**) is dehydrogenated to 24-ethylcholesta-4,22-dien-3-one with **11** in *t*BuOH / toluene, affording 80 % conversion after 36 h, whereas with **12** quantitative conversion is achieved after 20 h. With **11**, androstenedione is formed from *trans*-dehydroandrosterone (**S-3**) in low amount (45 % conversion in 46 h), while **12** afforded a higher conversion (86 % in 20 h). Interestingly, also pregnenolone (**S-4**) was efficiently oxidized to progesterone after 20 h with 87 and 95 % conversion using **11** and **12**, respectively.

These results indicate that osmium led to a better conversion respect to the analogous ruthenium complex and this may ascribed to the stronger thermal stability of the Os species respect to Ru, the deactivation being retarded.

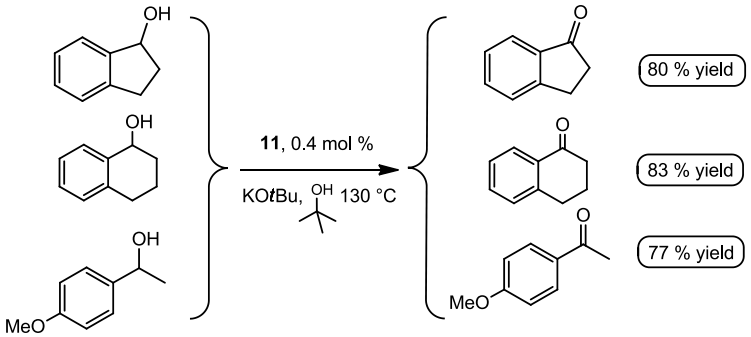
Apparently, this was the first report on the catalytic dehydrogenation of sterols promoted by a transition metal complex, without using an oxidant agent.

Finally, it is noteworthy that in the DHY of α-tetralol (**AL-11**), 4-methoxy-α-methylbenzyl alcohol (**AL-14**) and cholestereol (**S-1**) good results were achieved also with the ampy complexes ***cis*-1** and ***trans*-2**, found already active systems in TH and HY reactions Cap. 2, Par. 2.1).
These are promising data in order to extend the application of these complexes.
In the next chapters the study of the activity of the systems ***cis*-1** and ***trans*-2** in several reactions involving carbonyl compounds and alcohols was described.

5.2 Applications of catalytic DHY of alcohols in food, chemical and pharmaceutical industry

5.2.1 Preparation and isolation of ketones of interest

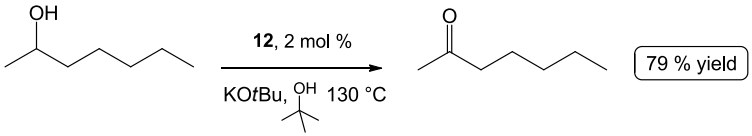
In order to show the potential of the catalytic dehydrogenation for synthetic applications, few ketones have been prepared. Thus, 1-indanone, α-tetralone and 4′-methoxyacetophenone were isolated in 80, 83 and 77 % yield, starting from a solution of the corresponding alcohol (1.25 M), complex **11** and KO*t*Bu in *t*BuOH at 130 °C (substrate / catalyst = 250 / 1).
Using 335 mg of 1-indanol, 370.5 mg of α-tetralol and 0.35 mL of 4-methoxy-α-methylbenzyl alcohol with 7.9 mg of **11**, complete dehydrogenation was obtained in an open system in few hours (4 - 7 h), affording, after filtration, evaporation of the solvent and purification on a SiO_2 chromatography column (CH_2Cl_2 / ether = 30 /1, in volume), 80 % yield of 1-indanone (265 mg), 83 % yield of α-tetralone (302 mg), 77 % yield of 4′-methoxyacetophenone (290 mg) (scheme 13).



Scheme 13

Among the products isolated in good yield, 1-indanone is known as an important drug intermediate for serotonin reuptake inhibitors and others. Indane class compounds find applications in perfumes, as fragrance enhancers, and as

intermediates in the production of drugs having analgesic, anaesthetic, sedative properties and antibiotics.
α-Tetralone is used as a reactive intermediate which is converted to target compounds including dyes, drugs (contraceptives)[52] and agrochemicals. It can be used also as solvent, softener of plastic and its chloride is used in preparing pesticides. Moreover, dihydro-2H-napthalene-1-ones are supposed to be useful in medicine for treating and preventing uncontrolled or abnormal proliferation of tissues, such as cancer, atherosclerosis, restenosis, and psoriasis.[53] Finally tetralone derivatives find extensive applications in color industry.
Interestingly, 4′-methoxyacetophenone is used as a component of perfumes and as chemical intermediate in the manufacture of pharmaceuticals, resins and flavoring agents. As flavoring agent can be employed in vanilla, nut, tobacco and butter flavors for its sweet, fruity, cherry with vanilla nuances taste.[12,39]
Moreover, following the procedure described above for 1-indanol, α-tetralol and 4-methoxy-α-methylbenzyl alcohol, using 20.9 mg of the osmium complex **12**, 0.11 mL of 2-heptanone (79 % yield) was prepared (20 h) and isolated from 0.14 mL of 2-heptanol, in an open system with KO*t*Bu in *t*BuOH at 130 °C (substrate / catalyst = 50 / 1) (scheme 14).



Scheme 14

As described in the Introduction, this ketone with a banana-like, fruity odor, is listed by the FDA as a food additive permitted for direct addition to food for human consumption, and acts also as an alarm pheromone.[39,47,48]
Besides this, it is noteworthy that 90 % yield of cholest-4-en-3-one (435 mg) was also isolated after filtration and evaporation of the solvents starting from 483 mg of cholest-5-en-3β-ol, using 7.9 mg of **11** at 145 °C in *t*BuOH / toluene (2 / 1 in volume) in an open system.
The ^{1}H NMR and ^{13}C NMR spectra of the isolated cholest-4-en-3-one, in figure 56 and 57, display the high purity of the product. NMR data were compared with those reported in the literature.[101]

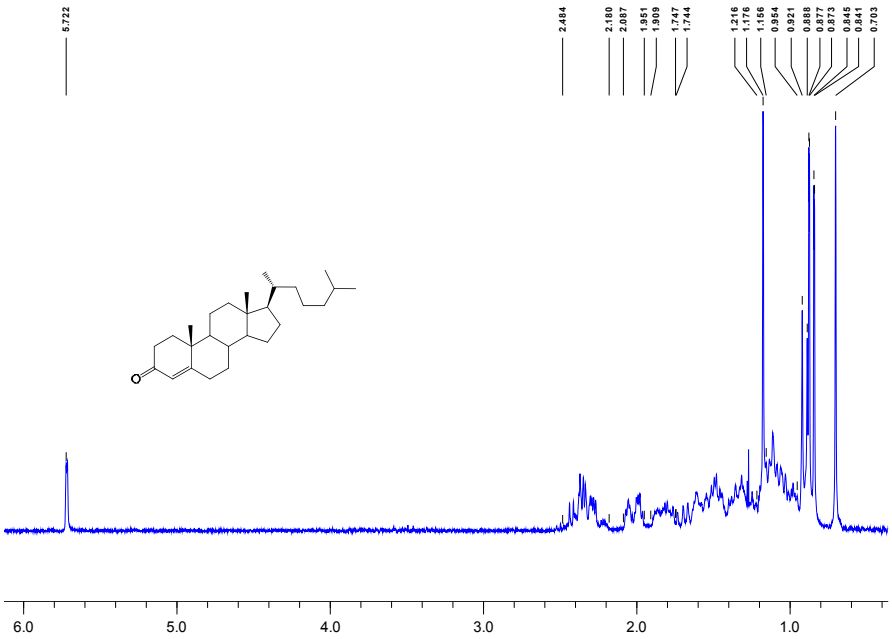


Figure 56. ^{1}H NMR spectrum in $CDCl_3$ of the isolated cholest-4-en-3-one

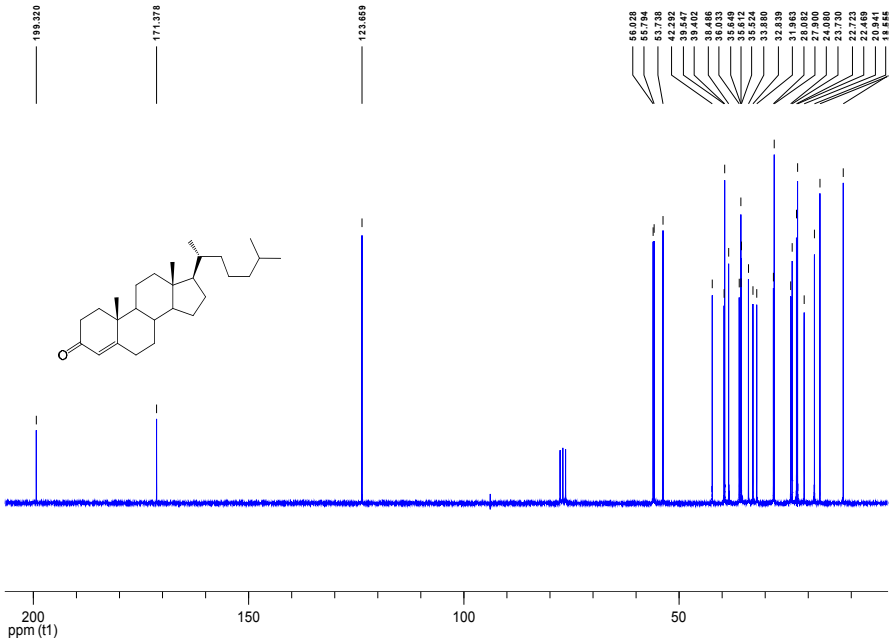


Figure 57. ^{13}C NMR spectrum in $CDCl_3$ of the isolated cholest-4-en-3-one

Cholest-4-en-3-one for its fat-accumulation inhibitory effect, can be used in the formulation of an anti-obesity agent which can be incorporated into food products or fats added to foods, or formulized into various pharmaceutical preparations. It is assumed that cholest-4-en-3-one antagonizes the action of the cholesterol and thus the transportation of the lipids through the cell membrane and the formation of adrenal corticoids.[131]

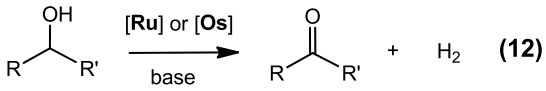
The isolation of cholest-4-en-3-one is a valuable application because by this way it is possible to isolate easily in good yield and in gram scale, progesterone and androstenedione. These are important steroidal hormones and thus vital regulators as well as precursors of other important hormones such as mineralocorticoids, glucocorticoids and sexual hormones, obtained with 95 % and 86 % final conversion respectively using **12** from the corresponding sterols (table 24).

5.3 Hydrogen production

In recent years a lot of attention has been devoted to hydrogen as suitable source for energy generation. This is in part a consequence of the progressive depletion of

fossil fuel reserves and the continuously increasing of energy demands. In addition, there exists a strong necessity to reduce the emission of green house gases. Apart from water cleavage, renewable resources such as biomass or its fermentation products, such as, alcohols are promising feedstocks for the generation of hydrogen. However, efficient hydrogen production from renewable resources remains difficult and improved technologies for generating hydrogen at higher reaction rates are required. In this respect, the development of new catalysts and their understanding will be a key issue.[86f] As described in the Chapter 1, there are examples of both homogeneous and heterogeneous catalysts capable of dehydrogenating alcohols.

Thus, we became interested in the generation of hydrogen under mild conditions from renewable resources, low molecular weight alcohols, at sufficient rate (TOF > 100 h^{-1}). On the basis of the previous studies on the activity of ruthenium catalysts containing amine and phosphine ligands for dehydrogenation of alcohols[90,94,97], a preliminary study on hydrogen production has been carried out using the secondary alcohols 2-propanol and 2-butanol as hydrogen donors. These compounds were chosen for the simplicity of the analysis, the availability and handling, as well as for the absence of side-reactions, such as aldol condensation or decarbonylationwhich may occur using primary alcohols. The catalytic reactions were performed with distilled alcohols at 110 °C (2-propanol) or 120 °C (2-butanol) in the presence of a base (NaO*i*Pr, KO*t*Bu) (eq. 12).



(12)

All the experiments were carried out in an open system under an inert gas atmosphere (argon) with exclusion of air, to promote hydrogen production and the removal of hydrogen from the reaction solution. The amount of hydrogen generated by the dehydrogenation of the alcohols was measured by a gas burette. Besides hydrogen, acetone and 2-butanone are formed which in the reaction were measured by GC analysis.

On account of the good results achieved by *trans*-[Os(dppf)(en)] (**12**) in the acceptorless DHY of alcohols (table 23 and table 24), the activity of this complex in the DHY of 2-propanol was tested changing the loading of NaO*i*Pr in the reaction solution (table 25).

Table 25. Influence of the base (NaO*i*Pr, 0.2 M) on the dehydrogenation of 2-propanol with catalyst **12** (0.005 mmol) at 110 °C

Entry	n_{base} / $n_{catalyst}$ [a]	H_2 tot. [mL][b]	Average TOF [h^{-1}][c]
1	0	10	–
2	4	99.5	415
3	10	125	425
4	20	136	567
5	50	127	529
6	100	111	367
7	200	104	433

[a] n_{base} / $n_{catalyst}$ = mmol of base / mmol of catalyst. [b] Measured by gas burette after 2 h. [c] The average TOF (mole of H_2 formed per mole of catalyst per hour) was calculated concerning to values measured by gas burette.

In agreement with the results shown in table 21 obtained in the dehydrogenation of α-tetralol with catalysts **11** and **12**, high catalytic activity occurs in a certain range of base concentration.

In absence of base (entry 1, table 21), catalyst **12** was found non active in the dehydrogenation of 2-propanol, only 10 mL of hydrogen were produced in 2 h. Using n_{base} / $n_{catalyst}$ = 4, 10 and 200, the complex shows apparently the same behavior with average TOF = 415, 425 and 433 h^{-1}, respectively. With n_{base} / $n_{catalyst}$ = 100, a lower hydrogen production was observed (88 mL of H_2 in 2 h, average TOF = 367 h^{-1}). Using n_{base} / $n_{catalyst}$ = 20 the osmium catalyst showed the best performance affording 136 mL of hydrogen in 2 h. It is worth noting that at higher loading of NaO*i*Pr (n_{base} / $n_{catalyst}$ = 50) the catalytic DHY of 2-propanol still occurs efficiently reaching average TOF = 529 h^{-1}, although the system undergoes deactivation.

These data show that the system **12** displays the best activity in the DHY of 2-propanol using 0.1 mmol of NaO*i*Pr (0.2 M). With this system, the dependence of the hydrogen production (mL of H_2) generated from the DHY of 2-propanol, from the ratio n_{base} / $n_{catalyst}$ is shown in figure 58.

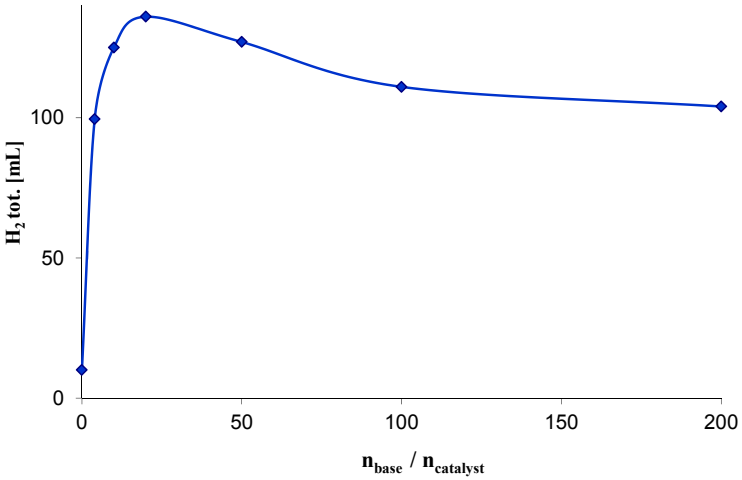
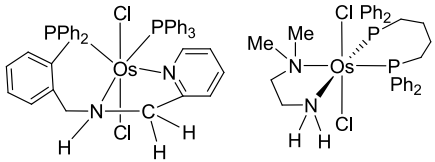


Figure 58

After this preliminary study to reach the ideal base concentration for this catalytic reaction, a number of catalysts of interest (see figure 59 and table 26) were tested in the DHY of 2-propanol and 2-butanol under the experimental conditions previously described. The catalytic results are shown in the table below.



26 **27**

Figure 59

Table 26. Catalytic dehydrogenation of 2-propanol at 110 °C and 2-butanol at 120 °C in the presence of base (NaO*i*Pr with 2-propanol or KOtBu with 2-butanol = 0.1 mmol) (final volume = 10 mL, catalyst = 0.005 mmol)

		2-Propanol		2-Butanol	
Entry	Catalyst	H_2 tot. [mL][a]	Average TOF [h^{-1}][b]	H_2 tot. [mL][a]	Average TOF [h^{-1}][b]
1	**9**	40	167	44	183
2	**12**	104	434	224	933
3	**19**	48.5	202	50	208
4	**26**	89	372	82	342
5	**27**	19.5	81	23	96

[a] Measured by gas burette after 2 h. [b] The average TOF (mole of H_2 formed per mole of catalyst per hour) was calculated concerning to values measured by gas burette.

The Os complexes, entry 2 and 4, displayed the best results, the system *trans*-[Os(dppf)(en)] (**12**), was found very active in the acceptorless dehydrogenation of a number of alcohol substrates,[122] reaching average TOF values up to 434 h^{-1} with 2-propanol and 933 h^{-1} with 2-butanol. These data show that from 2-butanol the hydrogen production is generally favored, except using Os PNN complex (**26**, entry 4). Interestingly, the Ru pincer catalysts **9** (entry 1) and **19** (entry 3) that catalyze the complete dehydrogenation of *α*-tetralol in *t*-BuOH at 130 °C in 24 h,[122] generate 40 mL and 48.5 mL of hydrogen in 2 h from 2-propanol (average TOF up to 202 h^{-1}) and 44 mL and 50 mL of hydrogen, respectively, in 2 h from 2-butanol (average TOF up to 208 h^{-1}).
On the basis of these promising catalytic results, a broad screening of various bi- and tridentate ligands has been carried out (table 27), preparing *in situ* catalysts by refluxing the ruthenium precursor $RuCl_2(dppb)(PPh_3)$ (figure 60) for 1 h in 2-propanol or 2-butanol with the ligands shown in figure 61 (**L-2 - 10**) (Ru : ligand = 1 : 2).

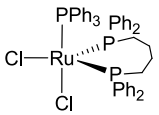


Figure 60. Ru precursor

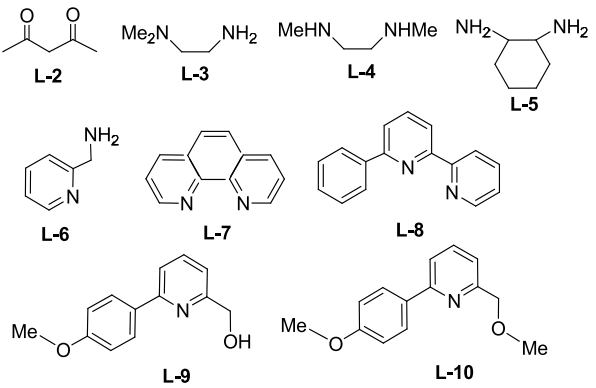


Figure 61. Ligands used to prepare the system $RuCl_2(dppb)(PPh_3)$ / **L-n** (**n** = **2** - **10**) ligand

Table 27. Catalytic DHY of 2-propanol at 110 °C and 2-butanol at 120 °C (final volume = 10 mL) with the system $RuCl_2(dppb)(PPh_3)$ / **L-n** (**n** = **2** - **10**) ligand (Ru = 0.005 mmol) in the presence of base (NaO*i*Pr with 2-propanol or KO*t*Bu with 2-butanol = 0.1 mmol)

	2-Propanol		2-Butanol	
Ligand	H_2 tot. [mL][a]	Average TOF [h^{-1}][b]	H_2 tot. [mL][a]	Average TOF [h^{-1}][b]
-	18.5	77	16	67
L-2	14	58	10	42
L-3	17.5	73	17	71
L-4	51.25	214	47	196
L-5	116	483	163	680
L-6	98.5	410	159	663
L-7	111	463	50	208
L-8	26.5	110	45	187.5
L-9	99	413	160	666
L-10	42.5	177	91	379

[a] Measured by gas burette after 2 h. [b] The average TOF (mole of H_2 formed per mole of catalyst per hour) was calculated according to the values measured by gas burette.

These results clearly show that the employment of the bidentate nitrogen ligand **L-5**, 1,2-diaminocyclohexane, resulted in the higher average TOF values with both 2-propanol (483 h^{-1}) and 2-butanol (680 h^{-1}). High activity was obtained also with the ampy ligand (**L-6**) and the tridentate **L-9**, reaching average TOF up to 413 h^{-1} in 2-propanol and up to 666 h^{-1} in 2-butanol. These data agree with those previously reported for the catalytic DHY of 2-propanol and 2-butanol (table 26). With these type of ligands the DHY of 2-butanol led to higher hydrogen production and it is faster than the DHY of 2-propanol.
A similar trend was observed with the tridentate ligands **L-8** and **L-10**, which gave respectively 45 mL and 91 mL of hydrogen from 2-butanol while with the same ligands only 26.5 mL and 42.5 mL of hydrogen from 2-propanol were formed.
On the contrary, using *ortho*-phenanthroline (**L-7**), the DHY of 2-propanol generated a double amount of hydrogen after 2 h (111 mL, average TOF = 463 h^{-1}) compared to the DHY of 2-butanol (50 mL, average TOF = 208 h^{-1}). With **L-2** and **L-3** poor hydrogen production was observed, obtaining respectively 14 mL and 17.5 mL of hydrogen from 2-propanol, 10 mL and 17 mL from 2-butanol. No significant difference in the hydrogen production was found using $RuCl_2(dppb)(PPh_3)$ in absence of the ligands **L-2** and **L-3**.

Chapter 6

α-alkylation of ketones with primary alcohols

In the previous chapters it has been described that the easily accessible complexes MCl_2(dppf)(ampy) (M = Ru ***cis*-1**, Os ***trans*-2**) are efficient catalysts for reducing reactions via transfer hydrogenation and hydrogenation reactions of carbonyl compounds as well as for dehydrogenation reactions involving alcohols and sterols. With these sytems good results have been achieved also in the racemization of chiral alcohols.

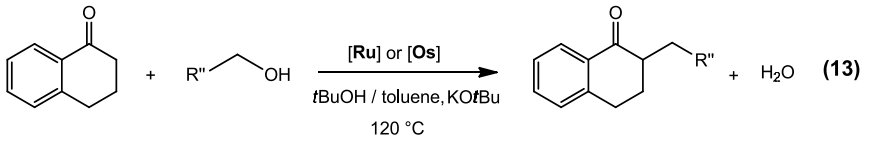
Recently, a great interest has been devoted to the preparation of efficient multitasking catalysts able to promote different organic transformations by a careful switching of the reaction parameters, namely temperature, solvent and co-catalyst concentration

In this part of the PhD thesis the study of the catalytic activity of the easily available ***cis*-1**, ***trans*-2** has been extended to other reactions of interest for industrial applications, involving carbonyl compounds and alcohols. Carbonyl compounds are reactive in a wider range of transformations than the precursor alcohols and can react *in situ* to give imines, alkenes, and α-functionalized carbonyl compounds such as α-alkylated ketones.

The α-alkylation of ketones with primary alcohols has been reported by several research groups as an important way to achieve valuable chemical intermediates with industrial applications (Cap. 1, Par. 1.5.2). The reaction proceeds via an oxidation of alcohol / aldol condensation / reduction of the unsaturated ketone pathway (Cap. 1, scheme 4).[86f] It is worth noting that the reduction of the unsaturated ketone intermediate may occur through hydrogenation at the C=C double bond or via reduction of the C=O bond, followed by isomerization of the allylic alcohol.

6.1 α-Alkylation of α-tetralone with ruthenium cis-1 and osmium trans-2

The complexes Ru ***cis*-1**, Os ***trans*-2** and the Ru **11**, which were found highly active in the DHY of alcohols and in the TH, HY reactions, were investigated in the alkylation of α-tetralone with several primary alcohols at 120 °C and in the presence of KO*t*Bu (30 mol %) in *t*BuOH / toluene (1 : 2, v / v) (eq. 13).



(13)

The alkylated ketones and the catalytic results are shown in figure 62 and in tables 28 - 29, respectively.

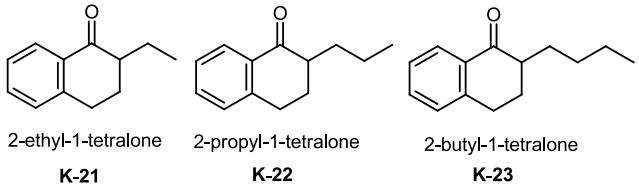


Figure 62

Table 28. α-Alkylation of α-tetralone (0.33 M) with primary alcohols (3 equiv.) using ***cis*-1**, ***trans*-2** (0.5 mol %) with KO*t*Bu (30 mol %) in *tert*-butanol / toluene (1 : 2, v / v) at 120 °C

		***cis*-1**		***trans*-2**	
Primary alcohol	Alkylated α-tetralone	Conv. [%] (h)[a]	TOF [h^{-1}][a]	Conv. [%] (h)[a]	TOF [h^{-1}][a]
EtOH	**K-21**	1 (8)[b]	–	–	–
EtOH	**K-21**	96 (4)	98	93 (1)	520
*n*PrOH	**K-22**	87 (2)	230	91 (30 min)	910
*n*BuOH	**K-23**	92 (3)	420	93 (10 min)	2800

[a] The conversion and TOF (moles of ketone converted into α-alkylated ketone per mole of catalyst per hour at 50 % conversion) were determined by NMR analysis. [b] Reaction in absence of ***cis*-1**.

Table 29. α-Alkylation of α-tetralone (0.33 M) with primary alcohols (3 equiv.) using **11** (0.5 mol %) with KO*t*Bu (30 mol %) in *tert*-butanol/toluene (1 : 2, v / v) at 120 °C

		11	
Primary alcohol	Alkylated α-tetralone	Conv. [%] (h)[a]	TOF [h^{-1}][a]
EtOH	**K-21**	89 (30)	29
*n*PrOH	**K-22**	93 (4)	95
*n*BuOH	**K-23**	90 (3)	410

[a] The conversion and TOF (moles of ketone converted into α-alkylated keton per mole of catalyst per hour at 50 % conversion) were determined by NMR analysis.

As shown in table 28, α-alkylation of α-tetralone with EtOH doesn't occur in the absence of ***cis*-1**, thus indicating that catalyst plays a fundamental role in this

reaction. By contrast, reaction of α-tetralone with EtOH (3 equiv.) and Ru ***cis*-1** leads to 96 % of the alkylated ketone in 4 h. Using *n*PrOH and *n*BuOH with the same catalyst, the conversion was 87 and 92 % in 2 and 3 h, respectively, with TOF up to 420 h^{-1}. The alkylated products were analyzed by NMR measurements and the data were compared with those reported in the literature.[105a,132] Apparently, no alkylation of ketones with simple alcohols (EtOH and *n*PrOH) has been described before this work. The relatively low loading of catalyst and the high rate indicate that ***cis*-1** is an efficient system for this reaction. Surprisingly, the osmium derivative ***trans*-2** displays a higher activity with respect to ruthenium ***cis*-1**. Thus, the alkylation of α-tetralone with EtOH, *n*PrOH and *n*BuOH is attained in 1 h, 30 min and 10 min, respectively, with TOF up to 2800 h^{-1}. No example on the use of Os in the α-alkylation of ketones has been reported. Interestingly, also the Ru complex **11** gave good results although displaying lower activity respect to the Os complex ***trans*-2**, especially in the α-alkylation of α-tetralone with EtOH (89 % conversion in 30 h). The results obtained by **11** with *n*PrOH and *n*BuOH are comparable with those achieved using the Ru catalyst ***cis*-1**, affording better results with *n*PrOH (93 % conversion in 4 h).

In conclusion, these data show that the Ru and Os systems ***cis*-**1 and ***trans*-**2 are highly active also in the ketone α-alkylation with primary alcohols.

Chapter 7

Isomerization of allylic alcohols to ketones

Redox isomerization of allylic alcohols into the corresponding saturated ketones mediated by transition metal complexes represents a useful way for the preparation of carbonyl compounds, which otherwise would require a two-step sequence of oxidation and reduction reactions (Cap. 1, Par. 1.5.3).
Among the several transition metal catalysts which have been developed for this transformation, particular attention has been devoted to ruthenium which led to the most active systems and some osmium complexes gave interesting results.[111,112]
To further extend the activity of the complexes ruthenium ***cis*-1** and osmium ***trans*-2**, they are also tested in the isomerization of allylic alcohols.

7.1 Isomerization of allylic alcohols with ruthenium cis-1 and osmium trans-2

Complex ***cis*-1** and ***trans*-2**, which were found active in the achiral TH and HY of aldehydes and ketones, racemization of chiral alcohols, DHY of alcohols and sterols and α-alkylation of α-tetralone with primary alcohols, were employed in the catalytic isomerization of allylic alcohols to obtain ketones of interest.
The ruthenium and osmium complexes (1 mol %) with KO*t*Bu (2 mol %) in *tert*-butanol catalyzes efficiently the isomerization of monosubstituted aliphatic alcohols (eq. 14) (figure 63), and the results of this study are shown in table 30.

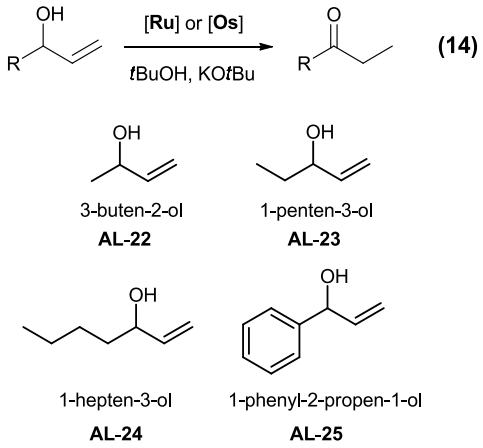


Figure 63. Allylic alcohols isomerizated to ketones

Table 30. Isomerization of allylic alcohols (0.33 M) with the Ru ***cis*-1** and Os ***trans*-2** (1 mol %) with KO*t*Bu (2 mol %) in *t*BuOH

	***cis*-1**			***trans*-2**		
Substrate	T °C	Conv. [%][a] (h)	TOF [h^{-1}][a]	T °C	Conv. [%][a] (h)	TOF [h^{-1}][a]
AL-22	70	94 (10 min)	6000	120	78 (1)	150
AL-23	70	93 (30 min)	480	120	90 (30 min)	300
AL-24	70	94 (30 min)	440	120	85 (1)	460
AL-25	120	93 (2)	160	120	62 (3)	150

[a] The conversion and TOF (moles of allylic alcohol converted into ketone per mole of catalyst per hour at 50 % conversion) were determined by GC analysis.

The substrate 3-buten-2-ol (**AL-22**) leads to 2-butanone in 64, 90 and 94 % conversion after 1, 5 and 10 min at 70 °C, respectively, affording a TOF = 6000 h^{-1} (table 30, entry 1). The substrates 1-penten-3-ol (**AL-23**) and 1-hepten-3-ol (**AL-24**) are isomerized to 2-pentanone and 2-heptanone in 30 min with TOF values 480 and 440 h^{-1}, respectively. The conversion of 1-phenyl-2-propen-1-ol (**AL-25**) to propiophenone occurs in 2 h at 120 °C, while at 70 °C the reaction is sluggish. With the osmium complex ***trans*-2**, the substrates 3-buten-2-ol, 1-penten-3-ol, 1-hepten-3-ol and 1-phenyl-2-propen-1-ol were converted into ketones at 120 °C with TOF up to 460 h^{-1}. These data clearly indicate the osmium ***trans*-2** displays also high catalytic activity, even though a higher temperature is required with respect to the ruthenium ***cis*-1**.

7.2 Applications in the industrial field

Among the ketones prepared by isomerization of the corresponding allylic alcohols which can be easily isolated after filtration and removing of the solvents by evaporation, 2-butanone is a manufactured chemical but it is also present in the environment from natural sources. It is a common solvent used in processes involving gums, resins, cellulose acetate and nitrocellulose coatings and in vinyl films. For this reason it finds use in the manufacture of plastics, textiles, in the production of paraffin wax, and in household products such as lacquer, varnishes, paint remover, a denaturing agent for denatured alcohol, glues, and other finishes, because it rapidly evaporates and will dissolve many substances, and as a cleaning agent. 2-Butanone is also used in dry erase markers as the solvent of the erasable dye.
As described in the Introduction, 2-pentanone is sometimes used in small amounts as a flavoring food additive for its sweet taste, and 2-heptanone, is an alarm

pheromone of insects and rats and a food additive used in particular in condiments, relishes, snack foods, baked goods.[39]
Besides, propiophenone is a useful intermediate to prepare nervous system drugs (anxiolytic and hypnotic drugs) (Cap. 1, figure 23) and in the formulation of perfumes and flavoring agents.

Conclusions

Chapter 8

In this PhD thesis a number of homogeneous ruthenium(II) and osmium(II) complexes, synthetized and characterized by the research group of inorganic and organometallic chemistry of the University of Udine, have been tested in a range of interesting reactions entailing carbonyl compounds and alcohols.

These systems have been prepared with chiral or achiral diphosphine and nitrogen ligands through an appropriate design of the complexes resulting in the formation of structurally well-defined catalysts.

High activity and reaction rate, at low catalyst loading, have been reached using ampy and pincer, ferrocenyl complexes ***cis***- / ***trans***-**1**, ***trans***-**2**, **3**, **4** and the pincer complex **5** (Cap. 2, figure 33) containing dppb, in the TH of aldehydes and ketones and with ***cis***-**1** and ***trans***-**2** also in HY reactions (5 atm H_2), using mild reaction conditions (82 °C for TH, 30 - 90 °C for HY). Through TH and HY, primary alcohols of interest such as *p*-anisyl alcohol, 2-methyl-1-butanol, hexyl alcohol, (±)-citronellol, (*S*)-citronellol, 2-phenylethanol and esters such as anisyl and hexyl acetate, citronellyl propionate and phenethyl propionate, have been synthesized and isolated in good to high yield. Interestingly, low concentration of metal residue (1,7 ppm of Ru) was found by ICP analysis in the isolated purified product (anisyl acetate) filtered over a short chromatography column filled with SiO_2 (10 cm) (Cap. 2, table 6).

The employment of the chiral pincer (*S*)-ligands (Cap. 3, figure 36), obtained via dynamic kinetic resolution (DKR) using lipase B from *Candida Antarctica*, and chiral Josiphos diphosphines, led to the preparation of chiral systems for the enantioselective reduction of ketones to (*R*)-alcohols in 2-propanol at 60 °C. Using the isolated complexes **6** and **8** (Cap. 3, eq. 8) in the asymmetric reduction of several alkyl aryl ketones, high purity (*R*)-alcohols have been obtained, namely (*R*)-1-phenylpropan-1-ol, (*R*)-3,5-bistrifluoromethyl-phenyl-ethanol (BTMP), which have applications in food and pharmaceutical industry. It is also noteworthy that the asymmetric reduction of (-)-menthone using the *in situ* system prepared with $RuCl_2(PPh_3)_3$ and the ligand (*S*)-**1b**, led to the synthesis and the isolation of (-)-menthol of 90 % purity (73 % yield).

In addition, the catalysts bearing bidentate and tridentate amino ligands, including the systems MCl_2(dppf)(ampy) (M = Ru, Os) ***cis***-**1**, ***trans***-**2**, found effective in TH and HY reactions, were found active for a number of organic transformations entailing the activation of the C-H bond close to the hydroxyl group of alcohols, thus broadening the alcohol reactivity. Complexes ***cis***-**1**, ***trans***-**2**, **3** - **5**, **9** - **18** (Cap. 4, figure 46), catalyze the racemization of optically active secondary alcohols in basic 2-propanol, and systems **3** - **5**, **9** - **10**, **17** - **18** are proven to be active for the deuteration of primary and secondary alcohols in basic 2-propanol-d_8. Racemization of alcohols in combination with DKR allows the preparation of chiral alcohols while deuterium-labeled compounds find application in pharmaceutical and analytical chemistry.

Interesting results have also been achieved in the accceptorless dehydrogenation of alcohols (DHY) using the complexes ***cis***- / ***trans***-**1**, ***trans***-**2**, **9** - **12**, **19** - **25** (Cap. 5,

figure 50, 51). These systems showed high activity in the oxidation of different substrates, including cyclic and linear alcohols and 5-en-3β-hydroxy steroids, in basic *t*BuOH at 130 - 145 °C. Thus, by this way, some compounds of interest in food and pharmaceutical industry: 1-indanone, α-tetralone, 4′-methoxyacetophenone, 2-heptanone, cholest-4-en-3-one, have been isolated in high yield and androstenedione, progesterone, have also been obtained. Moreover, the dehydrogenation of the secondary alcohols (2-propanol and 2-butanol) with hydrogen production as a potential method for energy generation, was also studied with complexes **9**, **12**, **19**, **26** and **27** (Cap. 5, figure 59) and with a number of *in situ* catalysts bearing nitrogen ligands (Cap. 5, figure 61). Promising results have been achieved especially with osmium complex **12** leading average TOF value of 933 h^{-1}.

In the final part of this PhD thesis, the α-alkylation of α-tetralone with several primary alcohols and the isomerization of allylic alcohols were studied using the easy accessible ampy, ferrocenyl complexes ***cis*-1**, ***trans*-2**. These catalysts, proven to be extremely versatile and efficient for a range of organic transformations such as TH and HY of carbonyl compounds, racemization of chiral alcohols, DHY of alcohols, showed good activity even in the α-alkylation of α-tetralone with primary alcohols and in the isomerization of allylic alcohols. All these reactions could have important applications to achieve valuable chemical intermediates (alkylated ketones) and for the preparation of carbonyl compounds through isomerization reactions. The comparison of the catalytic activity of the ruthenium(II) and osmium(II) complexes display that the first metal is generally active at lower temperature, whereas the second at higher temperature leading to better results for example in the oxidation of 5-en-3β-hydroxy steroids. Thus, osmium showed to be a valid complement to ruthenium also as regards enantioselectivity in asymmetric transfer hydrogenation, particularly at high temperature, where deactivation is retarded.

In conclusion, the ruthenium(II) and osmium(II) catalysts described in this PhD thesis have been found active in a number of redox reactions. The optimization of reaction parameters such as base concentration, substrate / catalyst ratio, type of solvents and reaction temperature, and even the design of the system, entailing the correct choice of phosphines and ligands, has led to good results in order to obtain and isolate interesting organic compounds.

The low metal concentration in the final purified product (< 5 ppm, the common limit of oral intake for Ru and Os), achievable simply by filtration over a suitable SiO_2 chromatography column, make these catalytic systems appealing for possible applications in the production of food aromas and additives, pharmaceuticals, agrochemicals. Furthermore, the straightforward catalyst preparation, in addition to the use of mild, environmentally friendly reaction conditions and low catalyst loading, represents a precondition for an efficient protocol for industrial utilizations.

Experimental Section

Chapter 9

9.1 Products, solvents and instruments

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. The solvents were carefully dried and distilled in the presence of Na and the substrates with $LiAlH_4$ before use. The diphosphine ligands, 1,1'-bis(diphenylphosphino)ferrocene (dppf) and all other chemicals were purchased from Aldrich or Fluka and used without further purification. HCNN (*S*) ligands were prepared according to literature procedures.[71e]
TLCs, were performed on silica gel 60 sheets. Chromatography separations and filtrations were carried out on columns having proper dimensions and using silica gel 60 (230 - 400 mesh). Optical rotations were measured with a digital polarimeter.
NMR measurements were recorded on a Bruker AC 200 spectrometer and the chemical shifts, in ppm, are relative to TMS for ^{1}H and $^{13}C\{^{1}H\}$ and 85 % H_3PO_4 for $^{31}P\{^{1}H\}$. The following abbreviations have been used: s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, b = broad. Elemental analyses (C, H, N) were carried out with a Carlo Erba 1106 elemental analyzer, whereas the GC analyses were performed with a Varian GP-3380 gas chromatograph equipped with a MEGADEX-ETTBDMS-β chiral column: length = 25 m, internal diameter = 0.25 mm, film thickness = 0.25 μm, column pressure = 5 psi, gas carrier = H_2 and a flame ionization detector (FID). Injector temperature = 250 °C. Detector temperature = 250 °C. Oven temperature programmed from 35 to 200 °C with temperature gradients from 0.4 to 40 °C / min. Peak identification was performed using the commercial reference substrates and products and checking complete conversion through NMR analyses.
For TH and HY reactions, acetophenone has been used as model substrate.
GC temperature program for acetophenone: 95 °C (0 min) - 1 °C / min - 110 °C (2 min) - 40 °C / min - 180 °C (3 min); $tr_{acetophenone}$ = 8.63 min; $tr_{(R)\text{-1-phenylethanol}}$ = 13.60 min; $tr_{(S)\text{-1-phenylethanol}}$ = 14.52 min.
The ICP analyses have been carried out on an ICP-OES Varian, VISTA MPX. The compounds $MCl_2(PPh_3)_3$ (M = Ru[60b], Os[133]), $RuCl_2(dppb)(PPh_3)$[134], catalysts **9**,[135] **10**,[71b] **11**,[94f] **12**,[103] **16**,[136] **17**,[137] **18**[72] **19**,[71a] **20**,[71a] **22**,[138] and the complexes shown in table 26 [71a,103,135] (Cap. 5, Par. 5.3), were prepared according to literature procedures. Derivatives ***cis*-1** and ***trans*-1**,[102] ***trans*-2**, **3**,[89] **4** and **5**,[89] **6**, **7** and **8**,[71e], **21**, **23**, **24** and **25**,[102] **13** and **14**[89]were isolated for the first time in the laboratories of Inorganic Chemistry of the Department of Chemistry, Physics and Environment (University of Udine).

9.2 Transfer hydrogenation and hydrogenation reactions with catalysts 1 - 5

*9.2.1 Synthesis of trans-[RuCl$_2$(dppf)(ampy)] (trans-**1**)*

$RuCl_2(PPh_3)_3$ (200 mg, 0.209 mmol) and dppf (127 mg, 0.229 mmol) were treated with toluene (2.0 mL) and the suspension was stirred for 1 h at 50 °C. After addition of ampy (23 mL, 0.223 mmol) the suspension was stirred for 2 h at 50 °C and then concentrated to about 0.5 mL. Addition of heptane (2 mL) afforded a yellow precipitate, which was washed with heptane (3 × 1 mL) and diethyl ether (3 × 1 mL) and dried under reduced pressure. Yield: 160 mg (92 %).
^{1}H NMR (200.1 MHz, CD_2Cl_2, 20 °C): δ = 8.51 (m, 1H), 8.10 (pseudo t, *J* = 7.9 Hz, 4H), 7.60 - 7.03 (m, 18H), 6.58 (t, *J* = 6.6 Hz, 1H), 4.73 (m, 2H), 4.31 (m, 2H), 4.22 (m, 2H), 4.14 (m, 2H), 4.03 (m, 2H), 3.05 (m, 2H); **^{13}C {^{1}H} NMR** (50.3 MHz, CD_2Cl_2, 20 °C): δ = 163.8, 156.3 (d, *J*(C,P) = 3.7 Hz), 139.2 - 120.1 (m), 89.9 (*J*(C,P) = 46.0 and 4.9 Hz), 82.4 (dd, *J*(C,P) = 46.8 and 0.8 Hz), 77.9 (d, *J*(C,P) = 7.7 Hz), 75.7 (d, *J*(C,P) = 7.1 Hz), 71.5 (d, *J*(C,P) = 5.8 Hz), 69.1 (d, *J*(C,P) = 5.0 Hz), 50.4 (t, *J*(C,P) = 2.3 Hz); **^{31}P{^{1}H} NMR** (81.0 MHz, CD_2Cl_2, 20 °C): δ = 51.6 (d, *J* = 38.3 Hz), 40.9 (d, *J* = 38.3 Hz); elemental analysis calcd (%) for $C_{40}H_{36}Cl_2FeN_2P_2Ru$: C 57.57, H 4.35, N 3.36; found: C 58.32, H 4.43, N 3.16.

9.2.2 Synthesis of cis-[RuCl$_2$(dppf)(ampy)] (cis-1)

Compound ***trans*-1** (120 mg, 0.144 mmol) was treated with toluene (2.0 mL), stirred for 24 h at 120 °C and then the suspension was dried under reduced pressure. Yield: 110 mg (92 %). **^{1}H NMR** (200.1 MHz, CD_2Cl_2, 20 °C): δ = 8.91 (m, 1H), 8.49 (pseudo t, *J* = 7.8 Hz, 2H), 8.16 (pseudo t, *J* = 8.1 Hz, 2H), 7.64 - 6.70 (m, 18H), 6.56 (s, 1H), 4.95 (m, 1H), 4.45 (m, 1H), 4.22 (m, 1H), 4.08 (m, 1H), 3.96 (m, 1H), 3.77 - 3.58 (m, 3H), 3.32 (m, 1H), 3.09 (m, 1H), 1.70 (m, 1H), 1.57 (m, 1H); **^{13}C {^{1}H} NMR** (50.3 MHz, CD_2Cl_2, 20 °C): δ = 158.6 (m), 151.0, 137.7 - 120.0 (m), 78.3 (d; *J*(C,P) = 12.8 Hz), 77.6 (d; *J*(C,P) = 8.4 Hz), 76.1 (d; *J*(C,P) = 2.9 Hz), 74.9 (d; *J*(C,P) = 6.9 Hz), 73.2 (d; *J*(C,P) = 5.8 Hz), 70.6 (d; *J*(C,P) = 3.9 Hz), 70.1 (d; *J*(C,P) = 5.5 Hz), 69.9 (d; *J*(C,P) = 5.6 Hz), 52.2 (d; *J*(C,P) = 2.6 Hz); **^{31}P{^{1}H} NMR** (81.0 MHz, CD_2Cl_2, 20 °C): δ = 57.8 (d, *J* = 35.6 Hz), 44.2 (d, *J* = 35.6 Hz); elemental analysis calcd (%) for $C_{40}H_{36}Cl_2FeN_2P_2Ru$: C 57.57, H 4.35, N 3.36; found: C 57.14, H 4.25, N 3.17.

9.2.3 Catalytic transfer hydrogenation of aldehydes and ketones with complexes cis-1, trans-1, 2, 3, 4 and 5

The ruthenium or osmium complex (1 - 1.3 μmol) was dissolved in 3 mL of 2-propanol. The aldehyde or ketone (1 mmol) was dissolved in 9 mL of 2-propanol and the solution was refluxed (100 °C, bath temperature) under argon. After addition of 200 μL of a NaO*i*Pr in 2-propanol (0.1 M, 20 μmol), 125 μL of the catalyst solution (0.05 μmol) and 2-propanol (final volume of the solution = 10 mL), the reduction of the aldehyde or the ketone starts immediately. The reaction was sampled by removing an aliquot of the reaction mixture and diethyl ether was added (1 / 1 in volume). The solution was filtered over a short silica pad and the conversion was determined by GC analysis (Ru or Os 0.005 mol %, NaO*i*Pr 2 mol %, aldehyde or ketone 0.1 M).

9.2.4 Preparation of anisyl alcohol by catalytic transfer hydrogenation with complex cis-1

The ruthenium ***cis*-1** (5.8 mg, 7.0 μmol) was dissolved in 50 mL of 2-propanol. After addition of *p*-anisaldehyde (1.7 mL, 14.0 mmol) and NaO*i*Pr (0.1 M, 2.8 mL, 0.28 mmol) the solution was refluxed under argon for 30 minutes. Diethyl ether was added to the solution (1 : 1, v / v), the mixture was filtered over a short column filled with SiO_2 (h = 10 cm, d = 10 mm) and the solvent was evaporated to afford the product which was analyzed through GC and NMR measurements (1.74 g, 90 % yield).
GC temperature program: 135 °C (0 min) - 1 °C / min - 158 °C (0 min) - 40 °C / min - 190 °C (2 min); tr $_{p\text{-anisaldehyde}}$ = 5.70 min; tr $_{\text{anisyl alcohol}}$ = 6.72 min.

Anisyl alcohol:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 7.30 - 7.25 (m, 2H), 6.94 - 6.87 (m, 2H), 4.57 (d, *J* = 4.7, 2H), 3.82 (s, 3H), 3.05 - 2.67 (br, 1H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 158.8, 133.0, 128.5, 113.7, 64.5, 55.1.

9.2.5 Preparation of 2-methyl-1-butanol by catalytic transfer hydrogenation with complex cis-1

2-Methyl-1-butanol was obtained following the procedure used for anisyl alcohol, using 2-methylbutyraldehyde (1.50 mL, 14.0 mmol) in place of *p*-anisaldehyde with ***cis*-1** and NaO*i*Pr (0.1 M, 1.4 mL, 0.14 mmol) in 50 mL of 2-propanol. The solution was refluxed under argon for 30 minutes and the product was analyzed through GC and NMR measurements (0.96 g, 78 % yield).
GC temperature program: 50 °C (0 min) - 2 °C / min - 75 °C (2 min) - 40 °C / min - 190 °C (1 min); tr $_{\text{2-methylbutyraldehyde}}$ = 3.79 min; tr $_{\text{2-methyl-1-butanol}}$ = 9.58 min.

2-Methyl-1-butanol:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 3.53 - 3.37 (m, 2H), 2.15 (s, 1H), 1.57 - 1.10 (m, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 8.0 Hz, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 67.8, 37.4, 25.9, 16.2, 11.3.

9.2.6 Preparation of hexyl alcohol by catalytic transfer hydrogenation with complex cis-1

Hexyl alcohol was obtained following the procedure used for anisyl alcohol, using hexanal (1.72 mL, 14.0 mmol) in place of *p*-anisaldehyde with ***cis*-1** and NaO*i*Pr (0.1 M, 1.4 mL, 0.14 mmol) in 50 mL of 2-propanol. The solution was refluxed under argon for 30 minutes and the
product was analyzed through GC and NMR measurements (1.31 g, 92 % yield).
GC temperature program: 45 °C (0 min) - 2 °C / min - 70 °C (2 min) - 40 °C / min - 190 °C (1 min); tr_{hexanal} = 8.66 min; $tr_{\text{hexyl alcohol}}$ = 15.45 min.

Hexyl alcohol:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 3.70 - 3.55 (m, 2H), 1.79 (s, 1H), 1.66 - 1.47 (m, 2H), 1.44 - 1.21 (m, 6H), 0.84 (t, *J* = 8.0 Hz, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 62.8, 32.8, 31.7, 25.6, 22.7, 14.1.

9.2.7 Preparation of (±)-citronellol by catalytic transfer hydrogenation complex with trans- 2

(±)-Citronellol was obtained following the procedure used for anisyl alcohol, using (±)-citronellal (2.52 mL, 14.0 mmol) in place of *p*-anisaldehyde with ***trans*-2** and NaO*i*Pr (0.1 M, 1.4 mL, 0.14 mmol) in 50 mL of 2-propanol and refluxing the solution for 2 h the product was analyzed through GC and NMR measurements (1.84 g, 84 % yield).
GC temperature program: 110 °C (0 min) - 3 °C / min - 120 °C (2 min) - 40 °C / min - 190 °C (1 min); $tr_{\text{(±)-citronellal}}$ = 4.87 min; $tr_{\text{(±)-citronellol}}$ = 7.18 min.

(±)-Citronellol
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 5.10 (m, 1H), 3.64 - 3.56 (m, 2H), 2.04 - 1.87 (m, 2H), 1.68 - 1.55 (m, 7H), 1.40 - 1.26 (m, 2H), 1.16 (m, 1H), 0.86 (m, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 131.0, 124.6, 61.7, 39.6, 37.1, 29.1, 25.6, 25.3, 19.4, 17.5.

9.2.8 Preparation of anisyl acetate

Anisyl alcohol (1.56 mL, 12.6 mmol) and acetic anhydride (15 mL) were refluxed for 1 h. The acetate was purified by elimination of the anhydride in excess through

distillation, obtaining 1.77 g of the product which was analyzed by NMR measurements (78 % yield). The ICP measurements of the Ru concentration in the final product have been carried out after filtration of the starting anisyl alcohol over a short column filled with SiO_2 (1° procedure: h = 2 cm of SiO_2, d = 10 mm; 2° procedure: h = 10 cm of SiO_2, d = 10 mm).

Anisyl acetate
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 7.29 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.04 (s, 2H), 3.79 (s, 3H), 2.07 (s, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 170.8, 159.5, 130.0, 127.9, 113.8, 65.9, 55.1, 20.9.

9.2.9 Preparation of hexyl acetate

Hexyl acetate was obtained following the procedure used for anisyl acetate, using hexyl alcohol (1.62 mL, 12.9 mmol), and the isolated product was analyzed through NMR measurements. Hexyl acetate 1.28 g (69 % yield).

Hexyl acetate
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 3.91 (t, *J* = 6.7 Hz, 2H), 2.07 (s, 3H), 1.62 (d, *J* = 7.1, 2H), 1.55 - 1.29 (b, 6H), 0.90 (t, *J* = 6.6 Hz, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 170.8, 64.3, 31.2, 28.3, 25.4, 22.3, 20.6, 13.7.

9.2.10 Preparation of citronellyl propionate

(±)-Citronellol (2.14 mL, 11.76 mmol) and propionic anhydride (20 mL) were refluxed for 3 h. Citronellyl propionate was purified by distillation obtaining 1.10 g of isolated product which was analyzed through NMR measurements (72 % yield).

Citronellyl propionate
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 5.02 - 4.92 (m, 1H), 3.99 (dt, *J* = 1.8 Hz, 6.8 Hz, 2H), 2.19 (q, *J* = 7.5 Hz, 2H), 1.94 - 1.81 (m, 2H), 1.56 (s, 3H), 1.49 (s, 3H), 1.43 - 1.08 (m, 4H), 1.02 (t, *J* = 7.6 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 174.1, 130.9, 124.4, 62.5, 36.8, 35.3, 29.3, 27.4, 25.4, 25.2, 19.2, 17.4, 8.9.

9.2.11 Preparation of (S)-citronellol by catalytic transfer hydrogenation with complex 4

(*S*)-(-)-β-Citronellol was obtained following the procedure used for anisyl alcohol, using (*S*)-(-)-citronellal (2.54 mL, 14.0 mmol) in place of *p*-anisaldehyde with **4** and NaO*i*Pr (0.1 M, 2.8 mL, 0.28 mmol) in 50 mL of 2-propanol. The solution was

refluxed under argon for 30 minutes and the product was analyzed through GC and NMR measurements (1.92 g, 88 % yield).
GC temperature program: 110 °C (0 min) - 3 °C / min - 120 °C (2 min) - 40 °C / min - 190 °C (1 min); tr $_{(S)\text{-citronellal}}$ = 4.92 min; tr $_{(S)\text{-citronellol}}$ = 7.21 min.

(*S*)-Citronellol
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 5.10 (m, 1H), 3.64 - 3.56 (m, 2H), 2.04 - 1.87 (m, 2H), 1.68 - 1.55 (m, 7H), 1.40 - 1.26 (m, 2H), 1.16 (m, 1H), 0.86 (m, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 131.0, 124.6, 61.7, 39.6, 37.1, 29.1, 25.6, 25.3, 19.4, 17.5.

9.2.12 Catalytic hydrogenation of aldehydes and ketones with complexes cis-1, trans-1

The ruthenium ***cis*-1** or ***trans*-1** complex (2.0 mg, 2.4 μmol) was dissolved in ethanol (2 mL). The substrate (2.0 mmol), 0.16 mL of NaOEt in ethanol (0.25 M, 0.04 mmol) and 0.33 mL of the catalyst solution (0.4 μmol) were added to ethanol (final volume of the solution = 4 mL). The solution was transferred into a thermostated reactor and the reduction was performed by introducing H_2 at 5 atm. The reaction was sampled by removing an aliquot of the reaction mixture and diethyl ether was added (1 / 1 in volume). The solution was filtered over a short silica pad and the conversion was determined by GC analysis (Ru 0.02 mol %, NaOEt 2 mol %, substrate 0.5 M).

9.2.13 Catalytic hydrogenation of aldehydes and ketones with complex trans-2

The osmium ***trans*-2** (2.0 mg, 2.2 μmol) was dissolved in methanol (2 mL). The substrate (2.0 mmol), KO*t*Bu (4.5 mg, 0.04 mmol), and 1.82 mL of the catalyst solution (2.0 μmol) were added to a methanol (1.2 mL) / ethanol (1 mL) mixture (final volume of the solution = 4 mL; MeOH / EtOH = 3 / 1 in volume). The solution was transferred into a thermostated reactor and the reduction was performed by introducing H_2 at 5 atm. The reaction was sampled by removing an aliquot of the reaction mixture and diethyl ether was added (1 / 1 in volume). The solution was filtered over a short silica pad and the conversion was determined by GC analysis (Os 0.1 mol %, KO*t*Bu 2 mol %, substrate 0.5 M).

9.2.14 Preparation of 2-phenylethanol by catalytic hydrogenation with complex trans-2

The osmium ***trans*-2** (18.5 mg, 0.02 mmol) was dissolved in 10 mL of a mixture MeOH / EtOH (3 / 1 in volume). After addition of phenylacetaldehyde (1.20 g, 10

mmol) and KO*t*Bu (22.4 mg, 0.2 mmol) the solution was transferred into a thermostated reactor at 90 °C affording complete reduction under H_2 (5 atm) in 8 h. Diethyl ether was added to the solution (1 / 1 in volume), the mixture was filtered over a short column filled with SiO_2 (h = 10 cm, d = 10 mm) and the solvent was evaporated to afford the product which was analyzed through GC and NMR measurements (1.04 g, 85 % yield).
GC temperature program: 110 °C (0 min) - 3 °C / min - 120 °C (2 min) - 40 °C / min - 190 °C (1 min); $tr_{phenylacetaldehyde}$ = 4.31 min; $tr_{2\text{-}phenylethanol}$ = 6.43 min.

2-Phenylethanol
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 7.40 - 7.22 (m, 5H), 3.82 (t, *J* = 6.8 Hz, 2H), 2.87 (t, *J* = 6.7 Hz, 2H), 2.7 (s, 1H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 138.5, 128.8, 128.3, 126.2; 63.3, 39.0.

9.2.15 Preparation of phenethyl propionate

2-Phenylethanol (1.02 mL, 8.5 mmol)) and propionic anhydride (15 mL) were refluxed for 3 h. Phenethyl propionate was purified by distillation obtaining 1.06 g of isolated product which was analyzed through NMR measurements (70 % yield).

Phenethyl propionate
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 7.38 - 7.20 (m, 5H), 4.32 (t, *J* = 7.0 Hz, 2H), 2.96 (t, *J* = 7.0 Hz, 2H), 2.33 (q, *J* = 7.6 Hz, 2H), 1.14 (t, *J* = 7.6 Hz, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 174.1, 137.7, 128.7, 128.3, 126.3, 64.5, 34.9, 27.3, 8.9.

9.3 Asymmetric transfer hydrogenation of ketones with chiral catalysts 6 - 8

9.3.1 Asymmetric transfer hydrogenation of acetophenone with the in situ catalyst [$MCl_2(PPh_3)_3$, M = Ru, Os] / (R,S)-Josiphos / (S)-1a - 1g ligand*

$RuCl_2(PPh_3)_3$ (1.0 mg, 1.04 μmol) and (*R*,*S*)-Josiphos* (1.1 mg, 1.57 μmol) or $OsCl_2(PPh_3)_3$ (1.0 mg, 0.95 μmol) and (*R*,*S*)-Josiphos* (1.0 mg, 1.43 μmol), respectively, were dissolved in 3 mL of 2-propanol and the solution was refluxed at 110 °C for 1 h (Ru) or 1.5 h (Os). The chiral pincer ligand (*S*)-**1a - g** (2.08 μmol for Ru and 1.90 μmol for Os) was added and the solution was refluxed at 110 °C for 1 h. Acetophenone (2 mmol) was dissolved in 2-propanol (18 mL) and the solution was heated at 60 °C under argon. By addition of NaO*i*Pr (0.1 M, 400 μL, 40 μmol) in 2-propanol, the appropriate volume of the solution of catalyst (0.1 μmol) and 2-propanol (final volume of the solution = 20 mL) the reduction of acetophenone starts immediately. The reaction was checked by removing an aliquot of the

reaction mixture and then diethyl ether was added (1 / 1 in volume). The solution was filtered over a short silica pad and the conversion was determined by GC analysis (Ru or Os 0.005 mol %, NaO*i*Pr 2 mol %, ketone 0.1 M).

9.3.2 Asymmetric transfer hydrogenation of ketones with catalysts 6 - 8

The ruthenium or osmium complex (1.0 mg) was dissolved in 3 mL of 2-propanol. The ketone (2 mmol) was dissolved in 2-propanol (18 mL), and the solution was heated at 60 °C under argon. By addition of NaO*i*Pr (0.1 M, 400 µL, 40 µmol) in 2-propanol, the appropriate volume of the solution of catalyst (0.1 µmol), and 2-propanol (final volume of the solution = 20 mL) the reduction of the ketone starts immediately. The reaction was checked by removing an aliquot of the reaction mixture and then diethyl ether was added (1 / 1 in volume). The solution was filtered over a short silica pad and the conversion was determined by GC analysis (Ru or Os 0.005 mol %, NaO*i*Pr 2 mol %, ketone 0.1 M).

9.3.3 Asymmetric transfer hydrogenation of (-)-menthone with the in situ catalyst [$MCl_2(PPh_3)_3$, M = Ru, Os] / P-n (n = 1 - 13) diphosphine / L-1 ligand

$RuCl_2(PPh_3)_3$ (2.0 mg, 2.08 µmol) and **P-1** - **13** (3.12 µmol) or $OsCl_2(PPh_3)_3$ (2.0 mg, 1.91 µmol) and **P-1** - **13** (2.86 µmol), respectively, were dissolved in 6 mL of 2-propanol and refluxed 110 °C for 1 h (Ru) or 1.5 h (Os). The CNN-pincer ligand **L-1** (4.16 µmol for Ru or 3.82 µmol for Os) was added and the solution was refluxed for 1 h. (-)-Menthone (1 mmol) was dissolved in 9 mL of 2-propanol and the solution was refluxed (100 °C, bath temperature) under argon. By addition of NaO*i*Pr (0.1 M, 200 µL, 20 µmol) in 2-propanol, the appropriate volume of the solution of catalyst (0.5 µmol) and 2-propanol (final volume of the solution = 10 mL) the reduction of (-)-menthone starts immediately. The reaction was checked by removing an aliquot of the reaction mixture and then diethyl ether was added (1 / 1 in volume). The solution was filtered over a short silica pad and the conversion was determined by GC and NMR measurements (Ru or Os 0.05 mol %, NaO*i*Pr 2 mol %, (-)-menthone 0.1 M).

9.3.4 Asymmetric transfer hydrogenation of (-)-menthone with the in situ catalyst $RuCl_2(PPh_3)_3$ / (S)-1b - 1f ligand

$RuCl_2(PPh_3)_3$ (2.0 mg, 2.08 µmol) and the chiral pincer ligand (*S*)-**1b** - **1f** (4.16 µmol) were dissolved in 6 mL of 2-propanol and refluxed at 110 °C for 1 h. The reduction of (-)-menthone was carried out following the procedure described in section **9.3.3**.

9.3.5 Preparation and isolation of (-)-menthol by asymmetric transfer hydrogenation with the in situ catalyst $RuCl_2(PPh_3)_3$ / (S)-1b ligand

The *in situ* catalyst $RuCl_2(PPh_3)_3$ / (*S*)-**1b** was prepared starting from 14 mg of $RuCl_2(PPh_3)_3$ (14.6 μmol) and 6.7 mg of (*S*)-**1b** (29.2 μmol) dissolved in 6 mL of 2-propanol and refluxed for 1 h. (-)-Menthone (2.4 mL, 14.0 mmol) was dissolved in 40 mL of 2-propanol and the solution was refluxed (100 °C, bath temperature) under argon. By addition of NaO*i*Pr (0.1 M, 2.8 mL, 0.28 mmol) and the appropriate volume of the solution of catalyst (7 μmol), the solution was refluxed under argon for 4 h. Diethyl ether was added to the solution (1 / 1 in volume), the mixture was filtered over a short silica pad and the solvent was evaporated to afford an oil which was analyzed through GC and NMR measurements (1.99 g, 91 % yield). The mixture containing 80 % (-)-menthol and 20 % of (+)-neomenthol, was dissolved in ethyl acetate and purified on a SiO_2 column (h = 60 cm, d = 26 mm, eluent: heptane / ethyl acetate = 9 / 1, in volume), obtaining 90 % of (-)-menthol as inferred from GC and NMR analyses (1.16 g, 73 % yield).
GC temperature program: 90 °C (0 min) - 1 °C / min - 110 °C (0 min) - 1 °C / min - 120 °C (5 min) - 20 °C / min - 130 °C (20 min) - 40 °C / min - 190 °C (1 min); $tr_{(-)\text{-menthone}}$ = 10.38 min; $tr_{(+)\text{-neomenthol}}$ = 13.51 min; $tr_{(-)\text{-menthol}}$ = 15.18 min.

(-)-Menthol
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 3.37 (dt, *J* = 4.3 Hz, 10.6 Hz, 1H), 2.16 (dqn, *J* = 2.5 Hz, 7 Hz, 13.9 Hz, 1H), 1.99 - 1.89 (m, 1H), 1.74 (s, 1H), 1.70 - 1.30 (m, 3H), 1.23 - 0.95 (m, 3H), 0.92 - 0.87 (m, 6H), 0.80 - 0.76 (m, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 71.4, 50.1, 45.0, 34.5, 31.6, 25.7, 23.1, 22.2, 21.0, 16.0.

9.4 Racemization of chiral alcohols

9.4.1 Synthesis of $RuCl_2$(L-1)(dppb) (9)

To a suspension of $RuCl_2(PPh_3)$(dppb) (1.17 g, 1.36 mmol) in 2-propanol (15 mL) were added the ligand **L-1** (0.300 g, 1.51 mmol) and triethylamine (1.9 mL, 13.6 mmol). The mixture was refluxed for 2 h, and the yellow precipitate was filtered, washed with methanol, and dried under reduced pressure. Yield: 810 mg (78 %).
^{1}H NMR (200.1 MHz, CD_2Cl_2, 20 °C): δ = 8.10 - 6.57 (m, 24H), 6.00 (t, *J* = 8.1 Hz, 2H), 4.12 (dd, *J* = 15.5 Hz, 4.4 Hz, 1H), 3.72 (td, *J* = 15.5 Hz, 4.1 Hz, 1H), 3.41 (m, 1H), 3.05 (m, 2H), 2.46 - 0.90 (m, 7H), 2.23 ppm (s, 3H); **^{13}C{^{1}H} NMR** (50.3 MHz, CD_2Cl_2, 20 °C): δ = 181.8 (dd, *J*(C,P) = 16.3 Hz, 7.8 Hz), 163.2, 155.9, 149.2 - 116.0, 52.5 (d, *J*(C,P) = 2.7 Hz), 33.4 (d, *J*(C,P) = 26.3 Hz), 30.7 (d, *J*(C,P) = 31.6), 26.8, 22.1, 21.8; **^{31}P{^{1}H} NMR** (81.0 MHz, CD_2Cl_2, 20 °C): δ =

57.3 (d, J = 38.3 Hz), 42.6 (d, J = 38.3 Hz); elemental analysis calcd (%) for $C_{41}H_{41}ClN_2P_2Ru$: C 64.77, H 5.44, N 3.68; found: C 64.36, H 5.52, N 3.70.

9.4.2 Racemization of chiral alcohols with catalysts cis-1, trans-2, 3 - 5, 9 - 18

The ruthenium or osmium complex (1.6 μmol), NaO*i*Pr (66 μL, 0.1 M solution in 2-propanol, 6.6 μmol) or KO*t*Bu, DBU, NEt_3, K_2CO_3 (8.2 μmol) and the chiral alcohol (0.16 - 0.33 mmol) were dissolved in 2-propanol (0.5 - 1 mL) under argon. The solution was stirred at the desired temperature. The reaction was sampled by removing an aliquot of the reaction mixture (25 μL) and diethyl ether was added. The solution was filtered over a short silica pad and the conversion was determined by GC analysis (Ru or Os 0.5 - 1 mol %, NaO*i*Pr 2 mol %, KO*t*Bu, DBU, NEt_3, K_2CO_3 5 mol %, chiral alcohol 0.33 M).

9.5 Deuteration of alcohols

9.5.1 Deuteration of alcohols with catalysts 3 - 5, 9 - 10, 17 - 18

In a NMR tube the catalyst (1.6 μmol) and KO*t*Bu (8.2 μmol) were dissolved in 2-propanol-d_8 (0.5 mL) and the substrate (0.164 mmol) was added under argon. The solution was kept at the desired temperature and the incorporation of D content was monitored over time by NMR spectroscopy. In the case of (*S*)-1-phenylethanol, the solution was also analyzed by chiral GC, according to the above procedure for the racemization of alcohols (2-propanol-d_8 / substrate = 40) (Ru or Os 1 mol %, KO*t*Bu 5 mol%, alcohol 0.33 M).

9.6 Dehydrogenation of alcohols and sterols

9.6.1 Catalytic dehydrogenation of alcohols with catalysts cis-1, trans-1, trans-2, 9 - 12, 19 - 20, 21 - 25

The ruthenium or osmium complex (0.01 mmol) was dissolved in *t*BuOH (2 mL). After addition of the alcohol substrate (2.5 mmol) and KO*t*Bu (0.05 mmol) the solution was heated at 130 °C (bath temperature) under argon in an open system. The reaction was sampled by removing an aliquot of the reaction mixture and diethyl ether was added (1 / 1 in volume). The solution was filtered over a short silica pad and the conversion was determined by GC and NMR analyses which revealed the absence of side products (Ru or Os 0.4 mol %, KO*t*Bu 2 mol %, alcohol 1.25 M).

9.6.2 Preparation of 1-indanone by catalytic dehydrogenation with catalyst 11

The ruthenium **11** (7.9 mg, 0.01 mmol) was dissolved in *t*BuOH (2 mL). After addition of 1-indanol (335 mg, 2.5 mmol) and KO*t*Bu (5.6 mg, 0.05 mmol) the solution was heated at 130 °C (bath temperature) under argon in an open system for 7 h. Diethyl ether was added to the solution (1 / 1 in volume), the mixture was filtered through a short silica pad, and the solvent was evaporated. The product was purified on a SiO_2 chromatography column (h = 50 cm, d = 10 mm, CH_2Cl_2 / ether = 30 : 1, in volume) to give the ketone which was analyzed through GC and NMR analyses (265 mg, 80 % yield).
GC temperature program: 135 °C (0 min) - 2 °C / min - 158 °C (1 min) - 20 °C / min - 170 °C (2 min) - 40 °C / min - 190 °C (2 min); $tr_{indanone}$ = 6.46 min; $tr_{indanol}$ = 7.12 min.

1-Indanone
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 7.70 - 7.30 (m, 4H), 3.07 (t, *J* = 5.8 Hz, 2H), 2.61 (t, *J* = 5.9 Hz, 2H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 206.9, 155.1, 137.0, 134.5, 127.2, 126.6, 123.6, 36.1, 25.7.

9.6.3 Preparation of α-tetralone by catalytic dehydrogenation with catalyst 11

The ketone α-tetralone was obtained by following the procedure used for 1-indanone, using α-tetralol as substrate and heating the solution for 4 h to afford the product which was analyzed through GC and NMR analyses (302 mg, 83 % yield).
GC temperature program: 135 °C (0 min) - 2 °C / min - 158 °C (1 min) - 20 °C / min - 170 °C (2 min) - 40 °C / min - 190 °C (2 min); $tr_{\alpha\text{-tetralone}}$ = 8.39 min; $tr_{\alpha\text{-tetralol}}$ = 9.21 min.

α-Tetralone
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 7.97 (d, *J* = 7.6, 1H), 7.39 (dt, *J* = 7.4 Hz, 1H), 7.26 - 7.16 (m, 2H), 2.88 (t, *J* = 6 Hz, 2H) 2.57 (t, *J* = 6.5 Hz, 2H) 2.05 (qn, *J* = 6.3 Hz, 12.6 Hz, 2H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 197.6, 143.9, 132.8, 132.0, 128.3, 126.5, 126.0, 38.6, 29.1, 22.5.

9.6.4 Preparation of 4'-methoxyacetophenone by catalytic dehydrogenation with catalyst 11

The ketone 4'-methoxyacetophenone was obtained by following the procedure used for 1-indanone, using 4-methoxy-1-phenylethanol as substrate and heating the

solution for 5 h to afford the product which was analyzed through GC and NMR analyses (290 mg, 77 % yield).
GC temperature program: 120 °C (0 min) - 1 °C / min - 152 °C (2 min) - 40 °C / min - 180 °C (1 min); $tr_{4'\text{-methoxyacetophenone}}$ = 12.79 min; $tr_{4\text{-methoxy-1-phenylethanol}}$ = 13.51 min.

4'-Methoxyacetophenone
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 7,93 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 2.54 (s, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 196.5, 163.3, 130.4, 130.1, 113.5, 55.2, 26.1.

9.6.5 Preparation of 2-heptanol by catalytic dehydrogenation with catalyst 12

The ketone 2-heptanone was obtained by following the procedure used for 1-indanone, using 2-heptanol (0.14 mL, 1 mmol) as substrate, the osmium **12** (20.9 mg, 0.02 mmol), KO*t*Bu (11.2 mg, 0.1 mmol) and heating the solution for 20 h to afford the product which was analyzed through GC and NMR analyses (90.2 mg, 79 % yield, Os 2 mol %, KO*t*Bu 10 mol %, 2-heptanol 0.5 M).
GC temperature program: 100 °C (0 min) - 1 °C / min - 120 °C (2 min) - 40 °C / min - 190 °C (2 min); $tr_{2\text{-heptanone}}$ = 3.06 min; $tr_{2\text{-heptanol}}$ = 3.61 min.

2-Heptanone
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 2.41 (t, *J* = 7.1 Hz, 2H), 2.13 (s, 3H), 1.54 (qn, *J* = 7.1, 14.2 Hz, 2H), 1.41 - 1.20 (m, 4H), 0.90 (t, *J* = 7.8 Hz, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 209.1, 43.6, 31.4, 29.6, 23.5, 22.5, 13.8.

9.6.6 Catalytic dehydrogenation of 3β-hydroxy sterols with catalysts 11 and 12

The ruthenium **11** or osmium **12** complex (0.01 mmol), the sterol substrate (1.25 mmol), and KO*t*Bu (0.05 mmol) were dissolved in *t*BuOH (2 mL) and toluene (1 mL). The solution was heated at 145 °C (bath temperature) under argon in an open system. The reaction was sampled by removing an aliquot of the reaction mixture and diethyl ether was added (1 / 1 in volume). The solution was filtered over a short Celite® column (h = 10 cm, d = 10 mm) and the conversion into the 4-en-3-one derivative was determined by ^{1}H NMR analysis (Ru or Os 0.8 mol %, KO*t*Bu 4 mol %, sterol 0.42 M).

Cholest-4-en-3-one:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 5.72 (s, 1H), 2.18 - 2.48 (several m, 4H), 2.09 - 1.95 (several m, 2H), 1.91 - 1.75 (m, 2H), 1.74 - 1.22 (several m, 12H), 1.17 (s, 3H), 1.15 - 0.95 (several m, 8H) 0.91 (d, *J* = 6.0 Hz, 3H), 0.86 (dd, *J* = 9.0 Hz, 3.0 Hz, 6H), 0.70 (s, 3H).

24-Ethylcholesta-4,22-dien-3-one:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 5.71 (s, 1H), 5.14 (dd, *J* = 15.0 Hz, 8.0 Hz, 1H), 5.00 (dd, *J* = 15.0 Hz, 8.0 Hz, 1H), 2.43 - 2.26 (several m, 4H), 2.05 - 1.96 (m, 3H), 1.81 - 1.37 (several m, 10H), 1.27 - 0.87 (several m, 8H) 1.17 (s, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.85 - 0.76 (complex m, 9H), 0.72 (s, 3H).

Androstenedione:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 5.74 (s, 1H), 2.55 - 2.27 (several m, 5H), 2.14 - 1.33 (several m, 10H), 1.18 (s, 3H), 1.30 - 0.95 (several m, 4H), 0.91(s, 3H).

Progesterone:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 5.69 (s, 1H), 2.55 - 2.50 (m, 1H), 2.47 - 2.14 (several m, 5H), 2.10 (s, 3H), 2.06 - 2.01 (m, 2H), 1.91 - 1.84 (m, 1H), 1.76 - 0.92 (complex m, 11H), 1.23 (s, 3H), 0.63 (s, 3H).

9.6.7 Preparation of cholest-4-en-3-one by catalytic dehydrogenation with catalyst 11

The ruthenium **11** (7.9 mg, 0.01 mmol) was dissolved in *t*BuOH (2 mL) and toluene (1 mL). After addition of cholest-5-en-3β-ol (483 mg, 1.25 mmol) and KO*t*Bu (0.05 mmol) the solution was heated at 145 °C (bath temperature) under argon in an open system for 20 h. Diethyl ether was added to the solution (1 / 1, v / v), the mixture was filtered over a short celite pad, and the solvent was evaporated to give the ketone which was characterized by ^{1}H NMR and ^{13}C NMR analyses (435 mg, 90 % yield).

Cholest-4-en-3-one:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 5.72 (s, 1H), 2.18 - 2.48 (several m, 4H), 2.09 - 1.95 (several m, 2H), 1.91 - 1.75 (m, 2H), 1.74 - 1.22 (several m, 12H), 1.17 (s, 3H), 1.15 - 0.95 (several m, 8H) 0.91 (d, *J* = 6.0 Hz, 3H), 0.86 (dd, *J* = 9.0 Hz, 3.0 Hz, 6H), 0.70 (s, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 199.3, 171.4, 123.6, 56.0, 55.8, 53.7, 42.3, 39.5, 39.4, 38.5, 36.0, 35.6, 35.6, 35.5, 33.9, 32.8, 31.9, 28.1, 27.9, 24.1, 23.7, 22.7, 22.5, 20.9, 18.5, 17.3, 11.8.

9.6.8 Catalytic dehydrogenation of 2-propanol and 2-butanol with ruthenium and osmium catalysts

The ruthenium or osmium complex (Cap. 5, table 26, 0.005 mmol) and the base (0.1 mmol), NaO*i*Pr (0.2 M, 0.5 mL) in 2-propanol or KO*t*Bu in 2-butanol, were added to 2-propanol or 2-butanol (final volume of the solution = 10 mL) in a schlenk, which was connected to a vigreaux column linked to a trap filled with NaOH and then to a gas burette for hydrogen measurements.
The reaction solution was refluxed at 110 °C for 2-propanol and 120 °C for 2-butanol, (bath temperature), under argon. Before starting the measurements, the system was purged with argon to remove air. The amount of generated hydrogen was measured by gas burette and the progress of the reaction was monitored through the production of acetone and 2-butanone by GC analysis.

9.6.9 Catalytic dehydrogenation of 2-propanol and 2-butanol with the in situ catalyst $RuCl_2(dppb)(PPh_3)$ / L-n (n = 2 - 10) ligand

$RuCl_2(dppb)(PPh_3)_3$ (3.5 mg, 5.0 μmol) and the ligand **L-2 - 10** (10.0 μmol) were dissolved in 9.5 mL of 2-propanol or 10 mL of 2-butanol and refluxed for 1h at 110 °C in 2-propanol and 120 °C in 2-butanol. The dehydrogenation of 2-propanol and 2-butanol were obtained following the procedure described above in section **9.6.8**.

9.7 α-Alkylation of ketones with primary alcohols

9.7.1 α-Alkylation of α-tetralone with primary alcohols catalyzed by cis-1, trans-2 and 11

The ruthenium or osmium complex (5.0 μmol), α-tetralone (146.2 mg, 1.0 mmol), the primary alcohol (3.0 mmol) and KO*t*Bu (34 mg, 0.30 mmol) were dissolved in 1 mL of *t*BuOH and 2 mL of toluene. The solution was heated at 120 °C (bath temperature) under argon. The reaction was sampled by removing an aliquot of the reaction mixture and diethyl ether was added (1 / 1 in volume). The solution was filtered over a short silica pad, the solvent was evaporated and the conversion was determined by NMR analysis (Ru or Os 0.5 mol %, KO*t*Bu 30 mol %, α-tetralone 0.33 M).

2-Ethyl-1-tetralone:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 8.04 (dd, *J* = 7.7 Hz, 1.2 Hz, 1H), 7.46 (ddd, *J* = 7.4 Hz, 7.4 Hz, 1.5 Hz, 1H), 7.32 (dd, *J* = 8.0 Hz, 7.7 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 3.03 - 2.98 (m, 2H), 2.49 - 2.35 (m, 1H), 2.26 (ddd, *J* = 13.2 Hz, 9.5 Hz, 4.6 Hz, 1H), 2.06 - 1.84 (m, 2H), 1.60 (dq, *J* = 21.3 Hz, 7.4 Hz, 1H), 1.01 (t, *J*

= 7.5 Hz, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 200.3, 143.9, 133.0, 132.5, 128.6, 127.3, 126.5, 48.8, 28.3, 27.6, 22.3, 11.4.

2-Propyl-1-tetralone:
^{1}H NMR (200.1 MHz, $CDCl_3$, 20 °C): δ = 8.03 (dd, *J* = 7.7 Hz, 1.5 Hz, 1H), 7.45 (ddd, *J* = 7.4 Hz, 7.5 Hz, 1.5 Hz, 1H), 7.30 (dd, *J* = 8.0 Hz, 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 3.02 - 2.95 (m, 2H), 2.53 - 2.42 (m, 1H), 2.23 (ddd, *J* = 13.3 Hz, 9.5 Hz, 4.7 Hz, 1H), 1.99 - 1.81 (m, 2H), 1.57 - 1.33 (m, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); **^{13}C {^{1}H} NMR** (50.3 MHz, $CDCl_3$, 20 °C): δ = 200.4, 143.9, 133.0, 132.5, 128.6, 127.4, 126.5, 47.2, 31.5, 28.2, 28.1, 20.2, 14.2.

2-Butyl-1-tetralone:
^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 8.03 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.45 (ddd, *J* = 7.4 Hz, 7.4 Hz, 1.5 Hz, 1H), 7.31 (dd, *J* = 7.9 Hz, 7.7 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 3.02 - 2.95 (m, 2H), 2.54 - 2.39 (m, 1H), 2.24 (ddd, *J* = 13.3 Hz, 9.5 Hz, 4.7 Hz, 1H), 2.03 - 1.79 (m, 2H), 1.50 - 1.31 (m, 5H), 0.92 (t, *J* = 6.6 Hz, 3H); **^{13}C {^{1}H} NMR** (50 MHz, $CDCl_3$, 20 °C): δ = 200.5, 143.9, 133.0, 132.5, 128.6, 127.4, 126.5, 47.4, 29.2, 29.1, 28.2, 28.1, 22.8, 14.0.

9.8 Isomerization of allylic alcohols to ketones

9.8.1 Isomerization of allylic alcohols with catalysts cis-1 and trans-2

The ruthenium ***cis*-1** or osmium ***trans*-2** (0.01 mmol), the allylic alcohol (1 mmol) and KO*t*Bu (2.2 mg, 0.02 mmol) were dissolved in 3 mL of *t*BuOH. The solution was heated at 70 °C (Ru) or 120 °C (Os, bath temperature) under argon. The reaction was sampled by removing an aliquot of the reaction mixture and diethyl ether was added (1 / 1 in volume). The solution was filtered over a short silica pad and the conversion was determined by GC analysis (Ru or Os 1 mol %, KO*t*Bu 2 mol %, allylic alcohol 0.33 M).

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