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To Andrei, Victor, mom and dad

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Abstract

This thesis describes a study of the hydrogenation of different functional groups in the presence of clays or metals anchored on clays as catalysts. The thesis also describes the selective aerobic oxidation of sulfides to sulfoxides using a palladium based catalyst .

Chapters 2 and 3 detail work on the hydrogenation processes. Ruthenium clays were prepared using montmorillonite-phosphine or montmorillonite-bipyridine and $RuCl_3 \cdot H_2O$. The clays obtained were found to be effective catalysts for the reduction of unsaturated esters, epoxides, sulfones and phosphonates. It was shown that Ru-phosphine clay is an efficient catalyst for reduction of the α-carbonyl group of α-ketoesters and α-ketoamides, and the α-imine group of α-iminoesters and α-iminoketones. The reductive amination of α-ketoesters with amines, catalyzed by ruthenium clay, was studied. The diastereoselectivity of the reactions was studied using chiral amines. Modification of the clay structure using organic ligands and/or metals was also investigated.

The reduction of aliphatic and aromatic ketones by hydrogen transfer was studied. The reaction was catalyzed by sodium montmorillonite and took place under basic conditions (0.06 M KOH in isopropanol). The *cis/trans* selectivity of the process was also examined.

The last chapter (Chapter 4) describes the selective oxidation of sulfides to sulfoxides. The palladium complex $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$, on exposure to oxygen in tetrahydrofuran, generates an active catalytic system for this reaction. The presence of other functional groups (amide, carboxyl) does not interfere with the oxidation process at sulfur. It was shown that this process is stereospecific in the case of (+)-biotin-sulfoxide 4-nitrophenyl ester.

Abbreviations

AAEMA$^-$	2-(acetoacetoxy)ethyl methacrylate (deprotonated form)
BDDP	2,4-bis(diphenylphosphino)pentane
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
(*R*,*S*)-BINAPHOS	(*R*)-2-diphenylphosphino-1,1’-binaphthalen-2’-yl (*S*)-(1,1’-binaphthalen-2,2’-diyl phoshite)
BOC	*tert*-butoxycarbonyl
br	broad
BPPM	1-(*t*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl] pyrolidine
bpy	2,2’- bipyridine
n-Bu	*normal*-butyl
t-Bu	*tert*-butyl
CI	chemical ionization
COD	1,5-cyclooctadiene
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
d	doublet
dd	doublet of doublets
DIOP	*trans*-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolan
DuPHOS	1,2-bis(phospholano)-benzene
ee	enantiomeric excess
EDS	energy dispersive spectrometry
EI	electron impact
Et	ethyl group
FT-IR	Fourier-transform infrared
GC	gas chromatography
ICP	inductive coupling plasma
J	coupling constant, in Hz

L	ligand
M	metal
MPV	Meerwein-Ponndorf-Verley reaction
M	molar concentration, mol/l
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl group
mp	melting point
MS	mass spectrometry
NBD	norbornadiene
ORTEP	Oak Ridge thermal ellipsoid plot
Ph	phenyl group
PNNP	*N,N'* bis[*R*(+)-α-methylbenzyl]- *N,N'* bis(diphenylphosphino) ethylenediamine
PROPHOS	1,2-bis(diphenylphosphino)propane
psi	pound per square inch
q	quartet
s	singlet
SEM	scanning electron micrographs
t	triplet
TBHP	*tert*-butyl hydroperoxide
THF	tetrahydrofuran
TLC	thin layer chromatography
TOF	turnover frequency
TON	turnover number
TPPMS	*m*-monosulfonated triphenylphosphine
TPPTS	*m*-trisulfonated triphenylphosphine
Ts	tosyl
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction

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Chapter 1.

Oxidation and Reduction Processes

1.1 Oxidation and Reduction

Oxidation and reduction processes play an important role in most synthetic sequences. They are indispensible when functional groups must be oxidized or reduced to the level required in the products, or in order to facilitate the introduction of other groups[1].

The number of oxidizing or reducing reagents employed in organic transformations is very large, and often many reagents effect the same type of transformation, but with different efficiencies and under different conditions[2]. At the same time the diversity of mechanisms involved in these processes covers a broad range and many mechanistic questions are still not clear. But important progress has been made and, due to the development of techniques and equipment, reactions could be examined almost step by step and experimental evidence was obtained for the composition and structure of reaction intermediates. Advances made in different fields contributed to the understanding of related areas (e.g. the research into homogeneous hydrogenation contributed to the development of homogeneous catalysis in general, but the ideas developed during this research were also important for heterogeneous catalysis)[3].

1.2 Oxidation and Reduction Reactions Catalyzed by Metal Complexes

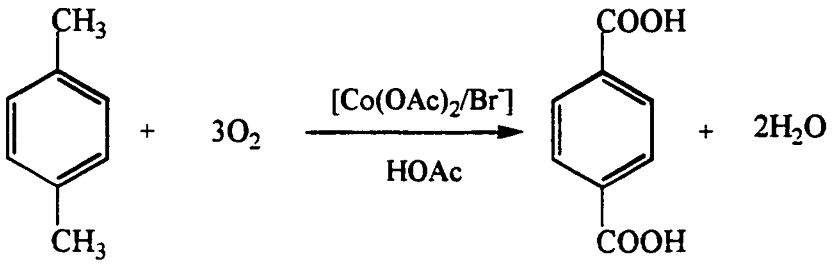
The majority of the processes employed industrially involve catalysis by metal complexes. Catalytic methods have the advantages, over non catalytic counterparts, of proceeding efficiently under milder conditions, thus leading to more energy-efficient processes. They are generally more selective and make possible the optimal utilization of raw materials. The catalytic processes, unlike the stoichiometric transformations, do not produce vast amounts of inorganic effluents which are difficult to dispose of (e.g. stoichiometric oxidation with traditional oxidants such as permanganate and dichromate).

The scope of catalytic hydrogenation and oxidation is very broad; most functional groups can undergo such transformations, in high yield, to any of several possible products. Molecules with various functional groups can often be reduced or oxidized at any of these functions with a high degree of chemoselectivity and stereocontrol.

The first observation of a catalytic oxidation can be attributed to Davy, who showed in 1820 that ethanol is oxidized to acetic acid in the presence of platinum[3]:

$$CH_3CH_2OH + O_2 \xrightarrow{[Pt]} CH_3COOH + H_2O \quad \text{(eq. 1)}$$

Initially, the majority of the important industrial processes involved vapor – phase oxidation over heterogeneous catalysts, like the oxidation of ethylene into ethylene oxide. Homogeneous catalysis in liquid phase became more important for larger scale applications in the late 1950s. Examples which illustrate this development are the production of terephthalic acid:



(eq. 2)

and the Wacker process for the synthesis of acetaldehyde:

$$2\ H_2C{=}CH_2 + O_2 \xrightarrow[H_2O]{[PdCl_2/CuCl_2]} 2\ CH_3CHO \quad \text{(eq.3)}$$

A variety of metal – catalyzed reactions have been developed for selective oxidations that can be carried out in laboratory scale synthesis.

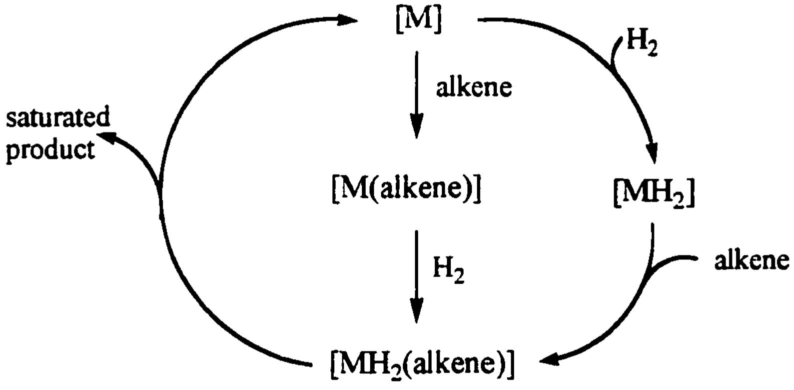
Metal – catalyzed oxidations may be conveniently divided into homolytic and heterolytic processes[3]. The first type of catalysis usually involves soluble transition metal salts (homogeneous) such as the acetates or naphthenates of Co, Mn, Fe, Cu, etc. or metal oxides (heterogeneous). Free radicals are formed as intermediates from organic substrates. Heterolytic catalysis involves reactions of organic substrates coordinated to transition metals. In this case the metal complex acts as a Lewis acid. For instance, transition metals such as V, Mo, W and Ti can promote heterolysis of the O-O bond in hydrogen peroxide and alkyl hydroperoxides[3]. The distinction between the two types of catalytic processes is not always clear and there are transition metal complexes that are capable of participating in both types of catalysis. The most important characteristics of metal catalysts used in oxidation reactions are the accessibility of several oxidation states as well as the accommodation of various coordination numbers. Both of these features are characteristic of transition metal complexes.

It is well known that many metals having partially filled *d* or *f* electron shells are also able to function as hydrogenation catalysts. Transition metal complexes present interesting features which make them suitable to act as hydrogenation catalysts[4]:

- capacity to coordinate compounds containing π-electron systems and to bind them through strong bonds;
- they can have different coordination numbers and can accommodate different ligands in their coordination sphere;
- they allow the choice of the ligand which has the best electronic and steric effect at the active site.

Under ambient conditions the H_2 molecule is not very reactive and catalytic hydrogenations, either homogeneous or heterogeneous, always involve steps of H_2 activation. In the process of activation molecular hydrogen is transformed either to hydride (H^-), hydrogen radical ($H^\cdot$) or proton (H^+). Hydrogen (H_2) is not the only possible source of hydrogen, and other molecules (hydrogen donors, DH_2) are also used as reactants in hydrogenations (*hydrogen transfer* reactions). Another process, *hydrogenolysis*, can take place during or subsequent to the addition of hydrogen. Hydrogenolysis is applied in the removal of protecting groups and unwanted functionalities or cleavage of small rings. During the reaction fragments (AH and BH) may be reductively removed from the initial substrate (AB).

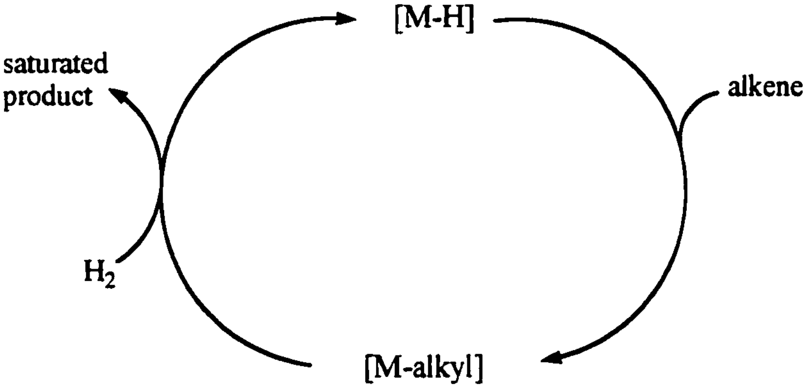
The pathways for some catalytic hydrogenation processes have been well established by mechanistic studies and an important step is represented by the discovery of dihydrogen complexes. Schemes 1 and 2 show idealized proposals for the homogeneously catalyzed hydrogenation of alkenes, but the actual mechanisms are, in general, more complex[4].



Scheme 1

Scheme 1 presents two possibilities for the hydrogenation of alkenes by metal complexes which do not contain a M-H bond[4]. The first possibility, the "alkene route", involves initial coordination of the substrate followed by activation of molecular hydrogen by the resulting complex. The second possibility, "the hydride route", implies initial reaction with molecular hydrogen followed by coordination of the substrate. The mechanism presented in Scheme 2 may be adopted by hydrogenation catalysts which contain an M-H bond[4]. The olefin inserts into the M-H bond to give a hydride alkyl species [M-alkyl], and then, the alkene is reductively eliminated to regenerate the catalyst.

The success of homogeneous catalysts in all types of hydrogenation reactions led to research on the attachment of the complexes onto a insoluble support. This new direction can take advantage of the properties of homogeneous complexes but it also facilitates catalyst removal and reuse. The supports used for metal complexes are very varied. Early work employed conventional polymers such as polystyrene and supports like silica and metal oxides have become more common recently due to the fact that they are inexpensive, easily functionalised and chemically, thermally and mechanically stable. More difficulties are encountered in mechanistic studies and often there are not many clues regarding the nature of the catalytically active species. Different techniques for solid surface analysis were developed to facilitate a better insight into the chemical process.



Scheme 2

1.3 Aims of Research

A large number of catalytic systems have been developed for the oxidation or reduction of a wide range of compounds, but the search for the improvement of the present technologies continues, with the goal of finding cheaper and recyclable catalysts and milder conditions for these very useful transformations. One of our objectives was to find very selective systems for both oxidation and hydrogenation processes. We focused on the "heterogenization" of homogeneous catalysts using clays as supports for anchoring transition metals (Chapter 2). There is an increasing interest in the use of clays as supports due to their low price, thermal and mechanical stability and the possibility of functionalization. The use of ruthenium complexes for the hydrogenation process is well documented but there are few reports of ruthenium anchored on clays. It was our intention to develop such a system and test its efficiency, selectivity and recycling possibility with a broad number of substrates.

During this study we also became interested in the catalytic activity of the clay itself. The structure of clays with Brönsted and Lewis acid sites made them useful in organic reactions. In Chapter 3 we show the results obtained in the transfer hydrogenation of ketones in the presence of Fluka K-10 montmorillonite as the catalyst.

In our search for new catalytic systems, we envisioned that a new palladium dimer, previously used in reduction processes could be successfully applied to oxidation reactions. The use of this complex for the selective oxidation of sulfides to sulfoxides is described in Chapter 4.

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Chapter 2.

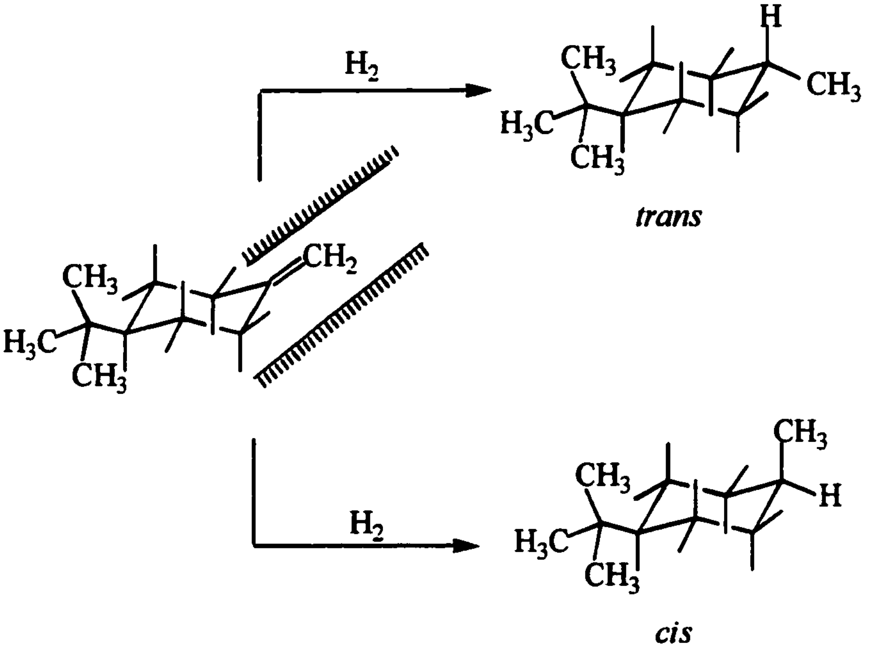
Hydrogenation Reactions Catalyzed by Ruthenium Clays

2.1 Hydrogenation Reactions by Heterogeneous Catalysis – Supported Metals

Catalytic processes are becoming more important for the large commodity chemicals business, as well as in the synthesis of fine chemicals and pharmaceuticals. Heterogeneous catalysts are involved in a variety of reactions among which hydrogenation is one of the most developed, due to its great utility and broad scope. This process has been applied to almost all groups of organic compounds: alkenes and dienes, alkynes, carbocyclic and heterocyclic aromatics, carbonyl compounds, nitroderivatives, nitriles, imines, etc.

The hydrogenation of molecules with a single functional group is now a common transformation. The search for new catalysts, has as an objective, the discovery of very selective systems, suitable for the hydrogenation of complex substrates. Much effort has been expended in finding catalysts with high chemoselectivity, regioselectivity or stereoselectivity[1]. Selectivity is difficult to attain when the two functional groups have similar activities, but it can sometimes be achieved by manipulating the reaction conditions. For instance, the formation of an allyl alcohol from an α,β-unsaturated aldehyde can be accomplished by modifying a platinum catalyst with Fe^{2+} and Zn^{2+} ions[1]. Without these modifications the main products would be the saturated aldehyde and the saturated alcohol.

One of the most important applications of the hydrogenation reaction is for the selective production of one stereoisomer over the other. The product stereochemistry can be controlled, in heterogeneous catalysis, by the manner in which the substrate is adsorbed on the catalyst. The hydrogenation of 4-*tert*-butyl methylene cyclohexane can be considered as an example. The formation of the *trans* or *cis* product depends on the steric hindrance on each side of the π cloud (Scheme 1).



Scheme 1

Another factor which has been observed to have a significant effect in determining the stereoselectivity of hydrogenation is the anchoring of the substrate onto the catalyst surface through a functional group present in the molecule (haptophilic effect). Hydroxy groups can play this role because they interact with the catalyst surface and determine a favored direction of adsorption. Many reactions of this type involve the hydrogenation of olefins over nickel or palladium catalysts.

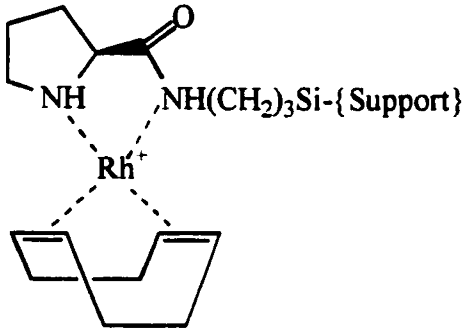
A heterogeneously catalyzed hydrogenation, as a particular case of heterogeneous catalysis, represents a complex process which occurs in several steps:

- ☐ Transport of the reactants to the catalyst.
- ☐ Interaction of the reactants with the catalyst (adsorption).
- ☐ Reaction of the reactants, adsorbed on the catalyst, to afford the products.
- ☐ Desorption of the products from the catalyst.
- ☐ Transport of the products from the catalyst.

There are some physical characteristics of the support which are important for the performance of the supported catalyst: hardness of the material, particle size and particle shape and surface area, which is directly related to pore size, pore distribution and pore volume. Among the inorganic solids which have been used as catalyst supports for the hydrogenation reaction the most common are alumina, silica, carbon, clays and titania.

There are several ways to incorporate the catalytically active species or the precursors onto the support. The process can involve surface bonding - through direct contact of the support with an impregnating solution, or by sublimation of a metal complex onto the solid, coating of the support with a liquid phase catalyst or attachment of the catalytic species through a chemical bond by reaction with functionalized supports. There is usually interaction between the functional groups on the surface of the support (e.g. OH groups) and the compound which is attached to it.

A major direction in catalysis research, and particularly in hydrogenation, is the "heterogenization" of homogeneous catalysts[2]. Following this methodology, different inorganic oxides were functionalized by reaction with organic compounds to yield chemically bound ligands. The most used organic molecules for this process are alcohols, which also contain another functional group [$HO(CH_2)_nL$, L=NH_2, PPh_2, SH], silanes that offer an option for the length of the alkyl chain ($RSiX_3$, X=Cl, OR', O_2CCH_3), or amines and aromatic compounds anchored on the surface after the treatment of the inorganic support with thionyl chloride. *N*-based chiral ligands were anchored on modified USY-zeolites, using the second route mentioned (silanes derivatives). The Rh complexes formed subsequently (**1**) proved to be effective in the enantioselective hydrogenation of *N*-acyldehydrophenylalanine derivatives with higher enantiomeric excess values than those obtained for the unsupported complex[3].



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The combination of the properties of solid supports with those of metal complexes can offer new possibilities to avoid the disadvantages of homogeneous and heterogeneous catalysts and to benefit from their advantages. The immobilization of metal catalysts on solid supports has different advantages, including the ease of separation of the catalyst from the reaction products. Many heterogenized complexes preserve the coordination sphere from the homogeneous phase but, in other cases, this approach gives information on the extent to which changes in the coordination sphere of the metal determine modifications in the activity or selectivity of the complex[4]. The ability of the supported catalyst to remain active at high temperatures, and their recycling capacity can not be neglected as advantages.

The complexity of catalyst surface (composition and structure) makes more difficult the investigation of the processes which take place. The development of modern science provides the means to have a deeper insight into the mechanisms of many catalytic reactions[5]. A wide range of surface science techniques have been developed to detect the intermediates formed and to probe the steps of the catalytic cycle:

- electron – mediated spectroscopy (X-ray photoelectron spectroscopy, Auger – electron spectroscopy);
- molecule – and ion – mediated spectroscopies (neutron/helium diffraction, ion scattering spectroscopy);
- photon – mediated spectroscopy (infrared, Raman, extended X-ray absorption fine structure; solid-state spin resonance)
- scanning probe microscopies.

There was an important progress in the field of heterogeneous hydrogenation in the past years. While the process is well developed for some metals (Ni, Pd, Pt, Rh) there are still metals (Ru, Ir, Co, Cu) for which the investigation of the heterogeneous process can contribute to new advances in catalysis .

2.2 Constitution and Properties of Clay. Organic Reactions Catalyzed by Clays.

Among the different metal supports, clays have good chemical and physical stability and the advantage that they are inexpensive. Their interlayer spacing can be adjusted by the introduction of substituents, by pillaring or by solvent swelling.

Clay minerals consist of silicate or aluminosilicate layers. These layers contain sheets of tetrahedrally coordinated cations (mainly Si^{4+} and varying Al^{3+} or Fe^{2+} content) and sheets of octahedrally coordinated cations (Al^{3+}, $Mg^{2+,}$ Fe^{2+}, Fe^{3+}) which are linked through shared oxygens. Each individual tetrahedron is connected with adjacent tetrahedra by sharing three corners and the fourth corner is oriented in a direction perpendicular to the sheet. The oxygen in the fourth corner belongs to the plane of junction between the tetrahedral and octahedral sheets. The junction plane also contains OH groups, but these groups are unshared (they belong only to the octahedral sheet) (Fig. 1). When one octahedral sheet is linked to one tetrahedral sheet a 1:1 layer is formed, as in kaolinite, and when one octahedral sheet is linked to two tetrahedral sheets, one on each side, a 2:1 layer is produced as, for example in talc or pyrophyllite[6]. The space between two successive layers is called an *interlayer* and the sum of a layer and an interlayer represents a *structure unit* [7].

The main groups of clay minerals are distinguished according to the following criteria:

- the ratio between the octahedral and tetrahedral sheets which constitute the layers,
- the nature of the cations at the tetrahedral or octahedral sites,
- the layer charge density

- the type of particles which are present in the interlayer space (water, cations, hydrated cations).

Montmorillonite, the clay used in the present work, belongs to the smectite type. It is characterized by 2:1 layers with hydrated cations (mainly Na, K, Ca) in the interlayer space and a low layer charge. The formula unit is $Na_{0.33}(Al_{1.67}Mg_{0.33})Si_4O_{10}(OH)_2 \cdot nH_2O$[7] and its structure is illustrated in Fig. 1[7].

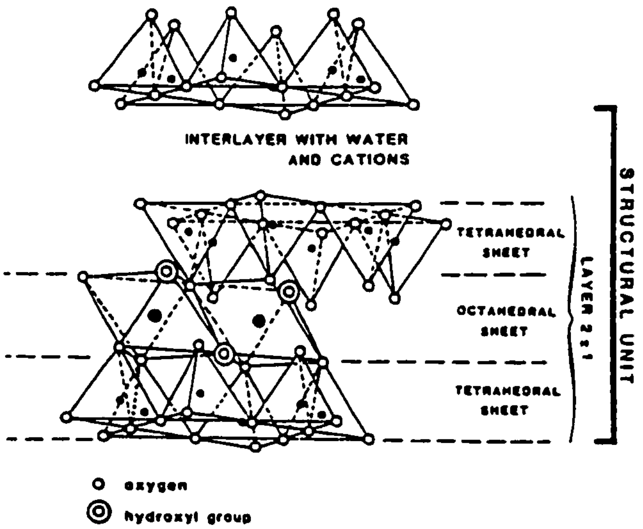


Fig. 1 2:1 layered structure of smectite (montmorillonite). (Chamley 1998)

The use of aluminosilicates in heterogeneous catalysis is mentioned beginning with Von Liebig (1865). He showed that hydrogen and oxygen or sulphurous acid and oxygen react in the presence of "powdered porcelain or ordinary pumice" to form water and sulfuric acid, respectively[6]. The reactions take place at temperatures at which the initial compounds would usually not react. Polygorskite (Florida earth) was found (1911) to catalyze the isomerization of pinene to camphene and to polymerize pentenes and hexenes to di- and trimers and higher polymers (1923). Clays were used as cracking catalysts for gasoline production (1923) and, when the problem of catalyst regeneration was solved[6], this process became commercial (1938). In 1952 clay catalysts accounted for 40 % of USA catalyst market of 470 tons/day[6] but, in recent years, the clay-based catalyst has been replaced by zeolites. One way to re-establish the importance of these minerals is the development of synthetic "clay-like" structures: 2:1 layer – lattice silicates.

There are several features of clay minerals which make them suitable to catalyze organic reactions[8].

- Clays are characterized by surface acidity.

The Brönsted acidity of clays is explained by the replacement of Si^{4+} with Al^{3+} in tetrahedral coordination. This gives rise to a negative charge which is balanced by H_3O^+. The Brönsted acidity is due also to the hydrate interlayer cations. This acidity, arising from protonic sites, is expressed by the H_0 value, application of the Hammett and Deyrup function to the clay surface – pH indicator interaction[6]. The acid strength of montmorillonite clays, after washing with mineral acid, corresponds to that of sulphuric acid solutions with concentration between 71 and 90 wt % H_2SO_4. A clay surface also bears Lewis acidic sites. Octahedral Al^{3+}, which is located at a platelet edge , can function as a Lewis acid site after dehydration[6].

- In a good approximation, clays can be considered as two-dimensional solids.

This characteristic can be a significant advantage for different types of reactions (e.g. bimolecular reactions). The reaction is constrained to occur on the surface of the clay sheets instead of taking place in a three-dimensional space. In this way the number of reactive collisions is increased, which corresponds to an enhancement of the rate of the reactions conducted on a clay surface[9].

- Clays have a ordered layered structure: the platelets are arranged like a "deck of cards". The ordered structure of clays can have a favorable effect for reactions (e.g. Diels-Alder) characterized by a highly organized transition state, due to the requirement of maximum overlap between the frontier molecular orbitals. Clays have the capacity to stabilize this transition state.
- The interface of clay minerals posses an electric double layer (i.e. positively charged ions in the interlayer space attracted by the negatively charged tetrahedral layer of montmorillonite clay). This characteristic can influence the transition state, especially for reactions which involve polar transition states or intermediates (e.g. Wheland intermediate). The electric field next to the clay surface can reach the value of 10^{10} $V \cdot m^{-1}$, which is sufficient to surmount the energy barrier for an S_N2 reaction[10].
- The high specific surface area (of the order of several hundred square meters/gram) represents another feature of clays which allows an increased adsorption capacity.
- Clay platelets offer protection against UV radiation of the molecules placed in the interlayer space.

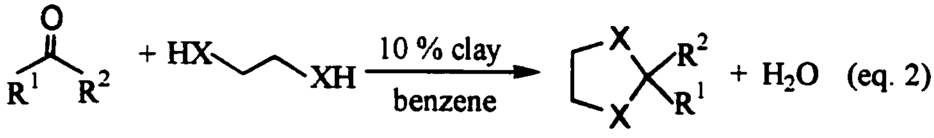
Clay minerals proved their effectiveness in electrophilic aromatic substitutions, addition and elimination reactions, oxidation and hydrogenation processes. Different types of clays (bentonite, Japanese acid clay, montmorillonite, franconite, etc) were used as catalysts in the alkylation of phenols with olefins and the catalytic activity was correlated with the acid strength[11]. The yields obtained in this process varied from 75 to 98%[8]. Acid activated montmorillonite – H_3PO_4 catalyst was used at 200-300 °C and 1-25 bar[12] for the industrial scale production of isopropanol from propene. Na montmorillonite catalyzed also the oxidation of benzylalcohol, benzylamine, thiophenol and aniline, under heterogeneous conditions, using potassium ferrate (VI)[13] as oxidizing reagent. Some of the results are summarized in Table 1.

Table 1. Oxidation Processes with K_2FeO_4 Catalyzed by Na Montmorillonite[13]

Substrate	Product	Yield (%)
benzyl alcohol	benzaldehyde	63
benzhydrol	benzophenone	100
cinnamyl alcohol	cinnamaldehyde	88

Texier-Boullet *et al.* reported[14], in 1986, a new preparative method for the synthesis of pyrroles and pyrazoles in 90-95 % yield, in the presence of montmorillonite as the catalyst (eq.1). Another type of clay – kaolinite- with a 6 % of Fe_2O_3 and 3.4 % TiO_2 catalyzed the chemoselective acetalization and thioacetalization of carbonyl compounds with 1,2-ethane-diols and 1,2-ethane-dithiols respectively (eq. 2)[15].

(eq.1)



(eq. 2)

$R^1, R^2 =$ alkyl, aryl, H
$X = O, S$

Yield: 72-98 %

These reactions represent just a part of the processes which involve clays. They take advantage of the low cost, ease of handling, non-corrosiveness and recycling capacity of clays, as well as of their Brönsted and Lewis acidity.

2.3 Transition Metals Immobilized on Clays

Clay minerals are among the inorganic supports used to anchor transition metals. In this category are also included other materials, which, similar to clays, possess a high surface area and are resistant to different reaction conditions (silica, glass, alumina, zeolites). The immobilization of metals or metal complexes on clays can be achieved in two major ways:

a) intercalation of metal complexes by ion exchange,

b) reaction of the metal complex with the clay which was previously functionalized.

a) Intercalation of metal complexes by ion exchange.

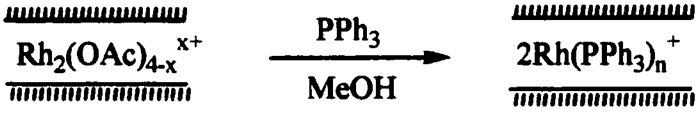
The layered structure of clays offers the possibility to conduct solution-like reactions in their interlayer space. This process approaches the reactions carried out under homogeneous conditions but, in the limited interlayer region, there are new forces which can change the course of the reaction. The cations present in the interlamellar spaces of clays can be exchanged, to a certain degree, with transition metal ions. The exchange reaction between cations M and N, with charges $m+$ and $n+$, in the interlayer space of the clay (C), can be expressed[6] (eq.3):

$$nMC_m + mN^{n+} \rightleftharpoons nM^{m+} + mNC_n \qquad \text{(eq. 3)}$$

In this process two phases are always involved: the solution containing the new cation and the surface region of the clay.

There are numerous examples of ion exchange clays acting as catalysts. Co^{3+}-exchanged montmorillonite was applied for the oxidation of cyclohexane to cyclohexanol and cyclohexanone (85% conversion at 125 °C and 2.8 bar air)[8]. Cu^{2+}-montmorillonite proved to catalyze the hydrolysis of thiophosphate esters and Al^{3+}-montmorillonite is active for the dehydration of primary alcohols to afford 1,1'-dialkyl ethers[6].

NMR and ESR experiments carried out by Pinnavaia, Fripiat and Stone brought more information about the interlayer environment in the presence of exchanged cations.[6]. Pinnavaia *et al.*[16] investigated the formation of $Rh(PPh_3)_n^+$ species, from intercalated di-rhodium acetate ions and a solution of triphenylphosphine in methanol.



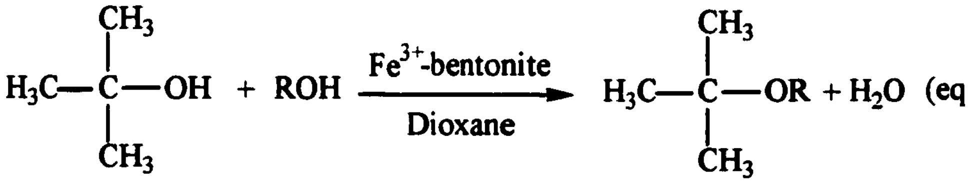
$$Rh_2(OAc)_{4-x}^{x+} \xrightarrow[MeOH]{PPh_3} 2Rh(PPh_3)_n^{+}$$

(eq. 4)

The intercalated species was tested in hydrogenation reactions and the results were compared with the corresponding homogeneous system. In the reduction of 1-hexene the rate of the reaction was lower for the clay based catalyst but the extent of isomerization to 2-hexene was decreased. This was explained by the fact that the clay can shift the equilibrium between the Rh monohydride and dihydride complexes, formed during hydrogenation, in favor of the dihydride complex which is a poor isomerization catalyst.

Studies made on this system or using $[Rh(NBD)(PPh_3)_2]^+$ (NBD=norbornadiene) as a precursor, showed the importance of other factors on the hydrogenation process: the water content of the solvent, the nature of the solvent (the swelling power of solvent decreases from methylene chloride and methanol to benzene[6]) and the size of the substrate. Another important factor to be considered in the intercalation process is the size of the metal complex. A large size complex can replace a smaller percentage of the ions initially present in the interlayers and, at increased loading of the metal complex, can reduce the rate of the reaction.

The literature mentions other different examples of intercalated cations with different applications[17]. A reaction with industrial importance is the etherification of *tert*-butanol with alcohols. It was observed that Fe^{3+}-exchanged Wyoming bentonite catalyzes the reaction and no symmetrical ethers are formed (eq. 5). The methyl tert-butyl ether can replace tetraethyl lead as a high-octane gasoline additive[18].



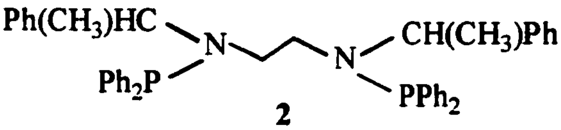
$$H_3C-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-OH + ROH \xrightarrow[\text{Dioxane}]{Fe^{3+}\text{-bentonite}} H_3C-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-OR + H_2O \quad \text{(eq. 5)}$$

R= Me, Pr, i-Pr

Hydroformylation processes using different interlamellar catalyst precursors – $[RhCl(COD)]_2$, $[Rh(CO)_2Cl]_2$ and positively charged ligands such

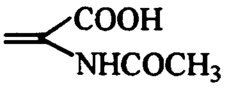
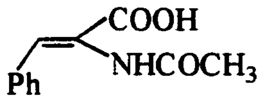
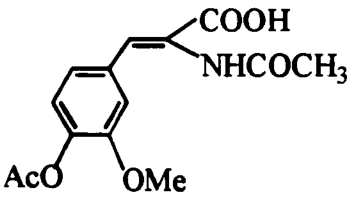
$[Ph_2PCH_2CH_2PPh_2(CH_2C_6H_4)]^+$ (P-P^+) showed better yields in the linear aliphatic aldehyde than the same complexes under homogeneous conditions[19].

Another step approaching the results obtained in solution was made by Mazzei *et al.*[20] who prepared an insoluble chiral complex of Rh using different mineral clays. Cationic Rh complexes were immobilized on clay by ionic exchange, at room temperature, in methanol. The optical yields in the hydrogenation of certain aminoacid precursors were close to those obtained with the soluble catalyst. The results obtained for different substrates with homogeneous and intercalated $[Rh(COD)(PNNP)(+)]^+$ [PNNP = N,N' bis(R(+)-α-methylbenzyl)-N,N'bis(diphenyl-phosphino) ethylenediamine] (**2**) are presented in Table 2.


2

In the above study it was observed that, in the case of α-acetamidocinnamic acid, the optical yield depends on the type of smectite used (hectorite, bentonite or nontronite).

Table 2. Optical Yields Obtained with $[Rh(COD)PNNP(+)]^+$ Complexes in Solution and Intercalated in Hectorite[20]

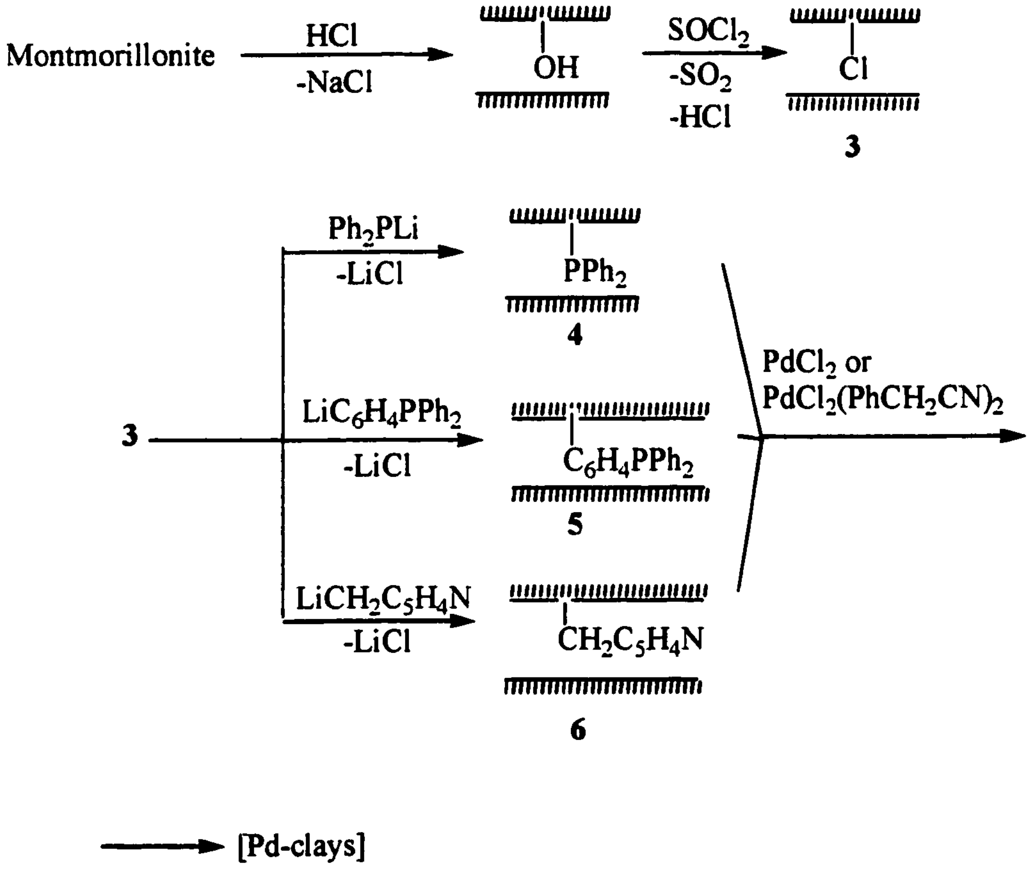
No.	Substrate	Homogeneous (%)	Intercalated (%)
1.		72-75	70
2.		80-85	49
3.		87	72

Reactions carried out at 25 °C, 20 atm H_2, $1.5\text{-}1.6 \cdot 10^{-1}$ molar concentration of the substrate, substrate/Rh=100.

b) Immobilization of metal complex by reaction with the clay which was previously functionalized.

The reaction of metal complexes with functionalized clays allows retention of the molecular character of the complex which can be altered under other conditions (direct reaction with the support). It brings also an improvement of the quality of the new species obtained, from the point of view of metal leaching. In the case of intercalated complexes, the formation of a neutral compound, during the reaction, has as a consequence the desorption of the new species from the support.

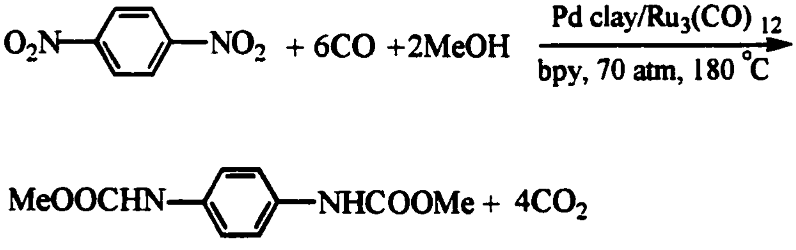
For solid supports, like silica, this method was developed and studied using mostly reaction between surface hydroxyl groups and a wide range of compounds of type $RSiX_3$. In the case of clays, Choudary and co-workers reported the immobilization of $PdCl_2$ using organofunctionalized montmorillonite[21,22,23]. The possibilities used by the above group to functionalize the clays are summarized in Scheme 2.



Scheme 2. Synthesis of Pd immobilized on clays

The above sequence represents a proposal for the reactions which take place between montmorillonite, phosphine and picoline ligands and the metal complex. The reactions written are based on the data obtained from solid-state CP/MAS ^{31}P-NMR, IR, X-ray diffraction and elemental analysis[22]. The palladium complexes obtained proved to selectively hydrogenate terminal alkenes and alkynes with the internal double bond or triple bond remaining unaffected[21]. Styrene is reduced to ethylbenzene under mild conditions (25 °C, 1 bar H_2)[24]. Palladium acetate immobilized on montmorillonite, using the phosphinated species **4,** catalyzed the hydroesterification of aryl olefins with very good regioselectivity (92 %) for the branched isomer[25].

Palladium (II) was also anchored on montmorillonite using bipyridyl ligands[23] obtained after reaction of chloromontmorillonite with *n*-BuLi and bipyridine. The clay modified in this way was used as a catalyst for the stereoselective hydrogenation of alkynes, alkenynes and dienes. The hydrogenation of 1,3-butadienes with substituents in positions 1 and 4 occurs with complete regioselectivty for the 1,2 addition. Unsymmetrical dienes are also hydrogenated at the less hindered double bond and internal alkynes are reduced with high *cis*-selectivity (98 %)[23]. The same clay-based catalytic system was used for the reductive carbonylation of nitroarenes to urethanes[26] (eq.6), the oxidative carbonylation of aliphatic mono, di- and triamines[27] (eq.7) and for the stereospecific synthesis of β, γ-unsaturated acids[28] (eq.8).

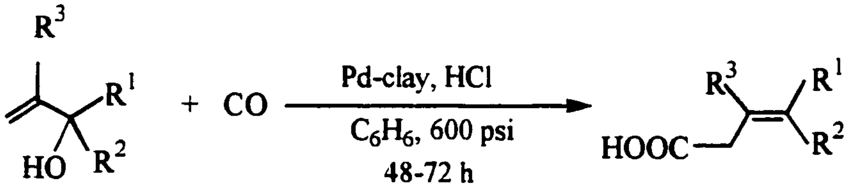


(eq.6)

67-72 % yield

$$R\text{-}NH_2 + CO + 1/2O_2 + MeOH \xrightarrow[\text{210 °C, 6-12 h}]{\text{Pd-clay, bpy, NaI}} RNHCO_2Me + H_2O \quad \text{(eq.7)}$$

60-94 % yield

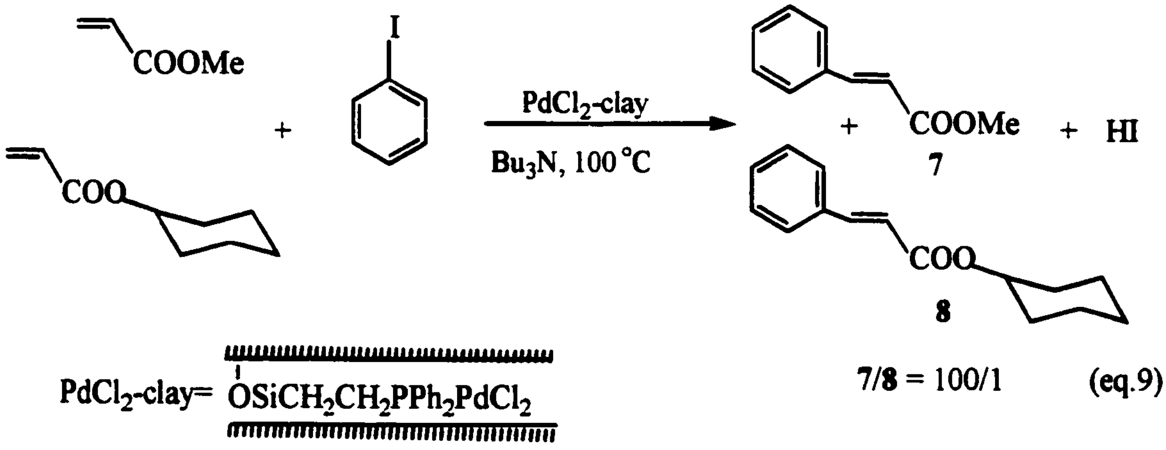


(eq.8)

39-56 % yield

The reaction of OH groups of H-montmorillonite with 3-aminopropyltriethoxysilane and 3-chloropropyltrimethoxysilane was reported as an intermediate step for the preparation of immobilized quaternary ammonium salts used as triphasic catalysts[29].

When $PdCl_2$ is reacted with ethylsilyldiphenyl-montmorillonite, obtained from H-montmorillonite, the new species formed catalyzes the preferential formation of only one product in the arylation of acrylates with iodobenzene [30] (eq. 9).



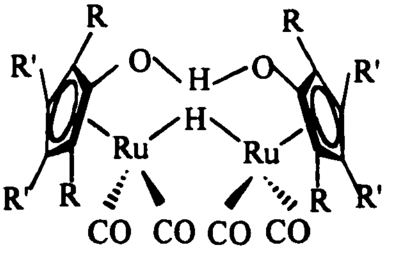
7/8 = 100/1 (eq.9)

Other methods for the immobilization of metal complexes on solid supports, like adsorption on the clay surface, are better developed for non-silicate oxides (oxides of Fe, Mn, Al, Ti, including also a second cation). The adsorption of metal cations on these type of soil oxides was investigated for the possible use in pollution control.

2.4 Results and Discussion

2.4.1 Ruthenium Based Complexes as Hydrogenation Catalysts

Several investigations concerning the catalytic activity of transition metals anchored on clays were made in our group, using palladium or rhodium compounds as catalyst precursors[26,27,28,31]. Our attention was now directed towards ruthenium which is known among transition metals for forming a wide variety of complexes which have catalytic properties. The activity of ruthenium compounds in homogeneous hydrogenation have been extensively studied. Compounds which contain ligands other than phosphines, like chlororuthenate(II), tetrachloro(bipyridyl)ruthenate (II)[32], were investigated in hydrogenation reactions. Complex **9**, containing cyclopentadienyl ligands, was found to be a precatalyst for the hydrogenation of alkenes, alkynes and carbonyl groups at moderate pressure of hydrogen (500 psi)[33].



R = Ph
R' = Ph, p-Cl-C_6H_4

9

Ruthenium catalysts which contain tertiary phosphine ligands can achieve very high hydrogenation rates of carbon-carbon multiple bonds and carbon-oxygen double bonds[34]. Chlorohydridotris(triphenylphosphine)ruthenium(II), $[RuHCl(PPh_3)_3]$, catalyzes the hydrogenation of terminal alkenes. It was observed that, when $[RuCl_2(PPh_3)_3]$ is used, the reaction time is increased, compared to $[RuHCl(PPh_3)_3]$ case, and an induction period is necessary for the formation of the hydridocomplex (eq. 10).

$$[RuCl_2(PPh_3)_3] + H_2 \longrightarrow [RuHCl(PPh_3)_3] + HCl \quad \text{(eq. 10)}$$

The measurement of the hydrogen uptake rate showed that the alkene hydrogenation rate is first order in alkene concentration and is inhibited by the addition of PPh_3. A possible mechanism was proposed (equations 11-13)[34]:

$$\begin{array}{rcll} [RuHCl(PPh_3)_3] & \rightleftharpoons & [RuHCl(PPh_3)_2] + PPh_3 & \text{(eq.11)} \\ [RuHCl(PPh_3)_2] + \text{alkene} & \rightleftharpoons & [Ru(\text{alkyl})Cl(PPh_3)_2] & \text{(eq.12)} \\ [Ru(\text{alkyl})Cl(PPh_3)_2] + H_2 & \rightleftharpoons & [RuHCl(PPh_3)_2] + \text{alkane} & \text{(eq.13)} \end{array}$$

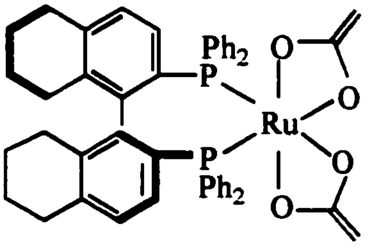
The kinetic study of the reduction of butenedioic acid in *N,N*-dimethyl-ethanamide as solvent supported the above mechanism and indicated that the rate of the hydrogenation is first order in hydrogen, between zero and first order in alkene and has an inverse dependence on the PPh_3 concentration[34]. A subsequent NMR study showed no detectable dissociation of $[RuHCl(PPh_3)_3]$ in solution (CH_2Cl_2) in contrast to $[RuCl_2(PPh_3)_3]$ which dissociates triphenylphosphine, detectable in $CHCl_3$, CH_2Cl_2 and toluene, forming $[RuCl_2(PPh_3)_2]_2$[35]. It was suggested that the life time of the catalitically active species is too short and they are undetectable by NMR spectroscopy.

Aldehydes and ketones are reduced to alcohols in the presence of $[RuHCl(PPh_3)_3]$ but it was observed that $[RuHCl(CO)(PPh_3)_3]$ is more efficient for the hydrogenation of these substrates[36]. Interesting results were obtained in catalysis with ruthenium compounds containing water-soluble phosphines[37,38]. Complexes of the type $[HRuCl(CO)P_3^*]$ (P^* =

sodium salt of *m*-monosulfonated triphenyl phosphine, TPPMS, or trisodium salt of *m*-trisulfonated triphenyl phosphine, TPPTS) are effective in the hydrogenation of *trans* – cinnamaldehyde with a product distribution (hydrocinnamaldehyde, cinnamyl alcohol and 1-phenylpropanol) which depends on pressure and temperature[37]. The use of $[RuCl_2(TPPMS)_2]_2$ in a biphasic system (water-toluene) affords better selectivity towards cinnamyl alcohol (83 %)[38].

Compounds containing carbon nitrogen double bonds, nitriles, nitro derivatives and aromatic compounds can also be reduced using ruthenium based systems[39].

Another important aspect of the use of ruthenium in catalysis is the high enantiomeric excess and turnover numbers obtained with binaphthyl-containing phosphines. This direction, derived from Noyori's work, is continuously diversified from the point of view of ligands, metal complexes and substrates. $[Ru(OCOCH_2)_2((S)\text{-}H_8\text{-}BINAP)]$ (**10**) and $[RuI((R)\text{-}H_8\text{-}BINAP)(p\text{-cymene})]I$ (**11**), for example, are effective catalysts for the asymmetric hydrogenation of α,β-unsaturated carboxylic acids[40] (ee = 41-96 %).



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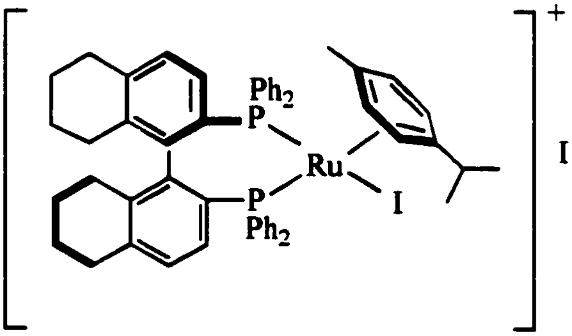
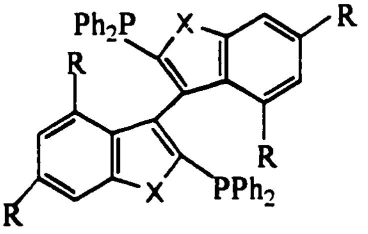


11

Another class of chiral diphosphine ligands was also reported[41]: bis(diphenylphosphino)five-membered biheteroaryls (**12**). With these type of ligands Ru(II) complexes were prepared using $[RuCl_2(C_6H_6)]_2$ and $[Ru(p\text{-cymene})I_2]_2$ and they were tested as catalysts in the asymmetric hydrogenation of α- and β-oxoesters and other olefinic substrates. The ee values obtained ranged from 78 to 99 %. Other ruthenium complexes, active in asymmetric hydrogenation reactions, are based on aminophosphine phosphinite ligands and on ferrocenyl biphosphines[42].

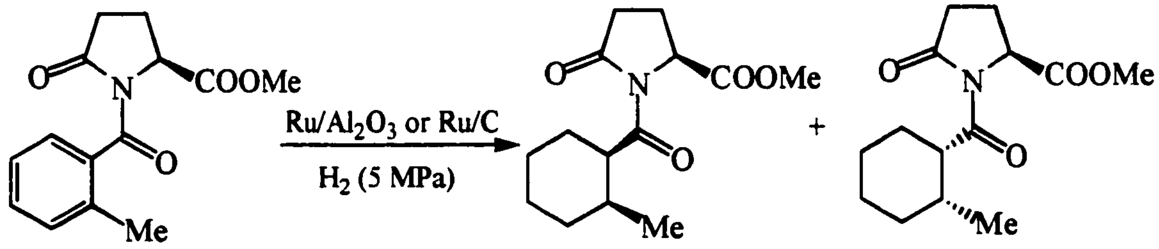


12

a) X = S; R = CH_3
b) X = S; R = H
c) X = O; R = H

The above results show the efficiency of ruthenium complexes as catalysts and they prompted us to investigate the possibility of immobilization of this metal on clay with analysis of the catalytic properties of the new species. This direction of research was also determined by the fact that there is a limited number of reports concerning heterogeneous ruthenium systems, which is in contrast with its wide use in homogeneous catalysis. The anchoring of organometallic ruthenium ions on clays through cationic exchange[17] has been mentioned before. There are also reports and patents regarding the use of supported ruthenium, sometimes in combination with other metals, for the reduction of aromatic hydrocarbons – a process important for the production of gasoline with reduced aromatics content[43]. These procedures involve Ru(0) supported on a carrier: carbon black, alumina, silica, titania, magnesia, zirconia, zeolites, naturally occurring silicates, clays or a combination of these materials. Heterogeneous ruthenium systems are also reported to be active for selective reduction of the carbonyl group of carboxylic acids[44], for the selective transformation of methyl oleate to oleyl alcohol[45] (Ru-Sn/alumina), or for the hydrogenation of nitrobenzene (Ru supported on the copolymer styrene-divinyl benzne)[46].

During our work on this project results were published using ruthenium supported on carbon and alumina for the selective hydrogenation of *o*-toluic acid derivatives to 2-methylcyclohexanoic acid with high diastereoselectivities (74-85 %)[47] (eq. 14), and on the reduction of olefins with ruthenium intercalated in pillared montmorillonite[48].



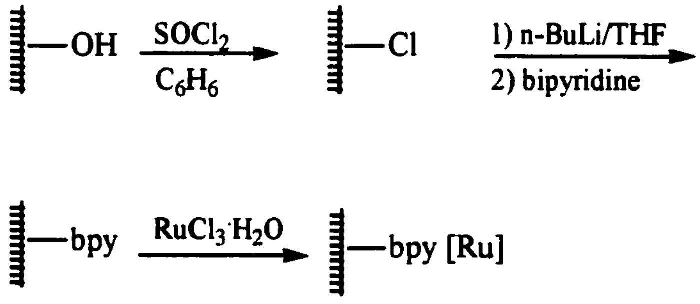
(eq. 14)

The immobilization of Ru (II) complexes on silica through thin films containing terminal donor ligands or the preparation of dendrimers, with $[Ru(bpy)_3]^{2+}$ as their core, have been reported[49,50], but their catalytic activity remains to be investigated.

2.4.2 Synthesis of Ruthenium Clays

Our approach was to use either phosphine or bipyridine as the ligands to attach to the clay, and these ligands serve as the link for binding ruthenium to the clay. The clay used in the study was Fluka K10 montmorillonite and in some experiments SWY-2 (Crook County, US).

Na montmorillonite was initially purified following the procedure described previously[23] and transformed into H-montmorillonite by stirring with 0.1 N HCl solution, followed by drying in air and then in vacuum. We chose two different methods to anchor ruthenium. The first route follows the procedure used by Choudary[23,51] and also by our group[26,27]. The clay, in its acidic form, is reacted with thionyl chloride , followed by treatment with *n*-BuLi and bipyridine and finally by addition of commercial ruthenium (III) chloride (Scheme 3).



13 **14**

Scheme 3. Synthesis of Ru bipyridine clays.

The reaction of bipyridine with lithiated substrates was also employed in the preparation of polymer-bound bipyridine[52]. In this procedure bipyridine is attached to phenyl residues of polystyrene-divinylbenzene copolymer after bromination and lithiation of the aromatic ring. The reaction of chloromontmorillonite with *n*-BuLi is based on the metal–halogen exchange process. Metal-halogen exchange reaction is in competition with alkylation reaction. Control of the reaction temperature [(-78) – (-80) °C] and the choice of *n*-BuLi as lithiation agent instead of PhLi or MeLi, favors the metal halogen exchange[53]. The reaction can be envisioned to proceed further by attack of the Li species on bipyridine. The addition of R-Li compounds to nitrogen heterocycles is documented in the literature[53] and it may proceed by the addition of the lithium derivative to the C-N double bond at low temperature followed by elimination of lithium hydride on heating.

The IR spectrum of species **13** showed the characteristic absorption of bipyridine in the region 1562-1438 cm^{-1} (Fig. 2a). After treatment with commercial ruthenium chloride the only absorption observed in the region 1600-1500 cm^{-1} is the one corresponding to the water contained in montmorillonite (1642 cm^{-1}) (Fig. 2b). In solution, the absorption due to dipyridyl ligands, to which ruthenium is coordinated, is reported[54] as a weak sharp peak at 1600 cm^{-1}. It was assumed that the amount of bipyridine that remained on clay after addition of ruthenium chloride, followed by washings with water and THF, was very small. This is in agreement with the ruthenium content of clay **14**, 0.18 mmol Ru/g clay, determined by flame emission spectroscopy (wavelength 372.8 nm). The modification of the clay was also followed by measuring the basal spacing, d(001), which was 14.1 Å compared to 9.9 Å in the initial Na-montmorillonite.

The second method used to anchor ruthenium on clay is based on the reaction of $Si(OMe)_3(CH_2)_3Cl$ with the OH groups present in the clay, followed by addition of $KPPh_2$ and subsequent treatment with commercial ruthenium (III) chloride hydrate (Scheme 4).

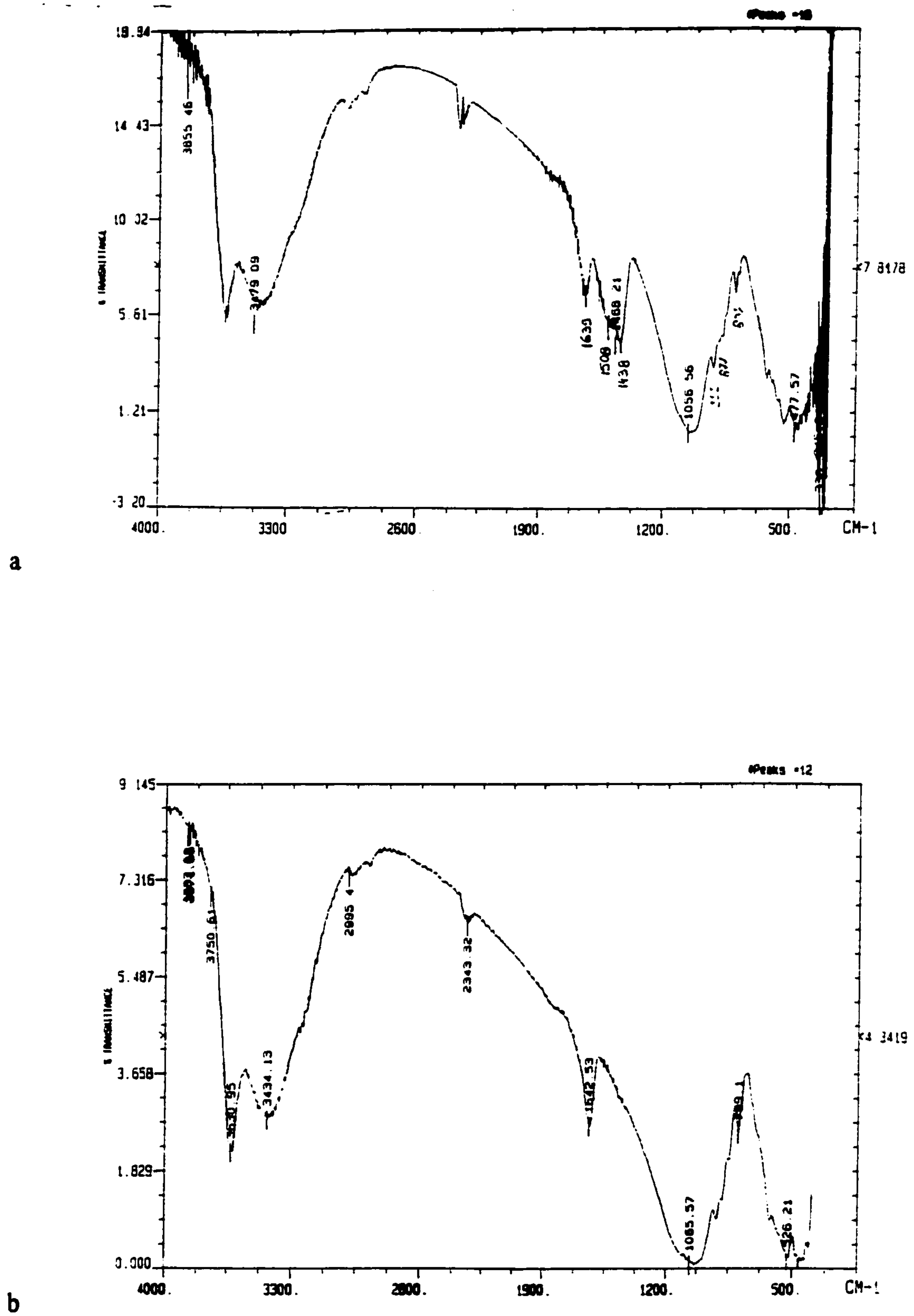
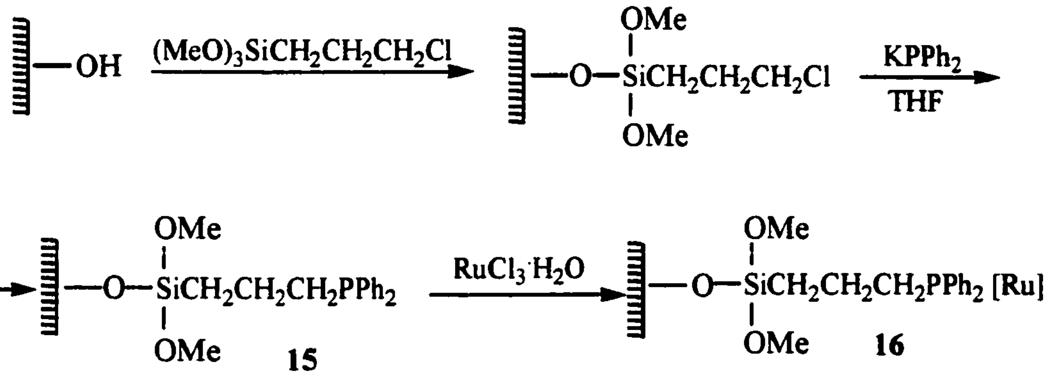


Fig. 2a,b IR spectra of 13 (a) and 14 (b)



Scheme 4. Synthesis of Ru phosphine clay.

This procedure was used by Allum *et al.*[55] to immobilize rhodium on silica. The reaction of silane compounds with the OH group of inorganic oxides is a known method for functionalization of solid supports[2]. For clays this method is less developed than the immobilization of metals through cationic exchange. Choudary and his group used a similar procedure in the preparation of triphasic catalysts and also in the synthesis of palladium clays[29,30].

The chlorine content, determined by X-ray fluorescence, was 2.9 mmol Cl/g after reaction with $(MeO)_3SiCH_2CH_2CH_2Cl$. The phosphination of chloromontmorillonite was carried out using a 0.5 M solution of $KPPh_2$ in THF followed by extraction with methanol and toluene. Commercial ruthenium (III) chloride was used as source of ruthenium to coordinate to the phosphine. The reactions were carried out under nitrogen in order to avoid the oxidation of phosphorus. The CP/MAS ^{31}P-NMR spectrum has a signal at −17.2 ppm (Fig. 3a) which was assigned to the phosphorus in siloxypropyldiphenylphosphine, which is close to the value reported for the same ligand grafted on silica (-16 ppm)[56]. After the

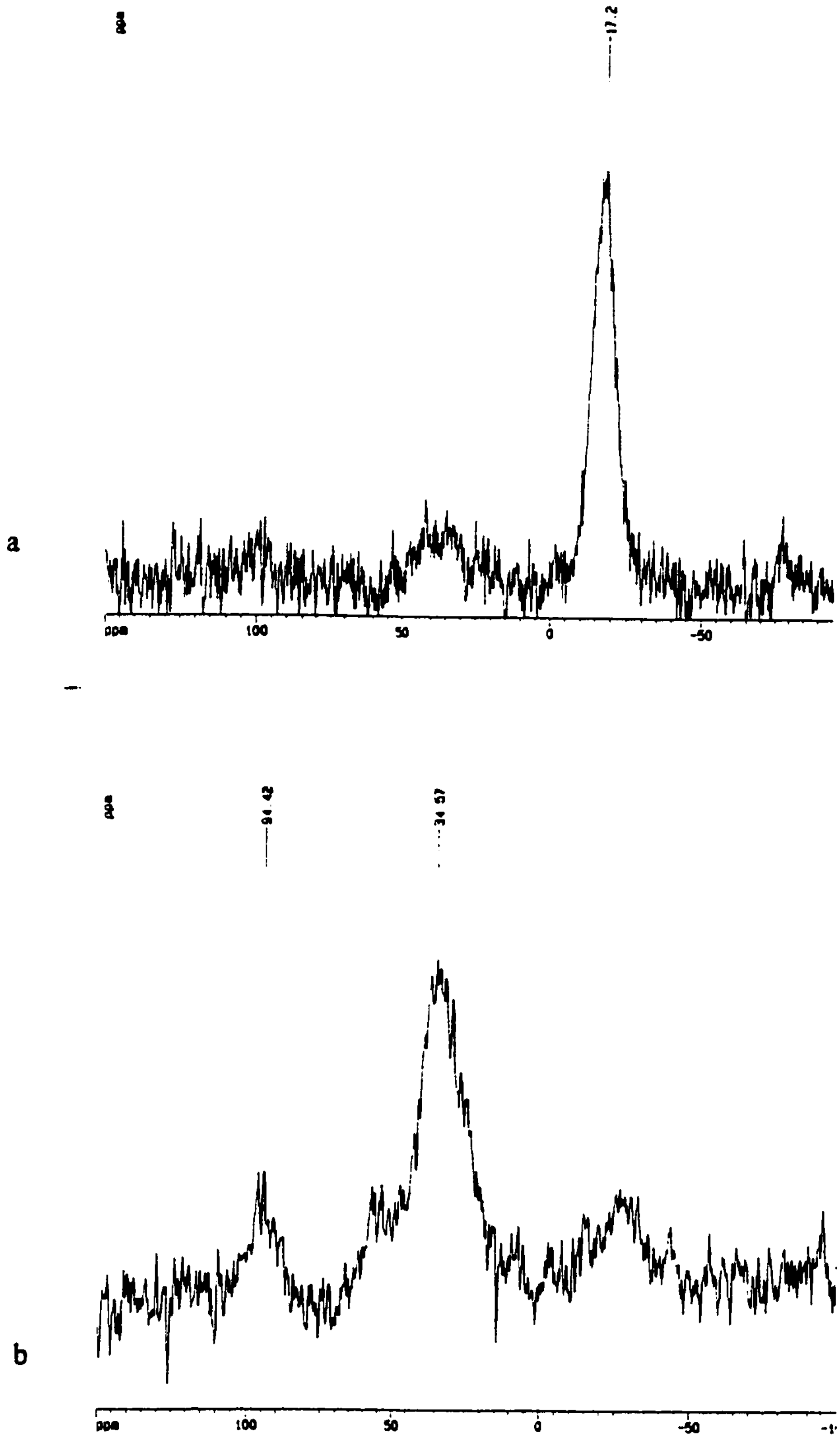
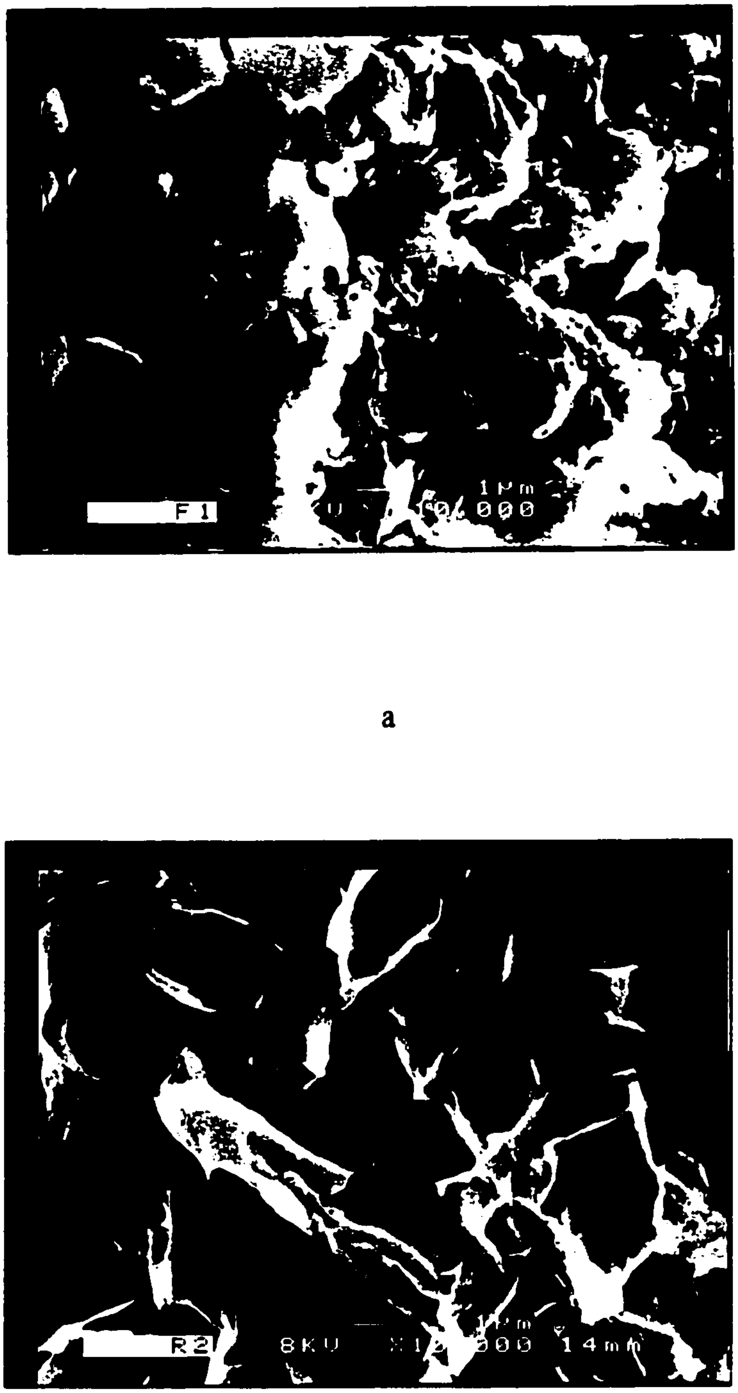


Fig.3 a,b. CP/MAS ^{31}P-NMR of **15** (a) and **16** (b) coordination of ruthenium the spectrum shows a broader peak at 34 ppm (Fig. 3b) and the signal at −17.2 ppm disappeared. It is known that the coordination of ruthenium to phosphorus generally leads to a shift of the ^{31}P signal to a lower field (40 ppm)[57]. A similar shift takes place in the case of Pd coordinated to phosphine on clay[22].

In the IR spectrum of species **15** the 2880-2900 cm^{-1} peak can be assigned to the carbon-hydrogen stretch for the propyl group attached to the phosphorus atom and the enhanced absorption between 770 - 665 cm^{-1}, compared to pure K10 montmorillonite, might be due to the presence of the aromatic rings bound to phosphorus. In aromatic phosphines the substitution pattern, in the region mentioned above, is known to be broken up into a number of strong absorptions. The IR spectra of both Ru clays show strong absorptions due to the montmorillonite which makes the identification of the attached organic molecules difficult to assign. X-ray powder diffraction of **16** showed a basal spacing d(001) of 13.3 Å and the ruthenium content, determined by flame emission and also by ICP analysis, was 0.17 mmol ruthenium/g clay. For different batches of catalyst, subsequently prepared, the ruthenium content of **16** varied from 0.13 to 0.17 mmol Ru/g.

On a macroscopic scale, both clays are powders, similar to the initial Na-montmorillonite. They have different colors: before complexation of ruthenium, **13** has a pink-violet color and **15** is pale yellow. After treatment with $RuCl_3$ the two compounds show different shades of grey.

On a microscopic scale (1-10 μm), the clays were observed by scanning electron micrographs (SEM). Figures 4 (a, b) show the SEM of Na montmorillonite in comparison to the clay treated with bipyridine and ruthenium chloride (**14**) (1 x 10 000 enhancement).



a

b

Fig. 4 a,b Scanning electron micrographs (SEM) of Na montmorillonite (a) and **14** (b)

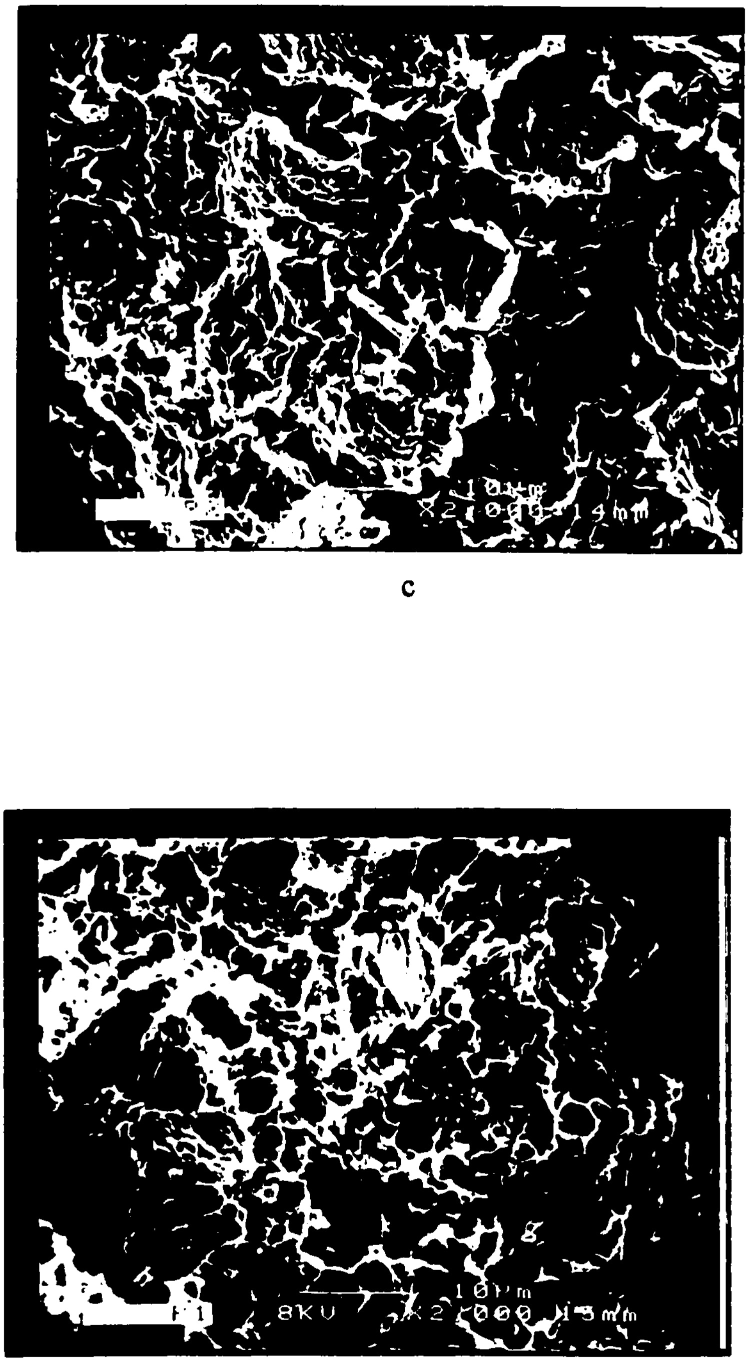


Fig. 4 c,d. Scanning electron micrographs (SEM) of **14** (c) and **16** (d)

Figures 4 (c, d) represent the SEM for the clay with bipyridine and ruthenium cloride **(14)** and the phosphinated clay reacted with ruthenium chloride **(16)** (1 x 2 000 enhancement).

The main characteristics of the ruthenium clays **14** and **16** are summarized in Table 3.

Table 3. Physical and Spectroscopic Data for Clays **14** and **16**

Ru clay	Color	Ru content (mmol Ru/g)	d(001) (Å)	^{31}P-NMR (ppm)
Ru-bipyridine clay **14**	grey (violet shade)	0.18	14.11	-
Ru-phosphine clay **16**	grey (slightly yellow)	0.17	13.36	34

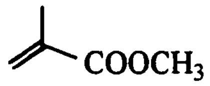
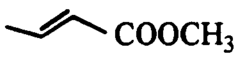
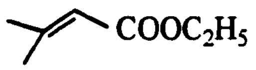
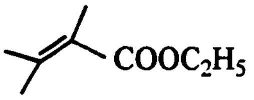
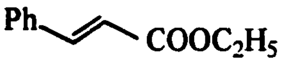
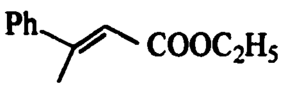
2.4.3 Reduction of Unsaturated Esters

Our objective was to investigate the catalytic activity of the ruthenium clays obtained, their stability and what advantages they have over other catalytic systems. First, the effectiveness of clays **14** and **16** was studied in the selective reduction of the double bond of unsaturated esters[58], a reaction of substantial interest in organic chemistry[59]. The hydrogenation of methyl methacrylate catalyzed by Ru clays **14** and **16**, with a substrate to catalyst ratio of 370:1 (30 mg clay which contained 0.005 mmol Ru) showed complete conversion to the corresponding propionate ester in 22 h at 300 psi H_2 and 75 °C. Clays **14** and **16** had comparable activity for selective reduction of the double bond of methyl methacrylate and methyl crotonate (Table 4 , entries 1, 2). In the case of methyl crotonate the complete hydrogenation takes longer (45 h) and a higher pressure is required (600 psi H_2). The reaction was stopped when no more increase in the conversion of the substrate was determined. The conversion was calculated from the ^{1}H-NMR spectrum , in the presence of an internal standard. The two catalysts behaved differently when both terminal hydrogens of the double bond are replaced by methyl groups, as in the case of ethyl 3-methyl-2-butenoate: **16** is inactive towards the substrate even at 600 psi H_2, while **14** catalyses the complete hydrogenation (600 psi H_2) in 45 h (Table 4, entry 3). Neither **14** or **16** was effective for the hydrogenation of ethyl 2,3-dimethyl-2-butenoate (Table 4 , entry 4). In contrast with the increased activity of Ru-bipyridine clay in the reduction of the carbon-carbon double bond of ethyl 3-methyl-2-butenoate, Ru-phosphine clay is the catalyst of choice for ethyl *trans*-cinnamate: 100 % conversion resulting in the formation of ethyl 3-phenylpropanoate in 85 % isolated yield (Table 4 ,entry 5). Catalyst **14** gave only 21 % conversion of ethyl *trans*-

cinnamate to the saturated ester, the rest being unreacted starting material. Ru clay **16** is also effective in the case of ethyl *trans*-β-methyl cinnamate with 100 % conversion to the saturated ester (Table 4, entry 6). The activity displayed by **14** for this substrate is similar to that of catalyst **16** (Table 4, entry 7). The difference in the value of the d(001) parameter for the two clays might explain the efficiency of the Ru-bipyridine clay in the hydrogenation of ethyl 3-methyl-2-butenoate and the inactivity of the phosphine based clay for the same substrate. The increased volume of the substrate (e.g. ethyl 2,3-dimethyl-2-butenoate) blocks the reaction even for catalyst **14**. This is in agreement with the previous observation that a Pd-clay catalyst hydrogenates preferentially the less hindered double bond in unsymmetrical dienes[23]. An increase of hydrogen pressure from 600 psi to 800 psi did not show any hydrogenated product for ethyl 2,3-dimethyl-2-butenoate. The planar geometry of the phenyl ring seems to fit better the clay catalytic system than the tetrahedral arrangement specific for a carbon sp^3 (Table 4, entries 5,6). These observations suggest that tuning of the interlayer space may be a useful process for the separation of mixtures of compounds.

The hydrogenation reactions were performed in benzene. Cyclohexane, obtained from reduction of the aromatic ring, was observed in the crude mixture. Several other solvents were used for the hydrogenation reaction with **16** as the catalyst. Reaction of methyl methacrylate catalyzed by **16** in methylene chloride gave complete conversion to methyl 2-methylpropionate, while in the reaction using methanol as the solvent, the starting material was recovered and only traces of hydrogenated product were found.

Table 4. Reduction of Unsaturated Esters Using **14** and **16** as Catalysts[a]

No.	Substrate	Catalyst	Pressure (psi H_2)	Time (h)	Conv. (Yield)[b] (%)
1.		**14** **16**	300	22	100 (90) 100 (87)
2.		**14** **16**	600	45	100 (91) 100 (85)
3.		**14** **16**	600	45 40	100 -
4.		**14** **16**	600	40	- -
5[c].		**14** **16**	800	63 52	21 100 (80)[d]
6[c].		**14** **16**	800	24	100 100 (84)[d]

a. Reaction conditions: substrate 2.0 mmol; 30 mg **14** or **16** (0.005 mmol Ru); temperature 75 °C; benzene 8 ml.

b. Determined by ^1H NMR using an internal standard.

c. 1 mmol substrate.

d. Isolated yield.

The recycling capacity of the catalyst (both **14** and **16**) was tested by reusing the Ru-clays three times consecutively, and no loss of activity was observed. In the three consecutive runs, using **16**, the conversion to saturated ester was always complete (Fig. 5). The benzene solution, which was obtained after the filtration of the clay, was analyzed for the presence of ruthenium by atomic absorption. No ruthenium wad detected. To confirm that the Ru-clay system is the active catalyst, the reaction of methyl methacrylate at 300 psi H_2 and 75 °C, using Na montmorillonite without any metal, was tested in which case no reaction was observed. The use of $RuCl_3{\cdot}H_2O$ as the catalyst for the same substrate, in benzene, gave only 27 % conversion to methyl 2-methylpropionate in 22 h. It was also demonstrated that the solid obtained by stirring a dry THF solution of Na montmorillonite and $RuCl_3$, under

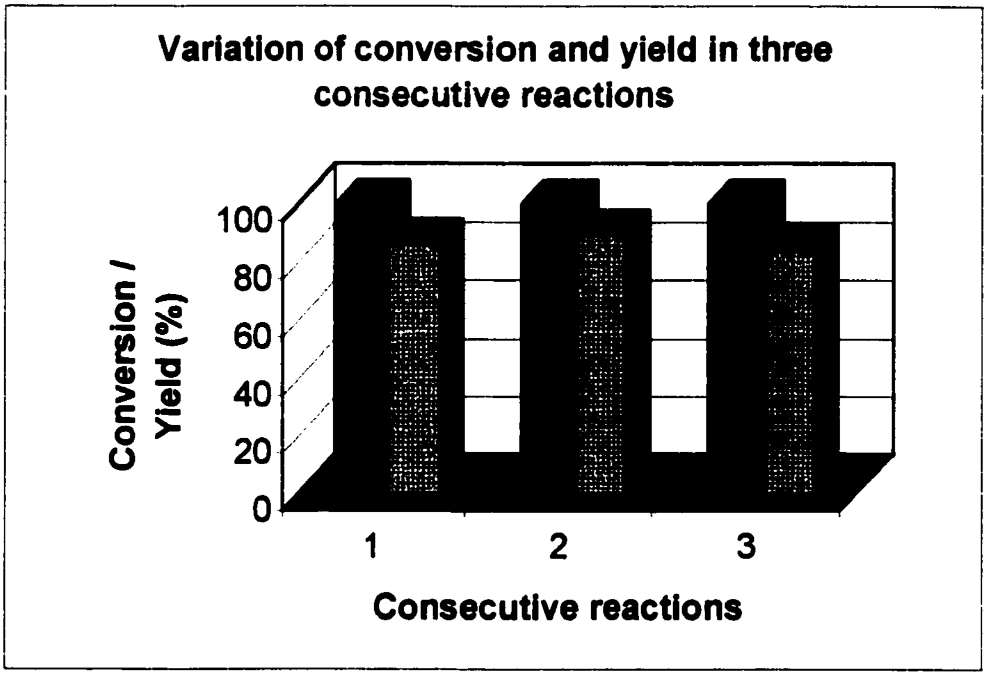
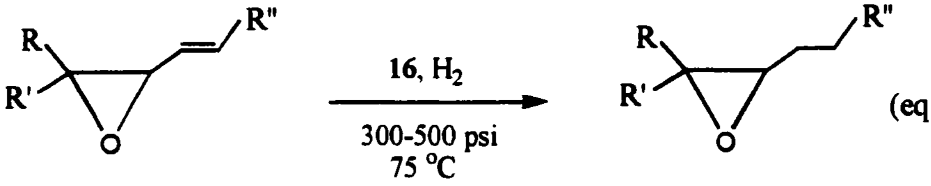


Fig. 5 Variation of conversion and yield in consecutive reactions

nitrogen, and then washing with water and THF, followed by drying in vacuum, does not give any reduction of methyl methacrylate.

Once the catalytic activity of the ruthenium clays was established our research focused on finding hydrogenation processes in which the new catalytic species could bring an improvement compared to the catalysts currently in use. The ruthenium–phosphine clay **16** was used for subsequent research. This decision was based on the comparable catalytic activity of the two species and also on the more documented hydrogenation process for homogeneous catalysis in the case of phosphine-based ruthenium compounds. Analogy with the homogeneous system might help us to understand better the present heterogeneous catalyst.

Catalyst **16** was tested for the selective hydrogenation of the double bond of vinyl epoxides (eq. 14’; Table 5). Reactions such as production of ethyl oxirane starting from butadiene are of industrial importance. Vinyl oxirane can be obtained with high selectivity from butadiene, using titaniumsilicates[60]. The next step to ethyl oxirane is selective reduction of the double bond. The use of palladium or rhodium on carbon was disclosed in a patent[61] while iridium and palladium are employed under homogeneous conditions[62].

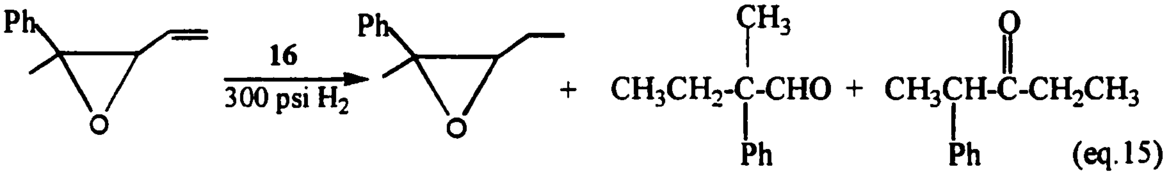


(eq. 14')

17a-20a **17b-20b**

R = alkyl, phenyl
R' = methyl, H
R''= alkyl, H

For the Ru-clay good selectivity was obtained for 2-phenyl-3-vinyloxirane, which afforded, at 500 psi H_2, 2-ethyl-3-phenyloxirane in 60 % isolated yield (Table 5, entry 1). In the case of 2-methyl-2-phenyl-3-vinyloxirane, an appreciable amount of saturated aldehyde (2-methy-2-phenylbutanal) **21** together with 2-phenyl-3-pentanone **22** was obtained in addition to the saturated epoxide **18b** (eq. 15), which represented only 30 % of the products (Table 5, entry 2). The hydrogenation of 1,3-cyclohexadiene monoxide at 500 psi H_2 gave



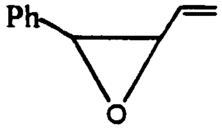
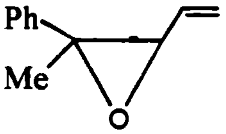
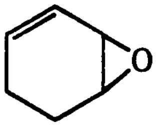
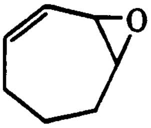
(eq.15)

18 a **18 b** **21** **22**

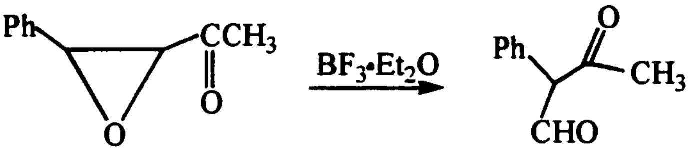
cyclohexene oxide in 16 % yield, the principal product being cyclohexanone (Table 5, entry 3). In the case of 1,3-cycloheptadiene monoxide the yield of cycloheptene oxide was higher (50 %) (Table 5, entry 4) with the accompanying product being cycloheptanone. Cycloheptene oxide is obtained in lower yield (33 %) when the hydrogen pressure is reduced to 300 psi H_2.

The Lewis acidic sites of the clay and the temperature used in the reaction might determine the rearrangement of the epoxide. Both the thermal and acid-catalyzed rearrangement of epoxides have been studied[63] and it is assumed that the ketones formed in these reactions result from hydride migration. The aldehydes observed as by-products in the case of substrates **17a** and **18a** may be formed through cleavage of the epoxide ring and generation of carbenium ion intermediates followed by ethyl migration. Similar behavior has been reported in the case of $BF_3 \cdot Et_2O$ which catalyzes the cleavage of the oxirane and migration of the acyl or phenyl groups (eq. 16) or in the reaction of cycloheptene oxide with $LiClO_4$ which affords cycloheptanone and cyclohexyl aldehyde (eq.17)[63]. It has also been reported that metal complexes like $[Rh(CO)_2Cl]_2$ and $Mo(CO)_6$ catalyze the alkyl or aryl migration of epoxides[64].

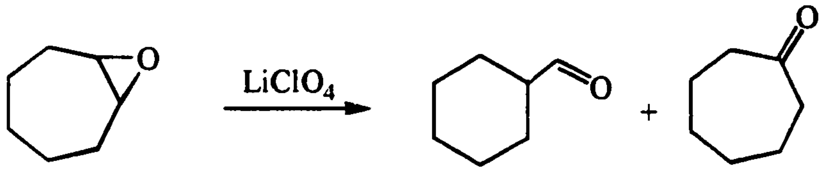
Table 5. Reduction of Unsaturated Epoxides Using **16** as the Catalyst

No	Substrate	Pressure (psi H_2)	Time (h)	Conversion (%)	Isolated yield (%)
1.	 **17 a**	500	24	100	60
2.	 **18 a**	300	24	100	30
3.	 **19 a**	500	48	100	16[a]
4.	 **20 a**	500	19	100	50[b]

a. GC isolated yield using an internal standard.
b. NMR yield (internal standard).



(eq. 16)

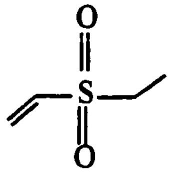
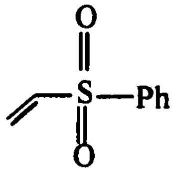
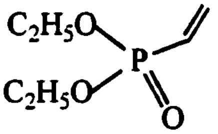


(eq. 17)

Considering the limited number of methods designed to selectively reduce the double bond of vinyl epoxides, the procedure involving Ru-clays represents an alternative with fair yields of alkyl oxiranes.

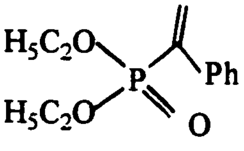
The catalytic activity of **16** was investigated for two other classes of functionalized olefins: α,β-unsaturated sulfones and phosphonates. Sulfur represents a very effective catalyst poison and sulfones, in which there are no unshared electron pairs on the sulfur atom, were chosen as substrates. Ethyl vinyl sulfone and phenyl vinyl sulfone (Table 6, entries 1,2) afforded diethyl sulfone and ethyl phenyl sulfone in 64 and 94 % yield, respectively. The use of ruthenium clay compares favorably, in terms of yield and selectivity for reduction of the carbon- carbon double bond, with commonly used hydride reagents such as $NaBH_4$ or $[(PPh_3)CuH]_6$[65] or with the catalyst generated from the reaction of $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$ with O_2 in THF[66].

Table 6. Reduction of Unsaturated Sulfones and Phosphonates Using **16** as the Catalyst

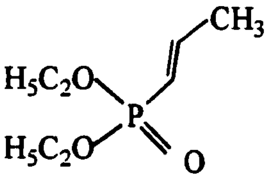
No	Substrate	Time (h)	Conversion (%)	Isolated yield (%)
1.		66	80	64*
2.		63	100	94
3.		22	100	90

Reaction conditions: 1 mmol substrate; 0.005 mmol Ru; temperature 125 °C (sulfones); 100 °C (phosphonate); 500 psi H_2; 8 ml benzene.
*Yield determined by GC using an internal standard.

Phosphorus containing moieties play a vital role in biological systems[67]. The problem of selective double bond reduction of a phosphonate without any secondary reactions (e.g. hydrogenolysis) may arise in organic synthesis. The use of Pd/C has been reported[68] as an heterogeneous catalytic system. In the presence of Ru-clay the hydrogenation proceeded readily (90 % yield) for diethyl vinyl phosphonate (Table 6, entry 3). As for basic alkenes, increasing degree of substitution at the double bond inhibits reduction. Either diethyl α-styrylphosphonate **23** or diethyl (1-propenyl)phosphonate **24** were recovered unchanged.



23



24

It can be concluded, for this part of our investigation, that ruthenium trichloride, immobilized on clay by means of phosphine or bipyridine containing units, showed good catalytic activity for the reduction of α,β-unsaturated esters. The phosphine-containing clay is an efficient catalyst for the reduction of unsaturated sulfones but is less selective for unsaturated epoxides and not generally effective for phosphonates.

High rates of hydrogenation for alkenes, alkynes or heteroaromatic compounds are achieved with [$RuHCl(PPh_3)_3$] in homogeneous catalysis. The Ru-phosphine clay system may involve a similar species. We observed that, in the hydrogenation reactions carried out, there is an initial period of time (3.5 - 4 h) before the pressure in the autoclave started to decrease. This observation may be associated with an induction period necessary to form a ruthenium hydrido derivative.

An XPS study, carried out on samples of Ru-clay, provided more information although the small concentration of ruthenium makes the analysis more difficult. The spectrum of clay **16** obtained by XPS is shown in Fig. 6 and that of $RuCl_3$ in Fig. 7[69]. In the spectra of $RuCl_3$ (Fig. 7) the peaks at 286.2 and 281.7 eV represent Ru^{3+} $3d_{3/2}$ and Ru^{3+} $3d_{5/2}$ signals. The carbon peak (C 1s) was used as an internal calibration signal (284.6 eV). The Ru-clay sample has an appreciable amount of carbon compared to ruthenium and the high resolution peak of ruthenium *3d* is almost covered by the carbon *1s* peak. The carbon peak has a shoulder at the low energy end (281.5 eV) and this could be the $3d_{5/2}$ peak for ruthenium. The signal at 281.5 eV is too high for Ru metal (280.0 eV) or Ru (IV) (280.7 eV) but is close to Ru (III) (281.7 eV)[70]. The ruthenium 3p peaks were also run at high resolution and appear at the proper position and the correct 22 eV apart but their position is not very informative about the oxidation state. A report[69] on hydrogenation reactions using Ru KL zeolite as a catalyst showed that the species present, according to XPS studies, are Ru (III) and Ru (0).

A Ru (II) hydride may be formed during the catalytic cycle, under hydrogen pressure, in the heterogeneous clay system. The alkene is adsorbed and coordinates to ruthenium. Hydrogen insertion gives the metal alkyl. According to the size of the functionalized olefin this step may or may not be likely. Addition of H_2 may lead to a dihydrido metal alkyl species. The alkane is formed by reductive elimination and the active catalytic species is regenerated (Scheme 5).The ruthenium system on clay, developed herein, has the general characteristics observed for Ru catalysts, homogeneous or heterogeneous: it is less active for the

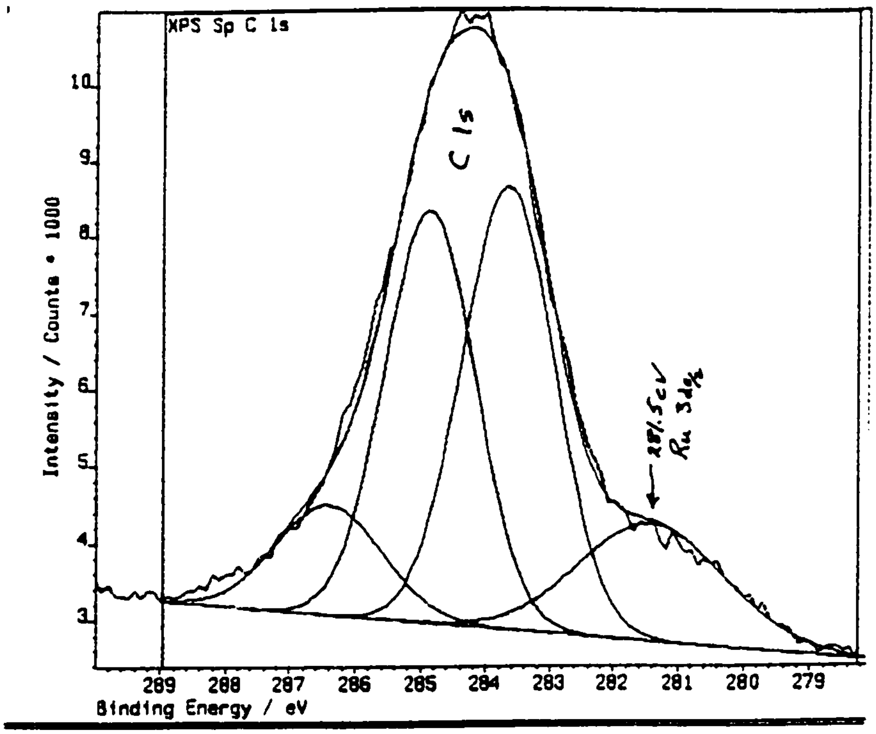


Fig. 6 XPS spectrum of **16**

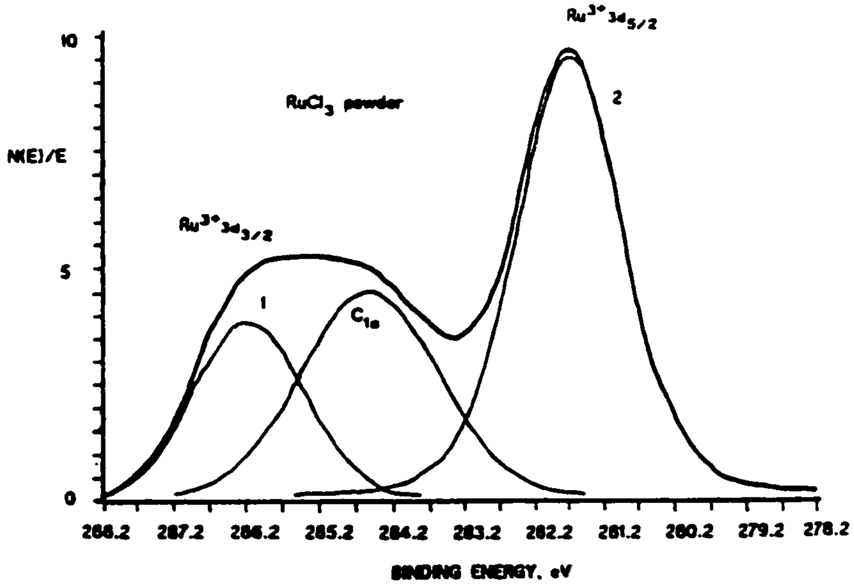
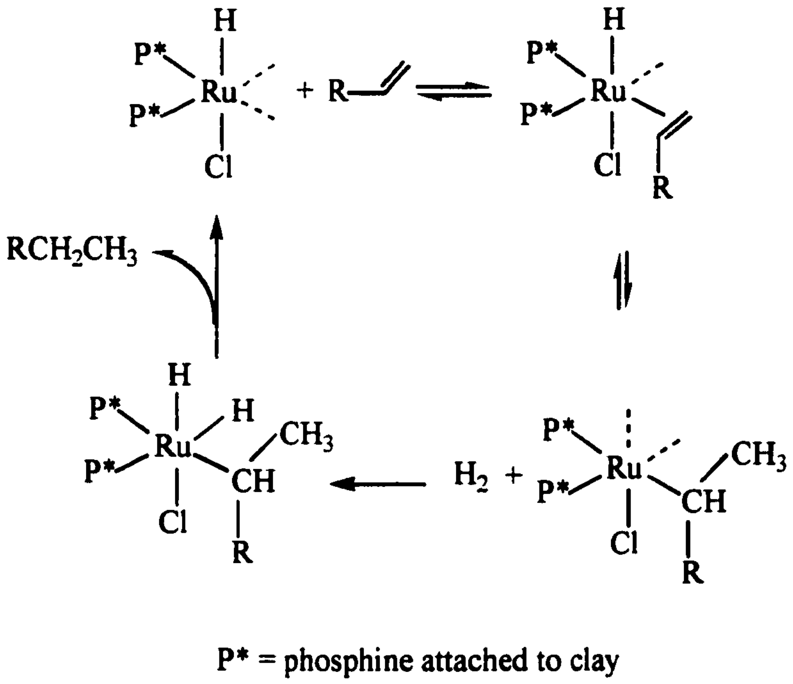
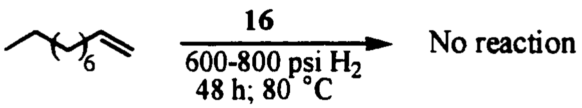


Fig. 7 XPS spectrum of $RuCl_3$

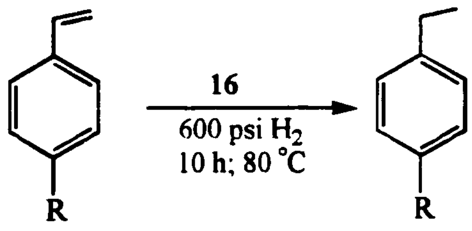
hydrogenation of non-activated olefins and it is efficient for the reduction of aromatics. Attempts to reduce 1-decene failed even when the reaction time was increased to 48 h (eq. 18) but the double bond in styrene or substituted styrene is selectively reduced (eq. 19).



Scheme 5. Possible catalytic route for hydrogenation of the carbon-carbon double bond.



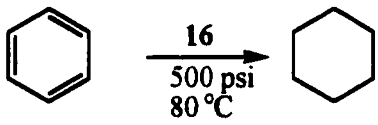
(eq. 18)



(eq. 19)

R=H, Bu^t

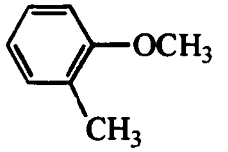
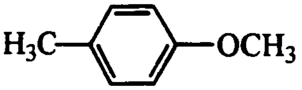
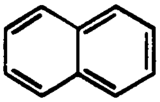
The formation of cyclohexane in the reaction carried out in benzene led us to investigate the efficiency of the Ru-phosphine clay for the reduction of different aromatic systems. In the reduction of neat benzene, after 2.5 h, 17 % conversion was obtained, corresponding to a turnover number (TON) of 3530 (mol product/mol catalyst) and a turnover frequency (TOF) of 1412 (mol product/mol catalyst · h) (eq. 20).



(eq. 20)

Methoxy benzenes are hydrogenated to the corresponding cyclohexanes. No hydrogenolysis of the carbon – oxygen bond occurs and *cis* substituted cyclohexane was the major isomer in the hydrogenation of *ortho* and *para* methylanisole (Table 7, entries 1, 2). For naphthalene, the fully hydrogenated product was obtained at 500 psi H_2 and 80 °C,

Table 7 . Reduction of Aromatic Rings Catalyzed by Ru - clay

No.	Substrate	Time (h)	*Cis*/*trans* ratio of the product*
1.		20	86/14
2.		21	62/38
3.		17	85/15

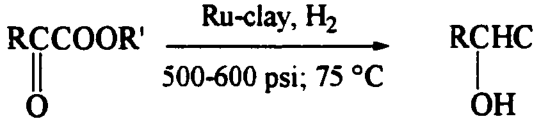
1 mmol substrate; 0.005 mmol Ru (30 mg clay); 500 psi H_2; 80 °C.
* Completely hydrogenated product.

with *cis* – decalin as the major isomer (*cis*-decalin/*trans*-decalin = 85/15) (Table 7, entry 3). The results obtained for the reduction of aromatic hydrocarbons show similar behavior to other ruthenium heterogeneous based catalysts (e.g. Ru/C) [1]. The reactions conditions employed are generally milder than those of other reported procedures (e.g. 150-200 °C and 140-1100 psi H_2) but other metals, like Rh or Co, are more efficient[71, 72].

2.4.3 Reduction of the Carbonyl Group in α-Ketoesters and α-Ketoamides

The reduction of α-ketoesters has attracted considerable attention in recent years[73]. This process represents an alternative approach to the synthesis of hydroxy acid derivatives. Very good results have been obtained using homogeneous rhodium catalysts. Rhodium phosphine systems with a neutral ligand (BPPM, CyDIOP) were found to be effective for the asymmetric reduction of α-ketocarboxylic esters[74], α-ketoamides[75], and ketopantolactone[76]. The most popular catalysts for heterogeneous hydrogenation of these type of substrates are based on platinum, palladium and nickel. The catalytic hydrogenation of α-ketoacids and α-ketoamides has been carried out using Pt/Al_2O_3, PtO_2, Pd/C, $Pd/CaCO_3$, $Pd/BaSO_4$ or Raney nickel[73,77]. Platinum supported catalyst can be chirally modified with cinchona alkaloids or other simple nitrogen containing compounds and this allows the synthesis of α-hydroxyesters and α-hydroxyamides with enantiomeric excesses up to 95 and 60 %, respectively[73,78]. A comparative study, on the enantioselective hydrogenation of pyruvate esters catalyzed by Pd and Pt in colloidal and supported form, was recently published[79]. It was concluded that the rate of the reaction is reduced in the case of palladium and the sense of the enantioselectivity is reversed with respect to that of the Pt system. Both systems used cinchonidine and cinchonine as chiral modifiers.

We were interested in investigating the activity of the Ru-phosphine clay **16** for the hydrogenation of α-ketoesters and α-ketoamides. The reaction of α-ketoesters with hydrogen in the presence of Ru clay proceeded for most of the substrates at 500 or 600 psi H_2 and 75 °C, affording the corresponding hydroxyesters in 60-100 % conversion and 80-89 % isolated yields (eq. 21).



$$\mathrm{RC(=O)COOR'} \xrightarrow[\text{500-600 psi; 75 °C}]{\text{Ru-clay, } H_2} \mathrm{RCH(OH)COOR'} \qquad \text{(eq.21)}$$

25a-28a **25b-28b**

Commercially available substrates were hydrogenated using the Ru catalyst. The conversion of methyl pyruvate to lactic ester was 60 % after 45 h at 500 psi H_2 and 100 %, in the same time, but at 600 psi H_2 (Table 8, entries 1,2). The same favorable pressure effect was observed for methyl benzoylformate – 100 % conversion at 600 psi H_2 but only 66 % conversion at 500 psi H_2 (Table 8, entries 4,5). The keto group connected to a longer alkyl chain, such as in ethyl 3-methyl-2-oxobutyrate, can be reduced completely at 500 psi H_2 (Table 8, entry 3). It was also observed that the reduction of substrates containing a phenyl ring, methyl benzoylformate and ethyl 2-oxo-4-phenylbutyrate, proceeds more rapidly (24 h and 18 h, respectively – Table 8, entries 4, 5, 6). The longest reaction time (66 h) and the highest pressure (850 psi H_2) was necessary for the reduction of ketopantolactone **29a** to pantolactone **29b** (Table 8, entry 7). Pantolactone was obtained in high yield (89 %) as the sole product of the reaction.

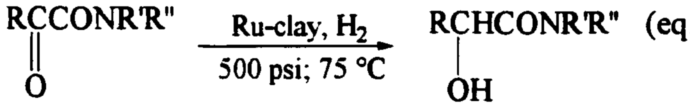
The results obtained for α-ketoesters prompted us to study the activity of the Ru catalyst for other derivatives of α-ketoacids such as α-ketoamides (eq. 22). The substrates were synthesized by the reaction of α-ketoesters with dimethylaluminum amides generated *in situ* from trimethylaluminum and the corresponding amine[80] (eq. 23, 24).

Table 8. Reduction of the Keto Group in α -Ketoesters and α -Ketoamides Using Ruthenium Clay[a]

No.	Substrate	Pressure (psi H_2)	Time (h)	Conversion (Yield)[b] (%)	
1.	$CH_3COCOOCH_3$ **25a**	500	45	60	
2.	$CH_3COCOOCH_3$	600	45	100	
3.	$CH_3CH(CH_3)COCOOC_2H_5$ **26a**	500	45	100	(80)
4.	$PhCOCOOCH_3$ **27a**	500	24	66	
5.	$PhCOCOOCH_3$	600	20	100	
6.	$PhCH_2CH_2COCOOC_2H_5$ **28a**	500	18	100	(87)
7.	$H_2CC(CH_3)_2C(O)C(O)O$ **29a**	850	66	100	(89)
8.	$PhCOCON(C_2H_5)_2$ **30a**	500	60	92	(50)
9.	$PhCOCONH(CH_2)_3CH_3$ **31a**	500	43	100	(68)
10.	$PhCOCONHCH_2Ph$ **32a**	500	50	90	(71)

[a] 1 mmol substrate; 30 mg Ru-clay; (0.005 mmol Ru); 8 ml benzene, 75 °C.

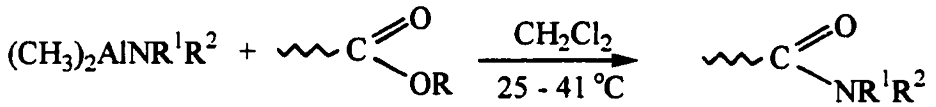
[b] Isolated yield.



$$\mathrm{R\underset{\overset{\|}{O}}{C}CONR'R''} \xrightarrow[\text{500 psi; 75 °C}]{\text{Ru-clay, }H_2} \mathrm{R\underset{\overset{|}{OH}}{C}HCONR'R''} \quad \text{(eq. 22)}$$

30a-32a **30b-32b**

$$(CH_3)_3Al + HNR^1R^2 \longrightarrow (CH_3)_2AlNR^1R^2 + CH_4 \quad \text{(eq. 23)}$$

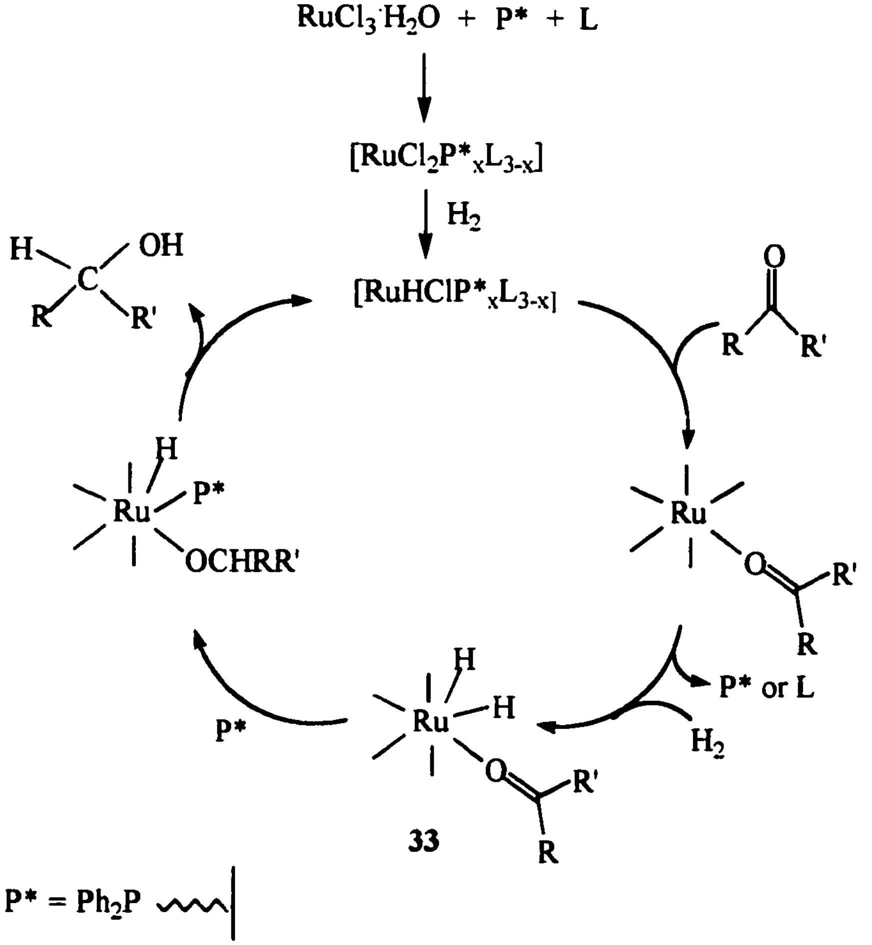


(eq. 24)

R^1; R^2 = H, alkyl; aryl

All the α-ketoamides were hydrogenated to α-hydroxyamides with high conversions (90-100%) without any competitive reactions taking place. A more rapid loss of hydrogen pressure was observed for *N*-butyl-benzoylformamide (43 h) than for *N*-benzyl-benzoylformamide (50 h) and *N,N'*-diethyl benzoylformamide (60 h). These differences may be attributed to the type of amide (primary or secondary) and the nitrogen substituent (aliphatic or aromatic). Neither of these two factors have a dramatic effect on the reaction time.

The reduction of the carbonyl group might involve a pathway similar to the homogeneous process like coordination of the oxygen of the CO group to ruthenium and hydride transfer to the carbon atom followed by reductive elimination giving the product alcohol (Scheme 6). Recent results[34] have shown that 7-coordinate 18-electron Ru (IV) –

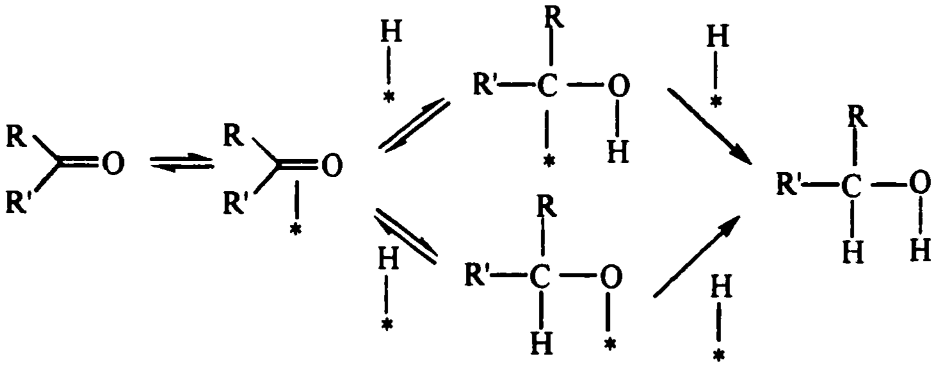


L = -OH;-O; solvent.

Scheme 6

intermediates are improbable and the complex **33** formed represents a Ru(II)-dihydride – dihydrogen complex. At the same time the modified Horiuti-Polanyi mechanism for the hydrogenation of carbonyl groups[1] assumes, as in the case of alkenes, the coordination of the carbon-oxygen bond through the π cloud of the double bond, followed by addition of hydrogen from the active site of the catalyst (Scheme 7). The effect of hydrogen pressure on the value of the conversion of the substrate (observed for methyl pyruvate and methyl benzoylformate) involves that the hydrogen availability to the catalyst is a determining factor in the mechanism of the reaction. A low hydrogen availability makes the addition of hydrogen-step the rate-determining step of the reaction. A hydrogen pressure higher than 600 psi (Table 8, entries 2, 5) means a high hydrogen availability and that the addition of hydrogen becomes a non-reversible step.

The distinction between the pathway similar to the homogeneous process and the Horiuti-Polanyi mechanism is not very strict, but the organic ligands anchored on solid supports might bring the reaction closer to the homogeneous mechanism.



Scheme 7. Horiuti-Polanyi mechanism for the hydrogenation of carbonyl groups

Quayle and Pinnavaia [81] in studies of intercalate Rh complexes in the interlayer of hectorite, proposed that the apparent substrate size selectivity arises from the spatial requirements of the reaction intermediate (Fig.8a). If the L-Rh-L axis is parallel to the clay layers and the carbon-carbon triple bond is perpendicular to the layers the intermediate could be less stable as the size of R increases due to repulsion between the silicate layers and R groups. The coordination of the keto-derivatives through the carbonyl oxygen (Fig. 8b) might make the dimensions of the substrate less critical for the reaction.

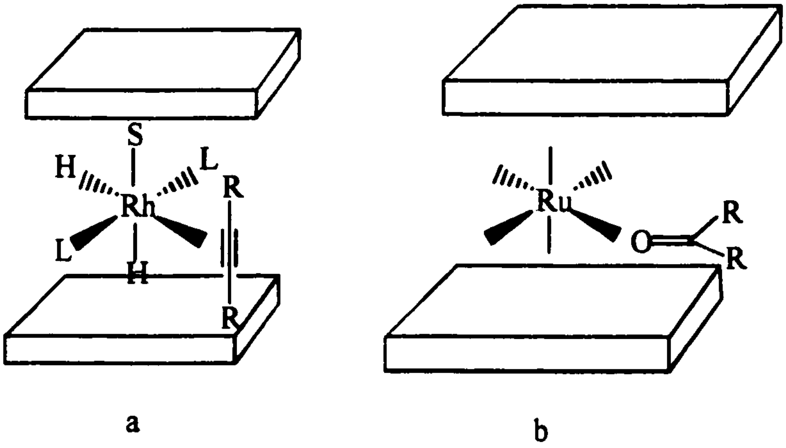


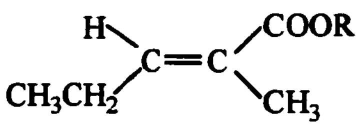
Fig. 8 a, b Metal complexes in the interlayer of clays

The results obtained in the hydrogenation of the α-carbonyl group in α-ketoesters and α-ketoamides demonstrate that the ruthenium-phosphine clay is a good hydrogenation system which is stable and retains high efficiency during consecutive catalytic cycles.

2.4.5 Attempted Asymmetric Hydrogenation Using the Ru Clay

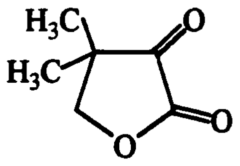
One of the important objectives in developing a new catalytic system for hydrogenation reactions is the achievement of an enantioselective process. Two main approaches were considered in attempting to realize asymmetric hydrogenations. The first approach was to adsorb a chiral ligand onto the catalyst. Platinum catalysts modified with cinchona alkaloids are effective for the hydrogenation of α-ketoesters[73a,b]. Naphthalene based aminoalcohols and aminoesters were developed as chiral ligands for the Pt catalyst used in the above process[73c]. Other examples of effective enantioselective heterogeneous catalytic systems are nickel complexes modified with tartaric acid and sodium bromide[1], which are most effective for the reduction of β-ketoesters, and palladium-cinchonidine catalysts used for the hydrogenation of (*E*)-α-phenylcinnamic acid to (*S*)-2,3-diphenyl propionic acid (44 % ee)[1].

For the Ru-clay system BINAP was the first chiral ligand to be used in the reduction process. The BINAP/Ru molar ratio was varied from 1 to 4. *Trans*-2-methyl-2-pentenoic acid, the corresponding ester (**34** or **35**) and also ketopantolactone **29a** were chosen as model substrates for reduction of the C-C and C-O double bond, respectively.



R = H, C_2H_5

34, 35



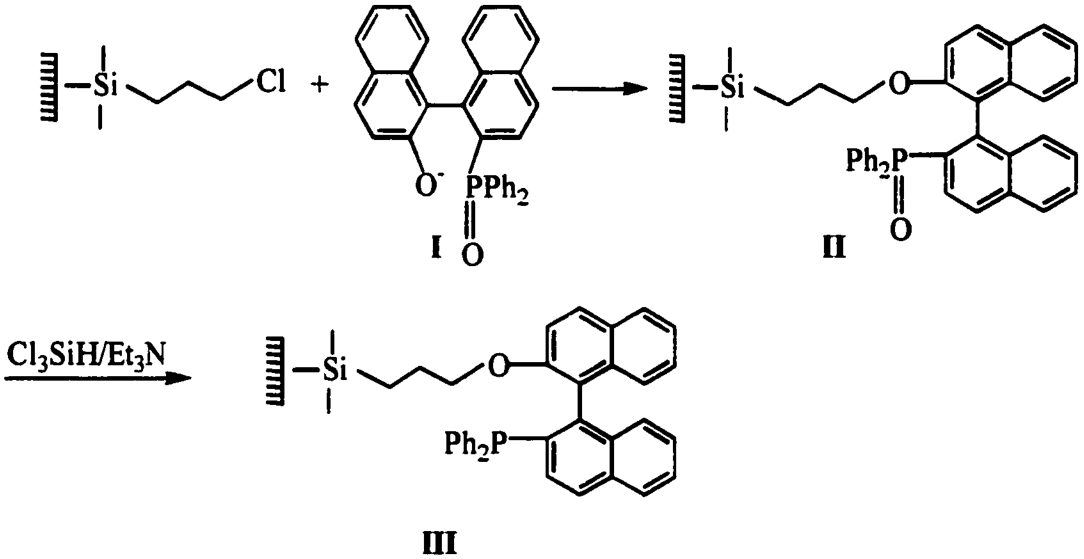
29 a

No favored formation of one enantiomer over the other one was observed (polarimeter or chiral gas chromatographic analyses). Similar behavior was observed when other chiral ligands were used: (-)-BPPM, (-)-DUPHOS, (R,S)-BINAPHOS. Pretreatment of the clay with hydrogen and pressure increases to 1200 psi did not show any improvement regarding enantioselectivity.

A recent study[82] analyzed the results reported previously regarding the variation of enantioselectivity with changes in pressure in asymmetric catalytic hydrogenation. The study shows that the increase in the value of enantioselectivity, observed with the increase of pressure, can be obtained by only changing the hydrogen concentration in the solution by variation of the gas-liquid mass transfer rate. The concentration of hydrogen in the liqiud phase, during the catalytic hydrogenation reaction, depends on the rate of gas-liquid mass transfer and on the kinetic rate law for the reaction. If the rate of mass transfer (gas-liquid) has a close value to that of hydrogen consumption in the reaction, the hydrogen concentration of the solution becomes very low. In the case of the reactors with inefficient stirring this condition persists throughout the course of the reaction and even the increase of pressure does not improve the enantioselectivity. This requirement of very efficient stirring is more difficult to satisfy in the laboratory apparatus which were used for the reduction (Parr autoclaves with magnetic stirrers) and can be a direction for further improvement.

The second approach involves immobilization of a chiral ligand onto the support through chemical bonding. There are few reports published using this route, but some of those have proved to afford good results regarding enantioselectivity (e.g. Rh on zeolites was reported for the catalytic hydrogenation of prochiral alkenes). For clays, only the intercalation of chiral complexes has been reported[20].

The method adopted in order to anchor the chiral phosphine ligand on clay is shown below (Scheme 8). It is based on similar reactions carried out in the homogeneous phase[83] and follows the same principle used for immobilization of the achiral ligand. The CP/MAS ^{31}P-NMR of the final product showed a chemical shift at 0.9 ppm (broad peak), which is different from that of the binaphthyl phosphine ligand in solution (-13 ppm). The long time (48 h) after which the spectrum could be recorded and the increased noise present, determined the conclusion that the amount of phosphorus containing compound on the clay is very small.



Scheme 8

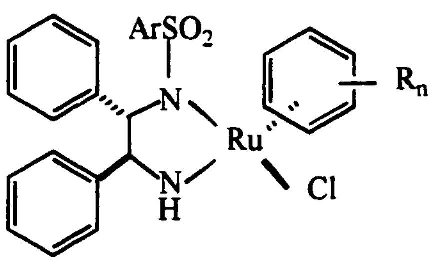
Other approaches could be of real value to try (i.e. reaction of the phosphine clay with a chiral ruthenium complex like [RuCl$_2$((*S*)-(-)-tol-BINAP)]$_2$ or reaction of the ruthenium-phosphine clay with the chiral complex of another metal).

2.4.6 Reduction of α-Iminoesters and α-Iminoketones and Reductive Amination of α-Ketoesters

The ability of the ruthenium clay system to reduce the α-imine moiety was invesigated. This process would lead, after hydrolysis of the ester group, to the formation of α-aminoesters and α-aminoacids respectively.

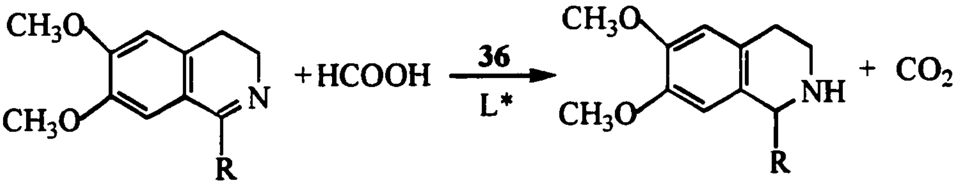
Transition metal complexes, such as $[Fe(CO)_5]$, $[Co_2(CO)_8]$, $[Mo(CO)_6]$/NaOMe, $[RhCl_2(DMF)(py)_2][BF_4]$ and $[(\eta^6\text{-}PhBPh_3)^-Rh^+(1,5\text{-}COD)]$ catalyze the reduction of the carbon-nitrogen double bond of imines in the homogeneous phase[34,84]. $Li[Ir(P\text{-}P)L_4]$ (P-P = chelating diphosphine)[85] was described as a catalyst which can tolerate ester, ketone, nitrile and nitro functional groups, and the species generated *in situ* from $[Ir(COD)Cl]_2$ and chiral diphosphines (BPPM, BDPP, DIOP) catalyzes the reduction of imines with hydrogen obtaining enantiomeric excesses up to 84 %[86].

The transfer hydrogenation of imines has been well developed over the past years. Ruthenium based catalysts showed high activity in this alternative route to imines. Bäckvall *et al.* demonstrated that imines are reduced by hydrogen transfer in propan-2-ol in the presence of catalytic amounts of $[RuCl_2(PPh_3)_3]$ and a base (K_2CO_3)[87]. $[Ru_3(CO)_{12}]$ also proved active for this process[34]. Significant progress was made by Noyori's group[88], showing that complex **36**, in the presence of suitable chiral 1,2-diamines (L*), efficiently catalyzes the asymmetric reduction of imines with a formic acid-triethylamine mixture (eq. 25). The number of heterogeneous systems reported for the reduction of the imine group is smaller than for the corresponding homogeneous catalytic systems. Usually palladium or Raney nickel are used[1], and the reaction conditions are mild (room temperature and atmospheric pressure).



η^6-arene: mesitylene; *p*-cymene; benzene

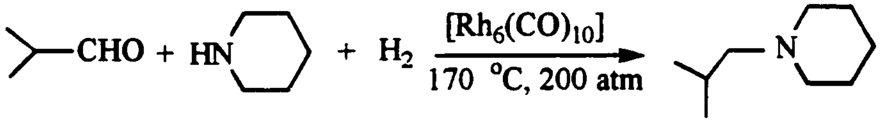
36



(eq. 25)

L* = chiral 1,2-diamines

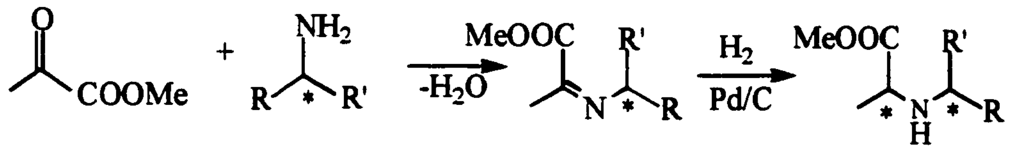
A related process is reductive amination, which assures the hydrogenation of an imine, formed *in situ* by condensation of an amine with a carbonyl compound (eq. 26)[1].



(eq. 26)

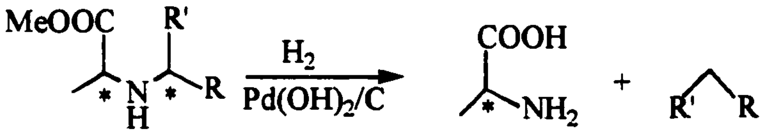
The most important heterogeneous catalysts for reductive amination are based on Pd/C or Raney Ni. The reaction can give a mixture of products if the amine produced competes with the reactant amine in the condensation step[1]. Based on this process another approach to the enantioselective synthesis of aminoacids was developed: the reductive amination of α-ketoesters using a chiral amine. Chiral amines (*R*)- and (*S*)-α-methylbenzylamine or (*R*)- and

(*S*)-phenylglycine are reacted with an α-ketoester and the Schiff base formed was reduced over a Pd catalyst (eq. 27)[89].



(eq. 27)

The substituent on nitrogen can be removed by hydrogenolysis after reductive amination (eq. 28).

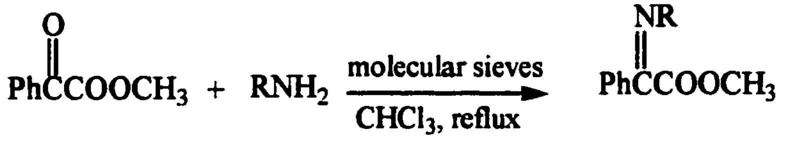


(eq. 28)

excess of *R* or *S*

2.4.6.1 Reduction of α-Iminoesters and α-Iminoketones

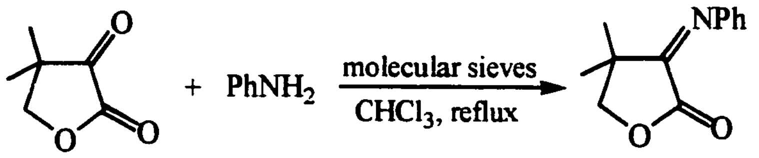
Several α-iminoesters were prepared by the known condensation reaction of an α-ketoester with different amines[90] (eq. 29, 30).



$$\mathrm{Ph\overset{\overset{O}{\|}}{C}COOCH_3} + \mathrm{RNH_2} \xrightarrow[\mathrm{CHCl_3,\ reflux}]{\text{molecular sieves}} \mathrm{Ph\overset{\overset{NR}{\|}}{C}COOCH_3}$$

(eq. 29)

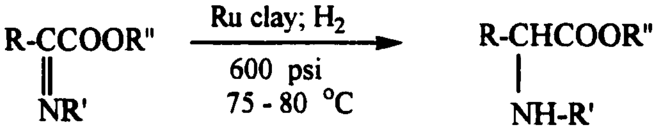
yield 62-71 %



(eq. 30)

yield 82 %

The hydrogenation reactions were carried out at 600 psi H_2 and 75-80 °C with 30 mg of Ru-clay (0.005 mmol Ru) (eq. 31).

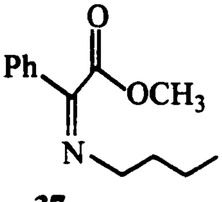
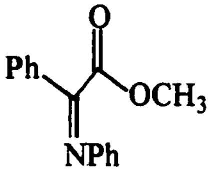
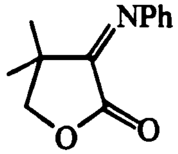
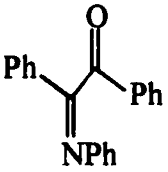
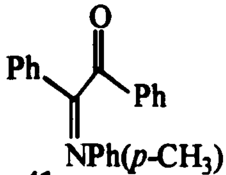


$$\text{R-}\underset{\text{NR}'}{\underset{\|}{\text{C}}}\text{COOR}'' \xrightarrow[\substack{600\ \text{psi} \\ 75-80\ ^\circ\text{C}}]{\text{Ru clay; H}_2} \text{R-}\underset{\text{NH-R}'}{\underset{|}{\text{C}}}\text{HCOOR}'' \qquad \text{(eq. 31)}$$

37a -39a **37b -39b**

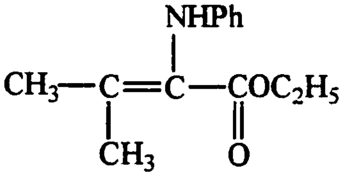
The reactions are clean, and the only product is the α-aminoester. For the α-iminoesters which are derivatives of aniline the conversion is almost complete after 41 h (Table 9, entries 2,3). In the case of the *N*-butyl derivative, after the same reaction time, the conversion to aminoester is 59 % (Table 9, entry 1). 3-Methyl-2-oxo-butyrate was also considered as a possible starting material. The preparation of the imine was carried out using the procedure mentioned above and also by a more recent reported synthesis involving the use of $TiCl_4$[91]. Both reactions gave more complex mixtures than the reactions which used ketoesters without a hydrogen in the α' position to the keto group. In this case a mixture containing the enamine **42** was formed.

Table 9. Hydrogenation of α-Iminoesters and α-Iminoketones Catalyzed by Ru Clay

No.	Substrate	Pressure (psi H_2)	Temperature (°C)	Time (h)	Conversion [isolated yield (%)]
1.	 **37a**	600	75	40	59 (51)
2.	 **38a**	600	75	41	97 (86)
3.	 **39a**	600	75	41	94 (82)
4.	 **40a**	900	100	44	100 (95)
5.	 **41a**	900	100	42	100 (60)

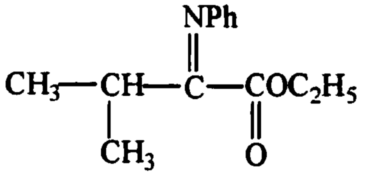
1 mmol substrate; 0.005 mmol Ru; 8 ml dry benzene.

Hydrogenation of the α-iminoester **43** resulted in incomplete conversion of the substrate after 64 h and the reaction mixture contained the aminoalcohol together with **42**.



$$CH_3-\underset{\underset{CH_3}{|}}{C}=\overset{\overset{NHPh}{|}}{C}-\underset{\underset{O}{\|}}{C}OC_2H_5$$

42

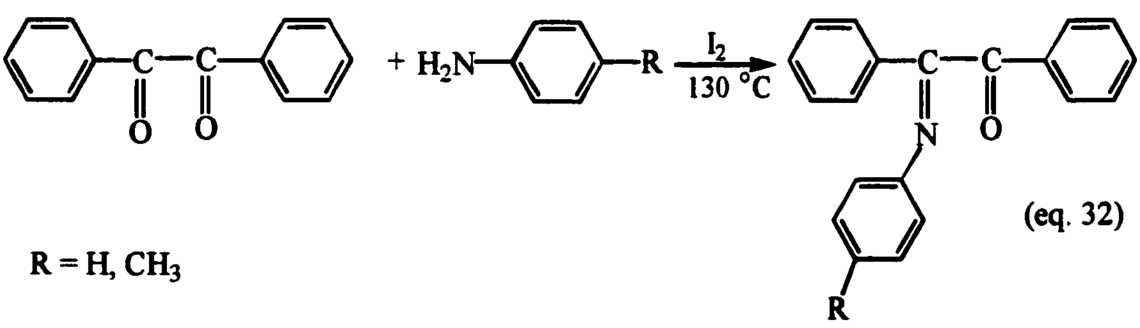


$$CH_3-\underset{\underset{CH_3}{|}}{CH}-\overset{\overset{NPh}{\|}}{C}-\underset{\underset{O}{\|}}{C}OC_2H_5$$

43

The tautomerization of the imine **43** to enamine **42** probably takes place under the reaction conditions and reduction of the C-C tetrasubstituted double bond is more difficult to accomplish with the present catalytic system. This fact is in agreement with our previous observations that a fully substituted alkene was not hydrogenated using the Ru phosphine clay.

The α-ketoimines used in the hydrogenation reactions were synthesized by direct condensation between benzil and aniline or an aniline derivative using the conditions described by Knoevenagel[92] (eq. 32).



R = H, CH_3

(eq. 32)

The main difference from the case of α-iminoesters is that more severe conditions are necessary: increase of pressure to 900 psi H_2 and increase of temperature to 100 °C. The reaction of the aniline derivative **40a** (R = H, Table 9, entry 4) afforded 95 % yield of the corresponding α-aminoketone which was the only product of the reaction. The reaction of **41a** (R = CH_3) gave complete conversion of the starting material (42 h) but α-aminoalcohol diastereoisomers are formed in addition to the aminoketone. The yield of α-aminoketone was only 60 %.

2.4.6.2 Comparison Between the Reduction of the Carbon-Nitrogen Double Bond Catalyzed by Ru Clay and Pd Clay.

A search for other efficient clay based catalytic systems was simultaneously conducted in our group. A palladium catalyst was synthesized based on the reaction of Na montmorillonite and $[Pd(PhCN)_2Cl_2]$[93] (eq. 33).

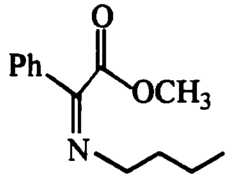
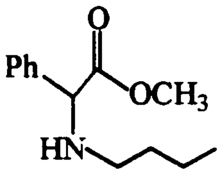
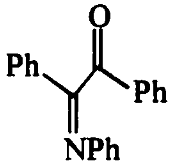
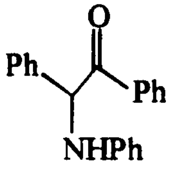
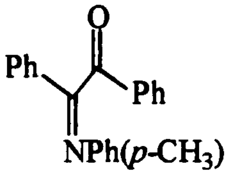
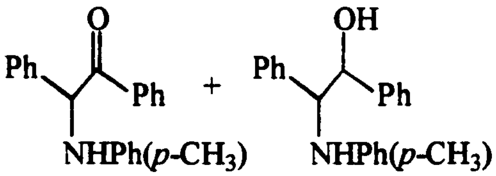
$$[\text{Clay-Na}^+] + [Pd(PhCN)_2Cl_2] \xrightarrow[\text{room temperature}]{CH_2Cl_2} \underset{\textbf{44}}{[\text{Pd-clay}]} \quad \text{(eq. 33)}$$

A similar process, using $[Rh(COD)Cl]_2$ has been previously reported[94]. The rhodium containing clay proved to be effective in catalyzing the hydroformylation of trialkylvinyl silanes with high selectivities (95-100 %) for linear silylaldehydes.

The Pd content of **44**, determined by inductively coupled plasma analysis (ICP), was 0.08 mmol Pd/g clay and the the basal spacing d(001) was 12.5 Å, as determined by X-ray diffraction.

The Pd-clay **44** confirmed the known behavior of palladium supported catalysts – efficient reduction of carbon–nitrogen double bond under mild conditions (room temperature and 100 psi H_2). Table 10 shows the results obtained with Pd-clay for some of the substrates which were also reduced in the presence of the Ru clay. The reduction of the *N*-butyl α-iminoderivative of benzoylformate, using the Pd catalyst, occurred in high yield (95 %), compared to 51 % yield obtained using ruthenium clay (Table 10, entry 1). The products obtained from the reduction of α-iminoketones were similar for the two systems. Reduction of **40a** afforded the α-aminoketone (88 % NMR yield) without any further reduction to aminoalcohol (Table 10, entry 2) while **41a** gave a mixture of α-aminoketone and α-aminoalcohols diastereisomers (Table 10, entry 3). In the Pd catalyzed reaction the percentage of aminoalcohols in the final mixture increases as the reaction time increases. After 7.5 h at 100 psi H_2 and room temperature the aminoalcohols represent 16 % of the total mixture, while after 19 h the aminoalcohols are 30 % of the reaction mixture. The reaction conditions used for the palladium system utilize lower hydrogen pressure (100 psi) and the reaction proceeds at room temperature , compared to the ruthenium clay system which uses a hydrogen pressure of 900 psi and needs a temperature of 100 °C.

Table 10. Hydrogenation of α-Iminoesters and α-Iminoketones Catalyzed by Pd Clay

No.	Substrate	Time (h)	Yield (%)	Product
1.		14	95^a	
2.		19	88^b	
3.		7.5 19	86^b 70^b	

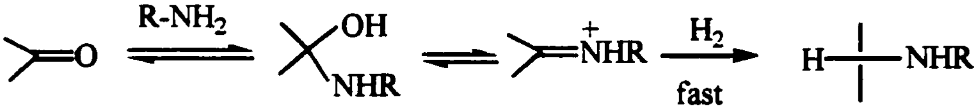
1 mmol substrate; 0.004 mmol Pd (50 mg clay); room temperature; 100 psi H_2; toluene 5 ml.
[a] Isolated yield.
[b] NMR yield, determined using an internal standard.

The same regioselectivity (formation of the aminoketone) in the hydrogenation process of α-iminoketones was observed when Pd/C was used[94] and previously for the hydrogenation of derivatives of benzilmonooximes in acidic medium[95].

The reactions carried out showed that ruthenium clay can efficiently catalyze this process which could be interesting to study for chiral α-iminoketones when α-aminoketones are obtained as mixtures of diastereoisomers. There was no diastereomeric excess obtained in the studies carried out using the Pd/C. Even if the ruthenium based catalytic system requires more severe reaction conditions, it represents a new and cheaper alternative for the reduction of iminoesters and iminoketones. The substrates are hydrogenated to the corresponding amino compounds in fair to high yield.

2.4.6.3 Reductive amination of α-ketoesters

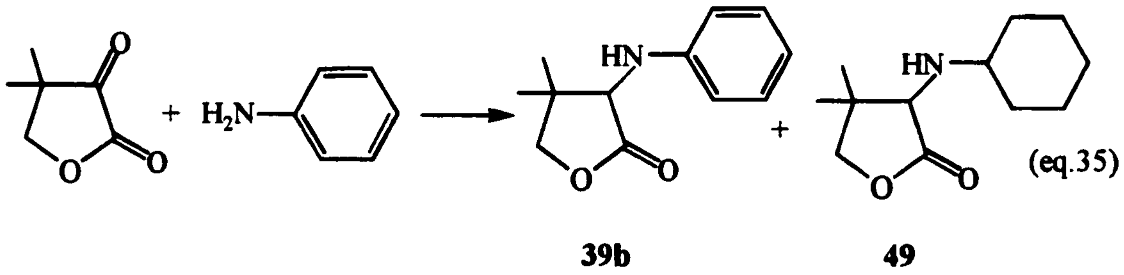
The good activity of Ru clay for the reduction of the imine bond of α-iminoesters suggested that direct formation of the α-aminoesters without isolation of the imine derivative may be possible. Reductive amination has previously been studied using heterogeneous catalytic systems based on palladium and nickel. The process is envisioned to proceed *via* the formation of an iminium ion which is then quickly reduced to the amine[89] (eq. 34). The possibility that species **16** catalyzes this process was first investigated using achiral amines.



(eq. 34)

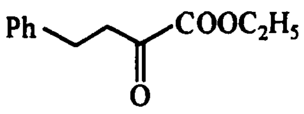
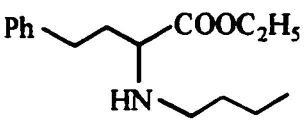
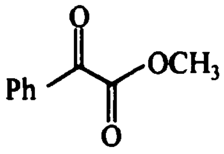
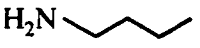
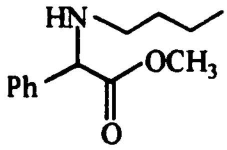
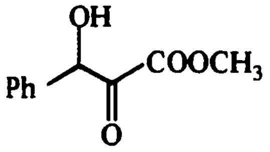
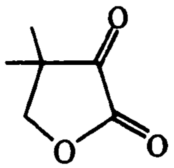
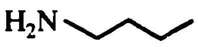
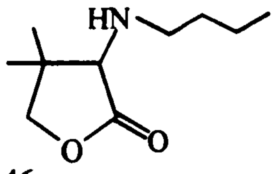
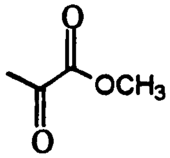
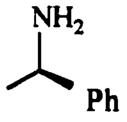
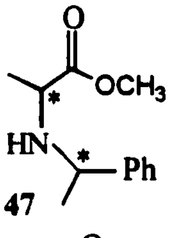
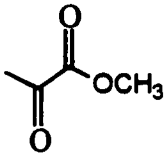
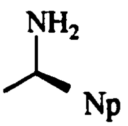
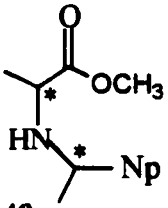
The reaction of ethyl 2-oxo-4-phenylbutyrate with *n*-butylamine at 600 psi H_2 and 100 °C, in the presence of Ru clay **16** gives the α-aminoester in 65 % yield (Table 11, entry 1). The reaction was carried out in the presence of molecular sieves as drying agents. No hydrogenation product is formed if the reaction proceeds only in the presence of molecular sieves, without Ru clay. The conversion of the α-ketoester is complete. The reaction mixture also contains unreacted amine (0.1 molar excess used in the initial mixture relative to α-ketoester), small amounts of α-hydroxyester and traces of another product which was not identified. For substrates in which the α-carbonyl moiety is bound directly to the phenyl ring the competitive process, formation of the α-hydroxyester, occurs more quickly. Methyl mandelate is formed in 72 % yield, while the aminoester constitutes the rest of the mixture (Table 11, entry 2).

In the reaction of ketopantolactone with *n*-butylamine, the aminoderivative **46** of pantolactone was obtained in 51 % isolated yield as the major product of the reaction (Table 11, entry 3). No ketopantolactone was recovered in the final mixture. If ketopantolactone is reacting with an aromatic amine (aniline) the products obtained suggest that a simultaneous reduction of the phenyl ring is occurring. *N*-phenyl and *N*-cyclohexyl amino derivatives of ketopantolactone are both obtained (eq. 35). *N*-Cyclohexylamine detected in the mixture suggests that the hydrogenation of the aromatic ring occurs before the reaction with ketopantolactone. As proven by the reduction of the *N*-phenyl-imino-derivative of ketopantolactone no hydrogenation occurs in the aromatic moiety once the imine bond is formed.



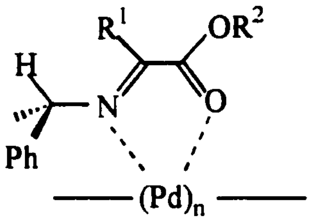
(eq.35)

Table 11. Reductive Amination of α -Ketoesters in the Presence of Ru Clay

No	α-Ketoester	Amine	Product	Yield (%)
1.			 **45**	65
2.			 **37b**	28
				72
3.			 **46**	51
4.		 (*R*)-(+)	 **47**	76 (75 % de)
5.		 (*R*)-(+)	 **48**	81 (78 % de)

1 mmol substrate; 1.1 mmol amine; 0.005 mmol Ru; 0.6 g molecular sieves; 600 psi H_2; 100 °C.

Reductive aminations are often utilized in organic synthesis in conjunction with the use of chiral amines. The reaction often leads to the formation of one major diastereoisomer. This can be used in the synthesis of α-aminoacids, formed by removal of the chiral auxiliary on the nitrogen. In reactions carried out using Pd/C, the diastereomeric excess was postulated to arise from interaction of the Schiff base with the catalyst - adsorption onto the catalyst from the less bulky face of the molecule (**50**).



50

In order to examine if any diastereoselectivity would be obtained using the Ru clay the substrates chosen were methyl pyruvate, (*R*)-(+)-α-methyl benzylamine and (*R*)-(+)-1-(1-naphthyl) ethylamine. These reactants were chosen due to the fact that the product of their hydrogenation is a precursor of the aminoacid alanine, and because in this way the results obtained with the new catalytic system can be compared with previous data.

The main concern was that use of chiral aromatic amines could be problematic as reduction of the aromatic ring may occur giving a complex mixture of products. Contrary to the result obtained with ketopantolactone and aniline, the reaction between methyl pyruvate and the chiral amines proceeded with very good selectivity towards the formation of *N*-arylaminoesters. The aminoesters represent the major product of the reactions which occur with complete conversion of the methyl pyruvate.

The reaction of methyl pyruvate with either a phenyl or a naphthyl amino derivative produced two diastereoisomers. In the case of (*R*)-(+)-α-methyl benzylamine the diastereomeric mixture was isolated in 76 % yield and with 75 % diastereomeric excess, determined by ^{1}H-NMR (Table 11, entry 4). Using (*R*)-(+)-1-(1-naphthyl) ethylamine the yield of aminoester was 81 % and the diastereomeric excess was 78 % (Table 11, entry 5). It was reported that for the hydrogenation of the Schiff bases of *i*-butyl pyruvate with (*R*) or (*S*) alanine, over palladium on charcoal, the measured diastereomeric excess was 71-81 % and the same catalyst afforded 40-70 % de in the hydrogenation of Schiff bases prepared from benzyl esters of pyruvic acid and amino acid esters[96].

The new catalytic system is, to our knowledge, the first which uses ruthenium on clays for the reductive amination process. The results obtained have similar or even higher values in terms of yield and diastereomeric excess compared to previously reported systems (palladium or nickel) for reductive amination.

Conclusions

The ruthenium clays prepared were found to be effective catalysts for the reduction of unsaturated esters, epoxides, sulfones and phosphonates. Ru-phosphine clay is an efficient catalyst for reduction of the α-carbonyl group of α-ketoesters and α-ketoamides and the α-imine group of α-iminoesters and α-iminoketones. Ruthenium clay is an alternative to other heterogeneous catalytic systems (palladium or nickel) for the reductive amination of α-ketoesters with amines.

2.5 Experimental Section

General Considerations

All ^{1}H and ^{13}C-NMR spectra were recorded on Gemini 200, Varian XL 300 and Bruker AMX 500 NMR spectrometers. Infrared spectra were recorded on a BOMEM MB 100 FTIR spectrometer. Liquid samples were run neat, and solid samples were run as KBr pellets. Mass spectra were obtained on a VG7070E mass spectrometer. Gas chromatography was carried out using a Varian 3400 chromatograph, fitted with a glass column packed with 1.5 % OV-17 & 1.95 % OV-210 on CHROMOSORB W HP 100/200 mesh. Column chromatography was performed with Merck Silica gel 60 (70-230 or 230-400 mesh) using solvent combinations determined *via* initial TLC analysis with Merck Silica gel 60 F_{254} plates. Chemicals were purchased from Aldrich, Lancaster, Fluka and Sigma, and were used as received unless otherwise noted. Solvents were purified and dried using standard techniques[97].

Synthesis of ruthenium clays

Synthesis of ruthenium-bipyridine clay **14**: H-montmorillonite was prepared from Na montmorillonite K10 (purchased from Fluka, surface 200±20 m^2/g and bulk density 810±40g/l). Na montmorillonite was treated with saturated NaCl solution followed by 0.1 N HCl solution. It was dried in air and then in vacuum. H-montmorillonite (7 g) was suspended in dry benzene (50 ml), and reacted with $SOCl_2$ (10 ml, 0.13 mol) under reflux for 24 h[23].

The chloromontmorillonite obtained was filtered and dried under vacuum. Chloromontmorillonite (2 g) was reacted with excess n-butyllithium (3.5 ml, 5.6 mmol, 1.6 M in hexane) at -78 °C in dry THF. The solution was stirred at 0 °C for 4 h and then allowed to warm to room temperature and stirred for 1 h. Bipyridine (1.18 g, 7.6 mmol) was added and the mixture was refluxed for 4 h. The reaction mixture turned purple during refluxing. It was then cooled to room temperature and air was bubbled through the solution. The montmorillonite was washed with THF, ethyl acetate and benzene followed by Soxhlet extraction with THF for 24 h. The solid obtained (**13**) was dried under vacuum and commercial (Aldrich) ruthenium chloride hydrate (0.20 mmol, 42 mg) was added to **13** (2.0 g) suspended in THF. The mixture was stirred for 8 h under nitrogen. The resulting Ru clay was thoroughly washed with water and THF to remove excess $RuCl_3 \cdot H_2O$ and dried in vacuum. The Ru content determined by flame emission spectroscopy (wavelength 372.8 nm) was 0.18 mmol Ru/g clay.

Synthesis of ruthenium-phosphine clay **16**: H-montmorillonite (4.0 g) was suspended in benzene (40 ml), (3-chloropropyl)trimethoxysilane (5.0 ml, 0.027 mol) was added and the mixture was refluxed for 12 h. The clay was extracted (Soxhlet) with toluene for 24 h, and dried[55]. The clay (2.5 g) was then suspended in dry THF (30 ml) and $KPPh_2$ (4 mmol, 8 ml 0.5 M solution in THF) was added dropwise. The mixture was refluxed overnight under nitrogen[55]. The excess $KPPh_2$ was quenched with methanol and the clay was subjected to extraction with methanol for 24 h and then toluene for additional 24 h, and subsequently dried in vacuum. The dried montmorillonite **15** (0.8 g) was suspended in THF (15 ml). $RuCl_3 \cdot H_2O$ (0.10 mmol, 21mg) was added and the mixture was stirred for 8 h under N_2 and then washed with water and THF and vacuum dried affording clay **16**. The Ru content determined by flame emission (wavelength 372.8 nm, slit width 0.1 nm, fuel - acetylene) was 0.17 Ru mmol/g clay.

XRD analysis was performed using a PW3710 BASED type diffractometer (start angle [° 2θ]: 3.000, end angle [° 2θ]: 80.000, and step size [° 2θ]: 0.040). The basal spacing d(001) was 14.1 Å and 13.3 Å for **14** and **16**, respectively.

XPS analysis was carried out by Kratos Axis XPS using monochromated Al K α x-radiation and charge neutralization.

Synthesis of ethyl 2,3-dimethyl butenoate[98]

Preparation of the enol phosphate of the β-keto ester:

A solution of 9 mmol of ethyl acetoacetate in dry ether was added to a suspension of 9.9 mmol of sodium hydride in ether, all under nitrogen, at 0 °C. After the mixture was stirred for 15-20 min at 0 °C, 9.9 mmol of diethyl chlorophosphate was introduced and stirring was continued for 2 h at room temperature. The reaction mixture was quenched with aqueous ammonium chloride solution. The ether solution was then washed with a saturated solution of sodium bicarbonate, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The enol phosphate was used directly in the dialkylcuprate coupling reaction.

Preparation of dialkylcuprate:

Methyllithium (9 mmol, 1.4 M solution in ether) was added to a suspension of cuprous iodide (4.5 mmol) in ether under nitrogen and at -20 °C. This solution was used directly.

Dialkylcuprate coupling:

The enolphosphate (4.0 mmol) in ether was added to a cooled -78 °C solution of dialkylcuprate (prepared as above). The resulting mixture was stirred at -78 °C for 2 h and then at – 47 °C for 1 h. The reaction mixture was worked up by pouring it into saturated ammonium chloride solution. The aqueous layer was extracted with ether. The extracts were combined, washed with dilute ammonia in brine and then brine, dried over magnesium sulfate, filtered, and the solvent was removed. The product was purified by column chromatography using hexane/ ethyl acetate (7/3) as eluent.

Ethyl 2,3-dimethyl butenoate (Table 4, entry 4)[98]

^{1}H-NMR ($CDCl_3$) δ 1.30 (t, 3H, -$CH_2C\underline{H_3}$, ^3J=7.4 Hz), 1.79 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 4.14 (q, 2H, CH_2, ^3J=7.4 Hz); IR (neat) 1705 (C=O) cm^{-1}, MS *m/e* 142 [M^+].

Synthesis of vinyloxiranes[99]

Synthesis of **17a** and **18a**

To a suspension of anhydrous zinc chloride (16.8 mmol, 2.3 g) in dry THF (200 ml), at -78°C, under a nitrogen atmosphere, was added allyl chloride (12.6 mmol, 0.97 g). Preformed LDA [10 mmol, prepared from BuLi (16.8 mmol) in dry THF (15 ml) and diisopropylamine (16.8 mmol, 1.69 g) in 15 ml dried THF, stirred at 0 °C for 0.5 h] was added dropwise during 20 min followed by stirring (10 min) and addition of benzaldehyde (8.4 mmol, 0.89 g). The reaction mixture was quenched after 0.5 h with saturated $NaHCO_3$

solution (150 ml) at the same temperature (-78 °C), extracted with ether, dried (Na_2SO_4) and concentrated to give the crude chlorohydrin. The product was purified by passing through a silica gel column using hexane/diethyl ether as eluent.

The chlorohydrin (2.5 mmol, 0.4 g) was reacted with 2.5 mmol $NaOCH_3$ (25 % weight solution) in 20 ml anhydrous ethanol. The mixture was stirred for 1 h at room temperature (reaction followed by GC). The reaction mixture was neutralised with a 0.1 N solution of HCl and extracted with diethyl ether, dried over $MgSO_4$ and the solvent removed under vacuo. The vinyloxiranes were pure by spectroscopic and chromatographic analysis, and they were used directly in reactions.

2-Phenyl-3-vinyloxirane **17a** (*cis* isomer)[99,100]

^{1}H-NMR ($CDCl_3$) δ 3.61-3.82 [m, 1H, C$\underline{H}$(CH=CH_2)], 4.22 (d, 1H, CHPh, ^3J = 4.8 Hz), 5.21-5.59 (m, 3H, HC=CH_2), 7.21-7.43 (m, 5H, ArH); IR 1640, 1250 (C-O) cm^{-1}; MS *m/e* 146 [M^+].

2-Methyl-2-phenyl-3-vinyloxirane **18a** (mixture of isomers *cis/trans*)[99,100]

^{1}H-NMR ($CDCl_3$) δ 1.66 (s, 3H, CH_3–one isomer), 1.70 (s, 3H, CH_3-the other isomer), 3.30 [d, 1H, C$\underline{H}$(CH=CH_2)-one isomer], 3.49 [m, 1H, C$\underline{H}$(CH=CH_2)-the other isomer], 5.11-5.95 (3H for each isomer, HC=CH_2), 7.20-7.41 (5H for each isomer, ArH); ^{13}C-NMR ($CDCl_3$) (two isomers) δ 17.5 (CH_3), 24.5 (CH_3), 64.0 ($\underline{C}CH_3Ph$), 65.7 [$\underline{C}$H(CH=CH_2)], 66.8 [$\underline{C}$H(CH=CH_2)], 120.7, 120.8, 124.9, 126.3, 127.2, 127.3, 128.0, 128.3, 132.8, 133.7, 139.5, 141.1 (aromatics and C=C); IR (neat) 1650, 1230 (C-O) cm^{-1}.

Synthesis of **19a** and **20a**[101]

m-Chloroperbenzoic acid (m-CPBA) (10.6 mmol) was added portion-wise to a stirred slurry of the diene (10.6 mmol) and sodium carbonate (22 mmol) in methylene chloride (30 ml) at 0 °C. After all the peracid was consumed (test with starch-iodide paper) the mixture was filtered and the precipitate was washed with methylene chloride. The solvent was removed and the product was purified by HPLC.

1,3-Cyclohexadiene monoxide **19a**[101]

^{1}H-NMR ($CDCl_3$) δ 1.53-1.66 (m, 1H), 1.96-2.27 (m, 3H), 3.19-3.24 [m, 1H, CH(O)], 3.47-3.51 [m, 1H, CH(O)], 5.88-5.94 (m, 2H, CH=CH), ^{13}C-NMR ($CDCl_3$) δ 20.5 (CH_2), 20.7 (CH_2), 47.0 [$\underline{C}(O)CH_2$], 55.1 [$\underline{C}$(O)HC=CH], 123.0 and 133.0 (C=C); IR (neat) 1639 (C=C), 9925, 806 (C-O) cm^{-1}; MS *m/e* 96 [M^+].

1,3-Cycloheptadiene monoxide **20a**[101]

^{1}H-NMR ($CDCl_3$) δ 1.49-1.61 (m, 2H), 1.85-2.39 (m, 4H), 3.18-3.32 [m, 1H, CH(O)], 3.38-3.48 [m, 1H, CH(O)], 5.69-5.96 (m, 2H, CH=CH); IR (neat) 1666 (C=C), 952, 881 (C-O); MS *m/e* 110 [M^+].

Synthesis of vinylphosphonates 23 and 24[102]

To a stirred mixture of dialkyl phosphite (8.8 mmol) and triethylamine (8.8 mmol) in toluene (5 ml) under N_2 was added $Pd(PPh_3)_4$ (0.4 mmol) and then vinyl bromide (8 mmol). The resultant mixture was stirred at 90 °C for different times, depending on the substrate used (40 h for **23** and 2 h for **24**) and after being cooled at room temperature was washed with brine in order to remove $Et_3N\cdot HBr$. The product was purified by column chromatography using a mixture of hexane/ethyl acetate as eluant.

Diethyl α-styrylphosphonate **23**[102]

^{1}H-NMR ($CDCl_3$) δ 1.25 (t, 6H, CH_3, ^3J = 7 Hz), 3.96-4.21 (m, 4H, CH_2 , ^3J = 7 Hz), 6.25 (br, 1H, $H_2C{=}C$), 6.38 (dd, 1H, $H_2C{=}C$, $^3J_{P\text{-}H}$= 72 Hz), 7.25-7.30 (m, 3H, ArH), 7.32-7.54 (m, 2H, ArH); IR (neat) 1235 (P=O), 1050-1020 (C-O) cm^{-1}; MS *m/e* 240 [M^+].

Diethyl 1-propenylphosphonate **24** (mixture of *E* and *Z* isomers)[102]

^{1}H-NMR ($CDCl_3$) δ 1.21-1.32 [m, $C\underline{H}_3(CH_2)$ for both isomers], 1.81-1.87 (m, CH_3) 1.98-2.04 (m, CH_3), 4.00-4.08 [m, $CH_3(C\underline{H}_2)$ for both isomers], 5.46-5.70 (m, one H for each isomer), 6.30-6.85 (m, one H for each isomer); ^{13}C-NMR ($CDCl_3$) δ 16.1 and 16.3 ($\underline{C}H_3CH_2$), 19.7/20.2 ($H_3\underline{C}C{=}$), 61.2, 61.3, 61.4, 61.5 [$CH_3(\underline{C}H_2)$], 115.5, 116.4/ 119.2, 120.1 (=$\underline{C}$(P)H, two isomers: $^1J_{C\text{-}P}$ = 43.3 Hz and $^1J_{C\text{-}P}$= 48.6 Hz), 148.7, 148.8, 148.9, 149.0 [=$\underline{C}(CH_3)H$]; IR (neat) 1635 (C=C), 1060-1040 (C-O) cm^{-1}.

General procedure for the hydrogenation reactions[59]

A mixture of unsaturated substrate (2 mmol) and Ru clay, **14** or **16** , (30 mg – 0.005 mmol Ru) in benzene (8 ml) was placed in a 45 ml autoclave. The autoclave was purged three times with H_2 and then pressurized to the desired level. The reactor was placed in an oil bath and maintained at constant temperature. The reactions were run until all the substrate was transformed or no significant change in the conversion of the starting material was observed.

The conversion of the substrate was determined from ^{1}H-NMR spectrum using an internal standard added to the mixture after reaction. After the appropriate reaction time, the autoclave was cooled to room temperature, excess H_2 gas was released and the reaction mixture was filtered through Celite and the solvent was removed by rotary evaporation. The products were purified by distillation or column chromatography.

Ethyl hydrocinnamate (Table 4, entry 5)[103,105]

^{1}H-NMR ($CDCl_3$) δ 1.21 (t, 3H, CH_3, ^3J=8 Hz), 2.61 [t, 2H, $C\underline{H}_2(COOC_2H_5)$, ^3J=10.4 Hz], 2.93 (t, 2H, $C\underline{H}_2Ph$, ^3J=10.4 Hz), 4.12 [q, 2H, $C\underline{H}_2(CH_3)$, ^3J=8 Hz], 7.12-7.40 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 14.1 (CH_3), 30.9 ($\underline{C}H_2COOC_2H_5$), 35.9 ($O\underline{C}H_2CH_3$), 60.3 (CH-Ph), 126.1, 128.2, 128.4, 140.5 (aromatics), 172.7 (C=O); MS *m/e* 178 [M^+].

Ethyl 3-phenyl-butyrate (Table 4, entry 6)[105]

^{1}H-NMR ($CDCl_3$) δ 1.18 [t, 3H, $C\underline{H}_3(CH_2)$, ^3J=7.2 Hz], 1.29 [d, 3H, $CH_3(CH)$, ^3J=8 Hz], 2.58 [m, 2H, $CH_2(CH)$], 3.25 (m, 1H, CHPh), 4.07 [q, 2H, $C\underline{H}_2(CH_3)$, ^3J =7.2 Hz], 7.13-7.32 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 14.1 (CH_3), 21.7 (CH_3), 36.4 ($\underline{C}H_2COOC_2H_5$), 42.9 ($O\underline{C}H_2CH_3$), 60.2 (CH-Ph), 126.3, 126.7, 126.7, 145.7 (aromatics), 172.3 (C=O); IR (neat) 1220 (C-O), 1739 (C=O) cm^{-1}.

2-Ethyl-3-phenyl oxirane 17b[62,105]

^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H, CH_3, ^3J = 7.4 Hz), 1.05-1.43 (m, 2H, CH_2), 3.11-3.19 [m, 1H, $C\underline{H}(CH_2CH_3)$], 4.07 (d, 1H, $C\underline{H}Ph$, ^3J = 4.2 Hz); ^{13}C-NMR ($CDCl_3$) δ 9.9 (CH_3), 20.1 (CH_2), 57.4 [C(O)], 60.5 [C(O)], 126.4, 127.3, 127.9, 135.9; MS *m/e* 149 [M^+].

2-Ethyl-3-methyl-3-phenyloxirane **18b**[62,105]

^{1}H-NMR ($CDCl_3$) δ 0.89 (t, 3H, CH_3, ^3J = 7.2 Hz -one isomer), 1.02-1.33 [m, 2H (CH_2-one isomer], 5H (CH_3CH_2-the other isomer), 1.62-1.78 [br s, $CH_3C(Ph)$ for both isomers], 2.80 [t, 1H, $C\underline{H}(CH_2CH_3)$-one isomer], 3.01 [t, 1H, $C\underline{H}(CH_2CH_3)$ ^3J = 6.4 Hz -the other isomer]; ^{13}C-NMR ($CDCl_3$) δ (major isomer) 9.9 ($\underline{C}H_3CH_2$), 21.9 and 24.5 [$\underline{C}H_3C(O)$] and [$\underline{C}H_2C(O)$], 62.6 (C-O), 67.9 (C-O), 126.3,126.9, 127.8, 139.7 (aromatics); IR (neat) 1210 (C-O), 1615, 1480 (Ph) cm^{-1}.

Ethyl phenyl sulfone (Table 6, entry 2)[105]

White solid: mp 42 °C; ^{1}H-NMR ($CDCl_3$) δ 1.18 (t, 3H, CH_3, ^3J = 7.3 Hz), 3.04 (q, 2H, CH_2, ^3J = 7.3 Hz), 7.49-7.69 (m, 3H, ArH), 7.80-7.93 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 8.0 (CH_3), 50.5 (CH_2), 128.3, 129.8, 134.9, 138.4 (aromatics); MS *m/e* 170 [M^+].

(*O, O*)-Diethyl ethyl phosphonate (Table 6, entry 3)[103]

^{1}H-NMR ($CDCl_3$) δ 1.09 [t, 3H, $C\underline{H}_3CH_2O$, ^3J = 7.5 Hz], 1.18 [t, 3H, $C\underline{H}_3CH_2O$, ^3J = 7.9 Hz], 1.30 (t, 3H, $C\underline{H}_3CH_2P$, ^3J = 7.1 Hz), 1.60-1.82 (m, 2H, $CH_3C\underline{H}_2P$, ^3J = 7.1 Hz, $^2J_{P\text{-}H}$=16 Hz), 3.98-4.16 (m, 4H, $C\underline{H}_3CH_2O$); IR (neat) 1739, 1217 cm^{-1}; MS *m/e* 166 [M^+].

General procedure for the reduction of the aromatic rings of benzene derivatives and naphthalene

A mixture of the substrate (1 mmol) and ruthenium clay (30 mg – 0.005 Ru) in dry benzene was placed in a 45 ml autoclave equipped with a glass liner and a magnetic stirrer bar. The autoclave was purged three times with hydrogen and then pressurized at 500 psi H_2. The reactor was placed in an oil bath and maintained at constant temperature (80 °C). In order to stop the reaction the autoclave was cooled to room temperature and the excess hydrogen gas was released. The reaction mixture was filtered to remove the ruthenium clay. The ratio of the *cis/trans* isomers in the filtrate was determined by ^{1}H-NMR or gas chromatography. The compounds were identified by comparison with literature data or with commercial products.

Synthesis of α-ketoamides[80]

In a typical experiment 1.2 ml (3 mmol) of a 2.5 M solution of trimethylaluminum in hexane was added, at room temperature, to a solution of amine (3.0 mmol) in dry methylene chloride (7 ml), under nitrogen. The mixture was stirred for 20 min at room temperature and then 3.0 mmol of α-ketoester was added. The flask containing the mixture was kept at 30 °C and the progress of the reaction was followed by TLC. The reaction times varied, according to the substrates used, from 5 to 23 h. The reaction was quenched with dilute HCl and extracted with methylene chloride. The organic phase was dried ($MgSO_4$) and concentrated by rotary evaporation. The α-ketoamide was purified by silica gel column chromatography using hexane/ethyl acetate as eluent.

N,N-diethyl benzoylformamide **30a**[106]

^{1}H-NMR ($CDCl_3$) δ 1.12 (t, 3H, CH_3, ^3J = 7.1 Hz), 1.26 (t, 3H, CH_3, ^3J = 7.1 Hz), 3.21 (q, 2H, CH_2, ^3J = 7.1 Hz), 3.53 (q, 2H, CH_2, ^3J = 7.1 Hz), 7.43-7.61 (m, 3H, ArH), 7.88-7.92 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 12.8 (CH_3), 14.0 (CH_3), 38.7 (CH_2), 42.0 (CH_2), 128.9, 129.5, 133.2, 134.5 (aromatics), 166.7 [$C(O)NC_2H_5$], 191.5 [C(O)Ph]; IR (neat) 1640 (C=O, amide), 1685 (C=O, ketone) cm^{-1}.

N-butyl benzoylformamide **31a**[106]

^{1}H-NMR ($CDCl_3$) δ 0.93 (t, 3H, CH_3, ^3J = 7 Hz), 1.36-1.61 (m, 4H, -CH_2CH_2-), 3.32-3.42 (m, 2H, -$\underline{CH_2}$NH), 6.95-7.20 (br, 1H, NH), 7.41-7.60 (m, 3H, ArH), 8.29-8.34 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.6 (CH_3), 19.9 (CH_2), 31.2 (CH_2), 39.0 (CH_2), 128.3, 131.0, 133.2, 134.2 (aromatics), 161.7 [CO(NH)], 187.9 [CO(Ph)]; IR (neat) 1666 (C=O, amide), 1690 (C=O, ketone), 3322 (NH) cm^{-1}; MS *m/e* 205 [M$^+$].

N-benzyl benzoylformamide **32a**[106]

^{1}H-NMR ($CDCl_3$) δ 4.57 (d, 2H, CH_2Ph, J = 6 Hz), 6.70-6.90 (br, 1H, NH), 7.26-7.64 (m, 3H, 5H, ArH), 8.34-8.39 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 43.4 (CH_2Ph), 127.7, 127.8, 128.4, 128.7, 131.1, 133.2, 134.4, 137.0 (aromatics), 165.5 [CO(NH)], 187.5 [CO(Ph)]; IR (neat) 1655 (C=O, amide), 1690 (C=O, ketone), 3259 cm^{-1}; MS *m/e* 239 [M$^+$].

General Procedure for the hydrogenation reactions of α-ketoamides and α-ketoesters

A mixture of the substrate (1 mmol) and ruthenium clay (30 mg, 0.005 mmol Ru) in dry benzene (8 ml) was placed in a 45 ml autoclave equipped with a glass liner and a magnetic stirrer. The autoclave was purged three times with hydrogen and then pressurized to the desired level. The reactor was placed in an oil bath and maintained at constant temperature. In order to stop the reaction the autoclave was cooled to room temperature and the excess hydrogen gas was released. The reaction mixture was filtered through Celite to retain the ruthenium clay and the solvent was removed by rotary evaporation of the filtrate. In the case of recycling the catalyst, the mixture was filtered through fine filter paper and the ruthenium clay was then washed several times with benzene, followed by THF, and subsequently vacuum dried. The purification of the products was made by silica gel column chromatography using different ratios of the mixture hexane – ethyl acetate as eluent.

Ethyl 2-hydroxy-3-methylbutyrate **26b**[107]

^{1}H-NMR ($CDCl_3$) δ 0.83 (d, 3H, $C\underline{H}_3CH$, ^3J = 6.9 Hz), 1.00 (d, 3H, $C\underline{H}_3CH$, ^3J = 6.9 Hz), 1.28 (t, 3H, $C\underline{H}_3CH_2O$-, ^3J = 7.1 Hz), 2.01-2.09 [m, 1H, $C\underline{H}(CH_3)_2$], 2.67-2.70 (d, 1H, OH), 4.01-4.02 (m, 1H, $C\underline{H}OH$), 4.23 (dq, 2H, $CH_3C\underline{H}_2O$-, ^3J = 7.1 Hz); ^{13}C-NMR ($CDCl_3$) δ 14.1 (CH_3), 15.1 (CH_3), 18.6 (CH_3), 32.0 [$\underline{C}H(CH_3)_2$], 61.4 ($CH_3\underline{C}H_2$), 74.8 ($\underline{C}HOH$), 174.8 (C=O); IR (neat) 1733 (C=O), 3479 (OH) cm^{-1}.

Ethyl 2-hydroxy-4-phenylbutyrate **28b**[107] (Figure 9)

^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 3H, $CH_2C\underline{H}_3$, ^3J = 7.1 Hz), 1.95-2.09 [m, 2H, $C\underline{H}_2CH(OH)$], 2.76 (t, 2H, $PhCH_2$), 2.87-3.10 (br, 1H, OH), 4.18-4.25 (m, 1H, $C\underline{H}OH$), 4.22 (t, 2H, CH_2, ^3J = 7.1 Hz), 7.12-7.32 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 14.1 (CH_3), 31.0 (CH_2), 35.9 (CH_2), 61.1 ($CH_3\underline{C}H_2O$), 69.6 [CH(OH)], 125.9, 128.3, 128.5, 141.1 (aromatics), 175.1 (C=O); IR (neat) 1732 (C=O), 3458 (OH) cm^{-1}; MS *m/e* 208 [M^+].

Pantolactone **29b**[103,104]

White crystals: mp 89 °C; ^{1}H-NMR ($CDCl_3$) δ 1.06 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 2.62 (d, 1H, OH, J = 3.1 Hz), 3.92 (d, 1H, CH_2, ^{2}J = 9 Hz), 4.02 (d, 1H, CH_2, ^{2}J = 9 Hz), 4.09 (d, 1H, CH, J = 3.1 Hz); ^{13}C-NMR ($CDCl_3$) δ 18.7 (CH_3), 22.8 (CH_3), 40.8 [$C(CH_3)_2$], 75.7 and 76.4 ($\underline{C}H_2O$ and $\underline{C}HOH$), 177.7 (C=O); IR (KBr) 1779 (C=O), 3417 (OH) cm^{-1}; MS *m/e* 130 [M^+].

N,N-diethyl mandelamide **30b**[108]

^{1}H-NMR ($CDCl_3$) δ 0.76 (t, 3H, CH_3, ^{3}J = 7.1 Hz), 1.11 (t, 3H, CH_3, ^{3}J = 7.1 Hz), 3.08 (m, 2H, CH_2), 3.46 (m, 2H, CH_2), 4.81 (d, 1H, OH, ^{3}J = 6.4 Hz), 5.12 (d, 1H, CH, ^{3}J = 6.4 Hz), 7.26-7.34 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 12.5 (CH_3), 13.0 (CH_3), 40.6 (CH_2), 40.9 (CH_2), 71.5 (CHOH), 127.4, 128.4, 129.4, 139.8 (aromatics), 171.4 (CO); IR (neat) 1636 (C=O), 3392 (OH) cm^{-1}.

N-butyl mandelamide **31b**[108] (Figure 10)

^{1}H-NMR ($CDCl_3$) δ 0.85 (t, 3H, CH_3, ^{3}J = 7 Hz), 1.18-1.44 (m, 4H, CH_2CH_3), 3.17 (q, 2H, CH_2NH, ^{3}J = 7 Hz), 4.10 (d, 1H, OH, ^{3}J = 3.7 Hz), 4.91 (d, 1H, CH, ^{3}J = 3.7 Hz), 6.28-6.41 (br, 1H, NH), 7.27-7.35 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.6 (CH_3), 19.8 (CH_2), 31.4 (CH_2), 39.1 (CH_2), 74.0 (CH), 126.7, 128.4, 128.6, 139.6 (aromatics), 172.1 (C=O); MS *m/e* 207 (1), 205 (17), 108 (15), 105 (100), 100 (9), 79 (14), 77 (58), 57 (57).

N-benzyl mandelamide **32b**[108]

White crystals: mp 98.8-99.3 °C; ^{1}H-NMR ($CDCl_3$) δ 3.65 (d, 1H, OH, ^{3}J = 3.5 Hz), 4.41 (dd, 2H, CH_2Ph, ^{3}J = 2.2 Hz, ^{2}J = 5.8 Hz), 5.04 (d, 1H, CHPh, ^{3}J = 3.5 Hz), 6.40-6.60 (br, 1H, NH), 7.13-7.39 (m, 10H, ArH); ^{13}C-NMR ($CDCl_3$) δ 43.4 (CH_2), 74.2 (CH), 126.8, 127.5, 128.6, 128.8, 137.6, 139.3 (aromatics), 172.0 (C=O); IR (KBr) 1624 (C=O), 3212, 3270 (NH, OH) cm^{-1}; MS *m/e* 241 [M^+].

Procedure for attempted asymmetric hydrogenation of α,β-unsaturated esters and α-ketoesters

A mixture of substrate **29**, **34**, or **35** (2 mmol), Ru clay **14** (30 mg, 0.005 mmol), chiral ligand, BINAP (molar ratio *m* = BINAP/ Ru, m =1, 2, 3 or 4 for different experiments), in dry benzene (8 ml) was placed in a 45 ml autoclave. The autoclave was purged three times with H_2 and then pressurized to the desired level. The reactor was placed in an oil-bath and maintained at constant temperature. Different experiments were run for 17 h, 30 h and 48 h. The reaction was stopped by cooling the autoclave to room temperature, excess H_2 gas was released and the reaction mixture was filtered through Celite. The solvent was removed by rotary evaporation. The chiral ligand present in the reaction mixture was removed by distillation or by column chromatography. The favored formation of one enantiomer over the other one was observed by chiral gas chromatographic analyses or polarimeter. In the case of gas chromatograph the result was compared to the racemic compound. The experiments which involved the pretreatment of the clay with hydrogen were run using the same amounts and ratios of substrate, catalyst and chiral ligand. The Ru clay was suspended in dry benzene and pretreated with hydrogen (300 psi) for 2 h at 80 °C. The autoclave was cooled to room temperature and the substrate and the chiral ligand were added. The autoclave was purged again with H_2, pressurized and placed in the oil-bath.

Attempted functionalization of montmorillonite with chiral ligand

(*S*)-2-(diphenylphosphinyl)-2'-hydroxy-1,1'-binaphthyl, **I**, (1.45 mmol, 0.680g) – previously synthesized in our laboratory – was reacted with sodium hydride (60 % oil suspension, 1.60 mmol, 0.038 g) in 5ml THF at 0 °C and the mixture was stirred for 5 min at room temperature. Montmorillonite, which was treated with (3-chloropropyl)trimethoxysilane (0.500 g, chlorine content 2.90 mmol/g), was added at 0 °C and the reaction mixture was stirred at ambient temperature for 5 h. The mixture was diluted with ether and quenched with small amount of water. The clay was separated by filtration, washed with methanol and dried in vacuum. It was subjected further to reaction with $HSiCl_3/Et_3N$. The clay obtained from the previous step was suspended in xylene followed by addition of Et_3N (29 mmol, 2.930 g) and $HSiCl_3$ (7.25 mmol. 0.980 g). The reaction mixture was stirred at 120 °C for 5 h, under nitrogen. After being cooled to room temperature the mixture was diluted with ether and quenched with 2 ml saturated solution of $NaHCO_3$. The clay was filtered under nitrogen atmosphere, washed with methanol and dried under vacuum. CP/MAS ^{31}P-NMR: 0.9 ppm.

Synthesis of α-iminoesters[90]

A mixture of α-ketoester (6 mmol), amine (7.2 mmol) and molecular sieves (4 Å) was refluxed in chloroform (10 ml). The progress of the reaction was checked by TLC and GC. The reaction time varied from 3 to 24 h according to the substrate used. The mixture was then filtered from molecular sieves which were washed with solvent. The solvent was removed from the filtrate and washings by rotary evaporation, and the product was purified by column chromatography using a mixture of hexane/diethyl ether as eluent.

Reaction of ethyl 3-methyl-2-oxobutyrate with aniline[91]

To an ice-cooled solution of ethyl 3-methyl-2-oxo-butyrate (5 mmol, 0.72 g) and aniline (20 mmol, 1.86 g) in diethyl ether (12.5 ml), $TiCl_4$ (2.5 mmol, 2.5 ml solution 1 M $TiCl_4$ in methylene chloride) was added dropwise. After complete addition, the ice-bath was removed and the reaction mixture was stirred at room temperature for 2 h. A red-brown precipitate, formed when $TiCl_4$ was added, disappeared after stirring and a yellow suspension was formed. After 2 h the suspension was cooled to (10 °C) and poured into NaOH (20 ml). The organic layer was separated and the water layer extracted twice with ether. The combined organic extracts were dried (K_2CO_3), filtered, and the solvent was removed in *vacuo*. The reaction mixture was worked-up by column chromatography using a ether-hexane (2/8) as eluent.

Methyl α-(*N*-butylimino) benzenacetate **37a**[109]

^{1}H-NMR ($CDCl_3$) δ 0.92 (t, 3H, CH_3, ^3J = 7.3 Hz), 1.39-1.51 (m, 2H, CH_2), 1.62-1.80 (m, 2H, CH_2), 3.50 (t, 2H, CH_2N, ^3J = 7.0 Hz), 3.90 (s, 3H, OCH_3), 7.37-7.40 (m, 3H, ArH), 7.64-7.72 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.8 (CH_3), 20.4 (CH_2), 32.7 (CH_2), 51.7 (CH_2), 55.0 (OCH_3), 127.0, 128.3, 130.7, 134.3 (aromatics), 159.6 (C=N), 166.1 (C=O); IR (neat): 1735 (C=O), 1634 (C=H) cm^{-1}; MS *m/e* 219 [M$^+$].

Methyl α-(*N*-phenylimino) benzenacetate **38a**[109]

^{1}H-NMR ($CDCl_3$) δ 3.62 (s, 3H, CH_3), 6.91-7.52 (m, 8H, ArH), 7.81-7.92 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 51.9 (CH_3), 119.4, 124.9, 127.9, 128.7, 128.8, 131.8, 133.7, 149.9 (aromatics), 160.7 (C=N), 165.4 (C=O); IR (neat) 1736 (C=O), 1630 (C=N), MS *m/e* 239 [M^+].

3-(*N*-phenylimino)-4,4-dimethyl-butyrolactone **39a**[110]

^{1}H-NMR ($CDCl_3$) δ 1.12 and 1.39 [both s, 6H, $C(CH_3)_3$, *syn* and *anti* isomers], 4.12 and 4.29 [both s, 2H, $CH_2(O)$, *sin* and *anti* isomers], 6.78-6.82 (m, 2H, ArH), 7.07-7.38 (m, 3H, ArH); ^{13}C-NMR ($CDCl_3$) δ 24.5 (CH_3), 40.5 [$C(CH_3)_2$], 77.2 (CH_2), 118.2, 124.5, 124.9 148.2 (aromatics), 161.2 (C=N), 166.5 (C=O); IR (KBr) 1685 (C=N), 1779 (C=O); MS *m/e* 203 [M^+].

Synthesis of α-iminoketones[92]

A mixture of benzil (9 mmol, 2 g), aniline (21 mmol, 2.0 g) and iodine (0.010 mmol, 2.5 mg) was heated for 5-10 minutes at 130 °C. Ethanol was added after the flask containing the mixture was removed from the oil-bath. The solid product was dissolved in ethanol and was allowed to stay at room temperature. The crystals formed were filtered, washed with cold ethanol on the filter and dried under vacuum.

N-phenyl-1-benzoylbenzylidenamine **40a**[92,111]

Yellow crystals: mp 105 °C; ^{1}H-NMR ($CDCl_3$) δ 6.81-7.55 (m, 11H, ArH), 7.70-7.79 (m, 2H, ArH), 7.82-7.91 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 120.3, 124.6, 128.2, 128.3, 128.5, 128.7, 129.2, 131.6, 134.2, 134.6, 135.0, 149.1 (aromatics), 166.2 (C=N), 197.5 (C=O); MS *m/e* 285 [M^+].

N-(*p*-tolyl)-1-benzoylbenzylidenamine **41a**[92,111]

Yellow crystals: mp 117 °C; ^{1}H-NMR ($CDCl_3$) δ 2.18 (s, 3H, CH_3), 6.78-6.96 (m, 4H, ArH), 7.31-7.58 (m, 6H, Ar H), 7.78-7.89 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 20.8 (CH_3), 120.5, 128.0, 128.7, 128.8, 129.2, 129.3, 131.4, 134.2, 134.3, 134.5, 135.2, 146.5 (aromatics), 165.7 (C=N), 198.0 (C=O); IR (KBr) 1665 (C=O), 1618 (C=N) cm^{-1}.

General procedure for the hydrogenation reactions of α-iminoesters and α-iminoketones

A mixture of the substrate (1 mmol) and ruthenium clay (0.005 mmol Ru) in dry benzene (8 ml) were placed in a 45 ml autoclave equipped with a glass liner and a magnetic stirrer. The autoclave was purged three times with hydrogen and then pressurized at the desired level (600-900 psi H_2). The reactor was placed in an oil-bath and maintained at constant temperature (75 or 100 °C). In order to stop the reaction the autoclave was cooled to room temperature and the excess hydrogen gas was released. The reaction mixture was filtered through Celite to retain the ruthenium clay and then the solvent was removed by rotary evaporation of the filtrate. The purification of the products was effected by silica gel column chromatography using different ratios of hexane and ethyl acetate as eluent.

Synthesis of Pd clay[93]

A mixture of $[Pd(PhCN)_2Cl_2]$ (38.3 mg, 0.10 mmol) and Na montmorillonite (1 g) in dry dichloromethane (25 ml) was stirred for 10 h at room temperature(under nitrogen). The resulting yellow solid material (Pd clay) was filtered, washed thoroughly with dry dichloromethane and dried by blowing with nitrogen and dried under vacuum. The Pd content, determined by ICP analysis, was 0.08 mmol Pd/g clay.

General procedure for the hydrogenation of α-ketoimines using Pd clay[93]

A mixture of substrate (1 mmol), Pd clay (0.050 g – 0.004 mmol Pd) and dry toluene (5 ml) was placed in a 45 ml autoclave equipped with a glass liner and a magnetic stirrer. The autoclave was flushed three times with hydrogen and then pressurized to 100 psi. The autoclave was kept at room temperature. After 7.5 –19 h the excess hydrogen was released and the reaction mixture was worked–up in a similar way to the reaction catalyzed by Ru clay. The yield of hydrogenated product was determined either by isolation of the product or by ^{1}H-NMR using an internal standard.

Methyl α-(*N*-butylamino) benzenacetate 37b[112]

^{1}H-NMR ($CDCl_3$) δ 0.86 (t, 3H, CH_3, $^3J = 7.1$), 1.22-1.55 (m, 4H, $-CH_2CH_2-$), 1.90-2.09 (br, 1H, NH), 2.48-2.63 (m, 2H, CH_2NH), 3.66 (s, 3H, OCH_3), 4.34 (s, 1H, CH), 7.28-7.42 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.8 (CH_3), 20.3 (CH_2), 32.0 (CH_2), 47.4 (CH_2), 52.1

(OCH_3), 65.5 (CHPh), 127.3, 127.9, 128.6, 138.2 (aromatics), 173.5 (C=O); IR (neat) 1739 (C=O), 3335 (NH); MS *m/e* 178 (8), 162 (100), 149 (31), 106 (65), 77 (30), 57 (14).

Methy α-(*N*-phenylamino) benzenacetate **38b**[112]

White crystals: mp 78 °C; ^{1}H-NMR ($CDCl_3$) δ 3.72 (s, 3H, OCH_3), 4.88-5.25 (br, 1H, NH), 5.07 (s, 1H, CH), 6.53-6.73 (m, 3H, ArH), 7.07-7.51 (m, 7H, ArH); ^{13}C-NMR ($CDCl_3$) δ 52.8 (CH_3), 60.7 (CHPh), 113.3, 118.0, 127.2, 128.2, 128.8, 129.2, 137.5, 145.8 (aromatics), 172.3 (C=O); IR (KBr) 1737 (C=O), 3345 (NH); MS *m/e* 241 [M^+].

3-(*N*-phenyamino)-4,4-dimethyl-butyrolactone **39b**[113]

Fine crystals, pale yellow: mp 108 °C, ^{1}H-NMR ($CDCl_3$) δ 1.05 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 3.97-4.08 (m, 4H, CH_2, CH, NH), 6.67-6.81 (m, 3H, ArH), 7.14-7.24 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 19.9 (CH_3), 24.0 (CH_3), 41.6 [$-C(CH_3)_2$], 62.9 (CH), 77.1 (CH_2), 113.4, 118.8, 129.3, 147.1 (aromatics), 176.3 (C=O); IR (KBr) 1766 (C=O), 3378 (NH); MS *m/e* 203 [M^+].

N-phenyl-(α-benzoyl)benzylamine **40b**[94]

Pale yellow crystals: mp 98 °C, ^{1}H-NMR ($CDCl_3$) δ 5.35-5.50 (b, 1H, NH), 5.90-6.09 (s, 1H, CH), 6.63-6.72 (m, 3 H, ArH), 7.01- 7.60 (m, 10H, ArH), 7.95-8.06 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 62.6 (CH), 113.4, 117.7, 128.0, 128.3, 128.6, 128.8, 129.0, 129.2, 133.5, 134.9, 137.6, 146.0 (aromatics), 197.0 (C=O); IR (KBr) 1682 (C=O), 3394 (NH) cm^{-1}; MS *m/e* 287 [M^+].

N-p-tolyl-(α-benzoyl)-benzylamine **41b**[94]

Fine yellow crystals: mp 146 °C; ^1H-NMR ($CDCl_3$) δ 2.11 (s, 3H, CH_3), 5.35-5.60 (br, 1H, NH), 6.00 (s, 1H, CHPh), 6.57-6.61 (m, 2H, ArH), 6.90-6.94 (m, 2H, ArH), 7.17-7.52 (m, 8H, ArH), 7.94-7.99 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 20.3 (CH_3), 63.1 (CH), 113.8, 127.6, 128.0, 128.1, 128.6, 128.8, 129.0, 129.7, 133.4, 134.7, 137.4, 143.5 (aromatics), 196.7 (C=O); IR (KBr) 1674 (C=O), 3397 (NH) cm^{-1}.

General procedure for the reductive amination of α-ketoesters in the presence of Ru clay

A mixture of α-ketoesters (1 mmol), amine (1.1 mmol), ruthenium clay (0.005 mmol Ru) and molecular sieves - 4 Å (0.6 g), in dry benzene (8 ml), was placed in a 45 ml autoclave equipped with a glass liner and a magnetic stirrer. The autoclave was purged three times with hydrogen and then pressurized to 600 psi H_2. The reactor was placed in an oil-bath and maintained at 100 °C. The decrease of the hydrogen pressure was observed on the manometer of the autoclave. In order to stop the reaction the autoclave was cooled to room temperature and the excess hydrogen gas was released. The reaction mixture was filtered through Celite. The molecular sieves and the Ru clay were washed with benzene and the solvent was removed from the filtrate and washings by rotary evaporation. The purification of the products was made by silica gel column chromatography using different ratios of hexane/ethyl acetate as eluent, or by HPLC.

Ethyl 2-(*N*-butylamino)-4-phenylbutanoate **45**[112](Figure 11)

^{1}H-NMR (CDCl$_3$) δ 0.88 (t, 3H, CH$_3$, ^{3}J = 6.8 Hz), 1.26 (t, 3H, CH$_3$CH$_2$O, ^{3}J= 7.1 Hz), 1.34-1.49 (m, 5H, CH$_2$CH$_2$, NH), 1.86-2.02 (m, 2H, CH$_2$NH), 2.35-2.62 (m, 2H, CH$_2$CHNH), 2.68 (t, 2H, CH$_2$Ph, ^{3}J = 7.8 Hz), 3.20 (t, 1H, C H$_2$CH, ^{3}J = 6.8 Hz), 4.15 (q, 2H, OCH$_2$, ^{3}J= 7.1 Hz), 7.14-7.32 (m, 5H, ArH); ^{13}C-NMR (CDCl$_3$) δ 13.9 (CH$_3$), 14.3 (CH$_3$), 20.3 (CH$_2$), 32.0 (CH$_2$), 32.6 (CH$_2$), 35.1 (CH$_2$), 47.8 (OCH$_2$), 60.5/61.1 (CHNH/CH$_2$Ph), 125.9, 128.3, 128.4, 141.4 (aromatics), 175.5 (C=O); IR (neat) 1731 (C=O), 3326 (NH) cm^{-1}.

3-(*N*-butylamino)-4,4-dimethyl butyrolactone **46**[113](Figure 12)

^{1}H-NMR (CDCl$_3$) δ 0.89 (t, 3H, CH$_3$CH$_2$, ^{3}J = 6.9 Hz), 0.98 (s, 3H, CH$_3$C), 1.16 (s, 3H, CH$_3$C), 1.28-1.53 (m, 5H, CH$_2$CH$_2$, NH), 2.56-2.71 (m, 1H, NHCH$_2$), 2.77-2.91 (m, 1H, NHCH$_2$), 3.11 (s, 1H, CHNH), 3.83 [d, 1H, C(O)H, ^{2}J = 8.8 Hz], 3.92 [d, 1H, C(O)H, ^{2}J = 8.8 Hz]; ^{13}C-NMR (CDCl$_3$) δ 13.9 (CH$_3$), 19.7 (CH$_3$), 20.1 (CH$_2$), 23.9 (CH$_3$), 32.3 (CH$_2$), 40.8 [C(CH$_3$)$_2$], 49.4 (CH$_2$NH), 66.5 and 76.5 (CHNH and CH$_2$), 177.9 (C=O); IR (KBr) 1777 (C=O), 3324 (NH) cm^{-1}; MS *m/e* 185 [M^{+}].

Methy 2-[*N*-(α-methyl)-benzyl] aminopropionate **47** (major diastereoisomer)[96]

^{1}H-NMR (CDCl$_3$) δ 1.20 [d, 3H, CH$_3$(CHCOOCH$_3$), ^{3}J = 7.1 Hz], 1.31 [d, 3H, CH$_3$(CHPh), ^{3}J = 6.4 Hz], 1.75-1.90 (br, 1H, NH), 3.09 [q, 1H, CH(COOCH$_3$), ^{3}J = 7.1 Hz], 3.68 (q, 1H, CHPh, ^{3}J = 6.4 Hz), 3.69 (s, 3H, OCH$_3$), 7.14-7.28 (m, 5H, ArH); ^{13}C-NMR (CDCl$_3$) δ 19.7 (CH$_3$), 25.2 (CH$_3$), 51.6, 54.1 and 56.8 (CHCOOCH$_3$/OCH$_3$/CHPh), 126.7, 127.0, 128.3, 144.8 (aromatics), 176.8 (C=O); IR (neat) 1736 (C=O), 3352 (NH) cm^{-1}; MS *m/e* 207 [M^{+}].

Methy 2- [*N*-1-(1-naphthyl)-ethyl] aminopropionate **48** (major diastereoisomer)[96]

^{1}H-NMR ($CDCl_3$) δ 1.26 [d, 3H, $C\underline{H}_3(CHCOOCH_3)$, ^{3}J = 7.1 Hz], 1.46 [d, 3H, $C\underline{H}_3$(CHNp), ^{3}J = 6.5 Hz], 1.90-2.10 (br, 1H, NH), 3.17 [q, 1H, $C\underline{H}(COOCH_3)$, ^{3}J = 7.1 Hz], 3.64 (s, 3H, OCH_3), 4.57 (q, 1H, C$\underline{H}$Np, ^{3}J = 6.5 Hz), 7.43-7.51 (m, 3H, ArH), 7.68-7.79 (m, 2H, ArH), 7.82-7.87 (m, 1H, ArH), 8.12-8.17 (m, 1H, ArH); ^{13}C-NMR ($CDCl_3$) δ 19.9 (CH_3), 24.4 (CH_3), 51.6, 52.4 and 54.2 ($\underline{C}HCOOCH_3/O\underline{C}H_3/\underline{C}$HNp), 122.9, 123.1, 125.2, 125.5, 125.6, 127.2, 128.8, 131.4, 133.9, 140.3 (aromatics), 177.1 (C=O); IR (neat) 1735 (C=O), 3370 (NH) cm^{-1}, MS *m/e* 257 [M^+].

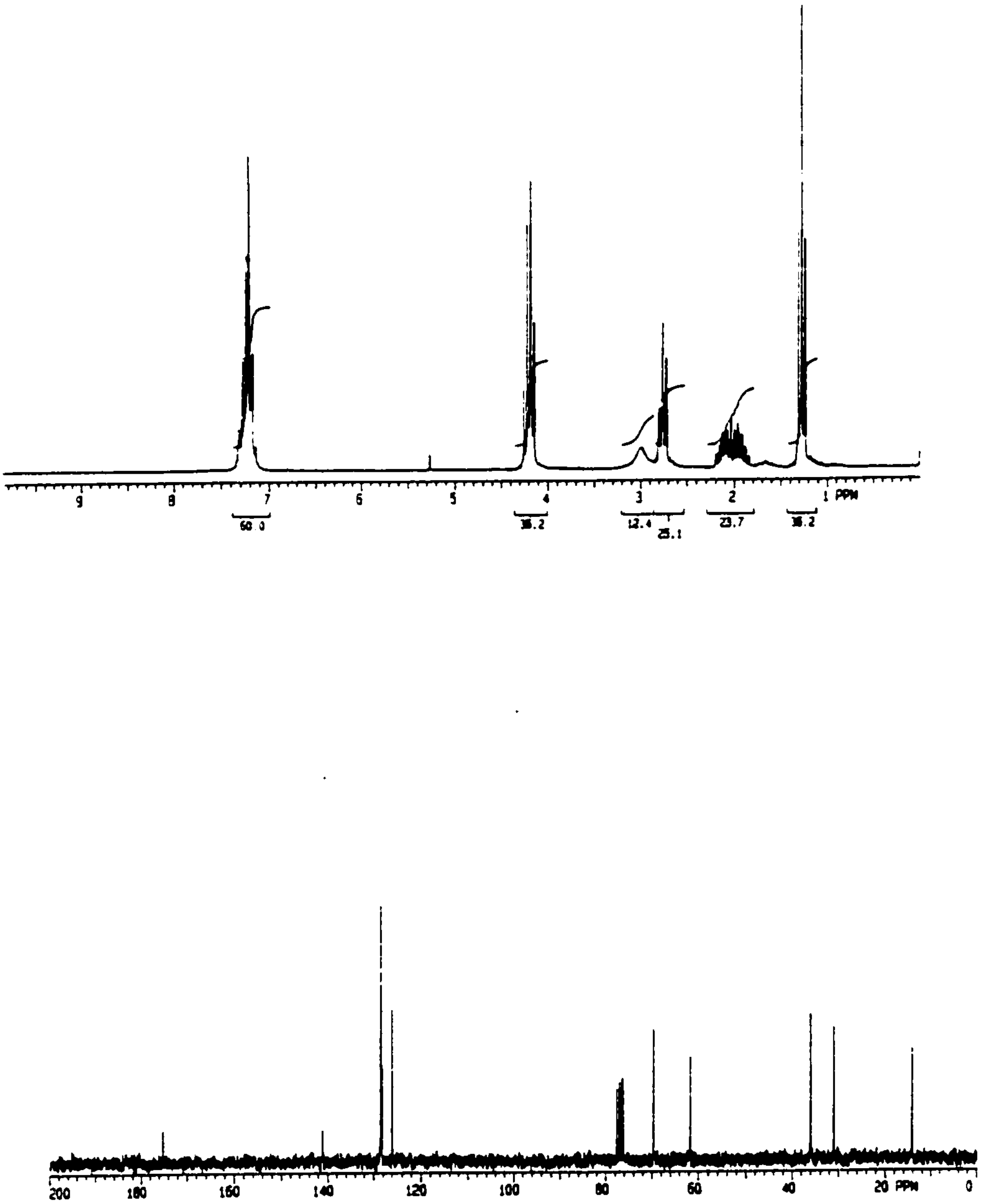


Fig. 9 ^{1}H- and ^{13}C- NMR of **28b** (CDCl$_3$)

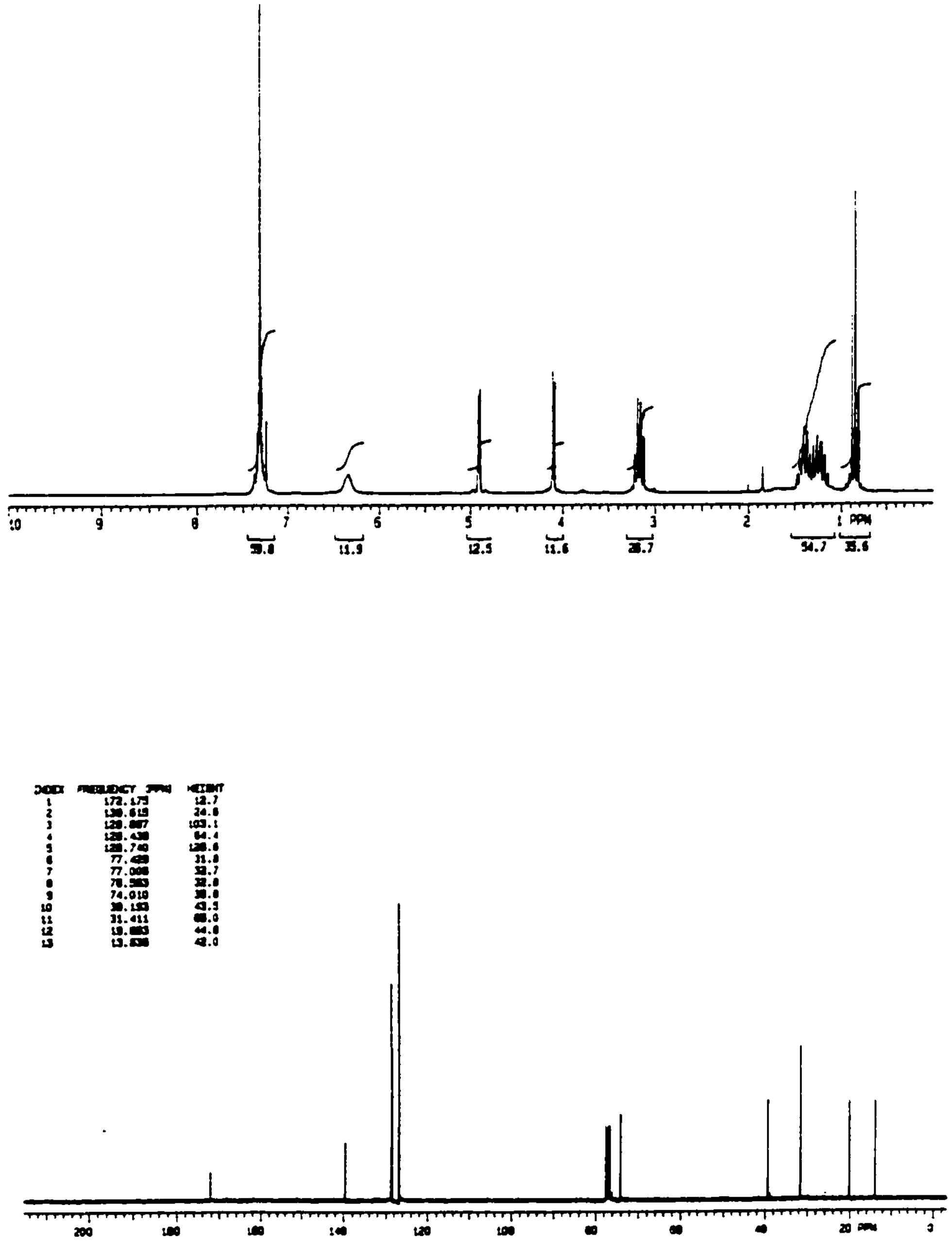


Fig. 10 ^{1}H- and ^{13}C- NMR of **31b** (CDCl$_3$)

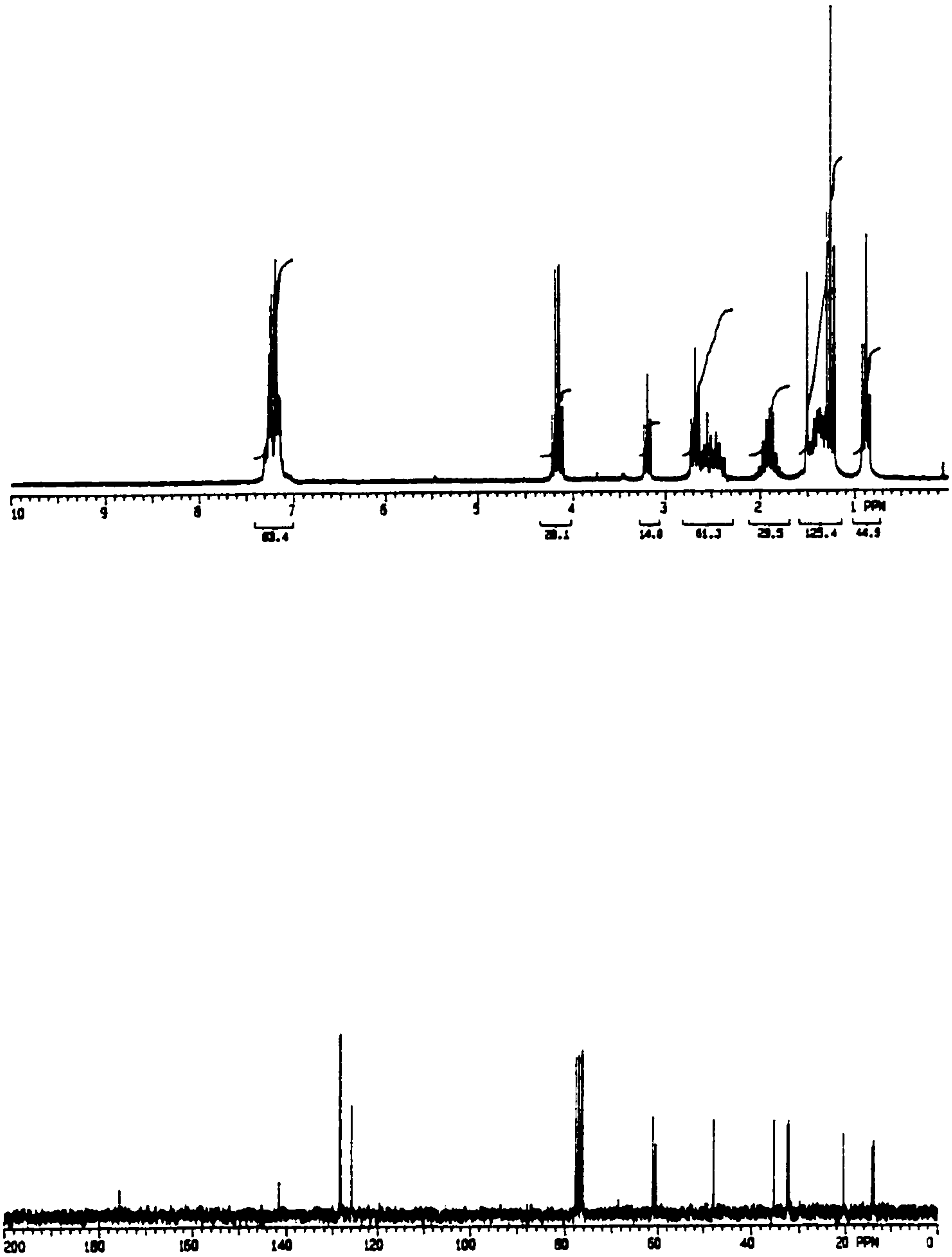


Fig. 11 ^{1}H- and ^{13}C- NMR of 45 ($CDCl_3$)

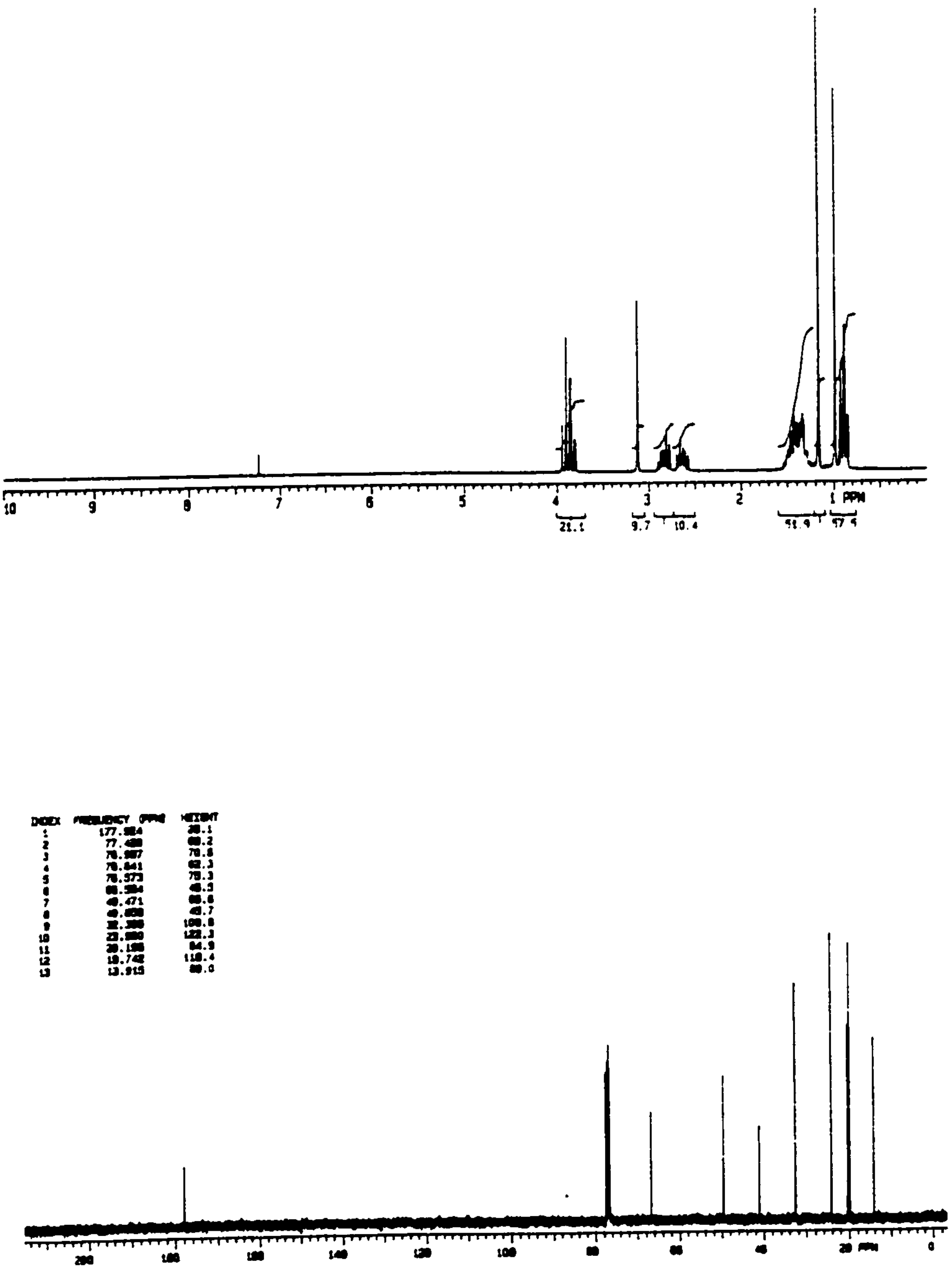


Fig. 12 ^{1}H- and ^{13}C- NMR of **46** (CDCl$_3$)

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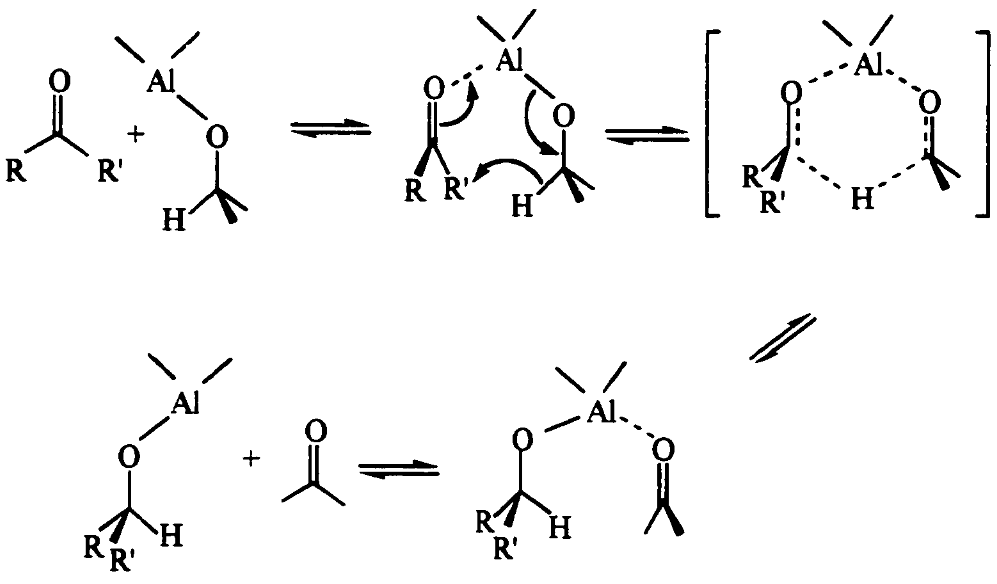
Chapter 3

Transfer Hydrogenation Reactions of Ketones

3.1 General Considerations and Mechanism

Hydrogenation reactions carried out with clay based catalytic systems, as well as hydroformylation, hydroesterification and oxidative carbonylation processes performed in our laboratory using metal anchored on clays[1], demonstrate the efficiency and wide applicability of these types of processes. We were interested in finding other chemical transformations which could benefit from the use of clays in terms of the reaction conditions, and regio- and stereoselectivity.

The transfer hydrogenation of ketones represents an attractive area of research due to the low cost of the reducing agent and simplicity in performing the reaction. This process is an attractive alternative to catalytic hydrogenation with molecular hydrogen. The classical Meerwein-Ponndorf-Verley (MPV) reduction of carbonyl compounds takes place in the presence of aluminum alkoxides (aluminum ethoxide, isopropoxide, *tert*-butoxide or phenoxide) and it has been applied to a great variety of substrates[2]. The generally accepted mechanism for the MPV reaction involves the formation of an intermediate complex in which both the carbonyl and alcohol are bound to the metal atom. Scheme 1 shows the formation of a six-membered transition state through which the hydride transfer takes place



Scheme 1

from the alcoholate to the carbonyl compound. Aluminum alkoxide is the most widely used metal alkoxide for this process, due to ease of preparation and good solubility in alcohols and hydrocarbons. The Lewis acidic character of aluminum (III) favors reaction with alcohols and carbonyl compounds. A drawback of this process is that stoichiometric amounts of reagent are usually necessary. Aluminum forms a stable metal complex with the carbonyl compound, or it may have a greater affinity for the alcohol produced during the reaction than for the reactant.

Alkali metal alkoxides (Na, K, Li) or lanthanide alkoxides have also been used as catalysts in the MPV process. Alkali metal alkoxides have low activity due to low metal charge density (Na, K) and small coordination sphere (Li)[2]. Ln (III) alkoxides are more active: Sm(O-*t*-Bu)I_2 (10 %) is active for the reduction process by transfer hydrogenation and

$Gd(O\text{-}i\text{-}Pr)_3$ (10 %) is almost one thousand times more reactive than $Al(Oi\text{-}Pr)_3$ for the reduction of cyclohexanone[3].

It was determined, by measurement of relative reduction potentials, that dialkyl ketones have the highest reduction potentials in a series of carbonyl compound (aliphatic and aromatic ketones and aldehydes)-alcohol systems. This explains the high reducing capacity of secondary alcohols used as a hydrogen source[2]. Alcohols are usually the hydrogen donors for carbonyl compounds, but hydrocarbons (alkanes, alkenes, aromatics), amines and cyclic ethers (dioxane) are also used in the hydrogen transfer reaction.

MPV reactions were also carried out using heterogeneous catalysts. Heterogeneous systems used in the transfer hydrogenation reaction include[2,4,5]: $\gamma\text{-}Al_2O_3$, chlorinated $\gamma\text{-}Al_2O_3$ and other metal oxides such as La_2O_3 or MgO. 2- Propanol on $\gamma\text{-}Al_2O_3$ reduces aldehydes to the corresponding alcohols[4] . Nitro, ester, amide, olefinic or benzylic bromide groups are stable to the reaction conditions. The function of alumina is not known exactly. The authors consider that an important feature of the heterogeneous system is the specific orientation of the substrate and the reagent once they are brought together. Alumina probably plays a role in activation of the substrate and/or of the reagent[4].

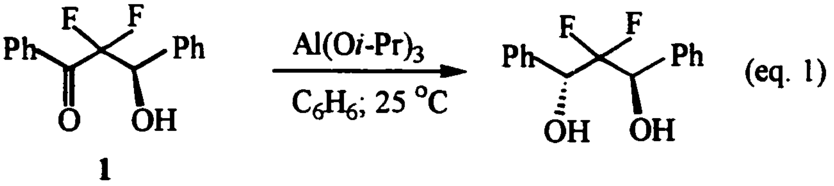
X-type zeolites with alkali or alkaline-earth counterions are active in the reduction of saturated and unsaturated aldehydes and ketones with isopropanol as the hydrogen donor[6]. The catalytic activity of these compounds was attributed to the metal cations but the Si- or Al-sites can also have a role in the process. Zeolite beta (BEA), which has a three-dimensional pore system, was employed for the reduction of 4-*t*-butylcyclohexanone to 4-*t*-butylcyclohexanol[7], using different secondary alcohols (propan-2-ol, butan-2-ol and pentan-2-ol) as the hydrogen source. The activity of this type of zeolite is related to the octahedrally coordinated aluminum formed following activation of the catalyst. The formation of the active site was observed by ^{27}Al MAS-NMR. Water or other oxygen containing ligands determine the modification of the tetrahedral geometry of aluminum atoms to octahedral geometry.

3.2 Transition Metals as Catalysts in Hydrogen Transfer Reactions. Selectivity of MPV Process.

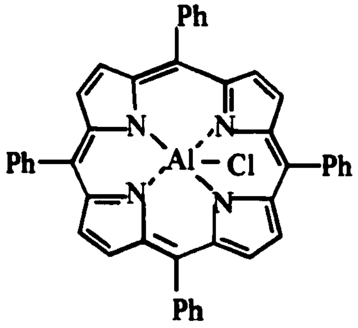
Much progress has been made in recent years regarding the use of more active catalysts and more efficient hydrogen donors for the MPV reaction. Many studies are concerned with the use of transition metals, primarily ruthenium, rhodium and iridium complexes[8]. This new development increased the importance of the hydrogen transfer reactions, and made them competitive with classical hydrogenation using molecular hydrogen. A general trend in MPV reductions is the faster reduction of aldehydes compared to ketones. Also hydrogenation of the carbonyl group prevails over hydrogen transfer to other groups, such as unsaturated carbon-carbon double bonds. An important objective of MPV reactions is selectivity of the process: chemo-, regio-, diastereo- and enantioselectivity.

Chemoselective reactions in which dialdehydes or diketones are reduced to hydroxy aldehydes and hydroxyketones, respectively , have been reported[9]. Cp_2ZrH_2 and Cp_2HfH_2[10] proved to be good catalysts for this transformation.

Diasteroselective MPV reductions can be regarded from the point of view of *syn* or *anti* diols formed or considered as a method to generate *cis/trans* selectivity of the substituted cyclohexanones. α,α-Difluoro-β-hydroxy ketones **1** are reduced in the presence of Al(O*i*-Pr)$_3$ with complete selectivity to the *anti*-form of the 1,3-diol[2] (eq. 1).

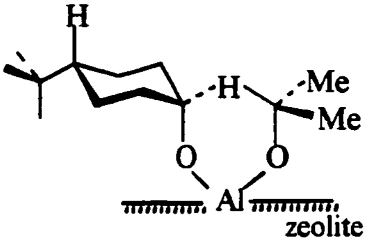


The homogeneous MPV reduction of substituted cyclohexanones usually yields the *trans*-isomer which is thermodynamically more stable, but the *cis*-isomer is also an important product (e.g. *cis*-4-*t*-butylcyclohexanol represents an intermediate in the fragrance industry). The yield of the *cis*-isomer is increased when a sterically hindered ketone[2] is used (attack of the hydride at the equatorial site which is less hindered), but due to reversibility of the reaction, the *trans*-isomer is formed after longer reaction times. The use of a more sterically demanding reducing alcohol butan-2-ol and Al(O-*s*-Bu)$_3$[2] or 5,10,15,20-tetraphenylporphyrinatoaluminum (III) chloride **2** afford a higher ratio of the *cis*-isomer.



2

High ratios of *cis* to *trans* isomers were obtained using the heterogeneous systems zeolite BEA[7]. It was assumed that the transition states which lead to formation of *cis-* or *trans-* 4-*tert*-butylcyclohexanol are different in size (**3**, **4**). The transition state **3** is thought to fit better than **4** in the zeolite pore and allows better coordination to the aluminum atoms.



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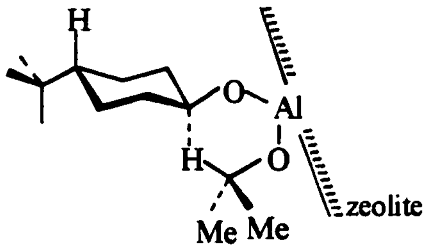

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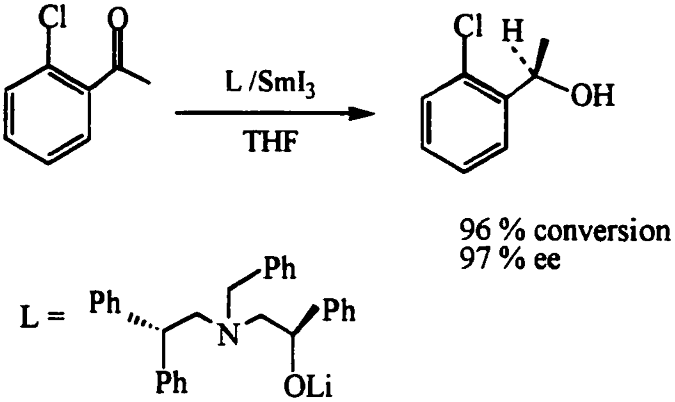
Enantioselective MPV reactions can be carried out using a chiral reducing agent or using a chiral catalyst. If the chiral reducing reagent is a strong reductant it can be applied in small amounts and the reverse reaction, which causes loss of ee, can be avoided. (*S*)-Butan-2-ol, used in the reduction of 3-methyl-heptan-2-one with aluminum 2-butoxide as catalyst, afforded 60 % conversion to the corresponding alcohol with 22 % ee in favor of (*S*)-3-methylheptan-2-ol[2]. Chiral lanthanide alkoxides, prepared *in situ* by addition of a chiral ligand to a solution of the lanthanide alkoxide, were reported[10,11]. A system of Ln(O*i*-Pr)$_3$ with dimethyl L-tartrate gave moderate enantiomeric excess (up to 30 %) for the reduction of acetophenone and pinacolone with *i*-PrOH[2]. Higher ee (46 %) in the hydrogenation of acetophenone was obtained when Er *tris*-isopropoxide was used with (*R*)-(-)-1-phenyl-2,2-

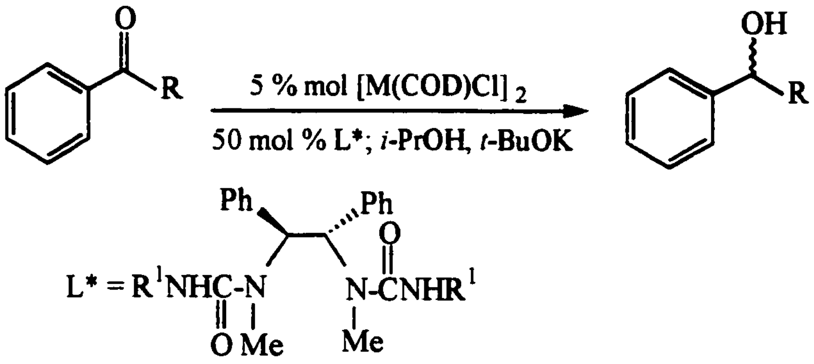
dimethyl-propane-1,3-diol[11]. An ee above 92 % was obtained by Evans *et al.*[12] with a catalyst prepared *in situ* from SmI_3 and a chiral lithium alkoxide (eq.2).



(eq. 2)

96 % conversion
97 % ee

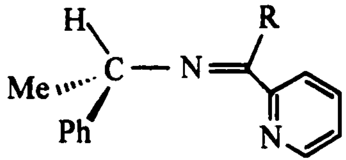
Ru(II), Rh(I), Ir(I) complexes with chiral phosphorus and nitrogen ligands were employed in enantioselective H-transfer reactions[13]. An interesting difference from the catalytic process with H_2 is that nitrogen-containing chiral ligands are the most used for enantioselective H-transfer reactions. Rh(I) or Ir(I) complexes with 2,2'-bipyridine or phenanthroline display high catalytic activity in this process. In the reduction of ketones with $[Rh(nbd)(P\text{-}P)][PF_6]$ (P-P = DIOP, PROPHOS, CHIRPHOS) in propan-2-ol the best ee is 34 %[13]. Recently, a higher enantiomeric excess was achieved with Rh or Ir complexes, in isopropanol, in the presence of *t*-BuOK (eq. 3)[14]. In this process the chiral ligands used were diureas (L*) and the highest ee was 80 % (Rh complex applied to propiophenone). Polyureas were previously used as ligands and as support for the heterogeneous H-transfer reduction of ketones[15].



(eq. 3)

M= Rh, Ir.

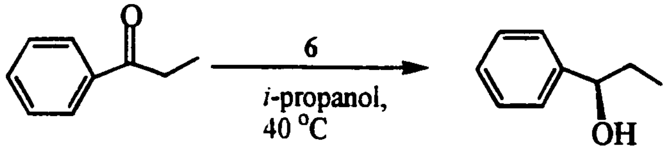
t-Butyl-phenyl ketone, which is usually reduced with difficulty due to steric hindrance, was hydrogenated to the corresponding alcohol in 84 % optical yield by [Ir(COD)(N-N)I] (N-N = 2-[*N*-alkylimino) pyridine (**5**)] in the presence of NaI[13].



5

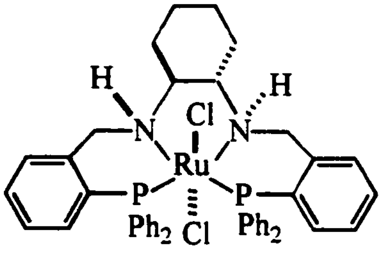
Initially, when asymmetric ruthenium-catalyzed H-transfer reductions were performed with chiral phosphine ligands, alcohols were obtained in low optical purity. For example, when $H_4Ru_4(CO)_8[(-)\text{-DIOP}]_2$ was used, the best result was 9 % ee in the case of phenyl isobutyl ketone. New chiral Ru complexes, which have soft phosphine and hard nitrogen ligands, were developed[16] and they afforded high optical yield (eq. 4).

Similar to Rh or Ir complexes, nonphosphine based chiral Ru catalysts show high activity. Complex **6** (*S,S*) or (*R,R*), reported by Noyori *et al*[17], catalyzes the hydrogen transfer



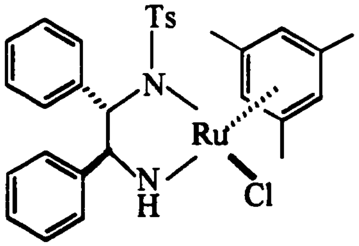
78 % yield
96 % ee (*R*)

(eq. 4)

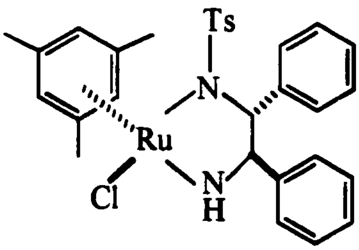


(*S*,*S*) - **6**

reaction in isopropanol with enantioselectivities up to 98 %.



(*S*,*S*)-**7**



(*R*,*R*)-**7**

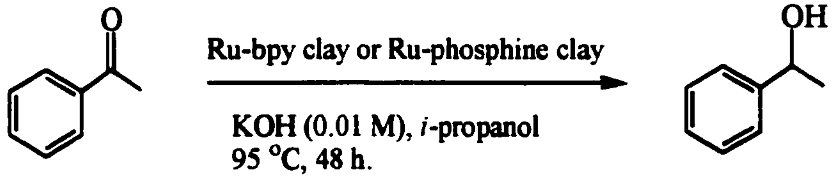
A problem which arises in this process is the decrease, with time, of the enantiomeric purity of the product due to the reversibility of the reaction. A solution to this problem is the use of formic acid instead of *i*-propanol. The hydrogen transfer reaction with formic acid-triethylamine (5:2) proceeds in the presence of (*S,S*) or (*R,R*) 7 as the catalyst with high yield (96 - 99 %) and enantioselectivities of 93 to 99 % [18]. Other complexes which were reported to afford good enantioselectivities use tridentate ligands with two oxazoline rings and one phosphine[19] or phosphinooxazoline[20]. The reactions are carried out in *i*-propanol, promoted with NaOH[20].

Important progress has been achieved in the area of hydrogen transfer reduction in the last years but there is a continuous effort to develop cheaper catalysts, to extend the applicability of the reaction to other substrates (epoxides, Schiff bases) and to better understand the mechanisms involved.

3.3 Results and Discussion

Many ruthenium catalyzed hydrogen transfer reactions have been studied. The reaction conditions are often mild[21,22] and usually the hydrogen source is propan-2-ol. Ruthenium catalysts are used together with a strong base as promoter (KOH, NaOH or sodium alkoxide) in order to increase the reaction rate[13]. The use of bases as promoters is a general feature of the hydrogen transfer process.

The fact that ruthenium clays were prepared (Chapter 2) and they proved to be catalytically active for hydrogenation reactions allowed us to assess their effectiveness for hydrogen transfer reductions[23]. The reduction of acetophenone with Ru-bipyridine clay and Ru-phosphine clay (species **14** and **16** described in Chapter 2) was performed in isopropanol at 95 °C, in the presence of KOH (0.01 M in isopropanol). When a ratio of 400:1 reactant to catalyst was employed, 1-phenylethanol was isolated in 10-70 % yield (Table 1). The yield of alcohol was good using the Ru-bipyridine clay while the Ru-phosphine clay was found to be a poor catalyst for this reaction (eq.5).



(eq. 5)

The difference in behavior of the two clay species is in agreement with the observed increased activity of metal complexes which contain nitrogen donor atoms[13], the low efficiency of the phosphine clay is still not well understood.

Table 1. Reduction of Acetophenone with Ru Containing Catalysts

No.	Catalyst	Ru content (mmol Ru/g catalyst)	Yield (% 1-phenylethanol)
1.	Clay-(bpy)-$RuCl_3$	0.18	70
2.	Clay-(phosphine)-$RuCl_3$	0.17	10

Reaction conditions: 2 mmol acetophenone, 30 mg catalyst (0.005 mmol Ru), [KOH] = 0.01M in isopropanol, 95 °C, 48 h.

Homogeneous systems based on $[RuCl_2(PPh_3)_3]$ are effective in hydrogen transfer reactions even if the yields are moderate to good[22,24,26]. When the hydrogen transfer reaction of acetophenone was run using ruthenium trichloride as the catalyst, the substrate was recovered unchanged. The same inertness was found using montmorillonite and 0.01 M KOH but no bound ruthenium. Reduction of acetophenone does proceed with 0.06 M KOH for the clay system (no ruthenium) in 52-64 % yield depending on the time the clay is pretreated with isopropanol and the temperature for such pretreatment (Table 2). The data in Table 2 show that the use of more concentrated base solution, 0.06 M KOH, has higher catalytic activity than the 0.01 M solution. When γ-Al_2O_3 was used as the catalyst[2] it was assumed that the base is required to deprotonate the *i*-propanol which is coordinated to the surface of alumina. In this way an aluminum isopropoxide catalyst is formed *in situ*. Similar processes may occur for clays. Figure 1 shows a possible configuration of a Lewis acid site for a 2:1 dioctahedral

Table 2. Catalytic Activity of the Commercial Clay (Fluka K10 Montmorillonite)

Conditions	[KOH] (mol/l)	Reaction time (h)	Yield (%)
Without activation	0.06	48	52
Activation at 100 °C [a]	0.01	24	0
Activation at 100 °C [a]	0.03	24	34
Activation at 100 °C [a]	0.06	24	56
Activation at room temperature (24 h) [b]	0.06	24	60
Activation at room temperature (1 h) [b]	0.06	24	64

Reaction conditions: 2 mmol acetophenone, 30 mg clay, 95 °C.
a) Clay pretreated with isopropanol for 24 h in a Soxhlet.
b) Clay stirred in isopropanol at room temperature.

clay mineral like montmorillonite[25]. The activation of clay by pretreatment with isopropanol (stirring in isopropanol at room temperature or treatment with the same solvent in a Soxhlet) has a favorable effect on the reaction time and yield. The reaction time (the conversion of the substrate was checked by gas chromatography analysis) decreased from 48 h (without activation) to 24 h (activated clay). The increase in yield for the reaction catalyzed by the pretreated clay is modest but nevertheless represents an improvement (52 % to 64 %). The suspension of clay in isopropanol, resulted at the end of the reaction, was filtered and the filtrate used in a subsequent reaction without any additional amount of clay. No conversion of acetophenone to 1-phenylethanol was observed and it was concluded that no catalytic species, like aluminum oxide, was leaching from clay at this concentration of KOH in isopropanol. Although the yield of 1-phenylethanol was similar using 0.06 M KOH – clay (56 – 64 %) and 0.01 M KOH–ruthenium bipyridine clay (70 %), the fact that no metal is

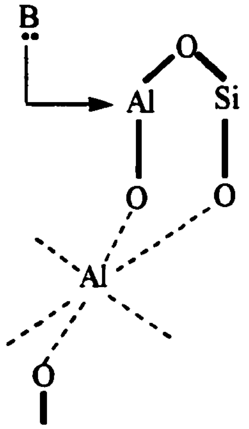
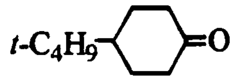
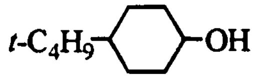
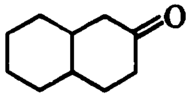
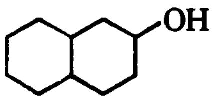
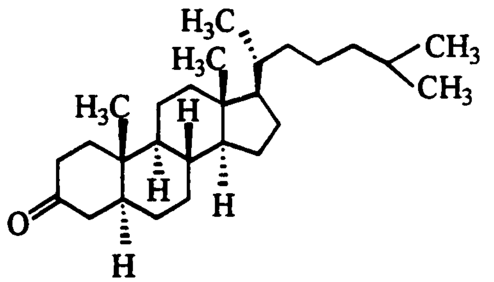
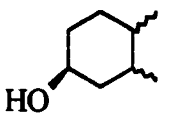
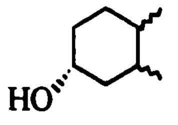


Fig. 1 Possible Configuration of a Lewis Acid Site in Montmorillonite

necessary led us to examine the scope of the H- transfer reduction process with 0.06 M KOH- montmorillonite. The results are presented in Table 3.

Aryl alkyl ketones, diaryl ketones and dialkyl ketones were used as substrates. Methyl aryl ketones are converted to the corresponding alcohols in good yields. *p*-Methoxy-phenyl methyl ketone was reduced to the alcohol in high conversion (87 %) (Table 3, entry 3). Lower conversion was obtained for acetophenone and *p*-ethyl acetophenone (64 and 58 %, respectively - Table 3, entries 1,2). The diaryl ketone, benzophenone also reacts, but yield of alcohol is appreciably lower (Table 3, entry 4). Dialkyl ketones such as 4-phenyl-2-butanone, 4-*t*-butylcyclohexanone, 2-decalone, and 5α-cholestan-3-one (Table 3, entries 5-8) give the corresponding alcohols in excellent yield. The results obtained for the reduction of dialkyl ketones are interesting due to the fact that many of the catalysts, developed previously, showed high efficiency only for aryl alkyl ketones. Recent work focused on development of the hydrogen transfer reduction for dialkyl ketones or ketones which contain other functionalities[19,20,23]. The *trans* / *cis* ratio for 4-*t*-butylcyclohexanol was 56/44 determined by ^{1}H-NMR[27] (Fig. 2).

Table 3.
Hydrogen Transfer Reduction of Ketones Using Na Montmorillonite as Catalyst

No.	Substrate	Product	Conversion[a] /Yield (%)
1.	$PhCOCH_3$	$PhCH(OH)CH_3$	64 (51)
2.	p-$C_2H_5C_6H_4COCH_3$	p-$C_2H_5C_6H_4CH(OH)CH_3$	58
3.	p-$CH_3OC_6H_4COCH_3$	p-$CH_3OC_6H_4CH(OH)CH_3$	87
4.	PhCOPh	PhCH(OH)Ph	52 (27)
5.	$PhCH_2CH_2COCH_3$	$PhCH_2CH_2CH(OH)CH_3$	85
6.			100 (72)[b]
7.			100 (85)
8.		 3β  3α	94 (88)[c]

Reaction conditions: 2 mmol (entries 1-6) and 1 mmol (entries 7,8), 30 mg Na montmorillonite, KOH solution 0.06 M in isopropanol, 95 °C, 24 h.
a. Determined by ^{1}H-NMR using an internal standard or from the recovered starting material. b. 56:44 *trans / cis* c. 63:37 3β/ 3α.

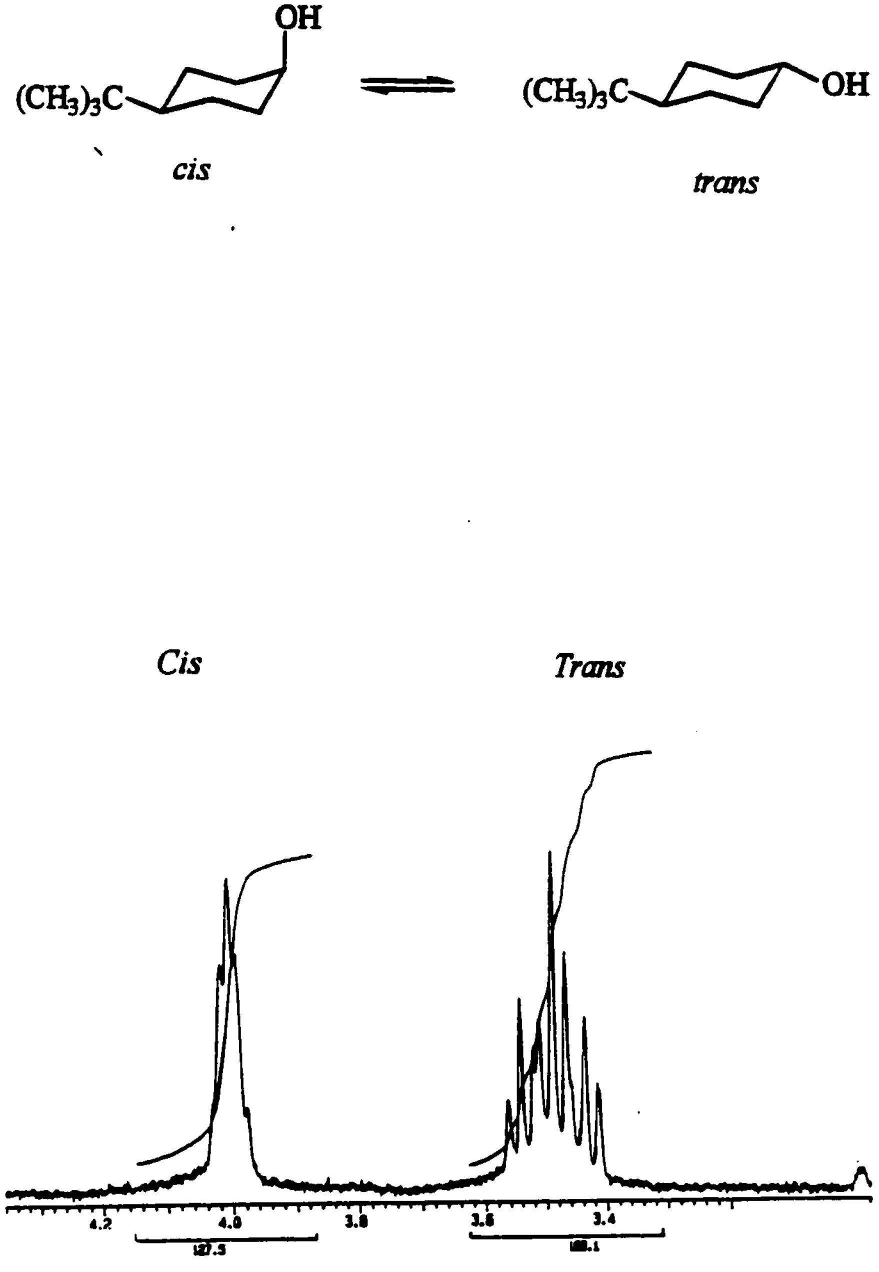
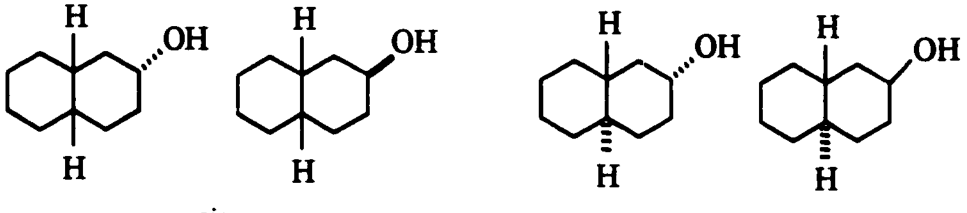


Figure 2

The reversible transformation between the two isomers has been studied[28] and it was shown that in MPV reactions an equilibrium is established between the epimeric alcohols. It was also shown that the values for the percentage of alcohols in the mixture, at equilibrium, are similar for different catalysts used, like aluminum alkoxide or Raney nickel. The percentage of the *trans* isomer of 4-*t*-butylcyclohexanol, at equilibrium is 79 % for aluminum isopropoxide, obtained after refluxing either the *cis* or *trans* isomer in isopropanol, for one week[28]. The value of 56 % *trans* isomer, found after 24 h in the experiments carried out with Na montmorillonite, must represent the result of a kinetically controlled hydrogen transfer. The same efficient reduction of the carbonyl group but low stereoselectivity was obtained for 5α-cholestane-3-one. The ratio of 3β- / 3α -dihydrocholesterol was found to be 63 / 37, based on the isolated amounts of each isomer.

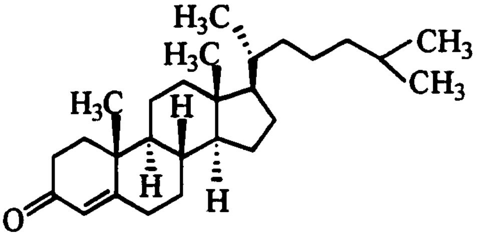
2-Decalol was obtained in 85 % yield from 2-decanone (mixture of *cis* and *trans*). The alcohol formed is a mixture of cis (*exo* and *endo* decalol) and trans decalol (with both axial and equatorial hydroxy epimers) (Fig. 3). The isomeric decalols were identified by the presence of different signals in the ^{13}C-NMR for the carbon which has the hydroxyl group attached[29].



cis *trans*

Fig. 3 *cis*- and *trans*-Decalols

Interestingly, α,β-unsaturated carbonyls such as cholestan-4-en-3-one **8** and testosterone **9** don't react with 0.06 M KOH – montmorillonite even if the reaction time is extended to 40 h. It was observed before[30] that in the presence of 2-propanol and alumina, the keto group in the steroidal enone **10** is completely stable, while the aldehyde group is reduced (eq. 6).



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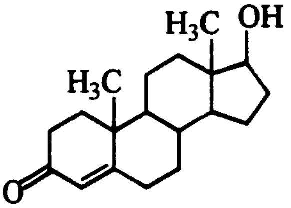

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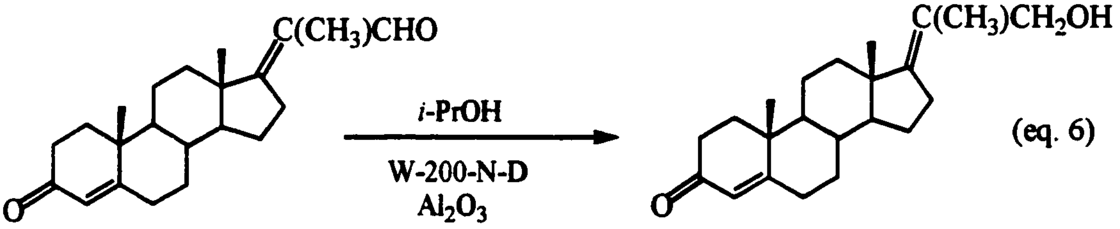
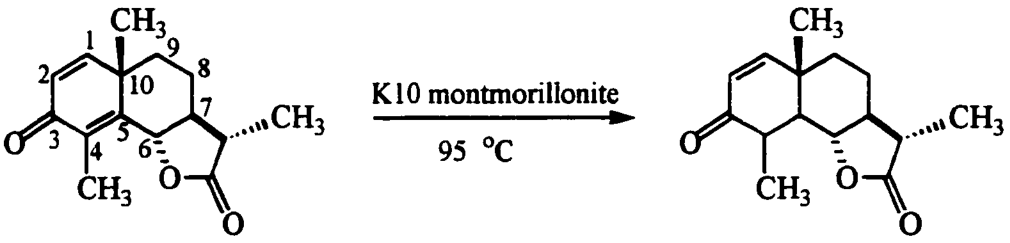


(eq. 6)

10

Santonin **11** did not undergo conversion to the alcohol. The α,β- unsaturated ketone **12** resulting from hydrogenation of the C(4)-C(5) double bond is formed instead (eq. 7). Some of the substrate is recovered unchanged (33 % conversion).



11 **12**

(eq. 7)

The structural assignment was based on the presence of a doublet of doublets in the ^{1}H-NMR, corresponding to the C(1)-C(2) double bond (δ 5.93, d, 1H, ^3J=10 Hz; δ 6.56, d, 1H, ^3J = 10 Hz) and the resonance of the proton attached to C(6) (δ 4.97, m). The ^{13}C-NMR indicated a different signal for the carbonyl group at C(3) (198.5 ppm) compared to the one in santonin (186.1 ppm) and the signals corresponding to the quaternary carbons C(4) and C (5) are not present in the spectrum. Results obtained previously[30] for the reduction of a series of steroid 3-oxo-1,4-dienes with $NaHFe(CO)_4$ showed that C(1)/C(2) unsubstituted compounds are preferentially reduced at the C(1)-C(2) double bond. The different nature of the reducing agent and catalyst in the Na montmorillonite system might be responsible for different regioselectivity of this reaction.

Conclusions

The reduction of ketones to alcohols by Na montmorillonite and KOH / isopropanol is of value as a new catalytic system for the hydrogen transfer reduction. The efficiency of this readily available system is comparable to that of other heterogeneous catalysts[2] and it can be applied to alkyl aryl ketones and dialkyl ketones with good yield of the corresponding alcohols. This is also an economical process.

3.4 Experimental Section

General procedure for the hydrogen transfer reduction using Fluka K10 montmorillonite

K10 montmorillonite (purchased from Fluka, surface 200±20 m^2/g) (30 mg) was suspended in isopropanol containing 0.06 M KOH (15 ml). The montmorillonite used was initially stirred in isopropanol for 1 h (1g clay in 20 ml of isopropanol), filtered, and then was dried in vacuum. The ketone (2 mmol) was added, and the mixture was heated to 95 °C, for 24 h. The reaction mixture was filtered through Celite and the solvent was evaporated. To the crude product was added ether (10 ml) and the suspension formed was washed with 2 N HCl solution. The aqueous layer was extracted three times with ether (15 ml). The combined organic layers were dried ($MgSO_4$). The compounds were purified by column chromatography, and identified by comparison of spectral data with literature results and/or with authentic samples.

Hydrogen transfer reduction using Ru-bipyridine clay and Ru-phosphine clay as catalysts

Ru clay (30 mg, 0.005 mmol Ru) was suspended in KOH (0.01 M) in isopropanol (12 ml). Acetophenone (2 mmol) was added and the mixture was heated (95 °C) under N_2 for 48 h. The reaction mixture was filtered through Celite and the solvent was evaporated. The crude mixture was analyzed by ^{1}H-NMR using an internal standard for determination of the yield of alcohol.

Spectral data for isolated compounds:

1-Phenyl ethanol (*sec*-Phenethyl alcohol) (Table 3, entry 1)[31,32]

^{1}H-NMR ($CDCl_3$) δ 1.49 (d, 3H, CH_3, ^3J = 7.4 Hz), 1.9 (broad s, 1H, OH), 4.89 (q, 1H, CH, ^3J = 7.4 Hz), 7.20-7.41 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 25.1 (CH_3), 70.3 (CH), 125.3, 127.4, 128.4, 146.0 (aromatics); IR (neat) 1070 (C-O); 3330 (OH) cm^{-1}.

1-Phenyl benzyl alcohol (benzhydrol)(Table 3, entry 4)[31,32]

White needles: mp 64.9-65.1 °C; ^{1}H-NMR ($CDCl_3$) δ 2.37 (broad s, 1H, OH), 5.81 (s, 1H, CH), 7.19-7.50 (m, 10 H, ArH); ^{13}C-NMR ($CDCl_3$) δ 76.1 (CH), 126.5, 127.5, 128.4, 143.7 (aromatics); IR (KBr) 1013 (C-O), 3338 (OH) cm^{-1}; MS *m/e* 184 [M^+].

cis-4-*t*-Butylcyclohexanol (Table 3, entry 6)[27,33,34]

^{1}H-NMR ($CDCl_3$) δ 0.85 [s, 9H, $C(CH_3)_3$], 0.92-1.60 [m, 8H, $-CHCH_2CH(C)CH_2CH$, OH], 1.75-1.89 [m, 2H, $C\underline{H}CH(OH)C\underline{H}$], 4.01 (m, 1H, $C\underline{H}OH$); ^{13}C-NMR ($CDCl_3$) δ 20.8 [$\underline{C}H_2CC(CH_3)_3$], 27.4 [$C(\underline{C}H_3)_3$], 32.6 [$\underline{C}(CH_3)$], 33.3 [$\underline{C}H_2CH(OH)$], 47.9 [$\underline{C}HC(CH_3)$], 65.8 [CH(OH)]; MS *m/e* 156 [M^+], significant peaks (intensities) 156 (1), 123 (18), 99 (28), 82 (41), 67 (33), 57 (100).

trans-4-*t*-Butylcyclohexanol (Table 3, entry 6)[27,33,34]

^{1}H-NMR ($CDCl_3$) δ 0.82 (s, 9H, $C(CH_3)_3$), 0.90-2.08 [m, 10H, $-(CH_2)_2CH(C)(CH_2)_2-$, OH], 3.50 (m,1H, $C\underline{H}OH$); ^{13}C-NMR ($CDCl_3$) δ 25.6 [$\underline{C}H_2CC(CH_3)_3$], 27.6 [$C(\underline{C}H_3)_3$], 32.2 [$\underline{C}(CH_3)_3$], 36.0 [$\underline{C}H_2CC(CH_3)_3$], 47.1 [$\underline{C}HC(CH_3)_3$], 71.1 (CH(OH)); MS *m/e* fragments (intensities): 138 (23), 123 (23), 99 (20), 81 (49), 57 (100).

cis- and *trans*-Decalols (*cis*- and *trans*-bicyclo[3,3,0] decan-3-ol) (Table 3, entry 7)[29]

Clear oil, mixture of *exo*- and *endo-cis*-decalols and *trans*-decalols.

^{1}H-NMR ($CDCl_3$) δ 0.8-2.1 (broad signal), 3.55 [m, $C\underline{H}(OH)$ in *endo-cis*-decalol], 3.80 [m, $C\underline{H}(OH)$ in *exo-cis*-decalol], 4.09 [m, $C\underline{H}(OH)$ *trans*-decalol]; ^{13}C-NMR ($CDCl_3$) Coincident signals in the region 20-40 ppm. Specific signals: δ 67.0 / 67.0 ($C\text{-}OH_{axial}$ in *trans*-decalol / $\underline{C}$-OH *in exo-cis*-decalol), 77.0 / 77.40 ($C\text{-}OH_{equatorial}$ in *trans*-decalol/ C-OH in *endo-cis*-decalol); IR (neat): 1054 (C-O), 3330 (OH) cm^{-1}.

(+)-Dihydrocholesterol (3-β-cholestanol) (Table 3, entry 8)[31,32,34]

White powder: mp 141-142 °C; ^{1}H-NMR ($CDCl_3$) δ 0.5-2.0 (m, 49H), 3.57 [m, 1H, $C\underline{H}(OH)$]; ^{13}C-NMR ($CDCl_3$) Signals above 40 ppm: δ 40.0, 42.5, 44.8, 54.3, 56.2, 56.4, 71.3; IR (KBr) 1042, 1077 (C-O), 2861, 2936 (C-H), 3342 (OH).

3-α-Cholestanol (Table 3, entry 8)[31,32,34]

White powder: mp 185-186 °C; ^{1}H-NMR ($CDCl_3$) δ 0.5-2.0 (49H), 4.02 (m, 1H, C<u>H</u>(OH)); ^{13}C-NMR ($CDCl_3$) Signals above 40 ppm: δ 40.0, 42.5, 54.3, 56.2, 56.5, 66.6; IR (KBr) 1034 (C-O), 2919 (C-H), 3285 (OH) cm^{-1}.

3.5 References

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Chapter 4.

Oxidation of Sulfides to Sulfoxides

4.1 Importance of Sulfoxides

Sulfoxides are one of the most important classes of organosulfur compounds. There are various ways for their preparation and they can be transformed into more complex sulfoxides[1]. Compounds containing a sulfoxide moiety are useful synthetic intermediates for the construction of various chemically and biologically significant molecules[2]. For example sulfoxides can be used in the preparation of allyl alcohols from aldehydes and ketones (methyl phenyl sulfoxide)[3] or in the synthesis of cyclohexane-1,3-dione derivatives as well as in cycloalkylation reactions (methyl ester of phenylsulfinyl acetic acid)[4,5]. Another important application is the synthesis of α, β-unsaturated carbonyl compounds by β-elimination of sulfenic acids from sulfoxides[6] and also the glycosidation of unreactive substrates by applying the sulfoxide activation method of Khane *et al.*[7]. The oxidation and reduction of sulfur has been used as a method for controlling the double bond position in cephalosporins[8]. Penicillin sulfoxide[8] made the first direct chemical correlation between a penicillin and a cephalosporin.

The configuration of sulfoxides is characterized by a pyramidal arrangement : three ligands and one lone pair of electrons around the central sulfur atom (Fig. 1). Optically active

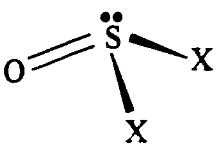


Fig.1 Configuration of sulfoxides

sulfoxides are well known and, in the absence of acids, racemization only becomes significant at temperatures above about 200 °C[1].

4.2 Routes to Sulfoxides

The oldest and generally applied sulfoxide synthesis consists of the oxidation of sulfides to sulfoxides. This reaction was reported for the first time by Märcker as early as 1865 and it involved the formation of dibenzyl sulfoxide from dibenzyl sulfide treated with nitric acid[9].

There are also other different possibilities to synthesize sulfoxides. The various methods used can be summarized as follows[1,9]:

- ☐ oxidation of sulfides
- ☐ co-oxidation of alkenes and thiols
- ☐ reaction of organometallic compounds with sulphurous acid derivatives
- ☐ reaction of organometallic compounds with sulphinic acid derivatives

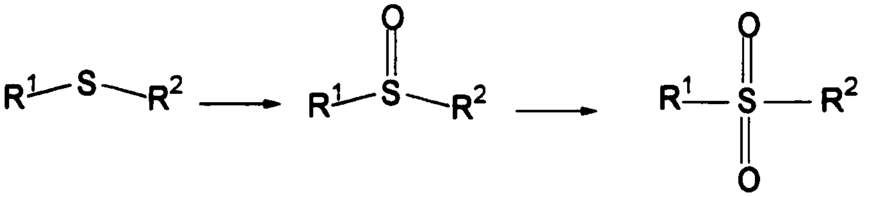
- reaction of aromatic derivatives and compounds containing active hydrogen with sulphinyl chlorides
- addition of sulphynyl chlorides and sulphenic acids to unsaturated compounds
- rearrangement of sulphenic acid esters
- cycloaddition of sulfur monoxide and sulphines to unsaturated compounds

Additional details concerning the oxidation of sulfides are presented in the following pages.

4.2.1 Oxidation of Sulfides

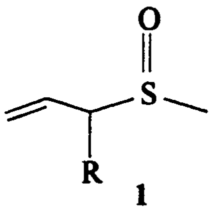
4.2.1.1. Oxidation by Different Chemical Reagents

The oxidation of sulfides gives the corresponding sulfoxides or sulfones or both, depending on the reaction conditions employed[10] (eq.1). In order to obtain sulfoxides selectively it is necessary to add equimolar or slightly excess amounts of oxidants to the sulfides under mild conditions.

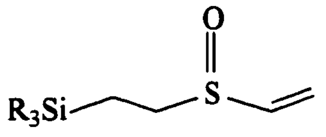


(eq.1)

One of the simplest methods of oxidation of sulfides to sulfoxides is the use of hydrogen peroxide. One drawback of this method is the relatively long reaction time for this transformation. The method can be applied to the preparation of various acid-sensitive sulfoxides such as allylic sulfoxides (**1**) or silyl substituted vinyl sulfoxides (**2**) and thietane sulfoxides (**3**). The yield in sulfoxide varies from 20 to 99 % and in some cases sulfone is obtained in almost equivalent amount to the sulfoxide. The oxidation is accelerated by the presence of acids (acetic acid, sulfuric and perchloric acids) and many metal salts such as SeO_2, V_2O_5, $TiCl_3$ and $VO(acac)_2$ also function as good catalysts. The main disadvantage in the acid-catalyzed oxidation is the relatively long reaction time and the facile over-oxidation to the corresponding sulfones[9].



1



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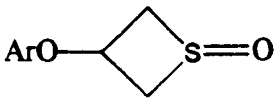
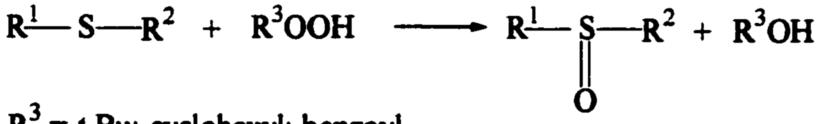


3

It was shown recently that the use of $H_2O_2/Ac_2O/SiO_2$ in methylene chloride represents a simple, inexpensive and highly efficient approach for both small and large scale preparation of glycosyl and non-carbohydrate sulfoxides from their corresponding sulfides. This procedure provides a convenient alternative to the standard *m*-chloroperbenzoic acid oxidation of glycosyl sulfides[2]. Also a molybdenum silicate catalyst combined with molecular sieves proved to be efficient for the oxidation of thioethers to sulfoxides using a solution of 30 % H_2O_2[11].

Organic hydroperoxides such as cyclohexyl hydroperoxide , *t*-butyl hydroperoxide and benzoyl hydroperoxide can oxidize various sulfides to the corresponding sulfoxides[10] (eq.2).

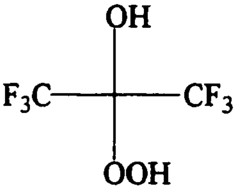


$$R^1\!-\!S\!-\!R^2 + R^3OOH \longrightarrow R^1\!-\!\underset{\displaystyle \overset{\|}{O}}{S}\!-\!R^2 + R^3OH \quad \text{(eq.2)}$$

R^3 = *t*-Bu; cyclohexyl; benzoyl.

It was found that oxygen transfer occurred in both polar and non-polar solvents to give quantitative yields of sulfoxides over a wide range of experimental conditions[9].

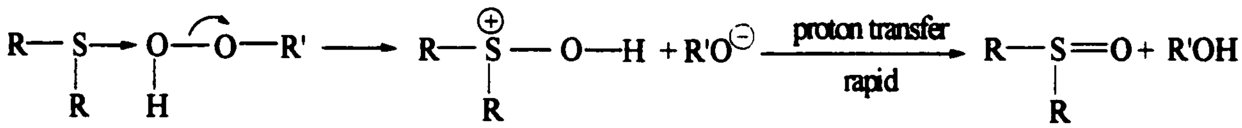
2- Hydroperoxyhexafluoro-2-propanol (4), formed *in situ* from hexafluoroacetone and hydrogen peroxide, is a convenient reagent for the conversion of sulfides into the corresponding sulfoxides under mild conditions[9].



$$F_3C-\overset{OH}{\underset{OOH}{C}}-CF_3$$

4

A variety of organic peroxy acids such as perbenzoic acid, *m*-chloroperbenzoic acid (MCPBA), peracetic acid and trifluoroperacetic acid are much stronger oxidants than H_2O_2[9]. The mechanism of oxidation to the sulfoxide was formulated in equation 3[12].

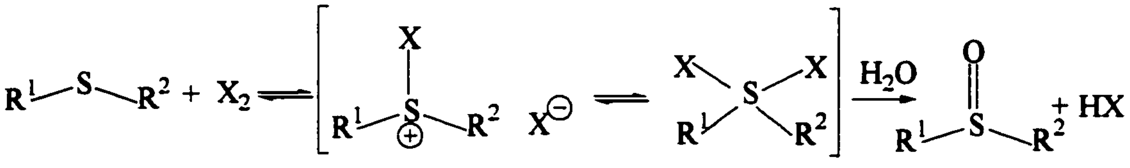


$$R-\underset{R}{S}\rightarrow\underset{H}{O}-O-R' \longrightarrow R-\underset{R}{\overset{\oplus}{S}}-O-H + R'O^{\ominus} \xrightarrow[\text{rapid}]{\text{proton transfer}} R-\underset{R}{S}=O + R'OH$$

(eq. 3)

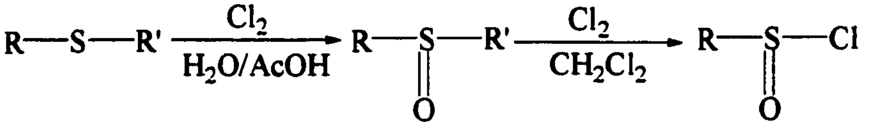
Since this kind of oxidation occurs under mild conditions (0 °C), it can be successfully applied to the preparation of base-sensitive sulfoxides.

Molecular halogens have been known to form addition compounds with organic sulfides which are readily hydrolyzed to sulfoxides[10] (eq.4).



(eq. 4)

But undesirable side-reactions often predominate over sulfoxide formation[13] (eq.5).



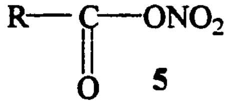
$$R-S-R' \xrightarrow[H_2O/AcOH]{Cl_2} R-\underset{O}{\underset{\|}{S}}-R' \xrightarrow[CH_2Cl_2]{Cl_2} R-\underset{O}{\underset{\|}{S}}-Cl$$

(eq.5)

The formation of by-products can be prevented by carrying out the reactions in the presence of amines or under two-phase conditions (CH_2Cl_2/H_2O) using $KHCO_3$ as a base[10].

Many "positive halogen" compounds such as *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), 1-chlorobenzotriazole (NCBT) oxidize sulfides to sulfoxides. The above reagents are sensitive to the nature of the solvent used and, according to the type of substrate and the experimental conditions, the C-S bond may be cleaved with no formation of sulfoxide. The yields obtained in the oxidation of sulfides to sulfoxides using *N*-halo compounds range from 62 to 93 %[9].

Nitric acid, inorganic nitrates [$Tl(NO_3)_3$; $(NH_4)_2Ce(NO_3)_6$] and organic nitrates (**5**) as well as nitronium salts (**6**) also have oxidative properties. Nitric acid, after its first use in 1865 by Märcker in the synthesis of dibenzylsulfoxide, was used as the oxidation reagent for the


$R-C(=O)-ONO_2$

5

R = Me, Ph

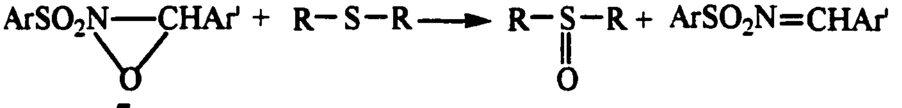
$NO_2^+X^-$

6

X = PF_6; BF_4

preparation of sulfoxides derived from alkyl aryl and long-chain sulfides. Trifluoromethyl methyl sulfide treated with concentrated nitric acid gave trifluoromethyl methyl sulfoxide in 30 % yield[9]. Recently a comparative study was published of the catalytic activity of $FeBr_3$ and the coordination compound $(FeBr_3)(DMSO)_3$, in the reaction of nitric acid with organic sulfides. It showed that higher yields in sulfoxide were obtained in the case when the complex is used as the catalyst, despite the fact that an induction period was necessary before the reaction started[14]. However, some of the reagents mentioned, like ceric ammonium nitrate, are not suitable for the oxidation of sulfides possessing α- hydrogens. This is most probably due to the Pummerer reaction which occurs in the presence of the nitrate[9].

Davies and coworkers[15] reported the selective oxidation of sulfides under aprotic conditions by 2-arenesulfonyl-3-aryloxaziridines (7). The reaction (eq.6) takes place at

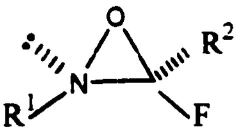

7

(eq. 6)

room temperature giving sulfoxides in yields exceeding 80 %. The yield of the reaction is strongly dependent on the structure of the oxaziridine. Stable oxaziridines give the sulfoxides in very low yield (5-7 %).

Recently, DesMarteau *et al* reported[16] that sulfides are oxidized to sulfoxides by stoichiometric amounts of perfluoro-*cis*-2,3-dialkyl oxaziridines (**8**). The reactions proceed at

– 40 °C with nearly complete selectivity to sulfoxides, but an increase of temperature (-20°C to 0 °C) drives the reaction to sulfones.


8

(a) $R^1 = n\text{-}C_4F_9$; $R^2 = n\text{-}C_3F_7$
(b) $R^1 = n\text{-}C_6F_{13}$; $R^2 = n\text{-}C_5F_{11}$

4.2.1.2 Aerobic Oxidation of Sulfides

Oxygen is a readily available and inexpensive oxidizing reagent. Under certain conditions, it can be used very efficiently for the oxidation of sulfides to sulfoxides without overoxidation to sulfones. A facile and selective oxidation of various aliphatic and aromatic sulfides was described recently[17]. Sulfoxides were obtained in very good yields (87–99 %), as the exclusive products of the reactions, when a combination of dioxygen and catalytic amounts of nitrogen dioxide was used at room temperature or below (eq. 7).

$$n\text{-}Bu_2S + 1/2\ O_2 \xrightarrow[CH_2Cl_2]{[NO_2]\ O_2} n\text{-}Bu_2SO \qquad \text{(eq. 7)}$$

The catalytic process was shown to proceed via a series of equilibria in which the first critical intermediate is the nitrosonium electron donor-acceptor complex (EDA): $[R_2S,NO^+]NO_3^-$.

Many procedures based on the use of transition metals as catalysts for the selective oxidation of sulfides to sulfoxides were reported. Oxidation of dibutylsulfide, chosen as a model substrate, has been studied at 120 °C and 5 MPa air pressure, without solvent, in the presence of halides, sulfates, acetates, butyrates, stearates, acetylacetonates and some other complexes of VO^{2+}, Co, Ni, Mn, Fe, Cr and Rh[18]. Metal acetylacetonates can be arranged in the following order of catalytic activity (r_{rel}) towards sulfoxide formation:

$$VO^{2+} \gg Cu^{2+} > Ni^{2+} > Co^{2+} \geq Mn^{2+} > Fe^{3+} = Mo^{6+}$$

r_{rel} [mol/ g-ion·l·h at 120 °C]	1200	20	13	10	9	1	1

The best results were obtained for vanadium complexes: formation of dibutylsulfoxide in 20-30 % yield in 3h. For different vanadyl complexes, the maximum yield of sulfoxide during dibutylsulfide oxidation without solvent was about 35 % and remains unchanged upon varying temperature, pressure and reaction time. The selectivity toward sulfoxide in the presence of the vanadyl complexes increases when the reaction is effected in solvents (alcohols or benzene) and achieves 70-80 % at a maximum yield of sulfoxide of 40 %.

The oxidation of dibutyl sulfide in the presence of $CuCl_2$, 100-130 °C, air pressure of 3-5 MPa and $[CuCl_2] = 0.03–0.04$ M, without solvent afforded a maximum yield of sulfoxide of 70 % with a selectivity of 80-90 %. Kinetic studies have indicated that the rate of sulfoxide formation increases proportionally with concentration of the catalyst and sulfide and is independent of air pressure.

Copper catalysts in acetone were found to be most efficient for the oxidation of sulfides[18]. Dialkylsulfides R_2S ($R = C_1 - C_5$), thiacyclohexane and thiolane are oxidized to the corresponding sulfoxides with 100 % selectivity at 80 –150 °C, 5-6 MPa, in 5-60 min with the catalytic systems containing 1-60 mmol $CuCl_2$ for a concentration in sulfide of 0.1-0.8 M (Table 1).

Table 1. Oxidation of Sulfides to Sulfoxides in Acetone in the Presence of Copper Complexes (reactions carried out at 5-6 MPa oxygen pressure, with 0.1 mol sulfide and in the presence of acetic acid or trifluoroacetic acid)[18]

Sulfide	Catalyst	Catalyst (mmol)	T (°C)	Reaction Time(min)	Sulfoxide (selectivity %)
Diethylsulfide	$CuCl_2$	3	120	30	100
	$CuBr_2$	8	130	30	85
	$(NH_2C_6H_4O)_2Cu$	1.3	150	20	77
Dibutylsulfide	$CuCl_2$	3	120	10	100
Thiolane	$CuCl_2$	3.9	100	25	95

Regardless of the nature of the copper catalyst and the oxidation conditions, the selectivity toward sulfoxide is close to 100 %, at a sulfide conversion below 80 %. At large conversions extra oxidation of sulfoxide to sulfone takes place. In acidic medium the reaction is facilitated, the rate being proportional to $[AcOH]^{1/2}$. The interaction of $CuCl_2$ with sulfide was demonstrated by ^{1}H-NMR and ^{13}C-NMR spectroscopy. In the formation of the complex, Cu^{2+} serves as the electron acceptor, while sulfide serves as the electron donor. The complex is relatively unstable: the lifetime of the sulfide molecule in the coordination sphere of Cu^{2+} is about 10^{-10} s and the formation enthalpy is 21 kJ/mol[18]. The complex formation leads to redistribution of electron density and to the appearance of a positive charge on the sulfur atom of sulfide; in other words, activation of the sulfide without the C-S bond rupture takes place.

The selective oxidation of thioethers by dioxygen was reported in 1992[19] and it involves the use of a Mn – porphyrin – based cytochrome P450 model system with Zn as the electron donor. This system, which proved also to be efficient for the selective oxidation of hydrocarbons, transformed di-*n*-butylsulfide into sulfoxide in 68 % yield with complete selectivity. It was also effective for the oxidation of alkyl aryl or diaryl sulfides, but the yield did not exceed 68 %, although the selectivity towards sulfoxide was always higher than 90 %. It is assumed that the active species responsible for oxidation by Zn-O_2 is a Mn(V)=O complex: [(TPP)(1-MeIm)Mn(V)=O] (TPP: tetraphenylporphyrin; 1-MeIm: 1-methylimidazole)[19].

The Co(II)-catalyzed oxidation of sulfides was achieved under homogeneous and heterogeneous conditions using oxygen or air as the oxidant. The heterogeneous reactions were carried out using copolymers obtained by reaction of $Co(AAEMA)_2$ [$AAEMA^-$ = deprotonated form of 2-(acetoacetoxy) ethyl methacrylate] with acrylamides[20] (Fig.2). The supported $Co(AAEMA)_2$ can catalyze the oxidation of diphenyl sulfide or dibutylsulfide to the corresponding sulfoxides (2-10 h), but at longer reaction times (15-40 h) the sulfone is formed predominantely. This result is very similar to that obtained in homogeneous system with $Co(acac)_2$ or $Co(AAEMA)_2$. When the reactions were carried out in air it was possible to determine the time when the conversion of the substrate into sulfoxide was optimal. When the reaction time was prolonged, the only sulfur compound detectable in the reaction medium was the sulfone[20].

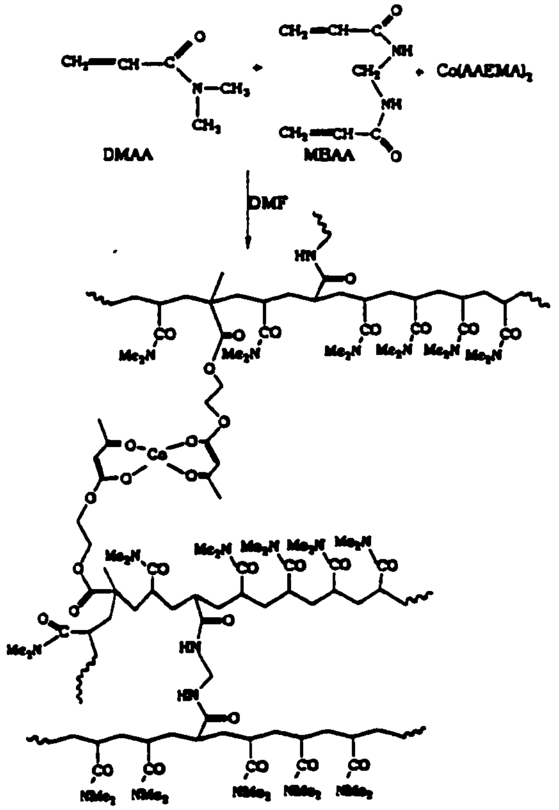


Fig. 2 Synthesis of supported $Co(AAEMA)_2$.

4.2.3 Asymmetric Oxidation of Sulfides

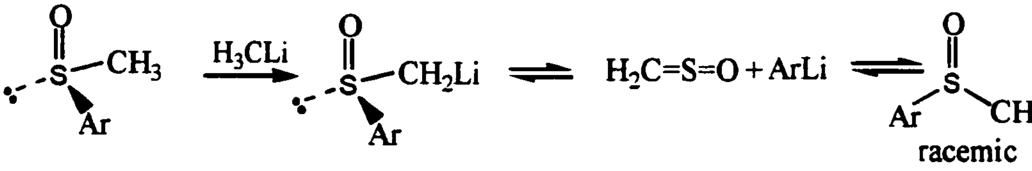
Substituted tricoordinate sulfur compounds having a pyramidal structure, such as sulfonium salts, sulfoxides, and sulfinate esters, contain a chiral sulfur atom and thus, in principle, are resolvable into optically active enantiomeric forms. The activation parameters for pyramidal inversion for several series of dialkyl, diaryl, and alkyl aryl sulfoxides have been determined[21]:


(eq. 8)

$$\Delta H^{\#} = 146 - 176 \text{ kJ/mol } (35 - 42 \text{ kcal/mol})$$

$$\Delta S^{\#} = (-8) \text{ to } 4 \text{ e.u.}$$

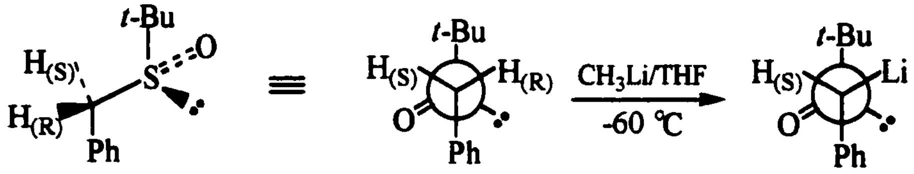
The thermal racemization of sulfoxides occurs only at about 200 °C. Sulfoxides therefore have good optical stability. In many cases, other thermal processes can occur and can lead to decomposition products at lower temperature than the racemization temperature (e.g. pyrolysis by *cis* –elimination for alkyl sulfoxides containing a β-hydrogen). While it was initially believed that sulfoxides are not racemized at moderate temperatures by strong bases such as potassium *t*-butoxide, it was later reported that, on treatment with methyllithium, methyl aryl sulfoxides racemized at room temperature[23]. One of the possible mechanisms involves a methylene sulfine intermediate (eq.9):



(eq. 9)

Sulfoxides have the ability to stabilize charges on an adjacent carbon atom and asymmetric synthesis using nucleophilic reagents containing a chiral sulfoxide group attracted considerable attention. In basic medium, the diastereotopic methylene protons of benzyl methyl sulfoxide undergo hydrogen-deuterium exchange at unequal rates; their relative ratio being 14/1.

Reaction of (+)-(*S*)-benzyl methyl sulfoxide with methyllithium in THF at (-60) °C yields the (*S*,*S*)-α-lithiobenzyl derivative with a selectivity of 15:1, whereas the same reaction of (+)-(*R*)-benzyl *t*-butyl sulfoxide (**9**) leads almost exclusively to the isomeric (*R*,*R*)-α-lithio derivative (**10**) (eq. 10).



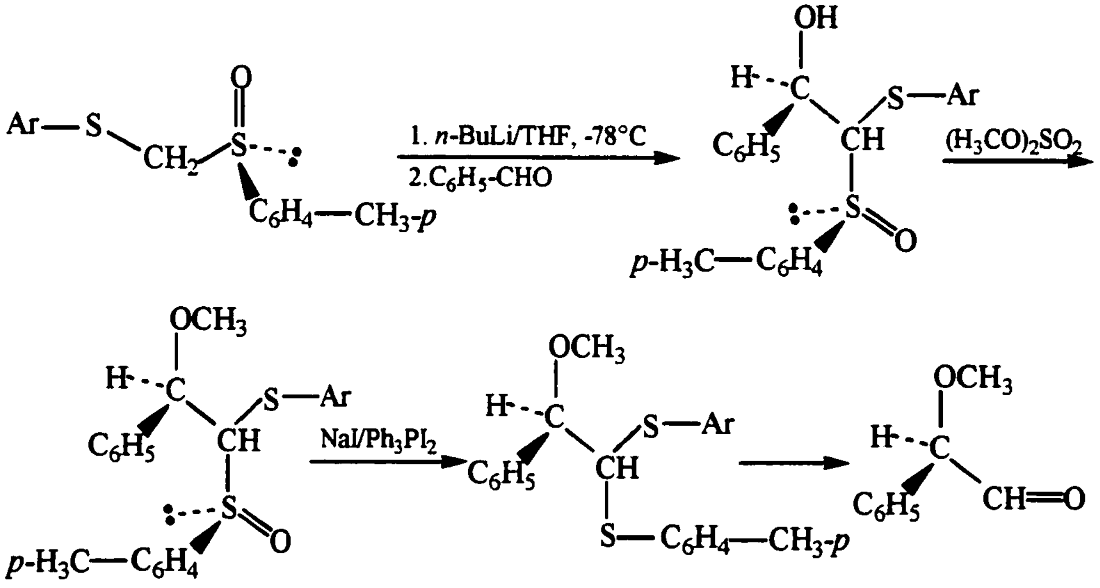
(+)-(*R*)-**9**

(*R*,*R*)-**10**

(eq. 10)

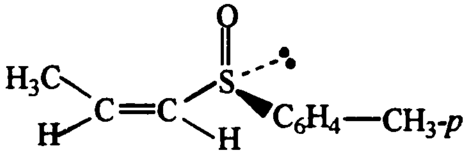
Such a preference has been explained from *ab initio* calculations[24] which indicated that the carbanion *trans* to oxygen was more stable than the one *trans* to the sulfur lone pair of electrons as a result of the *gauche* effect.

It has also been found that the electrophilic halogenation of carbanions α to a chiral sulfoxide group is a highly stereospecific reaction[25]. The condensation reaction of the anion of a chiral thioacetal monosulfoxide with benzaldehyde[26] was used to prepare optically active α-methoxyphenylacetaldehyde (70 %) (Scheme 1). Optically active sulfoxides were used to activate double bonds toward nucleophilic reagents: for example the addition of piperidine to optically active α, β-unsaturated sulfoxides (11) occurred with 74 % asymmetric induction[27].



Scheme 1

The reactions shown above prove that optically active sulfoxides can be very useful in asymmetric synthesis in certain cases. Therefore, much effort has been devoted to the elaboration of convenient methods for their synthesis[9]. Optically active sulfoxides have been obtained by optical resolution, asymmetric synthesis, kinetic resolution and

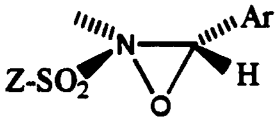


cis-(-)-(R)- **11**

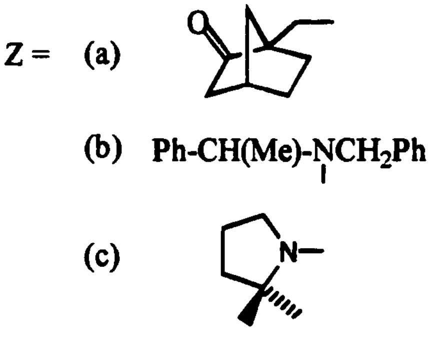
stereospecific synthesis. Some routes to chiral sulfoxides by asymmetric oxidation of prochiral sulfides will now be briefly described.

The standard Sharpless reagent [Ti (O*i*-Pr)$_4$ / (*R*,*R*)-diethyl tartrate/ *t*-BuOOH] oxidizes methyl *p*-tolyl sulfide into a mixture of racemic sulfoxide and sulfone[28]. This reagent, modified by addition of one molar equivalent of water, was found by Kagan and coworkers to give a new homogeneous reagent [Ti(O*i*-Pr)$_4$/(*R*,*R*)-diethyl tartrate/ *t*-BuOOH/ H_2O] which is able to oxidize various types of alkyl aryl sulfides to the corresponding chiral sulfoxides, with an enantiomeric excess in the range of 80-90 %[28].

Chiral 2-sulphonyloxaziridines (**12 a**) and 2-sulphamyloxaziridines (**12 b,c**) represent another type of efficient asymmetric oxidizing reagent which has been used by Davis and coworkers for the synthesis of chiral sulfoxides[29,30].



(12)

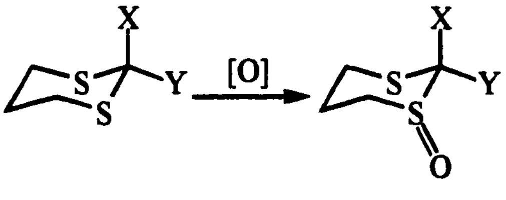


The oxidation of sulfides to sulfoxides proceeded catalytically often with good enantioselectivity when $Ti(Oi\text{-}Pr)_4$ was used in the presence of *R*-(+)-binaphthol instead of diethyl tartrate as a chiral source. Sulfides of the type Me-S-Ar were oxidized using *t*-butyl hydroperoxide (TBHP) in toluene, with high yields (70-90 %) and good enantiomeric excess (up to73 % ee)[31].

Microbiological oxidation (eq. 11) usually gives much better results.

$$R^1\text{—S—}R^2 \xrightarrow{\text{microrganism}} R^1\text{—}\underset{\substack{\| \\ O}}{\overset{*}{S}}\text{—}R^2 \quad \text{(eq. 11)}$$

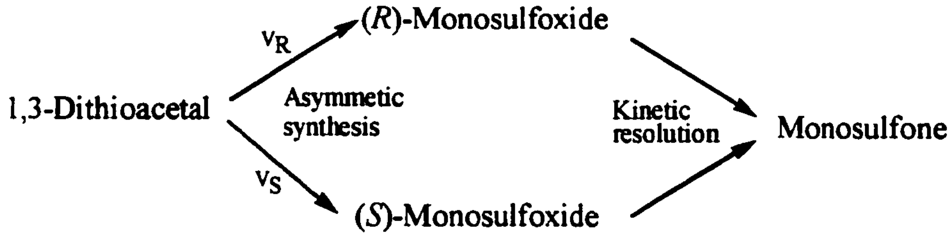
In the asymmetric oxidation of sulfides via fermentation with *Aspergillus niger* (NRRL 337) it was found that the chemical yield and stereoselectivity depend on the structure of the sulfide[32]. The highest optical purity (99 %) was observed in the case of *t*- butyl *p*-tolyl sulfoxide. With *Helmintosporium* cultures[33] high asymmetric induction was observed when 1,3-dithianes were used as substrates (optical yield up to 72 %) (eq. 12).



(eq. 12)

The oxidation of cyclic and acyclic sulfides by cytochrome P 450 from rabbit liver gave sulfoxides with R-configuration at sulfur[34]. The maximum enantiomeric excess (53.8 %) was observed for benzyl *t*-butyl sulfoxide.

Recently[35] cyclohexanone monooxygenase was found to catalyze the asymmetric aerobic oxidation of different alkyl aryl sulfides with the alkyl chain functionalized with Cl, CN, vinyl or hydroxy groups (ee between 14-99 %). The same enzyme can catalyze the oxidation of 1,3-dithioacetals and in combination with kinetic resolution gives pure (*R*)-monosulfoxides (Scheme 2).



Scheme 2

Sulfoxides are used synthetically in many different ways and this fact stimulates the search for new, simple and selective processes for their synthesis.

4.3 Results and Discussion

4.3.1 Synthesis and Characterization of the Complex $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$

The synthesis and the X-ray structural characterization of the new palladium complex $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$ (**13**) was reported in 1992[36]. The formation of this Pd dimer was observed when the reaction of phenols with $Pd(PR_3)_2$ (R = Cy; Bu^t) was investigated.

13 was formed in low yield and it did not incorporate any phenol molecules. The IR spectrum of **13** showed an absorption at 2280 cm^{-1} attributable to P-H stretching, and the formation of secondary phosphine PBu^t_2H and 2-methylpropene from metal coordinated PBu^t_3 is not unprecedented[37].

Complex **13** can be also prepared through the reaction[36]:

$$2\,CpPd(\eta^3\text{-}C_3H_5) + 4\,PBu^t_2H \longrightarrow \mathbf{13} + 2\,CH_3CH{=}CH_2 + 2C_5H_5 + H_2 \quad \text{(eq. 13)}$$

An X-ray study was undertaken and the ORTEP drawing of the complex **13** is shown in Fig.3. The Pd-Pd' distance of 2.594 (1) Å is slightly longer than that in $[Pd(\mu\text{-}PBu^t_2)(PMe_3)]_2$ [2.571(1) Å], in keeping with a metal-metal bond order of one based on a value of 1.30 Å for the covalent radius of palladium[36]. Pd^I - Pd^I bond lengths[38, 39] are usually in a range from 2.531 (1) Å in $[Pd_2(MeCN)_6]^{2+}$ to 2.699(5) Å in $[Pd(dppm)Br]_2$ (dppm = $Ph_2PCH_2PPh_2$). The Pd-P (terminal phosphine) distance is slightly longer than in related species: 2.287(2) Å in **13** compared to 2.250(5) Å in $[Pd(\mu\text{-}PBu^t_2)(PMe_3)]_2$. The authors attributed this lengthening to the presence of the bulkier *t*-butyl substituents and to the lower electron-donating ability of the dialkyl than of the trialkyl-phosphine.

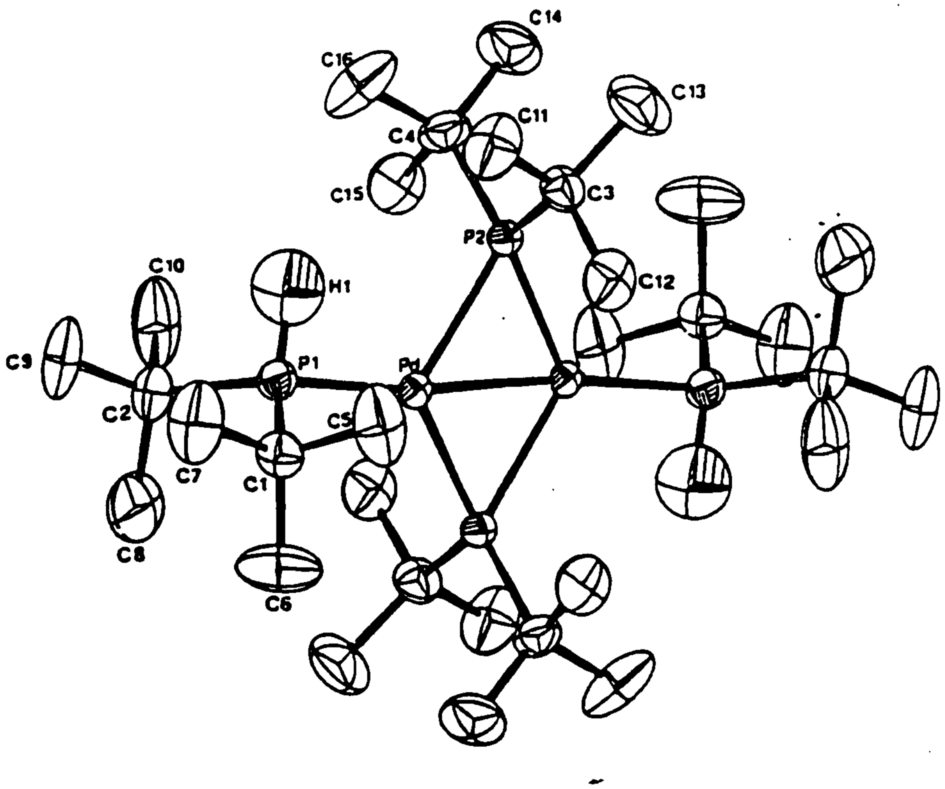
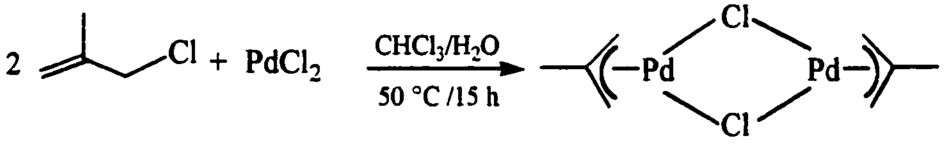


Fig. 3 ORTEP drawing of complex **13**. H (Me) atoms are omitted.

The Pd-P distance is longer in the bridging ligand [2.336(2) Å] than in the terminally bound one [2.287(8) Å].

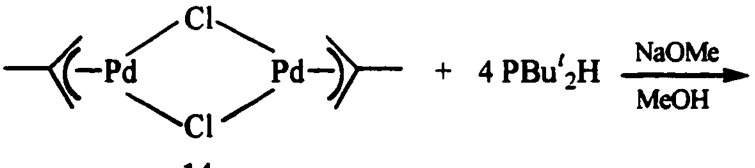
Previous work in our laboratory showed that complex **13** can be obtained by the above reaction (eq.13) but the yield was lower than 20 %. In order to obtain a better yield, the synthesis of **13** was made starting with $PdCl_2$ and 3-chloro-2-methylpropene[40] (eq. 14).



14

(eq. 14)

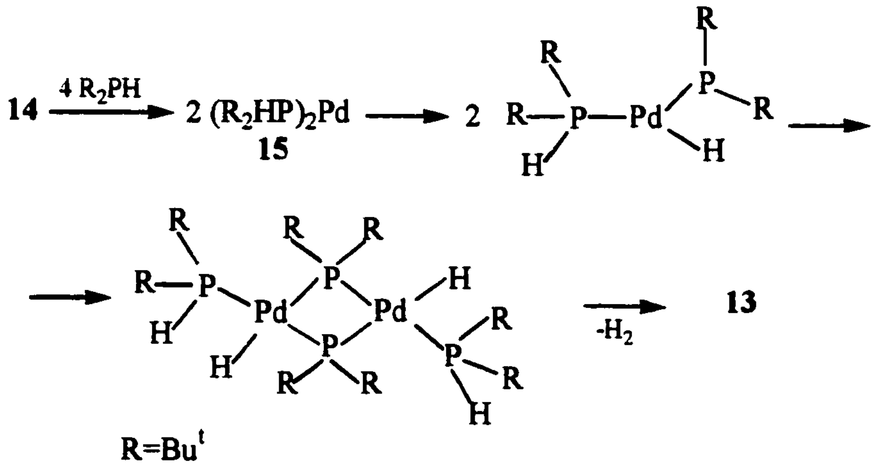
The dimer **14** obtained is then reacted with di-*t*-butyl-phosphine in the presence of NaOMe (eq. 15).



14

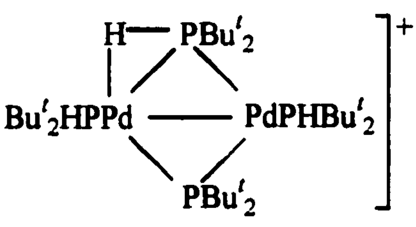
13 (eq. 15)

Complex **13** was obtained using the process described by eq. (14) and (15), in 35-45 % yield. A Pd(0) phosphine complex can be considered as an intermediate (**15**), and then the next step might involve the oxidative addition of P-H bonds to Pd (Scheme 2). This process is documented for nickel[41] and other metals[42] . The μ-phosphido ligand has been found to stabilize both early and late transition metal dinuclear systems. For Pd there are reported[43,44] complexes containing μ-phosphido ligands like: $[Pd_2(\mu\text{-}PBu^t_2)_2(PMe_3)_2]$ $[Pd_2(\mu\text{-}PPh_2)_2Cl_2(PPh_3)_2]$. At the same time it has to be mentioned that terminal phosphido derivatives are rare in late transition metal chemistry[45].



Scheme 2

More data on the structure of **13** were obtained indirectly, after it was reacted with CF_3SO_3H[46]. The cationic complex **16** was obtained and characterized by ^1H; ^{31}P-NMR; 2-D^{31}P; ^1H NOE experiments and X-ray diffraction methods.



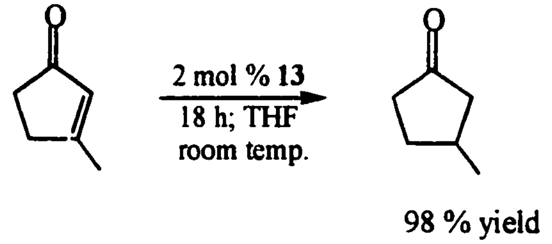
16

The structural features make complex **13** a potential precursor of new organometallics and favor its application in catalysis. The presence of a bis-μ-phosphido bridge should allow reactions of electrophilic reagents with the Pd-Pd bond without disruption of the dinuclear structure and the large bulk of the *t*-butyl groups of the phosphino and phosphido ligands could weaken the metal–phosphine bond, making substitution reactions easier[36].

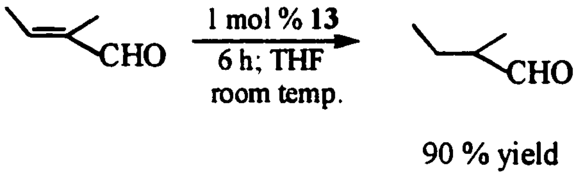
4.3.2 $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$ as Catalyst Precursor in Oxidation and Reduction Processes

Complex **13** was first evaluated as a catalyst for the hydrogenation of the carbon-carbon double bond of α,β-unsaturated ketones and aldehydes[47]. In this type of process, e.g. the reduction of 2-methyl-2-cyclopenten-1-one to 2-methylcyclopentanone in the presence of 2% of **13** in THF, inconsistent results were obtained: sometimes the saturated ketone was formed in excellent yield, while little or no reaction occurred on other occasions.By a careful examination of the reaction conditions it was discovered that the catalyst was not **13**, but an active species generated by reaction between **13** and traces of oxygen, present in the apparatus whenever purging with hydrogen was incomplete[47]. A solution, obtained by bubbling oxygen and stirring the suspension of **13** in THF, was found to be an extremely active catalyst for the reduction. Using this catalytic system the results were reproducible. If the reaction was carried out using standard Schlenk techniques (rigorous exclusion of oxygen), no reaction was detected.

Ketones containing a di- or trisubstituted double bond (eq. 16) and trisubstituted aldehydes (eq. 17) are reduced chemospecifically at the double bond using 1-2 mol% of **13**.

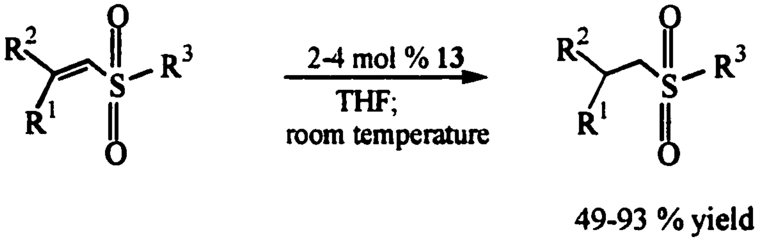


(eq. 16)



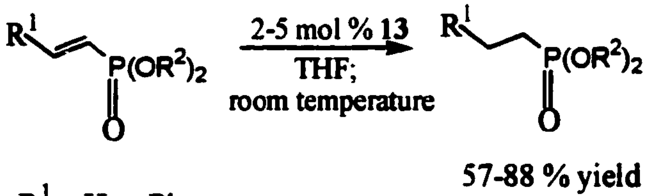
(eq. 17)

Also the reduction of α,β- unsaturated sulfones and phosphonates, under 1 atm pressure of hydrogen, in the presence of **13** pretreated with oxygen in THF, proceeds smoothly, affording the corresponding saturated sulfone or phosphonate in good to high yields (eq. 18 and 19)[48].



(eq.18)

R^1 = H or Ph;
R^2 = H or Me;
R^3 = Me, Ph, *p*-tolyl.

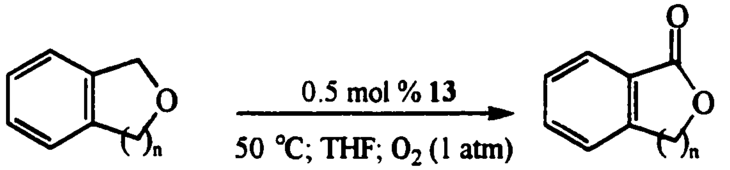


(eq.19)

R^1 = H or Ph
R^2 = Et or Ph

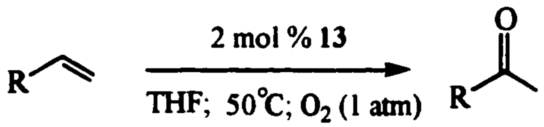
The same catalytic system proved to be effective for the reduction of the double bond in vinyl epoxides with yields varying from 60 to 88 %[49]. The interesting behavior of complex **13**, in the presence of O_2 in THF, enabled us to investigate not only reduction processes but also oxidation reactions.

Initially it was shown that **13** can catalyze the oxidation of ethers as well as alkenes[50]. The reactions were performed at 50 °C, in THF, and 1-isochromanone and phthalide were obtained from isochroman and phthalan, respectively (eq. 20). Simple olefins monosubstituted with an *n*-alkyl or cyclohexyl group were also transformed to methyl alkyl ketones with an average yield of 60 % (eq.21).



(eq. 20)

n = 1; 2.



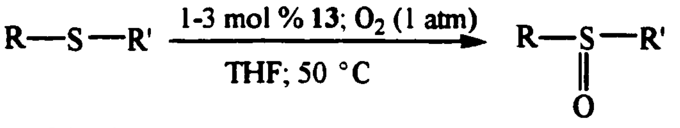
(eq. 21)

R = C_8H_{17}; $C_{12}H_{25}$; C_6H_{11}; C_6H_9.

Only traces of oxidation products were detected when oxygen was used, in THF, but in the absence of the metal complex.

4.3.3 Oxidation of Sulfides Using Molecular Oxygen and the Complex $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$

The catalytic system consisting of the complex $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$, THF and O_2, was used in the process for the oxidation of sulfides to sulfoxides. A mixture of **13** and THF was stirred under oxygen for 1-2 h at 50 °C, until a clear, yellow-orange, solution was formed. A wide variety of sulfides (i.e. aliphatic, aromatic, allylic, benzylic, and heterocyclic) were subjected to oxidation[51](eq. 22). The results are presented in Table 2.



$$R{-}S{-}R' \xrightarrow[\text{THF; 50 °C}]{\text{1-3 mol \% 13; }O_2\text{ (1 atm)}} R{-}\underset{\underset{O}{\|}}{S}{-}R' \qquad \text{(eq. 22)}$$

24 a-k **25 a-k**

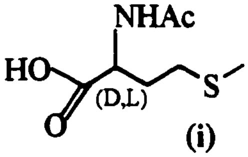
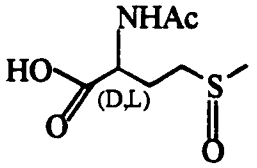
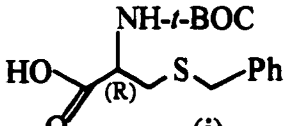
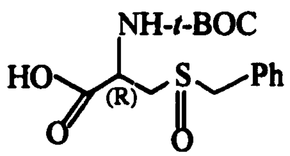
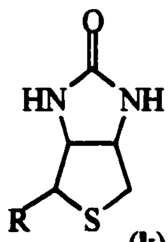
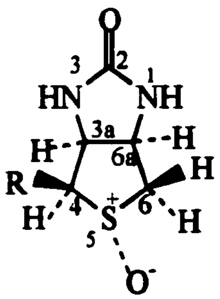
One of the best results for the oxidation reaction was obtained using dibenzyl sulfide (Table 2, entry 1) which afforded the sulfoxide in 83 % isolated yield (36 h). The replacement of the benzyl group, by an aliphatic or phenyl group, results in lower product yields. This was the case for benzyl phenyl sulfide, benzyl methyl sulfide and isopropyl phenyl sulfide (Table 2, entries 2-4 and Figure 4 – ^{1}H-NMR and ^{13}C-NMR of isopropyl phenyl sulfoxide). Even if the reaction time is extended to 48 h (e.g. for benzyl phenyl sulfide or benzyl methyl sulfide) the conversion to sulfoxide is incomplete, but no formation of sulfone is observed. Phenyl vinyl sulfide, in which two sp^2 carbons are directly bound to the sulfur atom, did not undergo oxidation. When phenyl allyl sulfide was used as substrate, the double bond remained unaffected in the oxidation process and the corresponding sulfoxide was obtained selectively, but only in 43 % yield (Table 2, entry 5).

A simple dialkyl sulfide, di-*n*-butyl sulfide, was oxidized to the sulfoxide in 37 % yield (Table 2, entry 6). Cyclic aliphatic sulfides (tetrahydrothiophene, tetrahydrothiopyran) are oxidized to the corresponding sulfoxides, without overoxidation to sulfone, with yields which varied from fair (56 % for pentamethylene sulfoxide) to good (76 % for tetramethylenesulfoxide) (Table 2, entries 7,8).

Interesting results were realized in the case of the derivatives of amino acids, methionine and cysteine. In these cases, the presence of amide and carboxylic groups does not interfere with the oxidation process at sulfur (Table 2, entries 9,10). *N*-acetyl-D,L-methionine and *N*-*t*-BOC-*S*-benzyl-L-cysteine give a 1:1 mixture of two diastereoisomers. Under similar reaction conditions, (+)-biotin 4-nitrophenylester led to the formation of (+)-biotin sulfoxide 4-nitrophenyl ester in 30 % yield. The conversion was incomplete after 48 h, but the reaction was chemoselective and stereospecific. The formation of (+)-sulfoxide is confirmed by the presence of a doublet of doublets for H-6(β) which has a smaller geminal coupling constant (J_{gem} = 13.2 Hz) compared to that for the (-)-stereoisomer[16] (reported as a doublet with J_{gem} = 15.1 Hz). In addition the C_{3a} and C_{6a} carbons are more shielded (54.0/56.9 ppm) compared to those in the (-)-sulfoxide (reported higher than 60 ppm) in accordance with the antiperiplanar effect of sulfoxide oxygen on carbons γ to the oxygen atom[52] (Figure 5).

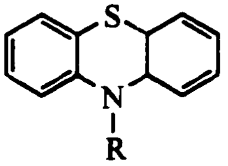
Attempts to oxidize phenothiazines (**17**) and dibenzothiophene (**18**) were unsuccessful. In these reactions the starting material was recovered unchanged. This result together with the previous observation that phenyl vinyl sulfide is completely unreactive under the reaction conditions suggests that electronic factors (determined by the substituents bound to sulfur atom) play an important role in this oxidation process.

Table 2. Oxidation of Sulfides to Sulfoxides by Oxygen Using **13** as the Catalyst Precursor*

Entry	Substrate (**24**)	Rxn. time (h)	Product (**25**)	Conversion (%)** (Isolated yield %)
1.	$PhCH_2SCH_2Ph$ (**a**)	36	$PhCH_2S(O)CH_2Ph$	100 (83)
2.	$PhCH_2SPh$ (**b**)	48	$PhCH_2S(O)Ph$	83 (60)
3.	$PhCH_2SCH_3$ (**c**)	48	$PhCH_2S(O)CH_3$	75 (50)
4	$PhSCH(CH_3)_2$ (**d**)	24	$PhS(O)CH(CH_3)_2$	83 (47)
5.	$PhSCH_2CH{=}CH_2$ (**e**)	48	$PhS(O)CH_2CH{=}CH_2$	82 (43)
6.	$(n\text{-}C_4H_9)S(n\text{-}C_4H_9)$ (**f**)	60	$(n\text{-}C_4H_9)S(O)(n\text{-}C_4H_9)$	60 (37)
7.	$(CH_2)_4S$ (**g**)	96	$(CH_2)_4S(O)$	100 (76)
8.	$(CH_2)_5S$ (**h**)	72	$(CH_2)_5S(O)$	75 (56)
9.	 (**i**)	48		(50)
10.	 (**j**)	50		(55)
11.	 (**k**) R = $4\text{-}NO_2C_6H_4COO(CH_2)_4$	48		(30)

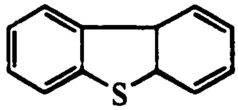
*Reaction conditions: 1 mmol sulfide; 0.01 mmol **13** (entries 1-9), 0.02 mmol **13** (entry10), 0.03 mmol **13** (entry 11); THF (10 ml); O_2 (1 atm);50 °C.

**Determined by GC using an internal standard or from the amount of unreacted sulfide.



17

$R = (CH_2)_3N(CH_3)_2;$
$CH_2CH(CH_3)N(CH_3)_2;$
$COCH_3$



18

The oxidation of sulfides to sulfoxides using our catalytic system was always carried out in THF. It was determined that other reaction solvents including methylene chloride, 1,2-dimethoxyethane and methanol were not useful for this reaction. Small amounts of by-products, resulting from the oxidation of THF, were formed in some of these reactions. Similar observations were made when the same catalytic system was used for the oxidation of ethers and alkenes[50]. The most important of the by-products detected is γ-butyrolactone. The amount of lactone increases, as anticipated, if the reaction time or volume of the solvent is increased. When the oxidation of THF was effected using 1,2-dimethoxyethane as the solvent, with a ratio THF/catalyst 1000/1[50] four products were detected: γ-butyrolactone (7.5 % yield), formate acetal (2.5 % yield) (**19**), traces of glycol formate $HO\text{-}(CH_2)_3\text{-}OOCH$ (**20**) and small amounts of another product, which remained unidentified.

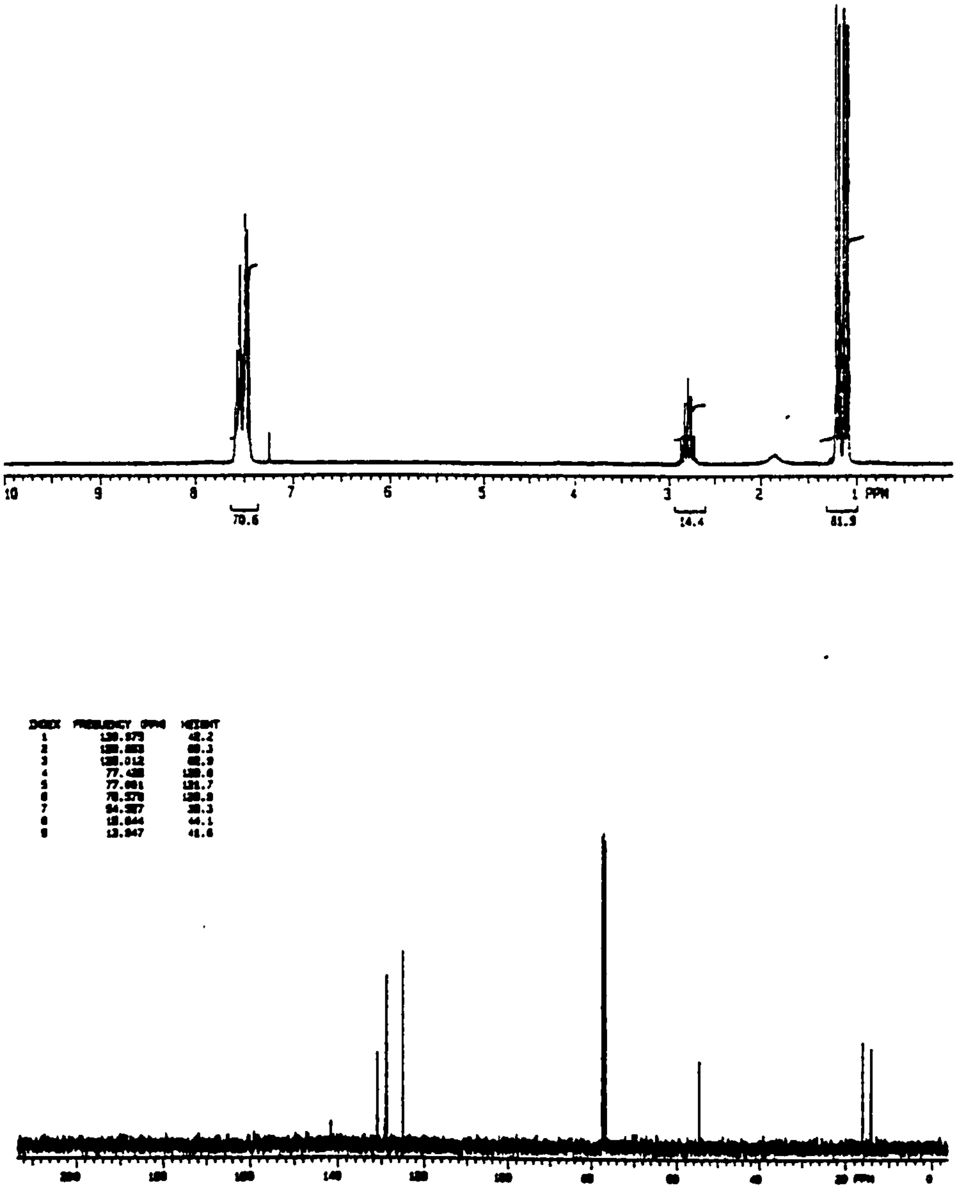


Fig. 4 ^{1}H-NMR and ^{13}C-NMR of 25 d (CDCl$_3$)

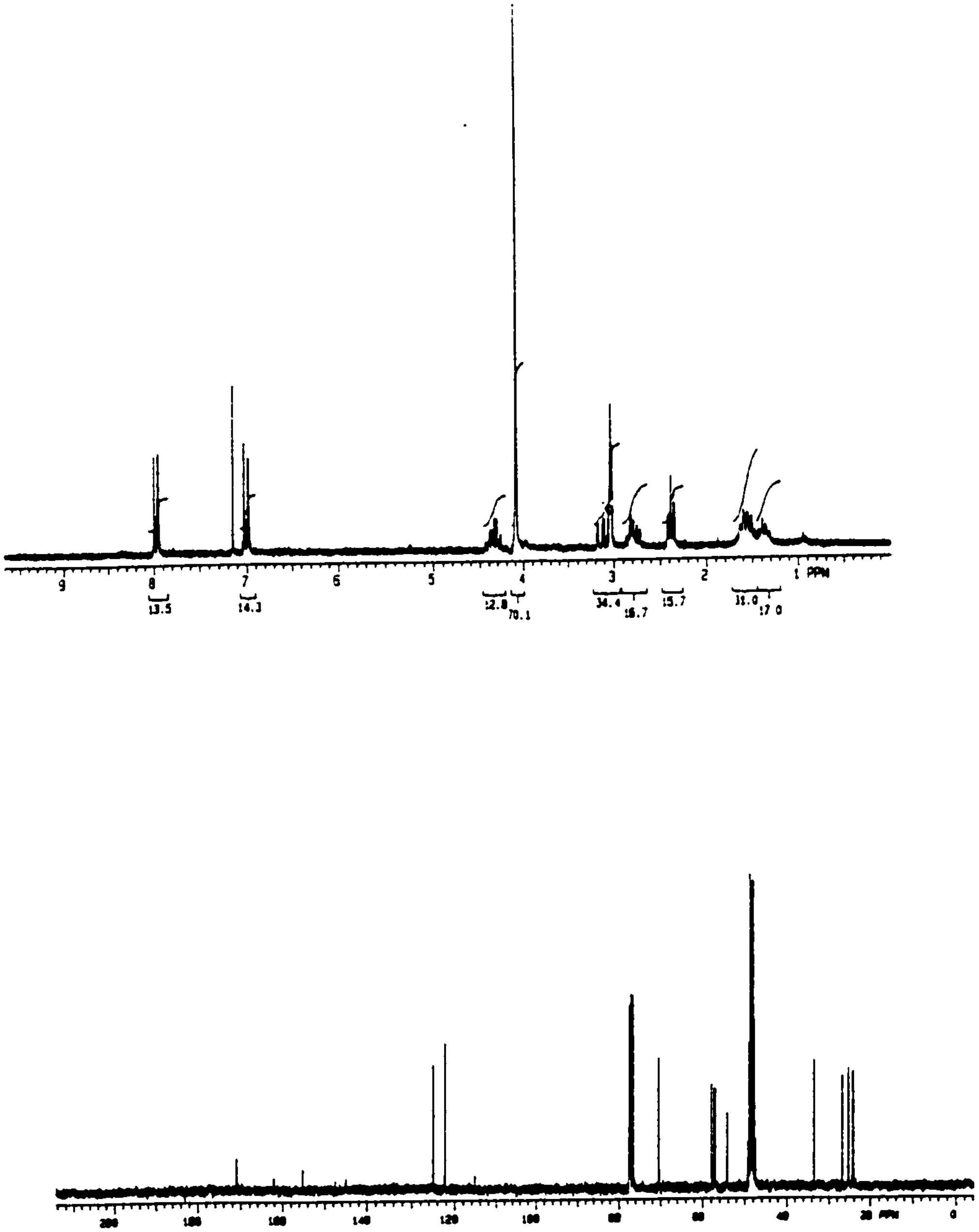
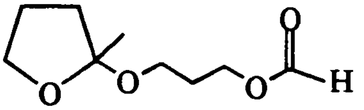
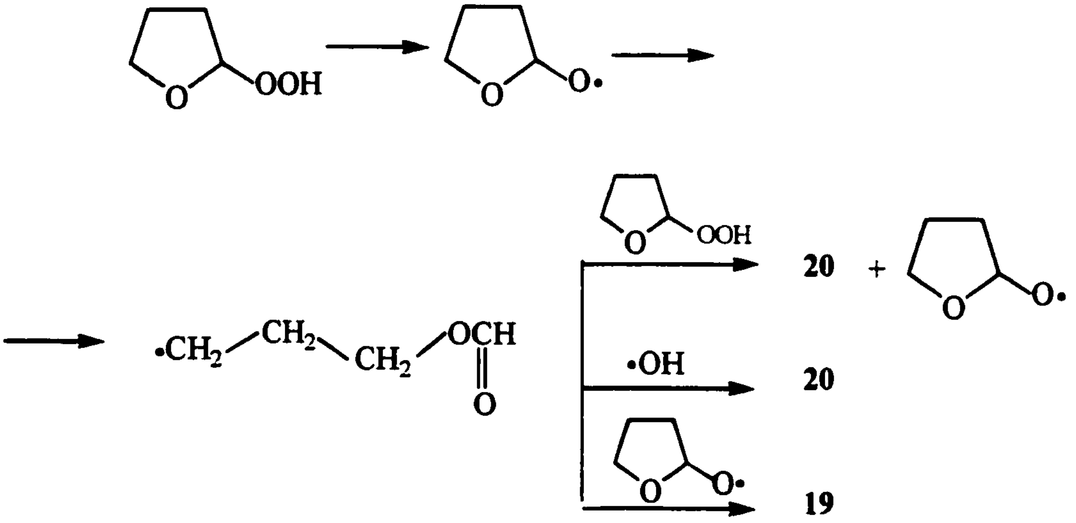


Fig. 5 ^{1}H-NMR and ^{13}C-NMR of **25 k** ($CDCl_3$+CD_3OD)



19

It is known that ethers form hydroperoxides upon exposure to atmospheric oxygen. By-products **19** and **20** are presumably formed by β-scission of an alkoxy radical resulting from decomposition of 2-hydroperoxytetrahydrofuran (Scheme 3) as previously reported[16].

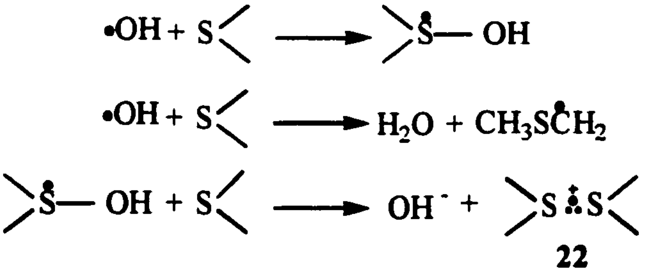


Scheme 3

Only traces of oxidation products were detected when THF was oxidized by O_2 in the absence of the metal complex. It was also noticed that no reaction took place when a sulfide was stirred in THF, under oxygen without any palladium catalyst.

A study undertaken by Pasquali's group[54], showed that when a suspension of **13** in toluene was stirred at 50 °C, under dioxygen, the red solid disappeared, yielding a clear orange solution. From this solution a complex $[Pd(O_2PBu^t_2)(PBu^t_2OHOPBu^t_2)]$ (**21**) was isolated which was characterized by ^1H, ^{13}C, ^{31}P-NMR spectroscopy and also by determination of the crystal structure[54]. The oxidation of phenyl methyl sulfide with O_2 using 2 mol % **21** gave only traces of sulfoxide and the rest of the sulfide was recovered unchanged. The reaction proceeds with almost complete conversion to sulfoxide when 11 % **21** is used. The possibility that the complex **21** is formed in the process of oxidation of sulfides can not be excluded.

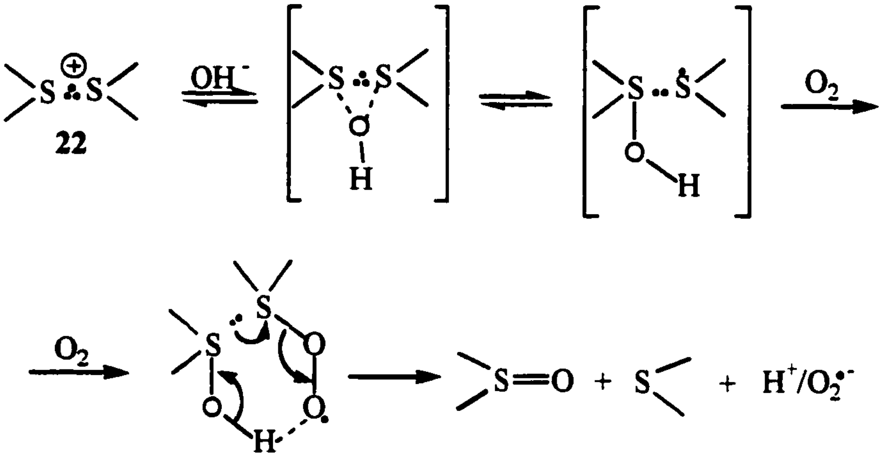
The fact that the reaction does not occur in a solvent other than THF and also the observed reactivity of **13** towards the oxidation of ethers, indicate that alkylhydroperoxides or ·OH species, arising from the oxidation of THF, may be involved in the process. It has been shown previously[55] that a sequence of reactions like that depicted in Scheme 4 can take place, once the ·OH radical is present in the system:



22

Scheme 4

The process is envisaged to continue by the association of the radical cation **22** with HO$^-$, followed by addition of oxygen and electron shift to lead to one molecule of sulfoxide (Scheme 5).



Scheme 5

The above reactions were assumed to take place when $HO^{\cdot}$ radicals were generated without the presence of a metal complex.

The palladium complex may become involved either through a alkylperoxopalladium (II), species which was reported to be capable of oxidizing terminal olefins to methyl ketones[56], or by coordination of the sulfur atom. In the case of Cu^{2+}, NMR studies showed complex formation of sulfide with copper acetylacetonate[18] which leads to the activation of the sulfide. Our studies indicated that when a stronger oxidizing reagent like Bu^tOOH (3.5 M solution) was used in reaction with the Pd complex in benzene, without any sulfide, two main products are formed. One of these was identified as $(Bu^t)_2P(O)OH$ (**26**) by spectroscopic means and comparison with literature data. The other is a solid residue, insoluble in pentane, which does not contain any P and has M_W up to 600. None of the two compounds compares with the initial complex as catalyst for the oxidation of sulfides, as demonstrated by our experiments.

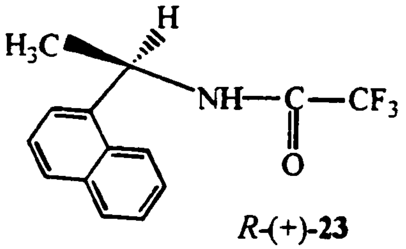
Molecular oxygen can oxidize the phosphine ligands of complex **13**, but probably at a slower rate than Bu^{t}OOH. The presence of the sulfide results in competitive oxidation at the sulfur atom. The fact that dioxygen is a mild oxidizing reagent and the competitive processes taking place in the system might account for the preferential formation of the sulfoxides.

4.3.4 Attempted Asymmetric Synthesis of Sulfoxides

The possibility of asymmetric synthesis of sulfoxides was investigated using **13**, O_2 and different chiral ligands:

(*R*)-(+)- and (*S*)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	BINAP
(2*S*,4*S*)-(-)-1-(*t*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl] pyrollidine	BPPM
(-)-1,2-bis(2*R*,5*R*)-2,5-dimethylphospholanobenzene	DUPHOS
(-)-dimethyl-2,3-*O*-benzylidene-*L*-tartrate	

Benzyl methyl sulfide was employed as the reactant and the ratio of ligand / catalyst was between 1 and 2. No measurable enantiomeric excess was detected in most cases. This was checked either by the use of a polarimeter or a gas chromatograph equipped with a chiral column. For some of the reactions the enantiomeric excess was determined by ^{1}H-NMR using the type of chiral shift reagents reported by Kagan[57] *et al.* to be suitable for alkyl aryl sulfoxides. These reagents are based on (*R*) or (*S*)- α-phenyl or naphthyl ethyl amine in which the amino group is acylated with 3,5-dinitrobenzoylchloride or trifluoroacetic anhydride. In our case the second route was chosen and the compound **23** proved to be efficient to resolve the mixture of enantiomers for benzyl methyl sulfoxide.



R-(+)-**23**

No significant enantiomeric excess could be detected by ^{1}H-NMR in the case of benzyl methyl sulfoxide, using R-(+)-BINAP, as chiral ligand (Fig. 6).

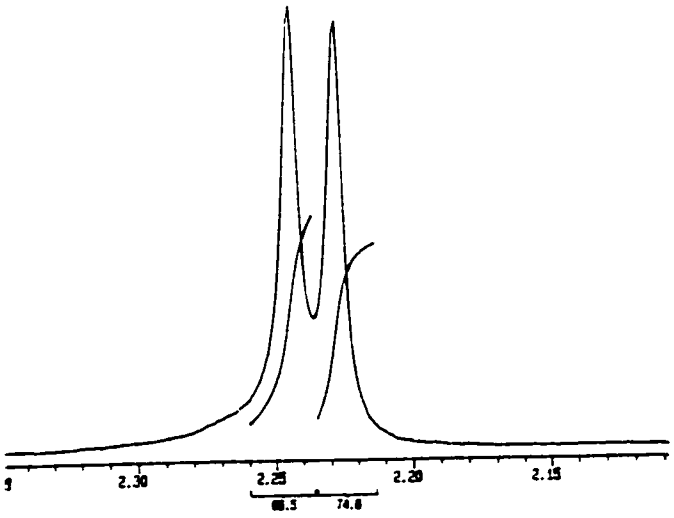
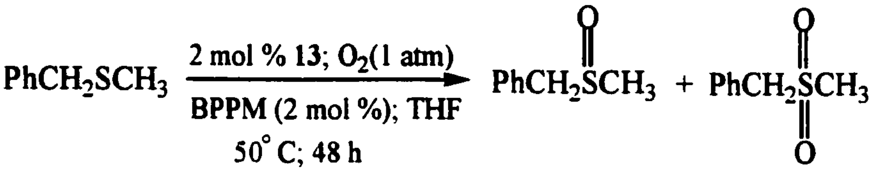


Fig. 6 Determination of enantiomeric excess by ^{1}H-NMR (the signal corresponding to the methyl group in benzyl methyl sulfoxide is split in the presence of the chiral shift reagent).

Attempts to increase the enantiomeric excess, by variation of the reaction conditions and of the chiral ligand, were not successful. It should be noted that the use of chiral phosphine ligands, sometimes resulted in a more facile oxidation process of $PhCH_2SCH_3$, and sulfone was formed as well as sulfoxide (eq. 23).



$$PhCH_2SCH_3 \xrightarrow[\substack{\text{BPPM (2 mol \%); THF} \\ 50^\circ\text{ C; 48 h}}]{\text{2 mol \% } \mathbf{13}\text{; } O_2\text{(1 atm)}} PhCH_2\overset{O}{\overset{\|}{S}}CH_3 + PhCH_2\overset{O}{\underset{O}{S}}CH_3 \quad \text{(eq. 23)}$$

In the above reaction the ratio of sulfone / sulfoxide was 2.4 / 1.

Conclusions

Different sulfides – aliphatic, aromatic, allylic, benzylic, and heterocyclic - can be selectively oxidized to sulfoxides by molecular oxygen, using a catalyst formed by the reaction of the palladium dimer **13** and oxygen. The reaction proceeds under very mild conditions (50 °C, 1 atm oxygen) and is simple in execution. The reaction is completely selective towards sulfoxide formation and can tolerate amide, carboxylic acid, imide, and nitro substituents. The process is stereospecific, as demonstrated in the case of (+)-biotin 4-nitrophenyl ester.

4.4 Experimental Section

General procedure for the oxidation of sulfides:

A mixture of **13** (8 mg, 0.01 mmol) and dry THF[62] (10 ml) was stirred under oxygen for 1-2 h at 50 °C, until a clear, yellow-orange solution, was formed. The sulfide (1mmol) was added at this time, and the reaction was stirred for 24-96 h (monitored by GC or TLC). The solvent was removed by rotary evaporation, and pure products were isolated by column chromatography on silica gel, using various ratios of ethyl acetate/hexane as eluant. If necessary Kugelrohr distillation was applied before column chromatography in order to remove the more volatile by-products. Solid products were further purified by recrystalization. The products were identified by comparison of spectral data with literature results and/or with authentic samples.

Benzyl sulfoxide (**25 a**)[58]

White crystals: mp 133.6-134 °C; ^{1}H-NMR ($CDCl_3$) δ 3.87 [d, 2 H, $-CH_2-S(O)-CH_2-$, ^2J=16 Hz], 3.88 [d, 2 H, $-CH_2-S(O)-CH_2-$, ^2J=16 Hz], 7.24-7.37 (m, 10 H, ArH); ^{13}C-NMR ($CDCl_3$) δ 57.1(CH_2), 128.2, 128.8, 130.0, 142.3 (aromatics); IR (KBr): 1030 (S=O) cm^{-1}.

Benzyl phenyl sulfoxide (**25 b**)[58]

Pale yellow needles: mp 122-123 °C; ^{1}H-NMR ($CDCl_3$) δ 4.02 (d, 2H, CH_2, ^2J=12.5 Hz), 6.93-7.43 (m, 10 H, ArH); ^{13}C-NMR ($CDCl_3$) δ 63.5 (CH_2); 124.4, 128.2, 128.4; 128.8, 130.3, 131.1, 141.5, 142.6 (aromatics); IR (KBr) 1047 cm^{-1} (S=O); MS (CI) 217 $[M+1]^+$.

Benzyl methyl sulfoxide (**25 c**)[65]

^{1}H-NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.89 (d, 1H, CH_2, ^2J= 12.8 Hz), 4.03 (d, 1H, CH_2, ^2J= 12.8 Hz), 7.23-7.38 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 37.2 (CH_3), 60.2 (CH_2), 128.4, 128.9, 129.9, 139.5 (aromatics); IR (KBr) ; MS *m/e* 154 $[M^+]$

Phenyl *i*-Propyl Sulfoxide (25 d)[59]

^{1}H-NMR ($CDCl_3$) δ 1.13 (d, 3H, CH_3, ^3J=6.9 Hz); 1.22 (d, 3H, CH_3, ^3J=6.9 Hz), 2.81 (m, CH, ^3J= 6.9 Hz), 7.41-7.60 (m, 5 H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.9 (CH_3), 15.8 (CH_3); 54.5 (CH); 125.0, 128.8, 130.9, 141.2 (aromatics); IR (neat): 1026, 1086 cm^{-1} (S=O).

Allyl phenyl sulfoxide (25 e)[64]

^{1}H-NMR ($CDCl_3$) δ 3.51 (m, 2H, $-CH_2-$), 5.22 (m, $=CH_2$), 5.56 (1H, m, -CH=); 7.42-7.68 (ArH); ^{13}C-NMR ($CDCl_3$) δ 60.8 ($-CH_2-$), 123.9, 124.3, 125.1, 129.0, 131.1, 142.5 (aromatic and C=C double bond); IR (neat) 1042, 1089 (S=O), 1634 (C=C) cm^{-1}; MS *m/e* 166 [M^+].

n-Butyl Sulfoxide (25 f)[63]

^{1}H-NMR ($CDCl_3$) δ 0.95 (t, 6 H, CH_3, ^3J=8 Hz), 1.5 (m, 4 H; CH_2),1.75 (m, 4 H, CH_2); 2.65 (m, 4 H, CH_2); ^{13}C-NMR ($CDCl_3$) δ 13.7 (CH_3), 22.0 (CH_2), 24.0 (CH_2), 52.14 (CH_2); IR (neat): 1070 (S=O), 2932 (alkyl) cm^{-1}.

Tetramethylene Sulfoxide (25 g)[63]

^{1}H-NMR ($CDCl_3$) δ 2.06 (m, 2 H), 2.45 (m, 2H), 2.87 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ 25.4 ($-CH_2-\underline{C}H_2-\underline{C}H_2-CH_2-$), 54.4 ($-CH_2-SO-CH_2-$); IR (neat) 1021 (S=O) cm^{-1}; MS *m/e* 104 [M^+].

Pentamethylene Sulfoxide (25 h)[60]

^{1}H-NMR ($CDCl_3$) δ 1.55 (m, 4 H), 2.15 (m, 2 H), 2.74 (4 H, m); ^{13}C-NMR ($CDCl_3$) δ 19.0 [$\underline{C}H_2-(CH_2)_2-S(O)-$], 24.5 [$\underline{C}H_2-CH_2-S(O)-$]; 48.8 [$-\underline{C}H_2-S(O)-$]; IR(neat):1027, 1068 (S=O), 2857, 2932 (alkyl) cm^{-1}; MS *m/e* 118 [M $^+$]

N-Acetyl-D,L-Methionine Sulfoxide (it was obtained as a 1:1 mixture of two diasteroisomers) (25 i)[16]

^{1}H-NMR ($CDCl_3$ and CD_3OD 3:1) δ 1.97 and 1.99 [s each, 3H, $CH_3C(O)$], 2.01- 2.36 [m, 2H, $-C\underline{H}_2CH_2S(O)$], 2.56-2.57 [s each, 3H, $CH_3S(O)$], 2.66-2.87 [m, 2H, $CH_2-S(O)$], 4.55 (m, 1H, CHN); ^{13}C-NMR ($CDCl_3$) δ 22.9 and 23.0 (CH_3), 25.4 and 25.6 [$CH\underline{C}H_2S(O)$], 37.4 and

37.5 [$CH_3S(O)$], 48.9 and 49.2 [$CH_2S(O)$], 51.4 and 51.6 [$CH\underline{C}(O)$], 171.2 and 171.6 [C(O)N], 172.40 and 172.44 [C(O)OH]; IR (KBr) 1009 (S=O), 1654 (amide) cm^{-1}.

N-BOC-*S*-Benzyl-L-Cysteine Sulfoxide (obtained as a 1:1 mixture of two diastereoisomers) **(25 j)**[16]

^{1}H-NMR [$CD_3C(O)CD_3$] δ 1.38 and 1.41 [s each, 9H, $C(CH_3)_3$], 3.02-3.21 [m, 2H, $CH_2S(O)$], 4.06-4.27 [m, 2H, ^2J=8.5 Hz for one diastereoisomer and ^2J=12.5 for the other diastereoisomer, $PhCH_2S(O)$], 4.59-4.70 (m, 1H, CHN), 7.23-7.41 (m, 5H, ArH), ^{13}C-NMR ($CDCl_3$ + CD_3OD) δ 28.1 [$C(\underline{C}H_3)_3$], 52.8 and 53.5 [$CH\underline{C}H_2S(O)$], 57.9 and 58.2 [$\underline{C}H_2Ph$ and $\underline{C}HC(O)$], 80.7 and 80.6 [$\underline{C}(CCH_3)_3$], 127.8, 128.8, 129,3, 137.9 (aromatics), 155.8 [$\underline{C}(O)\text{-}OC(CH_3)_3$]; 171.8 and 172.1 [$\underline{C}(O)OH$]; IR (KBr): 996, 1027 (S=O) cm^{-1}; MS (CI) 328 $[M+1]^+$.

Biotin (+)-Sulfoxide 4-Nitrophenyl Ester **(25 k)**[16,52]

White needles , mp 182-183 °C, ^{1}H-NMR ($CDCl_3$ and CD_3OD 3:1) δ 1.31-1.48 (m, 2H, $C\underline{H_2}CH$), 1.48-1.70 [m, 4H, $(CH_2)_2$], 2.40 [t, 2 H, $CH_2C(O)$], 2.70-2.89 (m, 2H,H-4 and H-6), 3.11 (dd, 1H, ^2J=13.2 Hz, ^3J=2.5 Hz, H-6), 7.0 and 7.98 (d each, 2H each, ArH); ^{13}C-NMR ($CDCl_3$ and CD_3OD 3:1) δ 23.9, 24.9, 26.5 (C-7,8,9), 33.2 (C-10), 54.0, 56.9 (C-6a, C-3a), 57.71 (C-6), 70.29 (C-4), 122.1, 124.7 (aromatics), 155.0 (C-2), 170.9 (C-11); IR (KBr) 1014 (S=O), 1683 (imide), 1748 (ester) cm^{-1}.

Synthesis of N-acetyl phenothiazine (17, R=$COCH_3$):

Phenothiazine free base (0.01 mol) and triethylamine (0.012 mol) were dissolved in THF. Acetyl chloride (0.012 mol) was added and the mixture stirred for 15 min. An insoluble precipitate was formed. The mixture was poured into cold water. The amide was extracted with ether , dried over $MgSO_4$, and the solvent removed by rotary evaporation.
^{1}H-NMR ($CDCl_3$) δ 2.19 (s, 3H, CH_3), 7.18-7.53 (m, 8H, ArH). IR (KBr) 1670 (C=O) cm^{-1}.

Synthesis of $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$ (13)[36,40]

A mixture of 3-chloro-2-methylpropene (8 mmol, 0.724 g), Pd Cl_2 (4 mmol, 0.709g), chloroform (4 ml) and 12 ml distilled water was placed in a round-bottom flask, equipped with a condenser, and heated at 50 °C, in an oil-bath. The color of the mixture turned dark red. After 15 h the mixture was cooled down and extracted three times with chloroform. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. A brown-red powder was obtained which represented the complex **14**. It was washed with hexane and dried in vacuum.

14 (1.18 mmol – 0.4 g) was placed in a dry flask. Methanol (25 ml) and NaOMe (2.36 mmol – 0.54 ml) were added under an inert atmosphere (N_2). The suspension of **14** in methanol becomes clear when NaOMe is added. Bu^t_2PH was added (4.72 mmol –0.974 g), very slowly at the beginning. The color started to change to yellow brown and the formation of a precipitate could be observed. The mixture was stirred overnight, at room temperature, under nitrogen. The precipitate was filtered under vacuum, using Schlenck techniques). Dry toluene was added and the suspension heated at 60 °C, under nitrogen, for 12 h. Finally, the solid was filtered and washed with toluene to afford **13** in 35-45 % yield.

$\underline{[C(CH_3)_3]_2P(O)OH}$[61]

^1H-NMR ($CDCl_3$) δ 1.29 [d, 18H, $^2J(^{31}P,^1H)$ =14 Hz]; ^{13}C-NMR ($CDCl_3$) δ 26.0 (CH_3), 34.6 [$\underline{C}(CH_3)_3$]; ^{31}P (H_3PO_4 85% as external standard) δ 65.8 $^2J(^{31}P,^1H)$=14 Hz. MS(m/e)=178[M^+].

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Conclusions

Ruthenium supported on montmorillonite (montmorillonite was pretreated with either bipyridine or phosphine containing silane) was used as catalyst for hydrogenation processes (Chapter 2). The ruthenium clays were found to catalyze the reduction of unsaturated esters, epoxides, sulfones and phosphonates. Ru-phosphine clay is an efficient catalyst for reduction of the α-carbonyl group of α-ketoesters and α-ketoamides and α-imine group of α-iminoesters and α-iminoketones. This catalytic system can be used in the reductive amination process of α-ketoesters with chiral amines in which case high diastereomeric excess is obtained.

Montmorillonite itself proved to be a useful catalyst in the transfer hydrogenation of ketones (Chapter 3). The system Na montmorillonite / KOH / isopropanol can be applied with good yields in the reduction of alkyl aryl ketones and dialkyl ketones to the corresponding alcohols.

The use of a palladium dimer, $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$, as catalyst precursor for the selective oxidation of sulfides to sulfoxides showed to be successful (Chapter 4). Aliphatic, aromatic, allylic, benzylic, and heterocyclic sulfides were selectively oxidized to sulfoxides by molecular oxygen. The reaction took place under mild conditions and was stereospecific as demonstrated in the case of (+)-biotin 4-nitrophenyl ester.

Claims to Original Research

1) Synthesis of ruthenium clays by reaction of phosphine montmorillonite and bipyridine montmorillonite with ruthenium chloride hydrate.

2) Use of ruthenium clays as catalysts for the:
   - selective hydrogenation of the carbon-carbon double bond in unsaturated esters, epoxides, sulfones and phosphonates;
   - selective reduction of the carbon-oxygen double bond in α-ketoesters and α-ketoamides;
   - selective reduction of the carbon-nitrogen bond in α-iminoesters and α-iminoketones.

3) Reductive amination of α-ketoesters with amines catalyzed by ruthenium phosphine clay.

4) Hydrogen transfer reduction of ketones using Fluka K10 montmorillonite as catalyst.

5) Selective synthesis of sulfoxides by oxidation of sulfides in the presence of $[Pd(PBu^t_2H)(\mu\text{-}PBu^t_2)]_2$ as catalyst precursor.

Publications

- ☐ Aldea, R. and Alper, H. "Selective Aerobic Oxidation of Sulfides Using a Novel Palladium Complex as the Catalyst Precursor" *J. Org. Chem.* **1995**, *60*, 8365.

- ☐ Aldea, R. and Alper, H. "Ruthenium Clay Catalyzed Chemoselective Hydrogenation of Unsaturated Esters, Epoxides, Sulfones and Phosphonates" *J. Organomet. Chem.* **1998**, *551*, 349.

- ☐ Dolmazon D., Aldea, R. and Alper, H. "Hydrogen Transfer Reduction of Ketones Catalyzed by Fluka K-10 Montmorillonite". *J. Mol. Catal.* **1998**, *136*, 147.

- ☐ Aldea, R. and Alper, H. "Hydrogenation of the Carbonyl Group in α-Ketoesters and α-Ketoamides Catalyzed by Ruthenium Clay" *J. Org. Chem.* **1998**, *63*, 9425.