Catalytic syntheses in non conventional media

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CATALYTIC SYNTHESES IN NON CONVENTIONAL MEDIA

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Every revolutionary idea -- in Science, Politics, Art or Whatever -- evokes three stages of reaction. They may be summed up by the three phrases:
"It is completely impossible -- don't waste my time."
"It is possible, but it is not worth doing."
"I said it was a good idea all along."

(Clarke's Law of Revolutionary Ideas, from "Murphy's Law")

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Preface

The attention for environmental and energetic problems, such as greenhouse effect and other pollution-related issues, and the need of new energy and raw materials sources, have been constantly growing during the last years. It is now widely acknowledged that the solutions for these problems can be provided with innovation in technology, which can lead to a more sustainable progress without affecting the economical and human development and the level of quality of life.

It is more and more diffuse conviction that scientific research can play a leading role in this field. Chemistry in particular is among the most involved disciplines, and a great effort is being made by many research groups in the world towards a "greener" chemistry. These works try to provide low-waste, low-energy consumption, low-hazard methods as candidates for replacing the traditional industrial processes.

The development of efficient catalytic systems and the use of alternative reaction media are powerful tools to reach the target of a sustainable chemistry in terms of both economy and ecology.

This thesis describes some examples of how the use of an appropriate catalytic system coupled with appropriate reaction media can provide a significant improvement of the results altogether with a decrease of the environmental hazard of the processes, and in some cases lead to new products.

Three independent experimental projects will be presented and discussed. All of them involve the use of transition metal complexes as efficient catalysts for the synthesis of different organic products in non conventional media such as water and carbon dioxide. Two of the projects (Chapters 2 and 4) were carried out at the Department of Organic and Industrial Chemistry of the University of Parma, Italy, under supervision of Prof. M. Costa, while one (Chapter 3) has been carried out at the Chemistry Department of Texas A&M University in College Station, Texas, under supervision of Prof. D.J. Darensbourg. An introduction will be provided focusing on general aspects and on the most interesting and recent applications of catalysis in non conventional media.

Chapter 1

Introduction

The health and environmental hazards related to the extensive use of conventional organic solvents have caused, together with the increasingly strict legislative regulations, several researchers to concentrate on finding alternative routes addressed to provide non-hazardous processes without affecting (or possibly improving) the process performance.

A combination of highly efficient catalysts and alternative reaction media can strongly improve the environmental impact of many processes that in several cases have proved to become also more efficient and economically advantageous than their conventional analogues.

Many examples of catalysis in non-conventional media have been published in the latest years. This chapter focuses on the general aspects of this matter and reviews some of the most interesting examples.

1.1 - Towards a greener chemistry: the problem of waste

Traditional industrial chemistry processes are usually focused on optimizing reaction efficiency and chemical yield. Due to the increasingly strict legislative regulations and the growing awareness in the scientific community and in the public opinion of the problems that arise from the intensive production of toxic and polluting waste, it is now widely acknowledged that the production of waste and/or the use of hazardous chemicals must be taken into account when estimating the efficiency of a process, and a trend has established towards a more sustainable technology or "green chemistry".

A general definition of "green chemistry" has been proposed by Roger Sheldon as follows[1]: "green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products."

Waste is defined as "everything produced in the process, except the desired product"[2]. The environmental impact of a chemical process can be expressed by the E factor, or environmental factor, defined as mass ratio of waste to desired product. The E factor of actual chemical processes significantly increases going from bulk to specialty chemicals. Table 1.1 reports the values of the E factors for different industrial processes. The E factors reported are

Industrial sector	Product tonnage/year	E (kg waste / kg product)
Oil refining	10^6-10^8	<1
Bulk chemicals	10^4-10^6	<1-5
Fine chemicals	10^2-10^4	5->50
Pharmaceuticals	10-10^3	25->100

TABLE 1.1. E factors for different chemical productions

theoretical values, derived from the stoichiometric equations, i.e. calculated on the basis of a 100% yield; the actual values are always higher than those reported.

From the data reported, it comes out clear that the amount of waste produced increases strongly going downstream from bulk to specialty chemicals, reaching values of over 100 kg waste / kg product in the pharmaceutical industry.

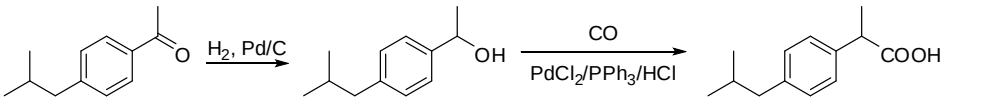
The production of waste derives from different sources. The most important ones are considered in the following paragraphs.

1.1.1 - Inorganic salts

Inorganic salts come from the use of stoichiometric amounts of inorganic reagents; for instance, Friedel-Crafts reactions that use stoichiometric amounts of Lewis Acids ($AlCl_3$) and Bronsted Acids (H_2SO_4); reductions with metal hydrides ($LiAlH_4$, $NaBH_4$); oxidations with potassium permanganate, etc.

The solution to this problem is switching to catalytic atom-efficient methodologies that employ molecules like H_2, CO, CO_2, O_2, H_2O_2, H_2O and NH_3 as direct sources of H, C, O and N for the organic synthesis. The above listed compounds can be obtained from renewable sources such as biomass, process exhausts, water and air. This switch might be a major challenge for the chemical industry of the future; nevertheless, several processes based on catalytic hydrogenation, hydroformylation, carbonylation, oxidation have been developed and applied in the industry during the past years.

An elegant example is the Hoechst-Celanese process for the synthesis of ibuprofen, a common pharmaceutical product presently manufactured in over 8000 t/y (scheme 1.1).[3]



conv. 99%, sel. 96%, TOF 375 h^{-1}

SCHEME 1.1. Hoechst-Celanese synthesis of ibuprofen

The synthesis is accomplished in a two-step 100% atom efficient catalytic process; however, the reagent is still obtained via a Friedel-Crafts acetylation of isopropylbenzene, so leaving space for a further optimization of the process.

1.1.2 - Undesired byproducts

Many processes are still affected by the production of non negligible amounts of byproducts. The problem consists in a lack of selectivity and can be avoided by developing new highly efficient catalytic systems.

For instance, most fine chemicals (pharmaceuticals, herbicides, etc.) require a high optical purity. Traditional organic processes often involve the production of a racemate and the consequent enantioseparation, thus wasting the undesired enantiomer or having it to undergo expensive and waste-producing recovery and racemization steps. An elegant way to avoid enantioseparation is the development of asymmetric catalyst suitable for producing only the desired enantiomer in high yields and purity. Many example of asymmetric catalysis are available in literature and have already gained widespread application in industry. Pioneers in these fields such as Noyori, Sharpless and Knowles gained the Nobel Prize in 2001 for their works in this field[4].

1.1.3 - Solvents

Solvents are a major issue in the production of chemicals. Glaxo-Smith-Kline researchers[5] have pointed out that about 85% of the total mass of chemicals involved in pharmaceutical production is constituted by solvents. Although solvents are recovered after each step, the recovery efficiencies generally range from 80% to 50%. This means that the environmental impact of specialty chemicals processes is dramatically affected by the problem of solvents.

Volatility. Solvents are usually chosen for their separation properties and for the solubility of substrates. Unfortunately, these are the same properties that affect their impact on environment. Most conventional solvents are highly volatile. This makes easier their separation from the product by distillation, but on the other hand volatility leads to losses by evaporation and spillage, therefore polluting the atmosphere and exposing workers to their vapors. VOCs (Volatile organic Compounds) for these reasons are now subjected to severe regulations in most developed countries.

Toxicity and regulations. Moreover, some of the formerly most common solvents for organic synthesis such as benzene or chlorinated hydrocarbons have proved to be major carcinogenics and their use has been banned or restricted in several countries.

Disposal and contamination. Some polar aprotic solvents such as DMF or DMSO are scarcely volatile and they are usually separated by washing the product with water. This leads to contaminated aqueous effluents that are difficult to treat and dispose of.

Flammability. The vast majority of conventional solvents are highly flammable. This implies that they need special care in handling and stocking, these precautions also contributing to increase the cost of the overall process.

Non renewability. Presently almost every available organic solvent is derived from oil processing. In the future, together with the shift to renewable energy sources, also raw materials including those for chemicals will be obtained from renewable sources such as biomass or atmosphere. Solvents like lower alcohols, natural esters etc., which can be easily obtained form natural sources and are biodegradable, are going to be privileged also in the choice of solvents for chemical manufacture.

1.1.4 - Catalysis in non conventional media as a solution

From the above considerations, it comes out clear that a major role on the road towards a more sustainable chemistry can be played by a combination of highly efficient catalysts and green solvents. Homogeneous catalysis has several advantages, including higher selectivities and activities, milder reaction conditions, efficient heat transfer, and minor mass transfer problems. Nevertheless, heterogeneous catalysis is usually preferred in the industry because of a single but essential reason: the easier separation and reuse of the catalyst.

A biphasic system of two mutually immiscible green solvents (or a green solvent and a conventional one) can be an elegant way to maintain the advantages of homogeneous catalysis in combination with an easy recovery of the catalyst.

In the next chapters the main alternative solvents presently available will be described and some of their most interesting applications in catalysis will be reviewed.

1.2 - Non conventional solvents

All the problems associated with the use of solvents can be overcome if the reaction can be run without the need of any solvent. However, in scientific literature and industrial applications there are only few examples of solvent-free systems, which are limited by the necessity of liquid reagents and products, concentration issues, and catalyst solubility.

If a solvent is needed, the ideal green solvent should be non volatile, non toxic, non hazardous, cheap, easy to recover, immiscible with water.

Several proposals have been made in the latest years; some of them have been applied with success in industrial production.

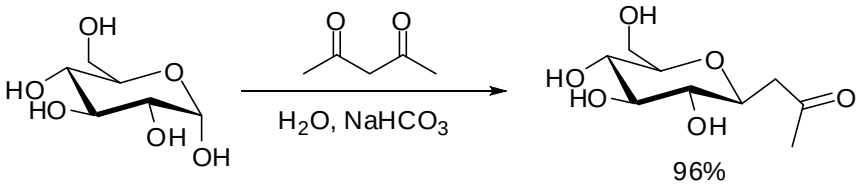
1.2.1 - Water

Water is the most abundant, inexpensive and less dangerous solvent available. Traditionally it has not been intensively used in organic chemistry because of the lack of solubility of most organic compounds and catalysts and of its possible reactivity. It is also to be taken into account that conducting a reaction in water implies that effluents should be conveniently purified; in fact, release of wastewater contaminated by traces of, for instance, heavy metals can be a serious environmental issue, thus invalidating the “greenness” of the whole process.

However, studies have shown that the unique properties of water as a reaction medium can be exploited to improve reaction performances, or to explore completely new reactivities of organic compounds.

Bulk water is in fact a system of small, highly polar molecules in a network of intermolecular hydrogen bonds, thus providing hydrophobic effects that can enhance the reactivity, and the low solubility of oxygen gas allows running in water air-sensitive organometallic catalyzed reactions.[6]

Moreover, being living systems essentially aqueous environments, water is a perfect solvent for many reactions that involve natural products. For instance, carbohydrates can be caused to react without further derivatization (that would be necessary for the use of organic solvents). Carbohydrates are common building blocks for the total syntheses of many natural products. An elegant example is the synthesis of β-C-glycosidic ketone that has been carried out in water in a single step with high yield. (Scheme 1.2). The same product had previously been obtained in seven steps via conventional organic reactions[7].

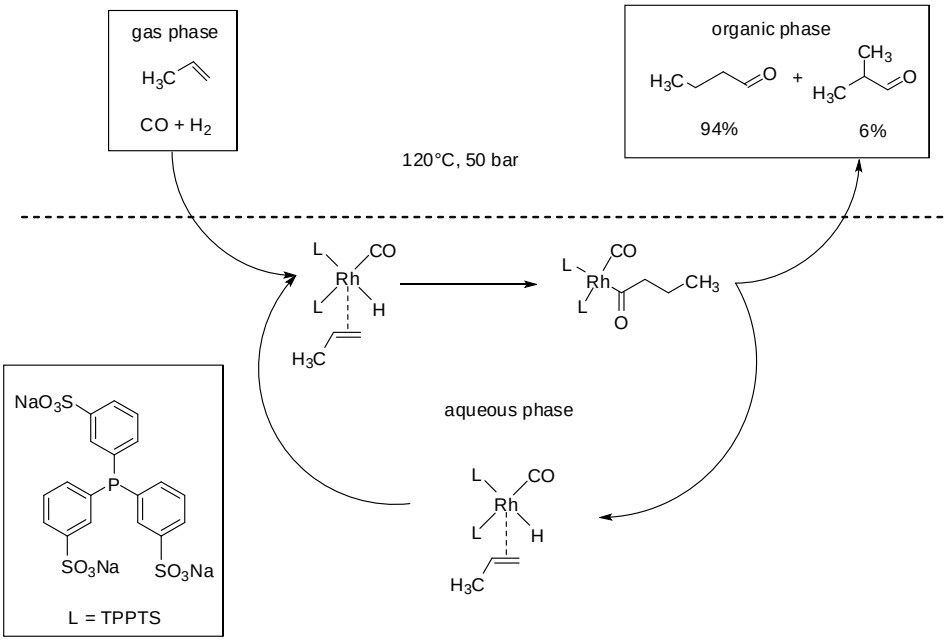


SCHEME 1.2. One step synthesis of β-C-glycosidic ketone in water

Several examples are available of transition metal catalysis in water. In contrast, traditionally water was avoided in transition metal catalyzed reactions because it may attack metal-carbon bonds or compete with chosen ligands for coordination on the metal centre, thus modifying the desired reaction pathway. In recent times it was demonstrated that the above mentioned properties can have a positive effect or be minimized by opportunely developing the catalytic system. Thus, transition metal catalysis in water has become a widely studied field. Solubilization of metal complexes in water can be achieved in two general ways: coordination of water-soluble ligands and direct interaction of H_2O molecules at the metal center[8].

Water soluble ligands for aqueous organometallic catalysis

New ligands and catalysts have been designed for this application, and presently several examples are available both in industry and in scientific literature. The most famous is the Rhone-Paulenc / Ruhrchemie hydroformylation process (scheme 1.3). This process is now reported to produce over 10% of the world's C4-C5 aldehyde capacity[9].



SCHEME 1.3. Rhone-Paulenc /Ruhrchemie hydroformylation process

The key for the development of this and several other reactions is the synthesis, accomplished in 1975, of the water soluble ligand triphenylphosphine trisulphonate (tppts), and of its mono- and di- sulphonated analogues (tppms and tppds) that allow to carry out the reaction in a biphasic water / organic system thus easily recycling the catalyst[10].

This class of ligands, along with others, is now widely used in homogeneous catalysis. Other suitable ligands for the preparation of water-soluble metal complexes include anionic phosphines bearing carboxylate groups and phosphonate groups, cationic phosphines such as AMPHOS, neutral phosphines bearing alkylhydroxilic groups[11], sulphonated and carboxylated diphosphines[12]. Less common are water soluble non-phosphorous containing ligands, such as bypyridines, EDTA, dithiolates and calixarenes[13]. Further development has been also introduced by the synthesis of chiral water soluble diphosphines (usually sulphonated analogues of BINAP) and by their use in asymmetric catalysis in water[14].

Metal-catalyzed reactions with water soluble catalysts are sometimes affected by problems due to the low solubility in water of some organic substrates (e.g., higher olefins in hydroformylation). This problem has been solved by preparing special surfactant-based phosphines. Their metal complexes show anphiphilic properties and are able to form micelles in water or to lower the interfacial tension thus enhancing the reactivity of the system [15].

Figures 1.1 – 1.4 report some of the most common water-solubilizing ligands available up to date.

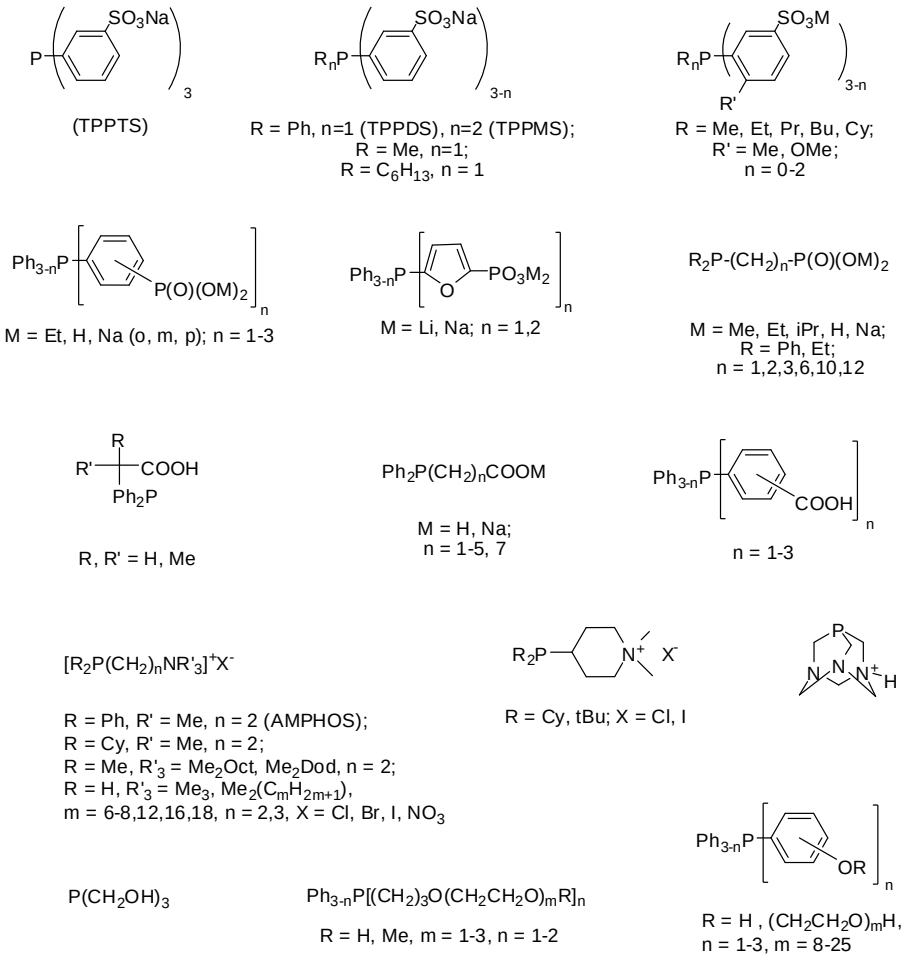


FIGURE 1.1. Water soluble monophosphines: sulphonated (first row), phosphonated (second row), carboxylated (third row), cationic (fourth row), neutral (fifth row).

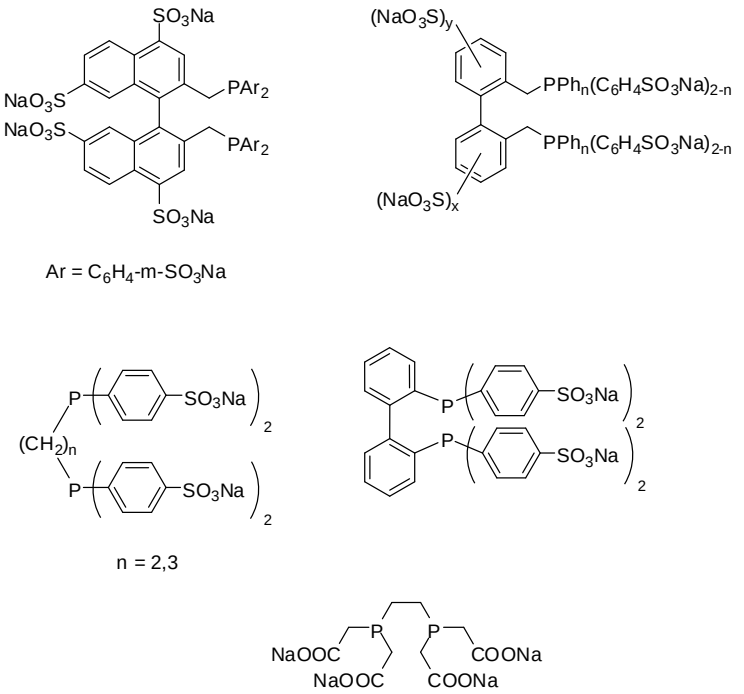


FIGURE 1.2. Water soluble diphosphines: sulphonated (first and second row) and carboxylated (third row).

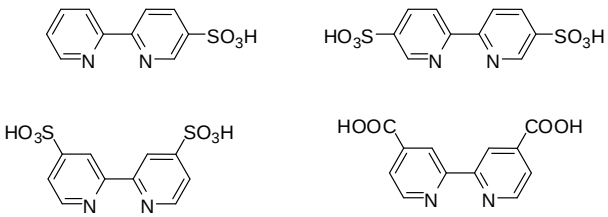


FIGURE 1.3. Water soluble sulphonated and carboxylated dipyridines.

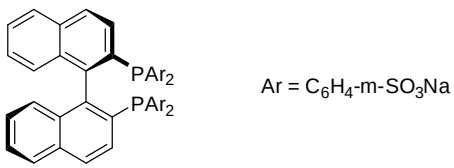


FIGURE 1.4. Water soluble sulphonated BINAP for aqueous asymmetric catalysis.

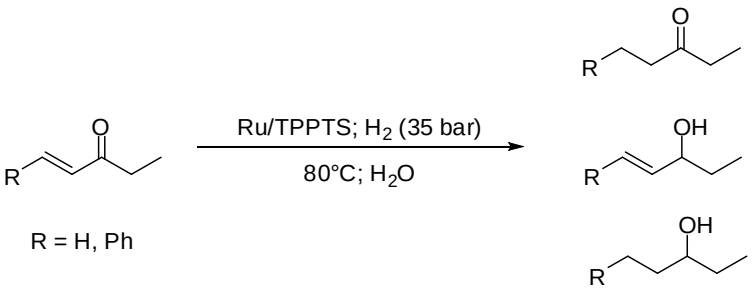
Aqueous organometallic catalysis via direct coordination of water

In the above mentioned case water solubility of the catalyst was attained due to the hydrophilic nature of the ligands. A different approach is the direct coordination of water molecules to the metal center. This allows to use less expensive metal complexes and to avoid the sometimes difficult and expensive synthesis of dedicated ligands. Although less studied, this field presents several examples of highly efficient catalyzed reactions in water. The most common catalysts used are hydrate late transition metal salts such as $[RhCl_n(H_2O)_{6-n}]_{3-n}$ and $[RuCl_n(H_2O)_{6-n}]_{3-n}$. which were first used in 1966 for the hydrogenation of maleic and fumaric acids[16].

Aqueous phase metal catalyzed reactions

Many kinds of reactions have been tested in aqueous phase. Examples include, apart from the aforementioned hydroformylation, hydrogenations, oxidations (including Wacker reactions), carbonylations, C-C coupling reactions (Heck, Stille, Suzuki, etc), metathesis, asymmetric syntheses, and polymerizations.

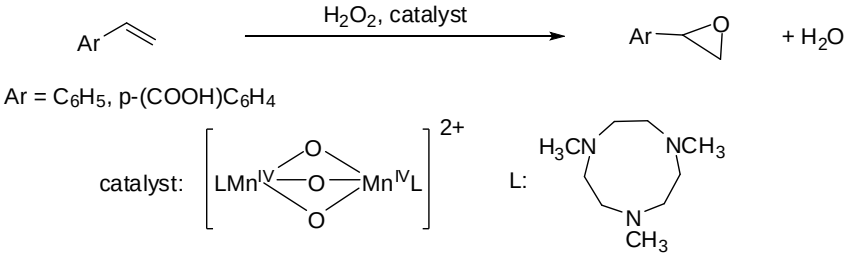
For instance, hydrogenation of 4-hexen-3-ones proceeds with good yields and selectivity to 3-hexanone with low production of C=O bond hydrogenation products if the catalyst is an hydride complex of ruthenium with TPPTS (scheme 1.4).[17]



SCHEME 1.4. Selective C=C bond hydrogenation on conjugated ketones in water.

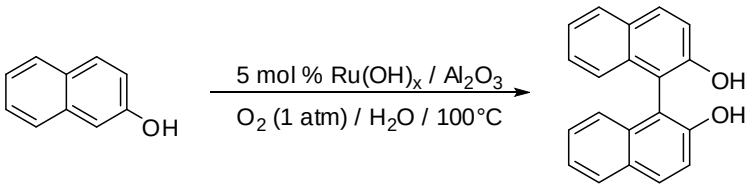
Catalytic systems for oxidations usually require the design of specific ligands. For the process to be both green and industrially attractive, it is necessary to employ an oxidizing agent both cheap and highly atom efficient: choices usually fall on O_2 or H_2O_2. For example, oxidation of terminal alkenes with a

Mn-based catalyst has proved to proceed with good yields in an aqueous solution of H_2O_2 (scheme 1.5)[18].



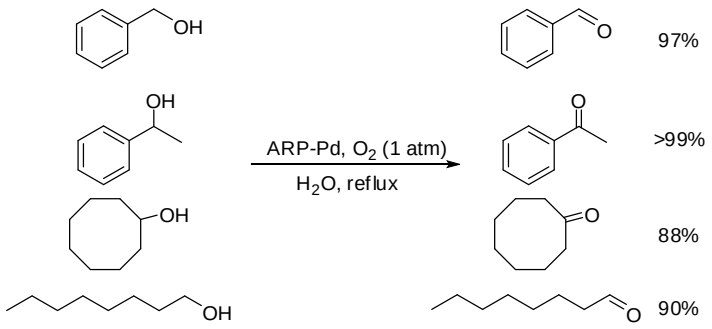
SCHEME 1.5. Epoxidation of terminal alkenes in water

Simple supported catalysts such as metal hydroxides on silica or alumina have been succesfully employed for oxidation reactions as well. For instance, Ruthenium hydroxides supported on alumina are able to promote the oxidative coupling of 2-naphtol in water (scheme 1.6)[19].



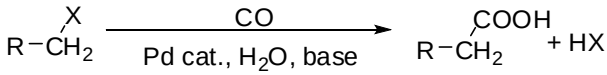
SCHEME 1.6. Oxidative coupling of 2-naphtol in water

Examples of palladium nanoparticles(Pd-ARP)-catalyzed alchols oxidations in water have been recently reported to take place in water with satisfactory yields (scheme 1.7)[20].



SCHEME 1.7. Alcohols oxidations in water

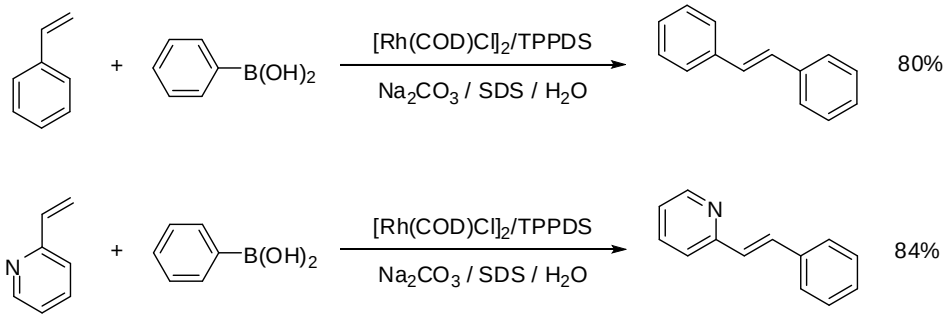
Several carbonylation reactions in water have been reported in literature. In most cases, they involve the use of allylic or aromatic halides and the use of a Pd catalyst such as $Pd(OAc)_2$ or $Pd(TPPTS)_2Cl_2$. Scheme 1.8 provides the general equation for the reaction[21].



X = Cl, Br, I
R = aromatic or allylic

SCHEME 1.8. General equation for carbonylation reactions in water.

Carbon-carbon bond formation reactions in water are less common. In most cases, they still require the use of very reactive derivatives such as arylboronic acids for the addition to styrenes. This reaction is catalyzed by water-soluble rhodium complexes. (Scheme 1.9)[22].



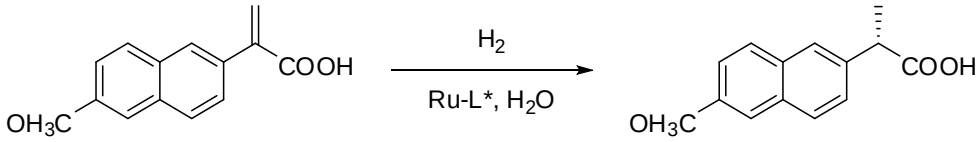
SDS = sodium dodecyl sulfate

SCHEME 1.9. Rh-catalyzed reaction of un-activated olefins with arylboronic acids in water.

An example of Rh-catalyzed carbon-carbon bond formation in water will be the subject of chapter IV.

Finally, asymmetric syntheses have been successfully performed in water. These reactions combine the efficient chiral catalysts developed for “classic “ asymmetric hydrogenations with water soluble moieties. This approach allows to elegantly solving the problem of recycling the expensive chiral catalysts via a simple extraction and recovery of the aqueous phase. The aqueous phase can be recycled several times without significant loss of activity and

enantioselectivity. Scheme 1.10 reports an example, studied by Davies and coworkers, which allows the synthesis of Naproxen utilizing a sulphonated Ru(BINAP) catalyst[23].



SCHEME 1.10. Enantioselective synthesis of Naproxen in aqueous phase.

1.2.2 - Supercritical fluids and carbon dioxide

Properties and advantages

Supercritical fluids (SCFs) are also an attractive alternative to standard solvents. Their main limitation are the technically challenging conditions required to reach the supercritical state for most compounds. Actually, the only supercritical fluid that has found a quite extensive application is carbon dioxide, due to its relatively low critical pressure (74 bar) and temperature (31°C). Most other molecules have critical points too high to be industrially attractive as reaction media. A list of critical points of common substances is given in table 1.2.

Studies have suggested possibilities for the utilization also of supercritical water (P_c = 220 bar, T_c = 374°C), hydrocarbons and fluorocarbons. A relevant application in this field is the industrial polymerization of ethylene, an homogeneously catalyzed process in which the supercritical fluid acts as both solvent and reagent.

However, supercritical carbon dioxide ($scCO_2$) is by far the most interesting and the most studied SCF so far. It is non toxic, non flammable, abundant and cheap. It is also non pollutant, as long as it is recycled from industry exhausts, since its use gives no further contribution to greenhouse effect. $scCO_2$ has a number of uses in fields other than synthetic chemistry, such as extraction solvent in food industry (with a very relevant role in caffeine extraction from coffee), in environmental decontamination, and as solvent or antisolvent for several industrial processes in the field of polymer manufacturing.

Substance	T_c °C	P_c MPa
Ethylene	9.3	5.04
Xenon	16.6	5.84
CO_2	31.1	7.38
Ethane	32.2	4.88
N_2O_3	36.5	7.17
Propane	96.7	4.25
NH_3	132.5	11.28
Butane	152.1	3.8
Pentane	196.5	3.37
Methanol	239.5	8.1
Toluene	318.6	4.11
H_2O	374.2	22.05

TABLE 1.2. **Critical points of some common substances.**

The reason of this success in separation technologies can be found in the fact that a supercritical fluid possesses the advantages of both liquids and gases. In fact, density is comparable to that of liquids, thus giving SCFs appreciable solvent capability, while viscosity and diffusivity are more similar to those of gases, thus overcoming most of mass transfer problems.

It is now widely acknowledged that these unique properties can be successfully exploited when a supercritical fluid is used as solvent. It is worth of note that some compounds can be soluble in a supercritical fluid and not in the corresponding liquid, or the opposite. This provides a potential way to separate catalyst and / or products from the reaction mixture just by a temperature or pressure change.

Interestingly, SCF density is strongly correlated to pressure and temperature. Figure 1.5 shows the relation between pressure and density of CO_2. The higher slope in the near-critical region indicates that CO_2 density rises strongly just on a slight pressure increase. The dielectric constant of CO_2 is almost linearly correlated with its density (figure 1.6). This allows fine-tuning solvent properties of SCF just by choosing the appropriate conditions.

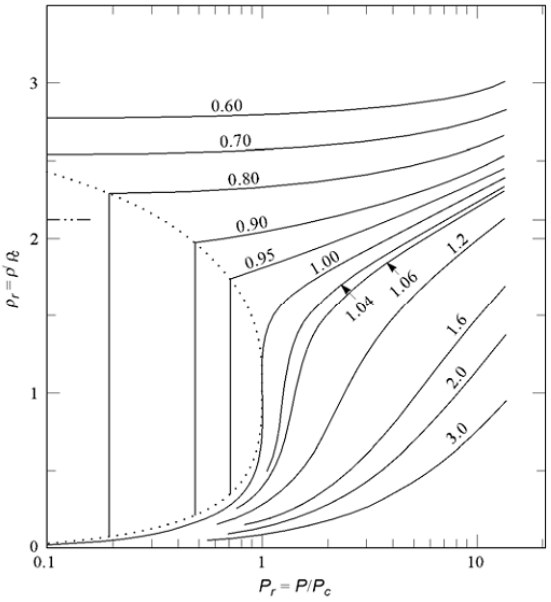


FIGURE 1.5. Reduced density (ρ/ρ_c) versus reduced pressure (P/P_c) of carbon dioxide, where ρ_c and P_c are the critical parameters. Taken from Kirk-Othmer, Encyclopedia of Chemical Technology, 2001, Wiley and Sons.

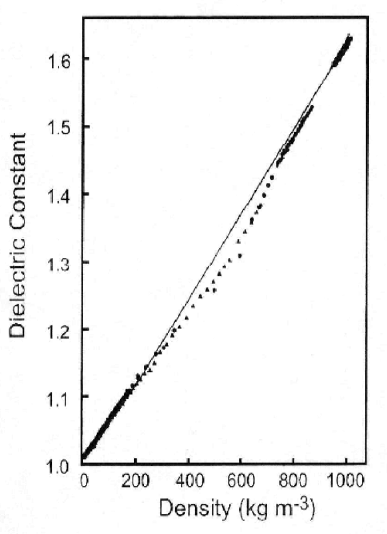


FIGURE 1.6. Relationship between density and dielectric constant of carbon dioxide in supercritical conditions.

Moreover, several researchers, including Noyori[24], Jessop[25], and Leitner[26] have reported that reactions involving gas reagents have been found to be faster in supercritical media, probably because mass transfer problems between different phases can be avoided. In fact, reactions of gaseous with liquid reagents with homogeneous catalysts dissolved in a liquid phase are usually limited by the mass transport at the interphase. The use of homogeneous catalyst systems in supercritical reaction media constitutes an elegant way to solve mass transport problems; in fact, supercritical fluids are in several cases able to dissolve both the gas and the liquids reagents thus forming an homogeneous mixture and then the reaction can be run with the fast kinetics typical of homogeneous catalysis. Moreover, in some cases, such as oxidations or hydrogenation, the use of non-flammable $scCO_2$ allows to reduce or avoid problems connected with flammability and explosion hazards.

Summarizing, SCFs allow potential advantages on several aspects of a catalytic reaction, including better yields and selectivities, easy recycle and longer lifetime of catalysts, enhanced mass and heat transfer.

Catalysis in SCF

Supercritical fluids have been discovered in 1822, and their first application in catalysis (in the polymerization of ethylene) dates back to 1913[27], but it was not until the mid 1990s that extensive studies were made about catalysis in SCFs. Since then, however, the field has been constantly and very rapidly growing. Reactions of almost any kind in both homogeneous- and heterogeneous- catalysis in $scCO_2$ have been attempted and published.

A recent comprehensive review from Philip Jessop[28] lists more than 150 different kind of homogeneous catalysis reactions published up to date in supercritical or liquid CO_2. Solubility of catalysts and/or reagents can be an issue in the development of a homogeneous reaction in $scCO_2$. Common aromatic ligands also are usually insoluble in $scCO_2$. However, several reactions have proved to proceed well even in these semi-heterogeneous conditions. Else, it is possible to develop CO_2-soluble catalysts or ligands, which are sometimes able to enhance the dissolution of the catalyst in the reaction media. Common strategies include the use of trialkylphosphines, the

attachment of perfluorurated chains on the aromatic rings, or even the use of a cosolvent.

Heterogeneous catalysis in $scCO_2$ is also being intensively studied. A review published by Alfons Baiker in 1999[29] lists about 30 different applications of SCFs in heterogeneous catalysis.

Some of the most recent and interesting examples of catalysis in $scCO_2$ will be described in the following paragraphs.

Examples of catalysis in CO_2

The use of $scCO_2$, as already pointed out, can be particularly useful in reactions involving gaseous reagents, allowing a liquid-gas system, whose performance is limited by mass transport at the interphase, to become an homogeneous phase.

Thus, several examples are available both in academic research and industrial applications in the fields of oxidation and hydrogenation.

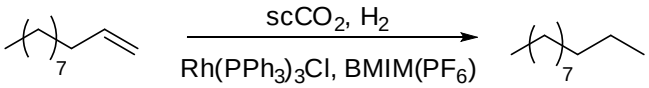
For instance, pilot plants or small scale industrial productions for the hydrogenation of various substances including fatty acids in supercritical fluids have been started some years ago[30].

On the side of oxidation, efforts have been made in the development of process capable of efficiently producing epoxides, in particular propylene oxide, in $scCO_2$ using oxygen or H_2O_2 as oxidant. Several researchers have been working in this area[31-36], although no economically competitive processes involving air as only oxidant have been described yet.

Supercritical carbon dioxide has also been extensively studied and applied in industry for the production and manufactory of advanced materials, such as polymers and nanoparticles[37], as well as a solvent for a number of organic reactions including, among others, Friedel-Crafts chemistry[38], enzymatic catalysis[39], C-C couplings[40-42].

Biphasic systems with CO_2

An interesting application of $scCO_2$ is its use as a second phase in a biphasic catalysis system; particularly in the case of using another green solvent as the first phase, it is clear that such a system would potentially allow recovering the catalyst and separating the product without the use of any organic solvent. Water and ionic liquids (ILs) are the most common phases chosen to dissolve the catalyst, while CO_2 is commonly used to extract the reaction products. An example is the work of Liu et al.[43], which shows that olefins such as 1-decene and cyclohexene could be hydrogenated by Wilkinson's catalyst dissolved in a ionic liquid phase and the product could be obtained via separation of the supercritical phase, allowing the recycle of the IL/catalyst phase for several times (scheme 1.11)



SCHEME 1.11. Hydrogenation of 1-decene in biphasic IL/ScCO2 system. BMIM = 1-butyl-3-methylimidazolium.

Miscibility switch systems

Eckert and coworkers have developed a new concept of multiphase catalysis involving "tunable solvents". Their work is aimed at coupling organic reactions with product separation, with considerable benefits for the sustainability of the whole process. The idea is to exploit the limited, but not negligible, solubility of CO_2 even at low pressures in organic media to alter the organic solvent properties, such as polarity, dielectric constants, and gas solubility.

It is thus possible, by adding and releasing CO_2 pressure, to "switch" the solvent between two different states, and exploit its different properties under different conditions to separate catalyst and products due to their different solubility.

Several techniques have been developed to take advantage of this effect[44]. One of the most elegant examples consists in the hydrogenation of styrene with a modified Wilkinson catalyst[45]. This reaction, similar to that described in the previous paragraph, takes advantage of a different approach. In this case,

the notorious CO_2-philicity of highly fluorinated hydrocarbons was exploited. A modified silica gel bearing fluorocarbon tails was used as the mean of separating the catalyst, a fluorinated version of Wilkinson's complex, $[RhCl\{P(C_6H_4\text{-}p\text{-}CH_2CH_2(CF_2)_6F)_3\}_3]$. The reagent was dissolved in a standard organic solvent, cyclohexane. Upon addition of CO_2 to the system, the catalyst was solubilized in the organic phase and the reaction took place homogeneously. After CO_2 pressure release, the catalyst was captured on the fluorinated silica gel beads and the liquid phase, containing the products, could be easily separated and recycled (figure 1.7).

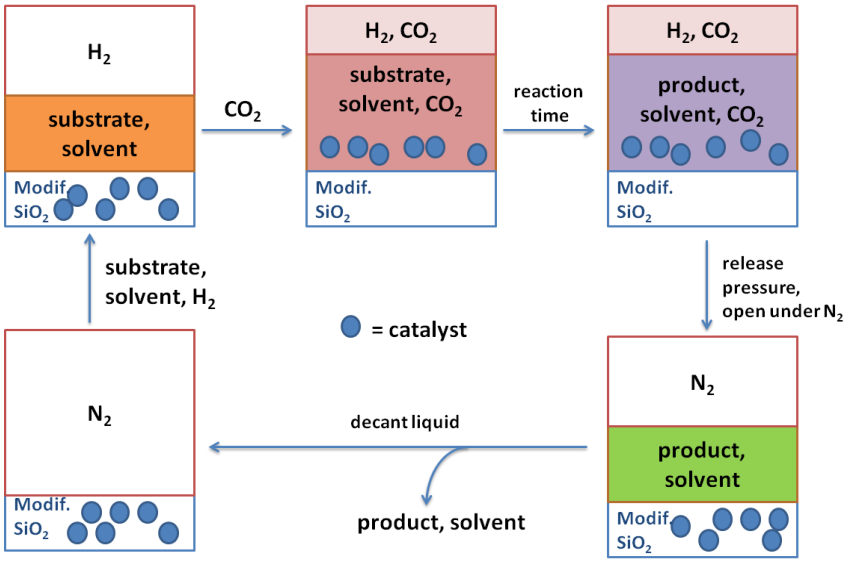


FIGURE 1.7. Solubility switch system for the recovery of the catalyst in the hydrogenation of styrene.

1.2.3 - Ionic liquids

Generalities

Ionic liquids (ILs) are commonly defined as salts with a melting point lower than 100°C. ILs that are liquid at ambient temperature are the most widely used because of their easiness of handling and are defined as Room Temperature Ionic Liquids. Over their melting points, ILs can be viewed as liquids composed entirely of ions.

ILs have received a great attention in recent years. They are usually non-volatile, easy to recover, and have a broad (300°C) liquid range. The interest of researchers in this field has exponentially grown in the last decade, and they are now recognized as one of the most attractive alternatives to conventional organic solvents. However, although academic research has produced a great number of works in which ILs are used as solvents, cosolvents and/or catalysts, they have not found an application in industry yet, mainly because of their usually very high cost, and secondarily for their, still to be determined, adverse effects and biodegradability.

The reason for the relatively low melting point of this salts is the low energy of their crystalline network. They are usually composed of a bulky and asymmetric organic cation (generally ammonium or phosphonium) with low charge density and low tendency to intermolecular interactions and an inorganic anion. However, carboxylate-based ionic liquids have been also synthesized in latest years.

The most common cations are 1,3-dialkylimidazolium salts, but 1,4-dialkylpyridinium and 1,1-dialkylpyrrolidinium salts are commonly used as well. The most common anions include BF_4^-, PF_6^-, $Al_2Cl_7^-$, RSO_3^-. The chemical, physical and solvent properties of the ILs depend on both the cation and the anion. Thus it is possible to design new ionic liquids with the desired properties by opportunely choosing the cation and the anion. This has granted them the name of “designer” or “task-specific” solvents. Some of the most common anions and cations are reported in figure 1.8.

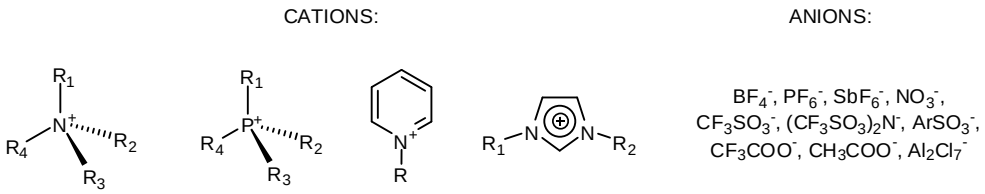
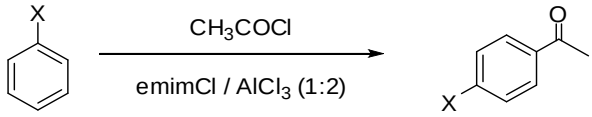


FIGURE 1.8. Commonly used cations and anions in ionic liquids.

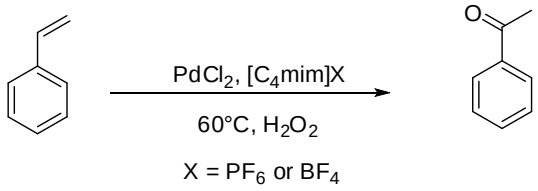
Catalysis in ionic liquids

One of the most interesting features of ILs is the opportunity of using them as both solvent and catalyst. Some examples of this kind have been reported by Seddon and coworkers, in the ionic liquid-catalyzed Friedel-Crafts acylation of substituted aromatics[46] (scheme 1.12).



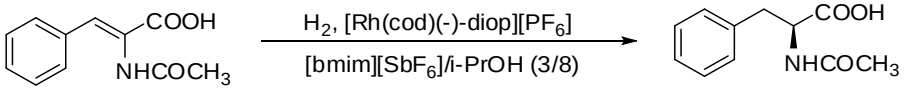
SCHEME 1.12. Friedel-Craft acylation in ionic liquids; X = Me, MeO, Cl; emim=methylethylimidazolium.

In other cases the ionic liquid acts as a cocatalyst, for instance in the Pd-catalyzed Wacker oxidation of styrene to acetophenone (scheme 1.13)[47]. It has been reported that in this case the imidazolium cation activates the H_2O_2 which, in turn, reoxidizes palladium(0) to palladium(II) to complete the reaction cycle.



SCHEME 1.13. Wacker oxidation of styrene to acetophenone in ionic liquid.

Obviously there are also several examples in which ILs act simply as a solvent without interacting in the reaction mechanism. A recent example is the enantioselective hydrogenation of enamide derivatives to optically active aminoacids. The reaction reported in scheme 1.14 shows high yields and good enantioselectivity and the product is easily extracted allowing the reuse of the IL-catalyst phase[48].



SCHEME 1.14. Enantioselective hydrogenation of acetamidocynnamic acid in IL.

It is worth noticing that ILs are also a good reaction medium for biocatalyzed transformations, in which they have several advantages over conventional organic solvents, including higher stabilities and enantioselectivity of the reaction system[49-50].

1.2.4 - Fluorous systems

Generalities

The term "fluorous" has been coined by Horvath and Rabai, in analogy with the term "aqueous"[51]. The term refers to reactions performed in fluorinated alkanes, ethers, or even tertiary amines. The properties of these compounds differ markedly from those of their organic analogues, with whom they are usually immiscible. Thus it is possible, through dissolving the catalyst in the fluorous phase by using special ligands designed for the task, perform reactions in a biphasic fluorous/organic systems. These reactions are commonly referred to as "fluorous biphasic catalysis"(FBC). The most common solvents and ligands for FBC are reported in figure 1.9.

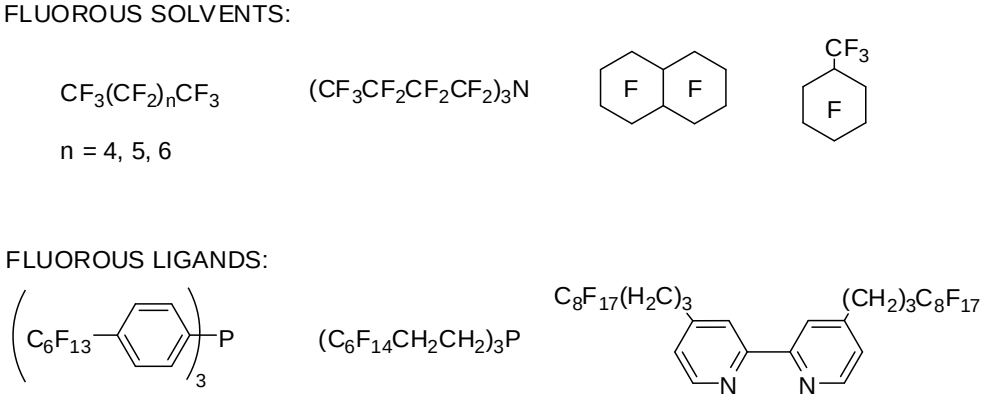


FIGURE 1.9. Common solvents and ligands for fluorous biphasic catalysis.

It is worth noticing that completely perfluorurated ligands would not be effective ligands for FBC, because their strong electron withdrawing effect would decrease the coordination ability of the donor atom (N or P). To circumvent this problem, ligands are usually designed with an organic non-fluorinated spacer between the donor atom and the fluorophilic moiety.

Two different approaches can be utilized when working with FBC. The first one is conventional biphasic catalysis, in which the catalyst is dissolved in the fluorous phase and the reactants and products in the organic layer. A different behavior can be obtained choosing accurately the two solvents so that they are immiscible at room temperature and miscible at reaction temperature. This approach, similar to the "pressure switch" described in chapter 1.2.2, allows to have the advantages of both homogeneous (no mass transport and solubility problems) and biphasic (easy separation and reuse of the catalyst) systems. Figure 1.10 represents the latter approach.

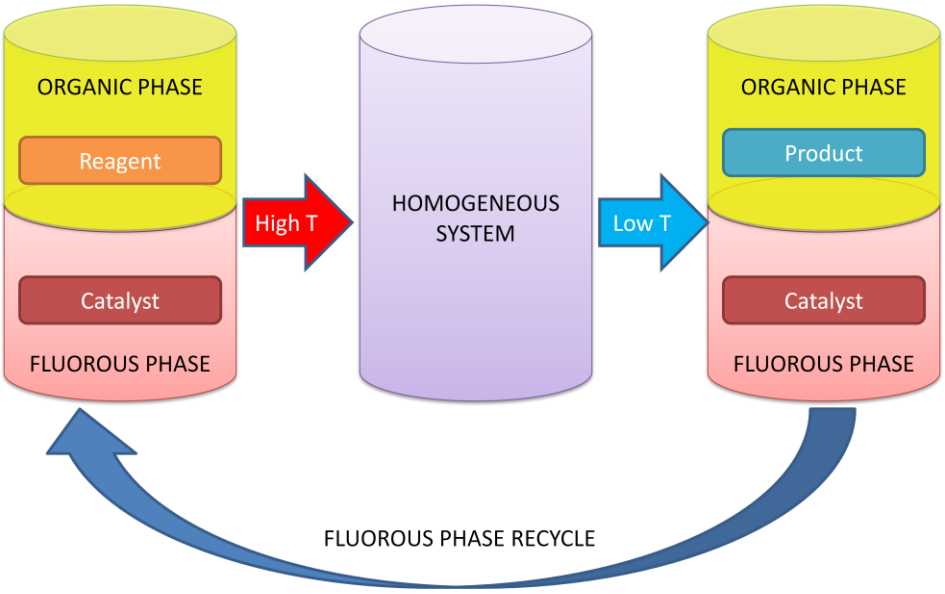
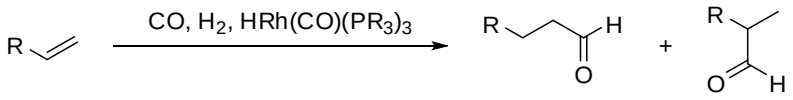


FIGURE 1.10. Temperature switch on miscibility in fluorous biphasic catalysis

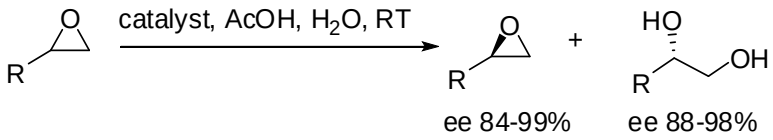
Examples of fluorous catalysis

The first published reaction that took advantage of FBC was the hydroformylation of 1-decene. (Scheme 1.15)[51]. The reaction proceeded with good yield and selectivities and the catalyst, namely an analogue of Wilkinson's catalyst with perfluoroalkyl "ponytails" attached on the aromatic rings) could be recycled for several times with negligible leaching[53].



SCHEME 1.15. Olefin hydroformylation in fluorous biphasic systems

FBC has more recently been applied to a number of different reactions. Oxidations have been successfully performed by virtue of high solubility of molecular oxygen in fluorous media. Pozzi and coworkers reported several examples of asymmetric epoxide ring opening in presence of air to yield 1,2-diols with good enantioselectivity[54]. Catalyst was a fluorinated version of Jacobsen's salen catalyst. (Scheme 1.16).



SCHEME 1.16. Asymmetric oxidative ring opening of epoxides in fluorous media.

Other reactions reported included hydrogenations[55], Heck and Suzuki couplings[56-58], and polymerizations[59].

Notwithstanding the growing amount of papers published on the subject, perfluorocarbons applications in industry have not been reported yet. This might be due to the high cost of these solvents and of the ligands required, together with the concerns about the long lifetime of fluorocarbons in the environment (although they are nor toxic or ozone-depleting agents as their analogues chlorofluorocarbons).

1.3 - Final remarks

In the previous chapters a quick review of the most important alternative reaction media has been presented. Although only catalytic reactions were taken in consideration as examples, since they match the subject of this thesis, it is not to underestimate the great potential these substances have also for replacing organic solvents in organic synthesis and in other technologies (e.g. extraction, purification, etc.). The number of papers and patents that came out

in the last years (figure 1.11) in this field is growing fast and some commercial applications have already shown to be not only environment-friendly but also economically competitive. In perspective, these applications should replace a large part of the existing chemical processes in order to achieve a more sustainable chemical industry.

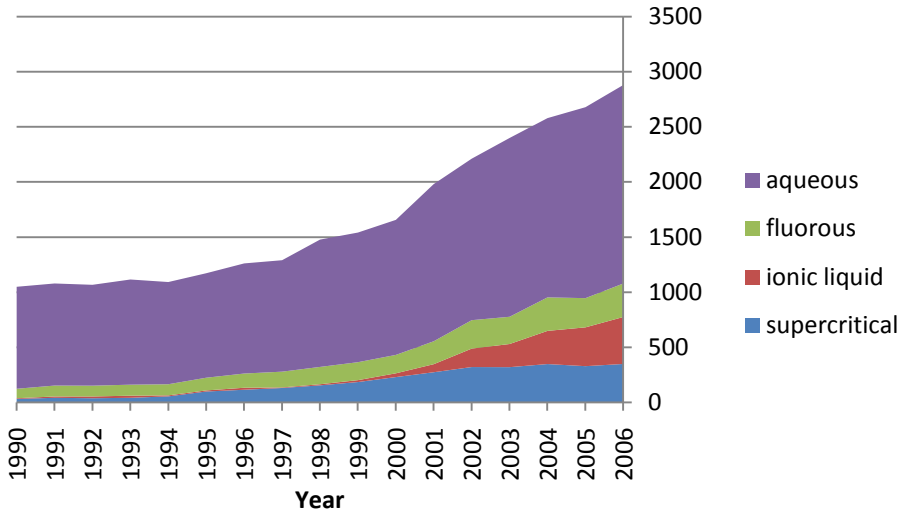


FIGURE 1.11.. Number of papers and patents published in the 1990-2006 period containing the indicated terms "closely related" with the term "catalysis" according to the program SciFinder™ Scholar 2006.

It is worth noticing that a lot of work is still to be done in optimizing the environmental friendliness of all secondary operations in the process. Even if the core reaction is sustainable, this has little effect if large amounts of waste are produced in the manufacture of, for instance, catalysts or ligands or if conventional techniques are employed in the purification steps. The ideal green process should be ecologically acceptable from the raw materials to the final product, including also the production of the necessary energy. It is clear that presently few, if not none, chemical processes satisfy these requests and a huge amount of research is still to be done by scientists working in this field.

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Chapter 2

Project I:

Oxidative carbonylation of amines in supercritical carbon dioxide

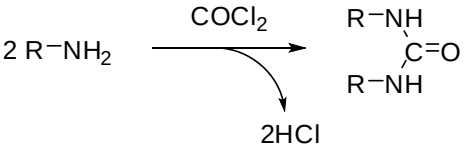
The industrial synthesis of ureas is presently accomplished by the use of highly hazardous and polluting reagents. In this chapter an efficient synthesis of symmetric disubstituted ureas via oxidative carbonylation of primary amines is described. The easy to synthesize and stable catalyst adopted, potassium tetraiodopalladate, allows the use of air as a cheap oxidizing agent. Using carbon dioxide in supercritical conditions as a reaction medium leads to a dramatic increase in the performance of the catalyst.

2.1 - Background

2.1.1 - Conventional and industrial synthesis of ureas

Ureas are an important class of organic chemicals which has found extensive use in the production of plant protection agents, in pharmaceutical and dye chemistry, as plasticizers, and as stabilizers (e.g. antioxidants in gasoline). Alkylureas and polyalkyleneureas are used as additives in the production of aminoplastics. They also find application in the chemical industry as intermediates for the production of carbamates, on their turn raw materials for several agrochemicals.

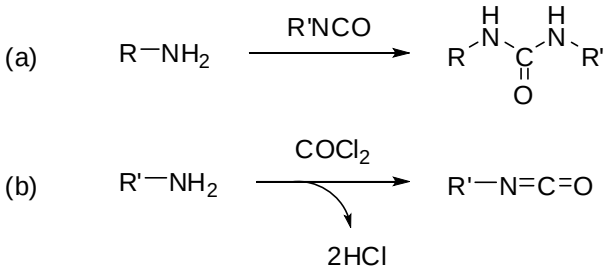
While non-substituted urea is produced by an high temperature equilibrium reaction between carbon dioxide and ammonia to give ammonium carbamate, followed by dehydration, the production of substituted ureas is mainly accomplished via reaction of amines with phosgene (scheme 2.1).



SCHEME 2.1. Synthesis of symmetrical N-N'-disubstituted ureas via reaction of amines and phosgene.

Phosgene is notoriously an extremely toxic gaseous substance. Its adverse effects on health start at 3 ppm concentration[1] and at increased concentration it may cause severe damage or death. For these reasons, the use of phosgene as a reactant in the chemical industry implies to take strict precaution in its transport, storage and manipulation. Presently storage and transportation of phosgene are avoided as far as possible for safety reasons. Generally, only the minimum amounts necessary in the course of the process are stored at intermediate stages. Unfortunately, phosgene production on site needs the use of chlorine as a reagent, with the consequent storage issues. Moreover, the reaction stoichiometry implies the production of 2 moles of hydrochloric acid per mole of product. This opens several other problems including the production of large amounts of waste water effluents.

In several industrial processes phosgene is replaced by isocyanates, which can react as well with amines yielding ureas (the synthesis of asymmetrically N-N' disubstituted ureas is possible and usually it is accomplished this way)(scheme 2.2 (a)). However, this is just a way of circumventing the problem since isocyanates require phosgene too for their synthesis(scheme 2.2(b)). The global stoichiometry of the process is the same as the formerly described

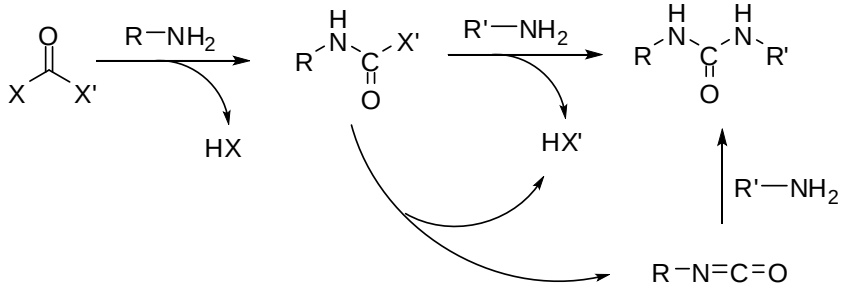


one.

SCHEME 2.2. (a)Synthesis of symmetrically and asymmetrically disubstituted ureas via isocyanates; (b) synthesis of isocyanates via phosgene.

2.1.2 - Alternatives to the use of phosgene: organic substitutes

Research provides several alternatives to phosgene, according to the general formula COX_2 where X is an organic leaving group. Most of these substances are less volatile and toxic than phosgene and thus can be handled more safely. Their general use strategy is reported in scheme 2.3.



SCHEME 2.3. General strategy for the synthesis of N, N'-disubstituted ureas with phosgene (X, X' = Cl) or phosgene substitutes.

The main alternatives to phosgene are reported in figure 2.1 and 2.2. They belong to two different categories, which have different applications in organic synthesis: reagents with two identical leaving groups, and reagents with two different leaving groups[2]. Although generally more expensive, the latter are more versatile and suitable for the synthesis of more complex targets.

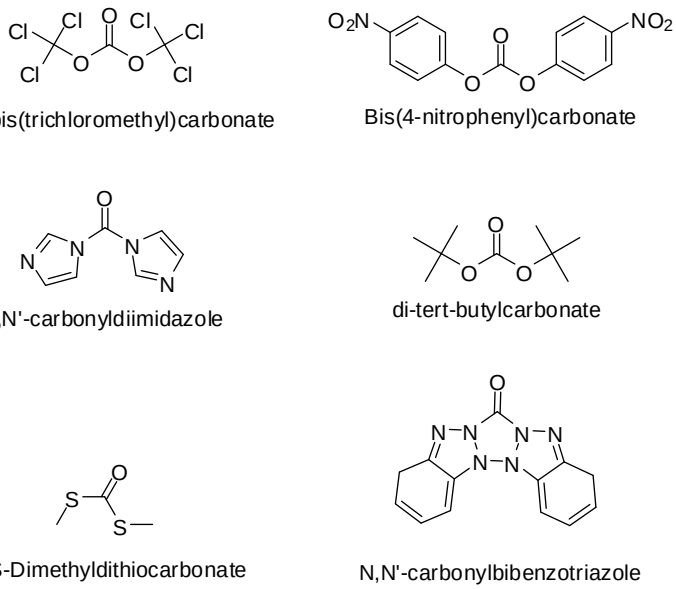


FIGURE 2.1. Some common phosgene substitutes with two identical leaving groups.

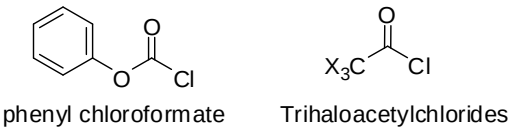


FIGURE 2.2. Phosgene replacements with two different leaving groups.

However, these compounds have several drawbacks. They are more expensive than phosgene; they usually require the use of stoichiometric amounts of bases or other reagents to efficiently provide the products; and, most notably, in most cases, they are prepared from phosgene on their turn. From the above mentioned reasons it is clear that phosgene replacements similar to those described are not suitable for large scale industrial preparations and do not solve the problem of the use of phosgene. However, they are still useful in

small scale laboratory preparation, especially if the target is a complex molecule difficult to synthesize by other pathways.

2.1.3 - Oxidative carbonylation reactions

Transition-metal-catalyzed carbonylation of amines offers a new and efficient methodology for the selective synthesis of ureas under relatively mild reaction conditions. Oxidative carbonylation defines a class of transition metal catalyzed CO additions to various organic substrates, while the active metal is reduced during the catalytic cycle. Therefore, an oxidizing agent is required to reconvert the metal to its original state in order to obtain a catalytic process. Use of CO as the carbonyl source in the presence of a catalyst and an oxidant provides an alternative to the traditional methods for conversion of amines to ureas, which involve stoichiometric use of phosgene and its derivatives.

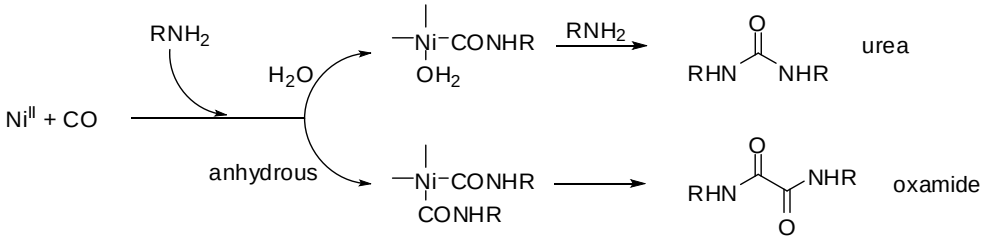
In fact, although CO itself is a toxic gas, it is already widely employed in the chemical industry and phosgene itself is prepared from reaction of CO and chlorine; thus, the direct use of CO in ureas synthesis would not add any dangerous compound to the global balance of the process. From the perspective of green chemistry, the replacement of phosgene and the minimization of the waste streams associated with phosgene derivatives would be beneficial.

Several transition metals have been found to be effective catalysts for the oxidative carbonylation of amines. The main targets are ureas; however, reactions are reported that produce mainly other products, such as carbamates[3], oxamides[4], urethanes[5], formamides[6], and oxazolidinones[7]. Other catalysts used include sulphur[8] and selenium[9] compounds; however, the latter two involve the production of dangerous acids such as H_2S and H_2Se, thus making the process less attractive.

Transition metals used as catalysts include Ni, Ru, Co, Rh, Ru and W.

For instance, nickel complexes such as $NiX_2(RNH_2)_4$ (X=Cl, Br; R = alkyl) were reported to produce by carbonylation of alkylamines N,N'-dialkylureas in anhydrous conditions and oxamides in presence of water. The differences in

selectivity are believed to be due to different intermediates[10] (scheme 2.4). However, yields reported were low and at higher than 50°C temperatures side reactions became predominant.



SCHEME 2.4. Ni-catalyzed oxidative carbonylations of primary amines.

Ruthenium catalysts such as $[Ru(CO)_3I_3]NBu_4$ in presence of NiI as the promoter catalyze the selective formation of N,N'-diphenylurea (DPU) from the oxidative carbonylation at ambient pressure of aniline with high selectivity (99%)[11]. The reaction proceeds under mild conditions, but the TON reported are fairly low (catalyst: substrate molar ratio = 1:16.5).

Cobalt(salen) complexes (salen= N,N'-bis(salicylidene)ethylenediamine) were also found to catalyze the carbonylation of anilines to cyclic and acyclic ureas[12]. Also in this case, the catalyst/substrate ratio was low (10:1).

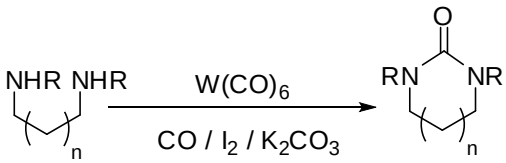
Interesting preliminary results have been by reported Deng and coworkers for the synthesis of ureas employing polymer-supported gold nanoparticles[13] (scheme 2.5).

SCHEME 2.5. Synthesis of ureas from amines on polymer supported gold nanoparticles.

Notably, in this case the carbonyl moiety derives from activation of CO_2 rather than CO, thus constituting a breakthrough in this field since the use CO_2 is for several obvious reasons preferable to that of CO. The catalyst shows satisfactory activity (TOF ≈ 3000). However, these researchers did not explain in detail the CO_2 activation mechanism and the eventual water elimination

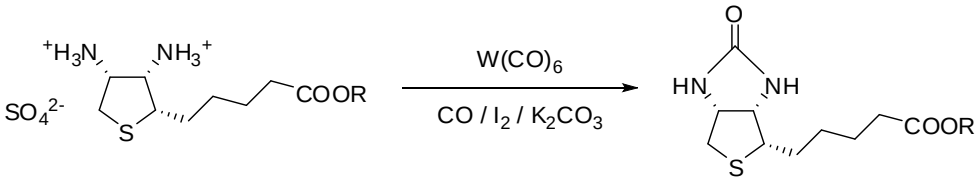
step and after the preliminary communication no further investigation on the subject has been published so far.

Finally, Mc Elwee-White and coworkers deeply investigated the possibility of using tungsten carbonyl complexes as catalysts for this process, alongside with the use of iodine as oxidant[14]. Aliphatic amines were found to react, with primary amines being more reactive than secondary, while anilines were not converted in the process. The yields were high but the catalytic efficiencies limited to TONs of about 40. This methodology was successfully extended to a series of primary diamines obtaining the respective cyclic ureas in satisfactory yields[15]. (Scheme 2.6)

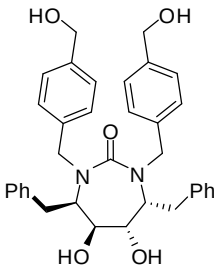


SCHEME 2.6. Oxidative carbonylation of primary diamines to cyclic ureas.

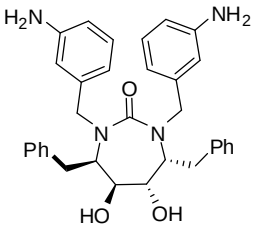
Biphasic aqueous – organic solvent systems were found to improve the efficiency of the reaction. The method was also tested in the synthesis of the methyl ester of biotin, also known as vitamin H[16] (scheme 2.7), and of some analogues of HIV protease inhibitors DMP 323 and DMP 450[17] (scheme 2.8)



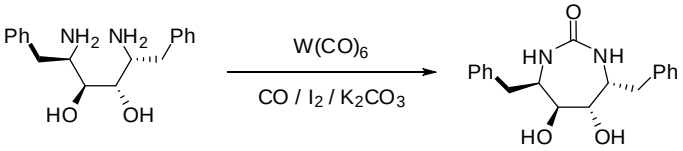
SCHEME 2.7. Biotin methyl ester preparation via carbonylation of the corresponding amine.



DMP 323



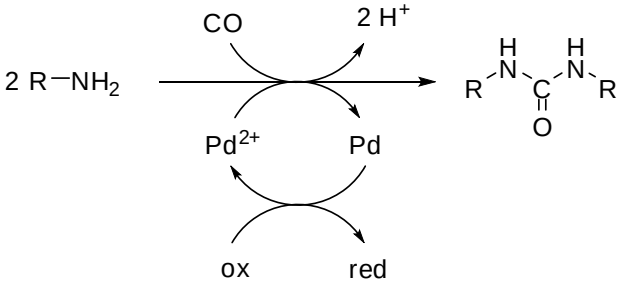
DMP 450



SCHEME 2.8. HIV-protease inhibitors DMP 423 and DMP 450 and the model analogue synthesized by oxidative carbonylation.

Pd-catalyzed oxidative carbonylations of amines

Palladium is by far the most studied catalyst for the oxidative carbonylation of amines. The general reaction scheme, reported in scheme 2.9, involves the reduction of Pd(II) to Pd(0) and its subsequent reoxidation by a reoxidizing system. Commonly the reoxidizing system is constituted by a copper(II) salt in catalytic amount and a stoichiometric oxidizer.



SCHEME 2.9. General scheme for the Pd-catalyzed oxidative carbonylation of amines to ureas.

The first example of Pd-catalyzed oxidative carbonylation of amines was reported back in 1966 by Tsuji[18]. Since then, many developments have

followed in the same field[19-20]. Different palladium(II) complexes, such as $PdCl_2$ and $Pd(OAc)_2$, show similar activities. In some cases, copper(II) salts are required in stoichiometric amount to ensure palladium reoxidation; in others, copper acts only as an intermediate reoxidizer, while oxygen is the stoichiometric reagent, according to the simplified processes:

$Pd(0) + 2Cu(II) \rightarrow Pd(II) + 2Cu(I)$

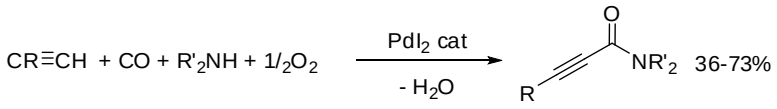
$2Cu(I) + ½O_2 \rightarrow 2Cu(II) + O^{2-}$

Recently, a similar system, based on $Pd(OAc)_2$ and $Cu(OAc)_2$ was shown to catalyze the formation of symmetrically and asymmetrically disubstituted ureas, with yields ranging from low (14%) to good (90%), at room pressure of CO and in presence of air; the TON reported are lower, requiring a high load of catalyst (substrate/catalyst molar ratio 20:1) and especially of cocatalyst (substrate / $Cu(OAc)_2$ molar ratio = 2:1)[21]. The process is however not suitable for an eventual industrialization, because of the high amount of palladium required and of copper salts produced.

A more efficient protocol for the synthesis of symmetrically and asymmetrically di- and tri-substituted ureas has been developed in a collaboration between our research group and Gabriele's one, reporting the highest catalytic efficiencies in this reaction up to date.

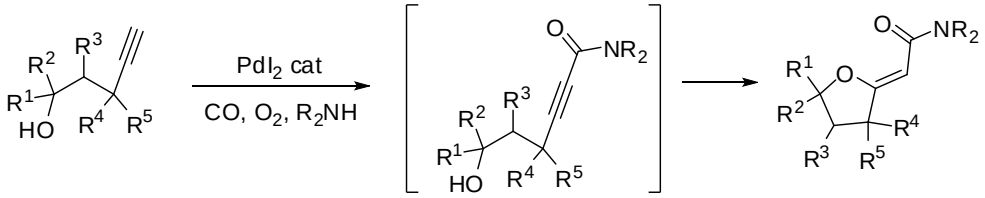
The process proposed is based on the use of the simple and extremely versatile catalytic system formed by PdI_2 in presence of a slight excess of KI that acts as a reoxidation promoter. This catalytic system has already been shown by us to be able to catalyze with high efficiencies oxidative carbonylations of many substrates, including alkyl- and arylacetylenes[22-23], and otherwise functionalized acetylenes[24-26]. Cyclization-alkoxycarbonylation was also successfully performed with the same catalyst system[27-28]. A recent comprehensive review of the reactions in which this catalyst system has been tested can be found in reference 29.

The first application of the PdI_2/KI catalytic system to the reaction of amines was the oxidative monoaminocarbonylation of terminal alkynes[30], according to scheme 2.10.



SCHEME 2.10. Monoaminocarbonylation of terminal alkynes catalyzed by PdI_2/KI.

The reaction was then extended to the reaction of 4-yn-1-ols that undergo intramolecular addition of –OH group to the triple bond providing tetrahydrofuran derivatives (scheme 2.11)[31].



SCHEME 2.11. Intramolecular cyclization- oxidative monoaminocarbonylation of 4-yn-1-ols.

Studies towards the synthesis of ureas with the same catalytic systems via carbonylation of primary and secondary amines were first reported in 2003[32]. In a subsequent paper, a deeper investigation was carried out and the reaction conditions were optimized[33]. Reactions were carried out at 90-100 °C in DME as the solvent in the presence of PdI_2 in conjunction with an excess of KI as the catalytic system and under 20 atm of a 4:1 mixture of CO and air. The presence of excess iodide ions in the reaction mixture ensures the ready reoxidation of the palladium catalyst, while oxygen acts as the stoichiometric oxidant according to the processes:

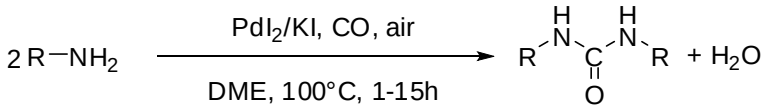
$PdI_2 + 2RNH_2 + CO \rightarrow Pd(0) + 2HI + (RNH)_2CO$

$2HI + ½O_2 \rightarrow H_2O + I_2$

$Pd(0) + I_2 \rightarrow PdI_2$

As it can be seen, the only byproduct in this process is one mole of water per mole of product. In some cases, the reaction was found to proceed more efficiently under CO_2 pressure (40 atm).

The reaction was applied to primary amines, which afforded the respective ureas in good yields and with the highest catalytic efficiencies reported in literature (scheme 2.12 and table 2.1)



SCHEME 2.12. General scheme for the oxidative carbonylation of primary amines to ureas

R	Yield	TON
Bu	96%	4800
$C_6H_5CH_2$	94%	4700
tBu	89%	4450
Ph	87%	4350
4-ClC_6H_4	68%	3400
4-iPrC_6H_4	94%	4700
4-$CH_3OC_6H_4$	98%	4900

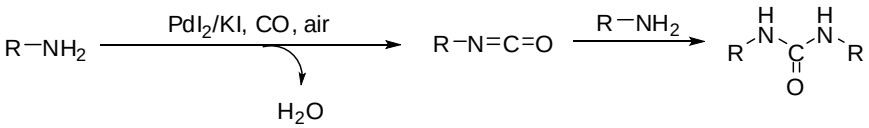
TABLE 2.1 **– Results of the oxidative carbonylation of primary amines to ureas according to figure 2.12. Conditions: PdI_2/KI/RNH_2 molar ratio = 1:100:5000, solvent: DME, substrate concentration) 1 mmol per ml of DME, T = 100 °C, t = 15 h, P(CO) = 16 atm, P(air) = 4 atm, P(CO_2) = 40 atm.**

Aromatic amines were found to be less reactive than aliphatic ones; this effect was ascribed to the lower nucleophilicity of such substrates. If CO_2 was added, it tended to inhibit reactivity for aromatic amines while promoting the reaction of aliphatic ones.

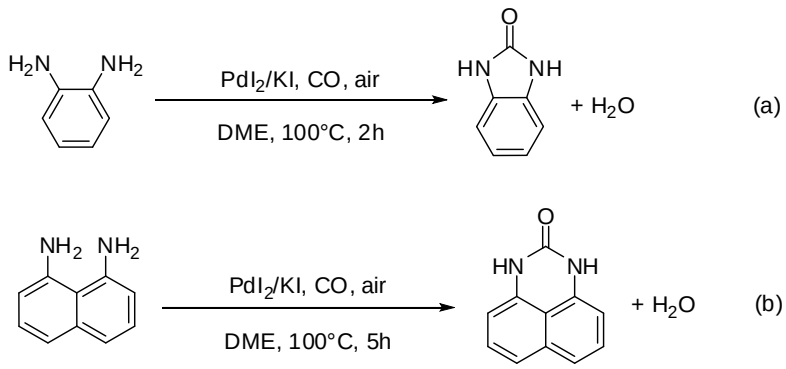
Secondary amines were not converted under the same conditions. This fact, and literature data, were taken as proofs of the formation of an isocyanate intermediate in the reaction mechanism (scheme 2.13); obviously, secondary amines cannot provide isocyanates thus becoming unreactive with this catalytic system. The detailed mechanism will be discussed in more detail later.

This methodology was then successfully applied to the oxidative carbonylation of primary aromatic diamines, leading to intramolecular cyclization and yielding cyclic ureas (scheme 2.14). High yields and selectivities were obtained in this case too.

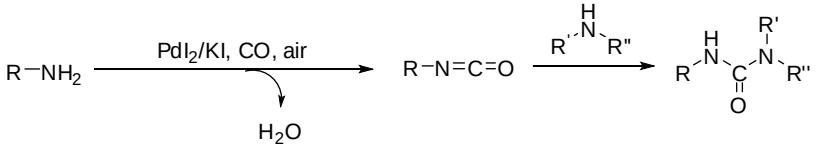
A further interesting application is based on the selective reactivity of primary amines. Since those molecules under the studied reaction conditions can react to yield isocyanates, if a secondary amine is present in the reaction mixture in opportune amount, it can react to yield asymmetrical N,N',N'-trisubstituted ureas according to scheme 2.15.



SCHEME 2.13. Mechanism of urea formation through isocyanate formation and subsequent condensation with a second molecule of amine.



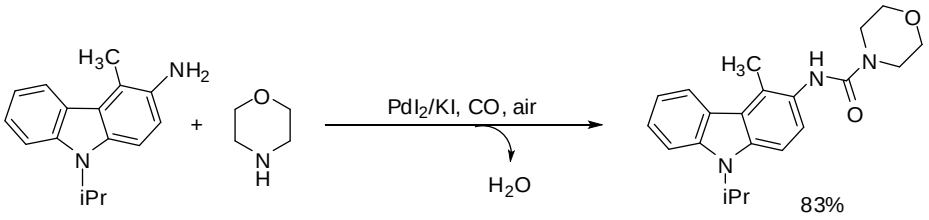
SCHEME 2.14. Synthesis of cyclic ureas via oxidative carbonylation of aromatic diamines.



SCHEME 2.15. Synthesis of asymmetrically N, N',N' trisubstituted ureas via condensation of a molecule of isocyanate, deriving from catalytic oxidative carbonylation of a primary amine, and a molecule of secondary amine.

By opportunely choosing the molar ratio of the two amines it was possible to selectively obtain the desired product in several cases (according to scheme 2.15, R = tBu, Ph, p-$CH_3OC_6H_4$, $MeOOCCH_2$; R', R''= nBu, -$(CH_2)_2O(CH_2)_2$-).

Finally, in order to show the wide potentials of this methodology, the synthesis of an important pharmaceutical product, the urea NP5RA-972 (N-(9-isopropyl-4-methyl-9H-carbazol-3-yl)morpholine-4-carboxamide), a potent antagonist of the neuropeptide N5 receptor, was accomplished with success[33] according to scheme 2.16.



SCHEME 2.16. Synthesis of NP5RA-972 via oxidative carbonylation and condensation of 9-isopropyl-4-methyl-9H-carbazol-3-amine and morpholine.

2.2 - Aim of the work

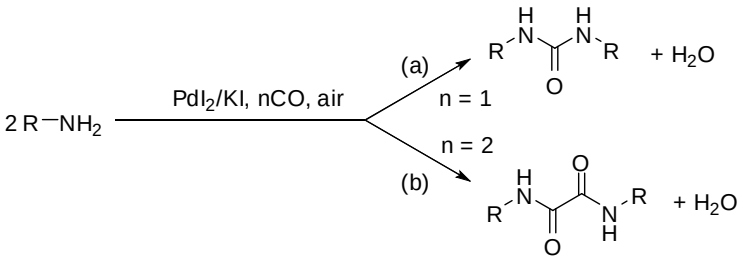
The above reported reactions were carried out in presence of organic solvents such as dimethoxyethane (DME). The presence of CO_2 was reported to improve the performance of the catalytic system. In this work the possibility of carrying out the reactions in absence of organic solvent and using supercritical CO_2 as the only reaction medium has been investigated, with particular attention devoted to the selectivity of the reaction towards ureas rather than the main undesired byproducts (oxamides). As a preliminary part of a more complex work in the present thesis only reaction of primary amines to symmetrically N,N'-disubstituted ureas are reported. The switch from a conventional "wet chemistry" system to a "dry chemistry" system, apart from the environmental advantages already described in the introduction of this thesis, has been shown to be particularly efficient in this case, providing the opportunity of avoiding explosion and combustion hazards connected with the use of carbon monoxide / air mixtures, of simplifying the workup procedures, and in some cases of improving even

dramatically the performance of the catalytic system, leading to unprecedented efficiencies in case of aromatic substrates.

2.3 - Results and discussion

2.3.1 - Preliminary work

The carbonylation of primary amines to the corresponding symmetrically N,N'-disubstituted ureas has been shown to proceed better if an aprotic and non polar solvent is utilized. In this cases, monocarbonylation (path (a) in scheme 2.17) is preferred over dicarbonylation (path (b) in figure X), thus yielding selectively ureas rather than oxamides.



SCHEME 2.17. Carbonylation of primary amines leading to ureas (a) or oxamides (b).

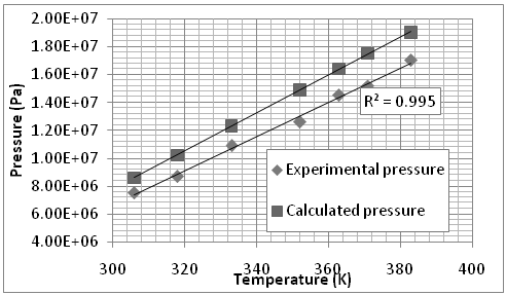
Supercritical carbon dioxide behaves like an almost aprotic solvent. It is thus a suitable reaction media for the selective synthesis of ureas. The reactions reported in this chapter were carried out in a stainless steel Parr high pressure reactor. The catalyst system used is the easily prepared and stable complex K_2PdI_4. The reagent and catalyst were loaded and then the reactor was closed, purged and loaded with the desired amount of liquid carbon dioxide, carbon monoxide and air. The amount of carbon dioxide loaded was determined by weighing the reactor prior to and after loading. The amount of carbon monoxide and air loaded were measured by reading the pressure on the reactor manometer at RT. The reactor was then heated by immersion in a preheated oil bath at the desired temperature. Since our apparatus did not allow the complete and uniform heating of the reactor, we first considered the behavior of CO_2 in our system to verify its coherency with theoretical properties of supercritical fluids, with special regard to the P-T relation. The

Morrison-McLindell state equation (eq. 2.1), which has been found to be very accurate for describing the behavior of CO_2 in supercritical phase[34], was used for comparing theoretical and experimental data.

$$P = [(nRT) (1 + \eta + \eta^2) / V (1 - \eta^3)] - [a_c \exp(\varepsilon) / (V/n) (V/n + b)]$$

EQUATION 2.1. Morrison-McLindell state equation, where $\eta = bn/ 4V$; $a_c = 0.4610\ R^2\ Tc^2 / Pc$; $\varepsilon = A_1 (T-T_c) + A_2 (T^2 - T_c^2)$ and $A_1 = -3.122 \cdot 10^{-3}$; $A_2 = 1.693 \cdot 10^{-6}$; $b = b_c \cdot \{1.065655[1-0.12 \exp(-2T_c/3T)]\}$ with $b_c = 0.1046\ RT_c / P_c$. (R expressed in J /K mol, V in m^3 , a = J m^3/ mol^2 and b = m^3/mol)

Our tests showed a slight, but non negligible difference between the experimental and the theoretical pressure of CO_2 at given temperatures, likely due to the above mentioned non-homogeneous heating between the bottom of the reactor, immerged in the oil bath, and the top which was in contact with the atmosphere. The temperatures reported are measured with a thermocouple and refer to the bottom of the reactor.



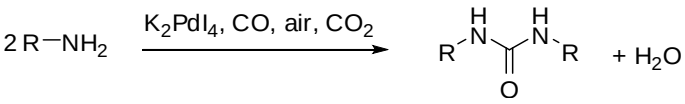
Temperature (K)	Experimental pressure(Pa)	Calculated pressure(Pa)
306	7.50E+06	8.57E+06
318	8.70E+06	1.02E+07
333	1.09E+07	1.23E+07
352	1.26E+07	1.49E+07
363	1.45E+07	1.64E+07
371	1.52E+07	1.75E+07
383	1.70E+07	1.90E+07

FIGURE 2.4. Experimental and calculated data for $scCO_2$ state in the reactor used in this work.

Thus, a correction factor was determined according to the experimental data reported in figure 2.4, and subsequently applied to the Morrison-McLindell state equation results in order to determine the theoretical partial pressure of CO_2 in our system (i.e. the pressure at the average temperature of the reactor). It is to be kept in mind, however, that the real partial pressure of CO_2 in the reaction system may vary due to the presence of non negligible amounts of other gases, namely CO and air, in the reactor.

2.3.2 - Oxidative carbonylation of primary aliphatic amines

The first substrate considered was butylamine that was reacted according to the equation specified in scheme 2.17.



SCHEME 2.17. General equation for the carbonylation of primary amines.

Entry	g CO_2	Urea Yield %
1	43	85
2	53	87
3	61	80
4	74	70

TABLE 2.2. **Results of the reaction of butylamine in presence of different amounts of CO_2. Reactor volume = 125 ml; catalyst = K_2PdI_4. Substrate / catalyst molar ratio = 1:1000, butylamine 20 mmol, P(CO) = 10 bar, P(air) = 15 bar, T = 70°C, t = 18 h. Isolated Yields.**

With the goal of optimizing the amount of CO_2 to be loaded, a series of experiments were carried out showing that the urea yield reaches a maximum in correspondence of about 50 grams of CO_2 loaded for the chosen conditions (see table 2.2). The following reactions were carried out with about the optimized amount of CO_2. It should be noted, however, that the amount of CO_2 necessary for the best results may vary in presence of different substrates.

The same substrate was then tested at different molar ratios with the catalyst. The results are reported in table 2.3. In one case (entry 6) the reaction was carried out in solvent-free conditions, i.e. not adding CO_2, and using a CO/air ratio of 4/1 in order to work outside the CO in air explosion range. (ca. 17-70% CO at 18-20 °C and atmospheric pressure, 14.8-71.5% CO at 100 °C and atmospheric pressure. At higher total pressure, the range of flammability decreases: for example, at 20 atm and 20 °C the range is ca. 20-60% CO[35]).

Entry	n-$BuNH_2$ mmol	Molar ratio. sub./cat.	t(h)	T(°C)	g CO_2	Urea yield %
5	20	2000	24	80	51	91
6[a]	20	2000	24	80	/	97
7	30	4000	48	90	49	93
8	40	10000	48	100	37	40

TABLE 2.3. **Results of the reaction of butylamine at different substrate/catalyst molar ratios. Reactor volume = 125 ml; catalyst = K_2PdI_4, Unless otherwise noted, P(CO) = 10 bar, P(air) = 15 bar. Isolated Yields. [a]: P(CO) = 20 bar, P(air) = 5 bar**

The results under these solvent-free conditions were slightly better than those in presence of CO_2. Other substrates did not show the same behavior: this can be ascribed to the different viscosity of the reagent/product mixture under reaction conditions. With reagents and products like n-butylamine and N,N'-dibutylurea, both liquid at reaction temperature, a solvent is not needed; in other cases, CO_2 dissolution in the amine phase prevents the mixture to became solid or very viscous thus ensuring higher conversions.

Yields were very satisfactory for molar ratios as high as 4000, although it was necessary to raise the reaction temperature and/or to extend the reaction time to achieve complete conversion. Selectivities were always high, with

negligible amounts of oxamides produced. For a substrate/catalyst molar ratio of 10000, a significantly lower yield was obtained.

T-Butylamine showed a remarkably different behavior. The yields were in fact significantly lower than those of its linear analogue, as reported in table 2.4.

Entry	t-BuNH$_2$ mmol	Molar ratio. sub./cat.	t(h)	T(°C)	g CO_2	Urea yield %
9	20	2000	24	80	53	22
10	20	2000	24	90	50	33
11	20	2000	24	100	42	50
12[a]	20	2000	24	110	38	60
13[b]	20	2000	24	110	37	90
14[c]	20	2000	24	110	/	90
15[c]	40	10000	24	110	/	67

TABLE 2.4**. Results of the reaction of t-butylamine at different substrate/catalyst molar ratios. Reactor volume = 125 ml; catalyst = K_2PdI_4, Unless otherwise noted, P(CO) = 10 bar, P(air) = 15 bar. Isolated yields.[a]: added 3 ml DME; [b]: added 15 ml DME; [c]: P(CO) = 20 bar, P(air) = 5 bar**

In this case, CO_2 showed a detrimental effect. In fact, in order to obtain improved yields, it was necessary to add DME or to run the reaction in solvent free conditions. This can be ascribed to the high stability of the carbamate formed between t-butylamine and carbon dioxide, which hinders the reactivity of the system. This hypothesis was confirmed by loading t-butylamine and CO_2 in the reactor and bringing it to the reaction conditions. t-butylcarbamate was isolated as an air-stable white solid. Running the reaction in absence of CO_2 avoids completely the formation of the carbamate, while the presence of DME is believed to enhance its dissolution or decomposition.

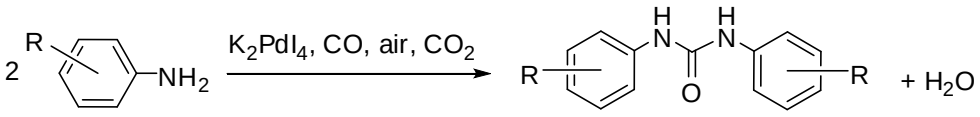
Benzylamine, on the other hand, afforded the expected dibenzylurea in high yields both in scCO_2 and in solvent-free conditions, according to table 2.5.

Entry	$BzNH_2$ mmol	Molar ratio. sub./cat.	t(h)	T(°C)	g CO_2	Urea yield %
16	20	2000	24	80	40	99
17	30	4000	36	100	32	96
18[a]	20	2000	24	100	/	98

TABLE 2.5**. Results of the reaction of benzylamine at different substrate/catalyst molar ratios. Reactor volume = 125 ml; catalyst = K_2PdI_4, Unless otherwise noted, P(CO) = 10 bar, P(air) = 15 bar. Isolated Yields.[a]: P(CO) = 20 bar, P(air) = 5 bar**

2.3.3 - Oxidative carbonylation of primary aromatic amines

Carbonylation of aromatic amines according to the general equation reported in scheme 2.18 had been found to be a challenging task when utilizing our catalytic system in a conventional organic solvent. As previously pointed out, yields and catalytic efficiencies were lower than those observed when reacting aliphatic amines. The reaction of aromatic amines in absence of organic solvent and in presence of supercritical carbon dioxide, on the other hand, proceeded with unexpected extraordinarily high turnover numbers, particularly with unsubstituted aniline: table 2.6 reports the results obtained when reacting aniline in *sc*CO_2 under our reaction conditions.



SCHEME 2.18. General equation for the oxidative carbonylation of variously substituted aromatic amines.

Entry	$PhNH_2$ mmol	Molar ratio. sub./cat.	t(h)	T(°C)	g CO_2	Urea yield %
19	20	2000	24	90	44	86
20[a]	20	2000	24	90	/	96
21	30	4000	32	90	43	90
22	40	8000	48	100	38	95
23	41	20000	48	100	41	92
24	40	60000	60	100	42	96
25	40	100000	72	110	45	87

TABLE 2.6. **Results of the reaction of aniline at different substrate/catalyst molar ratios. Reactor volume = 125 ml; catalyst = K_2PdI_4, Unless otherwise noted, P(CO) = 10 bar, P(air) = 15 bar. Isolated Yields.[a]: P(CO) = 20 bar, P(air) = 5 bar**

Aniline was found to react efficiently at substrate/catalyst ratios ranging from 2000 to 100000. In the latter case, it was sufficient to opportunely raise the reaction temperature and extend the reaction time. For comparison, the reaction in DME reached a maximum turnover number of 4350, while in $scCO_2$ the TON reached values of 87000. Here reported results are unprecedented in literature and are several orders of magnitude higher than the best results reported with other catalytic systems. The reason of this effect may be ascribed to an improved solubility of gases in the reagent and catalyst containing organic phase in presence of supercritical fluids rather than in organic solvents. In fact, while it is known that aniline is only slightly soluble in $scCO_2$ (3% at 32°C and 2500 psi[36]), it is widely acknowledged that gases with critical temperatures below 304 K, including CO and oxygen, are miscible with $scCO_2$ in all proportions[37]. Thus, the reaction would take place in a biphasic system consisting of a liquid phase formed by a solution of the catalyst in aniline (the catalyst has been found to be completely soluble in the amines

tested at reaction temperature) and a supercritical phase formed by carbon dioxide, nitrogen and oxygen. The mutual solubility of the two phases would be enhanced by the presence of the supercritical medium. This would allow overcoming mass transport problems at the interphase, leading to a faster and more efficient reaction, while in absence of CO_2 the gases would more difficultly reach the liquid phase[37]. In the case of aliphatic amines, which are likely soluble in the supercritical phase, this positive effect would be compensated by the catalyst dilution effect due to the formation of a single phase. Indeed this has already been verified in the case of oxidation of cyclohexene by oxygen. Wu and coworkers observed[38] that the efficiency of the reaction was dramatically decreased in connection with the formation of a single phase, while it proceeded very fast if the system was biphasic. Further experiments are being carried out in our laboratories to make this point more clear.

Entry	$CH_3OC_6H_4NH_2$ mmol	Molar ratio. sub./cat.	t(h)	T(°C)	g CO_2	Urea yield %
26	20	10000	24	80	41	77
27	35	6000	24	80	45	94
28[a]	35	6000	24	80	-	0

TABLE 2.7. **Results of the reaction of p-anisidine (R=CH_3O according to figure X). Reactor volume = 125 ml; catalyst = K_2PdI_4, Unless otherwise noted, P(CO) = 10 bar, P(air) = 15 bar. Isolated Yields.[a]: P(CO) = 20 bar, P(air) = 5 bar**

Other aromatic amines were then tested in the same reaction, both in presence and in absence of $scCO_2$. Tables 2.7-2.9 report the results obtained for the para- substituted anilines tested, namely, p-methoxyaniline (p-anisidine), p-trifluoromethoxyaniline, p-haloanilines, and p-nitroaniline.

Entry	$CF_3OC_6H_4NH_2$mmol	Molar ratio. sub./cat.	t(h)	T(°C)	g CO_2	Urea yield %
29	25	6000	24	80	42	70
30	25	6000	4	100	40	94
31[a]	40	6000	24	100	-	93

TABLE 2.8**. Results of the reaction of p-trifluoromethoxyaniline (R=CF_3O according to figure X). Reactor volume = 125 ml; catalyst = K_2PdI_4, Unless otherwise noted, P(CO) = 10 bar, P(air) = 15 bar. Isolated Yields.[a]: P(CO) = 20 bar, P(air) = 5 bar**

By comparing the results of p-methoxyaniline and p-trifluoromethoxyaniline (tables 2.8 and 2.9), a similar reactivity is noticed when the reaction is carried out in supercritical carbon dioxide (entries 27 and 30), while in solvent-free conditions the former shows no reactivity at all (entry 28). This behavior is ascribed to the different physical properties of the amines considered. In fact, p-anisidine has a melting point of 57-60°C, and in reaction conditions (80°C) is probably in a very aggregated molten phase, thus inhibiting the reactivity. In presence of CO_2 this phenomenon is less important and the reactivity is still high (entries 26-27).

Entry	X	Molar ratio. sub./cat.	Urea yield %
32	Br	2000	48
33	Br	5000	43
34	Cl	5000	41
35	F	5000	56
36	I	2000	32
37	I	5000	29
38	NO_2	2000	-
39	NO_2	5000	-

TABLE 2.9**. Results of the reaction of para-substituted haloanilines and p-nitroaniline. Reactor volume = 125 ml; reagent = 20 mmol, catalyst = K_2PdI_4, P(CO) = 10 bar, P(air) = 15 bar. CO_2 38-42g. T=80°C, t = 24h. Isolated Yields.**

P-trifluoromethoxyaniline is liquid already at room temperature: thus, no positive effect of CO_2 is observed and the reaction proceeds smoothly also in solvent free conditions (entries 30-31).

The same behavior was noticed when reacting halogen para-substituted anilines (table 2.9). These compounds have melting points close to or higher than reaction temperature and, as expected, no conversion at all was observed in absence of solvent. The melting points of all the examined anilines are reported in table 2.10 alongside with their reactivity in solvent free conditions and in supercritical CO_2 medium. The reactivity was found to decrease in the order F>Cl≈Br>I. The global efficiency of the reactions was however lower in comparison with the previously examined substrates. The low reactivity of p-iodoaniline can be also due to strong interactions between the iodine atom of the substrate and the palladium catalyst. P-nitroaniline showed no conversion under any conditions, due to the strong deactivating effect of the nitro group and/or to the very high melting point.

Substituent	MP, °C	TON (solvent free / $scCO_2$)
p-CH_3O	57-60	0 / 5640
p-CF_3O	<RT	5580 / 5640
p-F	<RT	3390. / 3360
p-Cl	69-72	0. / 2050
p-Br	62-64	0 / 2150
p-I	63-65	0 / 1450
p-NO_2	149-152	0 / 0

TABLE 2.10**. Comparison between some p-substituted anilines melting points.**

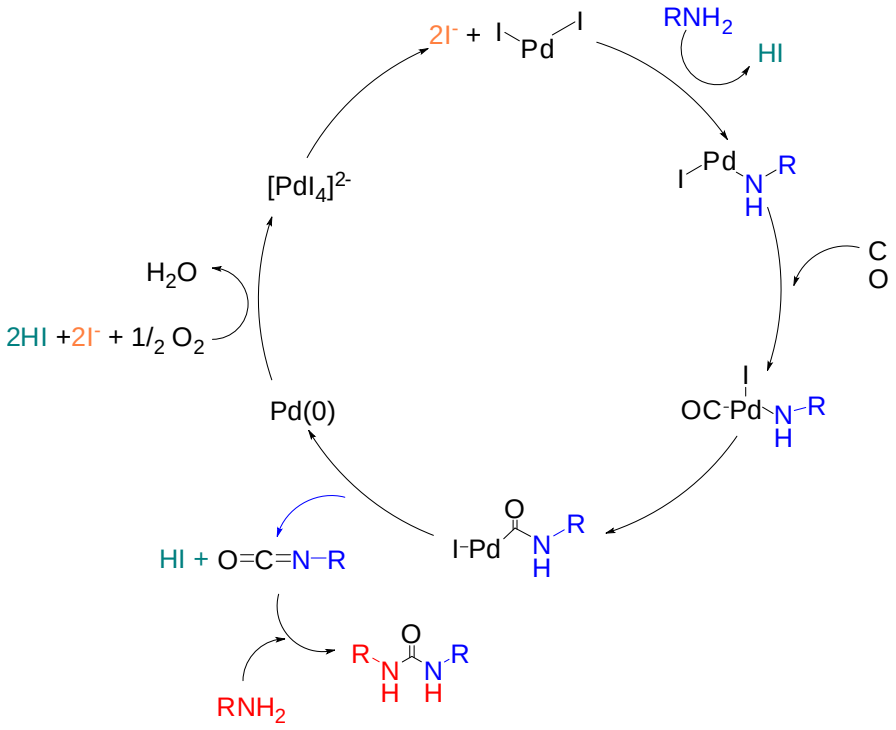
Entry	Substituent	Molar ratio. sub./cat.	Urea yield %
40	CH_3	6000	93
41	m-CF_3	6000	85

TABLE 2.11**. Results of the reaction of meta-substituted anilines. Reactor volume = 125 ml; reagent = 40 mmol, catalyst = K_2PdI_4, P(CO) = 10 bar, P(air) = 15 bar. CO_2 50g. T=80°C, t = 24h. Isolated Yields.**

Finally, the reactivity of some m-substituted anilines was tested in order to better demonstrate the general applicability of this process. The results obtained with m-toluidine and m-trifluoromethylaniline are reported in table 2.11. As already noticed (see tables 2.8 and 2.9), the presence of the fluorine atoms slightly decreases the reactivity of the system, due to the deactivating effect on the aromatic ring.

2.3.4 - Considerations on the reaction mechanism

As expected, secondary amines did not react at all under the above mentioned conditions. This fact is a further proof of the formation of an isocyanate intermediate in the mechanism. According to experimental data and theoretical considerations, a reasonable reaction mechanism is proposed as described in scheme 2.19.



SCHEME 2.19. Reaction mechanism proposed for the oxidative carbonylation of primary amines to N,N'-disubstituted ureas.

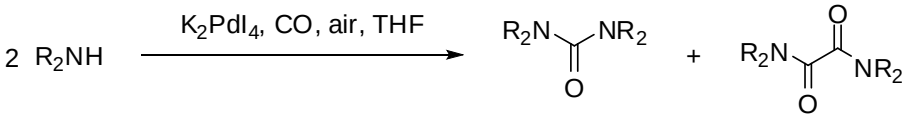
The first step is believed to be the attack of the amine on the palladium complex with production of one molecule of HI. Then, carbon monoxide coordinates on a free site of the metal complex, thus undergoing insertion by the aminic residue with formation of a carbamoylpalladium intermediate.

This intermediate gives a reductive elimination forming a molecule of isocyanate alongside with the reduction of palladium to its metallic state and liberation of HI. Isocyanate in fact was identified in the raw reaction mixtures. The urea product is formed by condensation of isocyanate with a second molecule of amine, while oxygen oxidizes the two molecules of HI formed to I_2. Iodine then reoxidizes palladium(0) to Pd(II). The key aspect of this reoxidation step is the formation of the $[PdI_4]^{2-}$ complex which was found to be thermodynamically more favored than the formation of PdI_2.

Since secondary amines are able to give the carbamoylpalladium intermediate, but not the isocyanate, attempts were made to react a secondary amine such as pyrrolidine and piperidine with the carbamoylpalladium species in order to obtain the symmetrically tetrasubstituted ureas. Preliminary tests were carried out in dry THF as solvent at low pressure of CO in order to avoid the formation of the undesired oxamides (scheme 2.20).

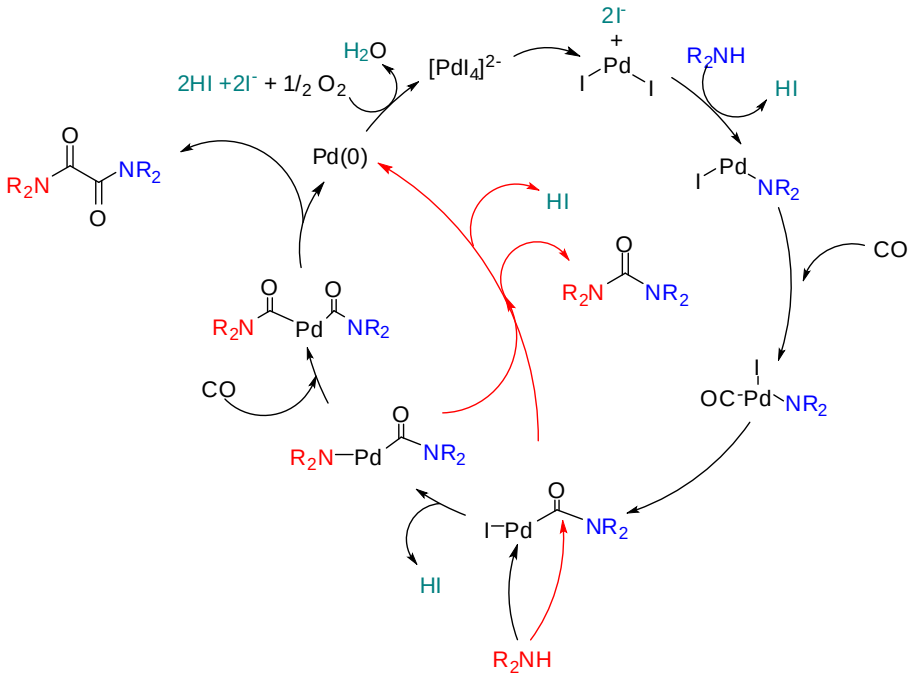
Entry	Reagent	mmol	THF (ml)	P(bar) CO	P(bar) air	T (°C)	T(h)	Urea yield (%)
42	Piperidine	5	1	4	30	80	24	0
43	Piperidine	5	20	1	30	80	24	0
44	Piperidine	5	2	1	30	25	24	8
45	Piperidine	5	2	2	30	80	24	30
46	Piperidine	5	1	2	30	100	24	25
47	Pyrrolidine	5	1	2	30	80	24	14

TABLE 2.12**. Reactivity of secondary amines in THF. Reactor volume 125 ml, Catalyst K_2PdI_4, substrate /catalyst molar ratio 250. Isolated yield. The molar balance is completed by the formation of the oxamide.**



SCHEME 2.20. Oxidative carbonylation of secondary amines to give ureas and oxamides. R_2 = -$(CH_2)_5$- (piperidine); R_2 = -$(CH_2)_4$- (pyrrolidine).

The results, reported in table 2.12, were not satisfactory and in some cases the reaction completely failed to afford the desired product. The predominant product was the oxamide. The mechanism hypnotized is reported in scheme 2.21.



SCHEME 2.21. Mechanism for the parallel formation of oxamides (black) and ureas (red) in the reaction of secondary amines.

The key difference with the mechanism reported for primary amines is the attack of the second molecule of amine. In absence of an isocyanate intermediate, in fact, the attack can take place on the electrophilic carbon of the carbamoylpalladium intermediate, leading to the formation of urea, or on the palladium metal. In this latter case, which is favored in the reaction conditions as pointed out by the experimental results in table 2.12, a second

molecule of carbon monoxide can coordinate and insert on the N-Pd bond thus forming, after the reductive elimination step, a molecule of oxamide.

2.4 - Conclusions

A green and efficient catalytic system has been proposed and investigated for the oxidative carbonylation of primary amines. The reactions yield no other byproduct than water and proceeds with high performance on both aromatic and aliphatic amines. In some cases it was possible to run the reactions in solvent-free conditions without any effect on the reactivity. The use of $scCO_2$ as a reaction medium allows several advantages: it configures a greener process since no organic solvent is needed; moreover, the safety of the process is improved since the excess of carbon dioxide prevents any explosion or combustion hazards. While primary aliphatic amines show only slight improvements in performance when using carbon dioxide as a solvent, the unexpected success of the reaction of anilines, which showed the highest performances up to date in this process under our conditions, is a further proof of the fact that the switch to non-conventional reaction media can not only improve the environmental feasibility of a chemical process, but in some cases also lead to strongly more productive reaction systems.

2.5 - Experimental

2.5.1 - Materials and methods

All solvents were dried over activated molecular sieves for 24 hours or freshly distilled. All amines were freshly distilled. Purified air, carbon monoxide and carbon dioxide were purchased from Sapio srl. All other reagents were purchased from commercial sources and utilized as received.
Reactions under pressure were performed in stainless steel 125 ml Parr autoclaves, equipped with manometer and thermocouple. Carbon dioxide was loaded as a liquid from a dip tube cylinder and the amount was measured by weighing. The temperatures reported in the Results and Discussion chapter refer to the values measured by the internal thermocouple.
Unless otherwise specified, yields reported refer to an isolated product.
Elemental analyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106. ^{1}H and ^{13}C NMR spectra were taken on a Bruker AC300 (300 MHz) spectrometer. IR spectra were taken on a Nicolet 5700 FT-IR spectrometer. Mass spectra were obtained using a GC system HP6890 Series coupled with a HP 5973 Mass Selective Detector at 70 eV ionization voltage. GC analyses were performed on a HRGC Mega 2 series Fisons Instruments equipped with a polymethylsilicone + 5% phenylsilicone as a stationary phase (HP-5) capillary column. Column chromatography was performed on silica gel 60 (Merck, 70-230 mesh).

2.5.2 - Procedures

Synthesis of potassium tetraiodopalladate. 1 mmol of PdI_2 (360 mg), 2 mmol of KI (332 mg) and 15 ml of methanol were introduced in a round-bottom single necked flask. The mixture was heated at reflux for one hour. After evaporating the solvent under vacuum, the product was collected as a black powder (Yield: 98%).

General procedure for the carbonylation reactions. A 125 ml stainless steel reactor was dried in oven for 12 hours, then cooled under argon to room temperature. The desired amounts of amine and catalyst, as reported in the Results and Discussion chapter, were loaded. Then the reactor was closed and purged three times with purified air. The desired amount of liquid CO_2 was loaded and subsequently the desired pressures of air and CO were loaded. The reactor was set in a thermostated bath at the desired temperature for the desired time under magnetic stirring.

After the reaction, the reactor was cooled to room temperature and slowly vented. The product was recovered with 5-10 ml of CH_2Cl_2 and the catalyst was separated by filtering through Celite. The raw mixture was analyzed by GC and GC-MS. If necessary, the product was purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate) followed by recrystallization from boiling acetone.

Characterizations

1,3-dibutylurea. White solid. **Melting point**: 71-72°C (lit. 73 °C). **MS** (EI, 70 eV,): m/z (relative. abundance): 172 (M+, 100), 157 (17), 143 (17), 130 (39), 129 (33),101 (45), 100 (33), 87 (31), 74 (69), 73 (27), 72 (33), 58 (16), 57 (67), 56 (33), 55 (17). **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 4.85 (bd, 2 H), 3.08(t, 4H, *J* =5.9 Hz), 1.16-1.61 (m, 8 H), 0.91 (t, 6 H, *J*= 6.2 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$): 159.5, 40.0, 32.6, 20.2, 13.9; **IR** (KBr): ν(cm^{-1}) 3300, 1620. **Elemental analysis**: Theoretical C 62.75%; H 11.68%; N 16.26%; Experimental C 62.52%; H 11.70%; N 16.08%

1,3-ditertbutylurea. White solid. **Melting point**: 252-254°C (lit. 251-254°C). **MS** (EI, 70 eV,): m/z (relative. abundance): 172(M+ ,100), 157(16), 143 (10), 130(32), 117(5), 101(50), 87(38), 74(90), 57(77) **^{1}H NMR** (300 MHz, DMSO-d): δ (ppm) 5.45(s, 2 H), 1.23 (s, 18 H). **^{13}C NMR** (DMSO-d) δ (ppm) 157.0, 48.7, 29.3; **IR** (KBr): ν(cm^{-1}) 3340, 2955, 2918, 1627, 1595, 1547, 1470, 1442, 1382, 1357, 1287, 1227, 1200, 632. **Elemental analysis**: Theoretical C 62.75%; H 11.68%; N 16.26%; Experimental C 62.76%; H 11.96%; N 16.04%.

1,3-dibenzylurea. White solid. **Melting point**: 171-174°C (lit. 170-173°C). **MS** (EI, 70 eV,): m/z (relative abundance): 240(M+ ,85), 149(40), 133 (15), 106(100), 91(70). **^{1}H NMR** (300 MHz, DMSO-d): δ (ppm) 7,35-7.21 (m, 10 H); 4,71(bs, 2H); 4.37(s, 4H) **^{13}C NMR** (DMSO-d) δ (ppm) 158.1, 140.8, 128.1, 126.9, 126.5, 42.9; **IR** (KBr): ν(cm^{-1}) 3320, 3030, 2922, 1627, 1575, 1453, 1266, 696. **Elemental analysis**: Theoretical C 74.97%; H 6.71%; N 11.66%; Experimental C 74.33%; H 6.88%; N 11.72%.

1,3-diphenylurea. White solid. **Melting point**: 239-241°C (lit. 239-241°C). **MS** (EI, 70 eV,): m/z (relative. abundance): 212(M+,23), 119(8), 94(27), 93(100), 92(7), 77(8), 66(12), 65(8) **^{1}H NMR** (300 MHz, DMSO-d): δ (ppm) 8.69 (s, 2 H), 7.50 (d, 4 H, *J*=7.5 Hz), 7.29(t, 2 H, *J*=7.5 Hz),6.97(t, 4 H, J=8.3 Hz). **^{13}C NMR** (DMSO-d) δ (ppm) 152.5, 139.7, 128.7, 121.7, 118.1; **IR** (KBr): ν(cm^{-1}) 3320, 3030, 2922, 1627, 1575, 1453, 1266, 696. **Elemental analysis**: Theoretical C 74.97%; H 6.71%; N 11.66%; Experimental C 74.33%; H 6.88%; N 11.72%

1,3-bis(4-methoxyphenyl)urea. White solid. **Melting point**: 238-240°C (lit. 240-241°C). **MS** (EI, 70 eV,): m/z (relative. abundance): 272 (M_+, 44), 149 (19), 134 (11), 123 (100), 108 (91), 95 (6), 80 (12). **^{1}H NMR** (300 MHz, DMSO-d): δ (ppm) 8.69 (s, 2 H), 7.50 (d, 4 H, *J*=7.5 Hz), 7.29(t, 2 H, *J*=7.5 Hz),6.97(t, 4 H, J=8.3 Hz). **^{13}C NMR** (75 MHz, DMSO-d):δ (ppm) 154.3, 152.7, 133.1, 119.6, 113.7, 54.7. **IR** (KBr): ν(cm^{-1}) 3300, 1634. **Elemental analysis**: Theoretical C 66.16%; H 5.92%; N 10.29%; Experimental C 66.06%; H 5.79%; N 10.21%.

1,3-bis(4-(trifluoromethoxy)phenyl)urea. White solid. **Melting point**: 238-240°C (lit. 240-241°C). **MS** (EI, 70 eV,): m/z (relative. abundance): 409(M+29,24), 381(M+1,100), 361(68), 295(32), 219(5), 203(5), 177(68), 108(24), 69(5), 59(5) **^{1}H NMR** (300MHz, DMSO-d): δ (ppm) 8.88(bs), 7.56(d, 4H, J=9.1 Hz), 7.28(d, 4H, J=8.4 Hz). **^{13}C NMR** (75 MHz, DMSO-d):δ (ppm) 152.3, 142.5, 138.7, 129.3 (q, J = 502 Hz), 121.6, 119.4. **IR** (KBr): ν(cm^{-1}) 3296, 1634, 1602, 1551, 1507, 1409, 1267, 1202, 1169, 1155, 1101, 1016, 922, 851, 800, 755, 703, 673. **Elemental analysis**: Theoretical C 47.38%; H 2.65%; N 7.37%; Experimental C 47.71%; H 2.51%; N 7.30%.

1,3-bis(4-fluorophenyl)urea. White solid. **Melting point**: 259-263 °C). **^{1}H NMR** (300MHz, DMSO-d): δ (ppm) 6.43 (s, 2H), 7.34 -7,29 (m, 4H), 7.01-7.06 (m, 4H). **^{13}C NMR** (75 MHz, DMSO-d):δ (ppm) 157(d, J=236Hz), 152.6, 135.9, 119.8 (d, J=7.6 Hz), 115.1 (d, J=19.4Hz). **IR** (KBr): ν(cm^{-1}) 3296, 1634, 1602, 1551, 1507, 1409, 1267, 1202, 1169, 1155, 1101, 1016, 922, 851, 800, 755, 703, 673. **Elemental analysis**: Theoretical C 47.38%; H 2.65%; N 7.37%; Experimental C 47.71%; H 2.51%; N 7.30%.

1,3-bis(4-chlorophenyl)urea. White solid. **Melting point**: 292-294 °C. **^{1}H NMR** (300MHz, DMSO-d): δ (ppm) 8.85 (s, 2H), 7.47 (d, J=8.9Hz, 4H), 7.31 (d, J=8.9 Hz, 4H). **^{13}C NMR** (75 MHz, DMSO-d):δ (ppm)152.2, 138.4, 128.5, 125.3, 119.7. **IR** (KBr): ν(cm^{-1}) 3269, 1633, 1591, 1559. **Elemental analysis**: Theoretical C 55.53%; H 3.58%; N 9.96%; Experimental C 55.37%; H 3.66%; N 9.84%.

1,3-bis(4-bromophenyl)urea. White solid. **Melting point**: 265-268 °C **^{1}H NMR** (300MHz, DMSO-d): δ (ppm) 8.84 (s, 2H), 7.40 -7.46 (m, 8H). **^{13}C NMR** (75 MHz, DMSO-d):δ (ppm)152.1, 138.8, 131.3, 120.1, 113.2. **IR** (KBr): ν(cm^{-1})3299, 2922, 2848, 1638, 1583. **Elemental analysis**: Theoretical C 42.20%; H 2.72%; N 7.57%; Experimental C 42.06%; H 2.79%; N 7.49%.

1,3-bis(4-iodophenyl)urea. White solid. **^{1}H NMR** (300MHz, DMSO-d): δ (ppm) 8.62 (s, 2H), 7.43 (d, J=7.7 Hz, 4H), 7.26 (d, J=7.7 Hz, 4H). **^{13}C NMR** (75 MHz, DMSO-d):δ

(ppm)152.2, 139.5, 128.6, 121.6, 118.0. **IR** (KBr): ν(cm^{-1}) 3298, 1638, 1594, 1551. **Elemental analysis**: Theoretical C 33.64%; H 2.17%; N 6.03%; Experimental C 33.25%; H 2.06%; N 5.91%.

1,3-bis(3-(trifluoromethyl)phenyl)urea. White solid. **Melting point**: 197-198°C (lit. 199°C). **MS** (EI, 70 eV,): m/z (relative. abundance): 377(M+29,15), 363(M+15,4), 349(M+1,95), 329(100), 161(66), 145(4). **^{1}H NMR** (300MHz, DMSO-d): δ (ppm) 9.20(s, 2 H), 8.04(s, 2 H), 7.57(d, 2 H, J=8.4 Hz), 7.57(t, 2 H, J=7.7 Hz), 7.34(d, 2 H, J=7.5 Hz). **^{13}C NMR** (75 MHz, DMSO-d):δ (ppm) 152.1, 139.8, 129.5, 128.8, 126.5, 121.0, 117.9, 114.0. **IR** (KBr): ν(cm^{-1}) 3325, 3311, 1661. **Elemental analysis**: C 51.74%; H 2.89%; N 8.04%; Experimental C 52.31%; H 2.84%; N 8.05%;

1,3-di-*m*-tolylurea. White solid. **Melting point**: 224-225°C (lit. 225°C). **^{1}H NMR** (300MHz, DMSO-d): δ (ppm) 8.58(s, 2 H), 7.12-7.38(m, 6 H), 6.79(d, 2 H, J=7.7 Hz), 2.29(s, 6 H). **^{13}C NMR** (75 MHz, DMSO-d):δ (ppm) 152.1, 140.3, 137.5, 128.2, 122.1, 118.2, 114.9, 20.8**.** **IR** (KBr): ν(cm^{-1}) 3299, 1635. **Elemental analysis**: Theoretical C 74.97%; H 6.66%; N 11.66%; Experimental C 74.97%; H 6.88%; N 11.54%.

dipiperidin-1-ylmethanone. White solid. **Melting point**: 41°C (lit. 42-45°C).: **^{1}H NMR** (300MHz, DMSO-d): δ (ppm) 1.53(m, 12 H), 3.13(m, 8H), 6.79(d, 2 H, J=7.7 Hz), 2.29(s, 6 H). **^{13}C NMR** (75 MHz, DMSO-d):δ (ppm) 177.6, 47.8, 25.7, 24.7**.** **IR** (KBr): ν(cm^{-1}) 2934, 2847, 1759, 1644. **Elemental analysis**: Theoretical C 67.31%; H 10.27%; N 14.27%; Experimental C 67.11%; H 10.78%; N 13.99%.

dipyrrolidin-1-ylmethanone. White solid. **^{1}H NMR** (300MHz, DMSO-d): δ (ppm) 1.76(m, 8 H), 3.33(m, 8H),. **^{13}C NMR** (75 MHz, DMSO-d):δ (ppm) 161.3, 46.5, 25.4**.** **IR** (KBr): ν(cm^{-1}) 2965, 2867, 1652, 1451. **Elemental analysis**: Theoretical C 64.25%; H 9.59%; N 16.65%; Experimental C 64.21%; H 9.30%; N 16.23%.

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Chapter 3

Project II:

Carbon dioxide as carbon feedstock for the production of plastics: copolymerization of epoxides and CO_2

The use of carbon dioxide as a carbon feedstock in replacement of non-renewable oil and natural gas derived raw materials has attracted growing attention in the chemical research. Due to the scarce reactivity of carbon dioxide, only few applicable processes have been developed. One of the most interesting is the copolymerization of CO_2 and epoxides, which is, nevertheless, affected by some problems, among those the formation of non negligible amounts of byproducts such as cyclic carbonate and polyethers, and the difficult separation of the catalyst from the product.

In this chapter an investigation on the mechanism and kinetics of formation of byproducts is presented, and the synthesis of a catalyst potentially suitable for supercritical separation is described.

Part of this work has been published as:

Darensbourg D. J.; Bottarelli P.; Andreatta J. R., "Inquiry into the formation of cyclic carbonates during the (Salen)CrX catalyzed CO_2/ cyclohexene oxide copolymerization process in the presence of ionic initiators", *Macromolecules*; **(2007)**, 40, 7727-7729.

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3.1 - Background

3.1.1 - Generalities

The use of carbon dioxide as both reagent and solvent has received great attention as it may lead to incorporation of CO_2 in important industrial products or intermediates. Although this might not have a strong impact on the greenhouse effect, because of the relatively small amount of CO_2 that would be utilized if compared to that produced in fossil fuel combustions, this still appears as a benign process since it allows the use of a cheap, non toxic and renewable carbon source in replacement of environmentally dangerous reagents and solvents.

Not many options are available for the conversion of CO_2 into something capable of generating profit. The key issue is the highly negative free energy of formation of CO_2, which results in unfavorable equilibriums. So far, research has investigated incorporation of CO_2 into organic carbonates and polycarbonates, and reduction of CO_2 via reverse water gas shift reaction. This latter process is very energy-intensive because of the above mentioned thermodynamic reason. Preliminary studies have demonstrated the possibility of producing acetic acid from carbon dioxide and methane[1]. A recent paper[2] reports the formation of vinyl acetate from CO_2, CH_4 and C_2H_2 over a Pt/Al_2O_3 catalyst under harsh conditions. In both cases, the authors report only instrumentally determinable yields and conversions, thus the process is not suitable for any industrial application and is so far limited to theoretical studies.

The incorporation of CO_2 into organic carbonates and polycarbonates is a more attractive solution from an industrial point of view. In fact, since this kind of reaction does not involve the reduction of the carbon atom of carbon dioxide, it is usually possible to perform it under common laboratory and industry high pressure conditions. In both cases the most common pathway is to react carbon dioxide with an epoxide, an alcohol or a diol. The reagent, together with the reaction conditions and the catalyst employed, drives the reaction towards mono or polycarbonates.

In most cases, organic cyclic carbonates, however a useful product as solvent and reaction intermediates, are also a byproduct of the copolymerization process.

It is worth noticing, although it is not subject of this thesis, that the synthesis of organic carbonates has made some good progresses recently[3-5].

In the next chapter a short account of the development of the epoxide and CO_2 copolymerization process will be given.

3.1.2 - Development of the epoxide-CO_2 copolymerization process

The first reported copolymerization of epoxides and carbon dioxide dates back to 1969 when Inoue and coworkers at Tokyo University utilized a 1:1 molar mixture of diethyl zinc and water as a catalyst system[6-7]. Still the efficiency of the process was very low and turnover frequencies were lower than 1 h^{-1}.

Several years later, zinc dicarboxylates such as zinc glutarate were reported to be a more efficient and air-stable catalyst for the copolymerization of propylene oxide and CO_2[8]. This process, although still affected by several problems including low reproducibility and activity, has been patented and is now the basis of a commercial process for the production of polyethylene and polypropylene carbonate[9].

Zinc glutarate has then been subject of intensive investigation by several researchers, including Darensbourg[10], and Zheng[11]. After some years, Darensbourg's group reported that zinc phenoxide catalysts could catalyze the copolymerization process with high efficiency in absence of organic solvent[12]. Figure 3.1 reports the structure of a representative catalyst of this generation.

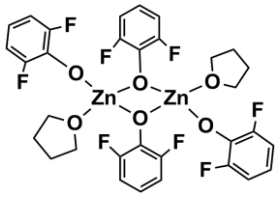


FIGURE 3.1. Zinc phenoxide catalyst. The complex was isolated as di-THF adduct.

These catalysts were quite active (TOF ≈ 16.5 h^{-1}) but suffered of the incorporation of the phenoxide into the polymer chain as end group, thus leading to ill-defined catalytic species and to highly disperse products.

A further improvement in zinc-based catalyst was due to the work of Coates and coworkers, that in 1998 reported[13-14] that zinc β-diiminate alkoxides(figure 3.2) were able to catalyze the copolymerization of both propylene and cyclohexene oxide and CO_2 affording with good (TOF ≈ 200 h^{-1}) to excellent (TOF = 2290 h^{-1}) efficiencies copolymers with narrow molecular weight distributions. Variations in the structure of the catalysts strongly influenced the results of the process.

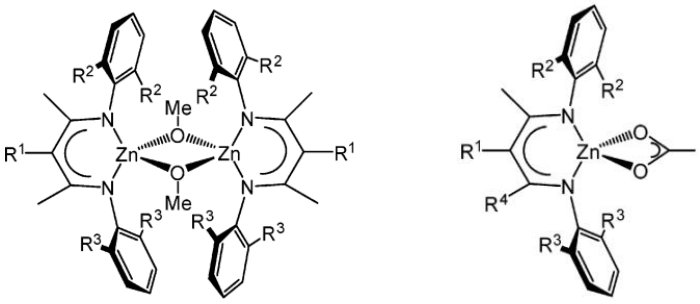


FIGURE 3.2. Dimeric (left) and monomeric (right) zinc β-diiminate catalysts suitable for copolymerization of cyclohexene oxide (dimeric, R^1 = H, R^2, R^3 = *i*Pr) or propylene oxide (monomeric, R^1=H, R^2=Et, R^3 = *i*Pr, R^4 = CF_3) and CO_2.

In the meantime, in a work aimed to the synthesis of cyclic carbonates[15], the first chromium-based catalysts, based on a porphyrin ligand, were reported to afford copolymers in the reaction of cyclohexene oxide and CO_2. On the side of the polymer production, a catalyst of this class was reported to catalyze the synthesis of polycyclohexylcarbonate in *sc*CO_2. The activities reported are limited to about 150 h^{-1}; nevertheless, this catalyst (figure 3.3) is the first reported to be soluble in *sc*CO_2.

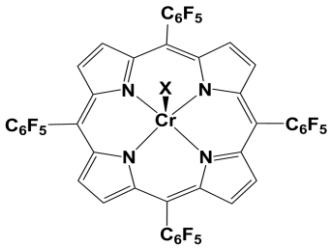


FIGURE 3.3. Cr(III) complex with fluorinated porphyrin.

The next breakthrough in this field came from Darensbourg's group, whose work on a Cr(III)salen (salen = N,N'-Ethylenebis(salicylimine)) catalyst was first published in 2002[17]. The choice of the ligand had been inspired by Jacobsen's work[18] in which a similar complex (figure 3.4) was utilized for the asymmetric ring opening of epoxides. Although the initial goal of obtaining a stereoregular polymer from the asymmetric epoxide ring opening favored by Jacobsen's catalyst was not reached, this work opened a new field that was going to be extensively studied in the next years[19-21].

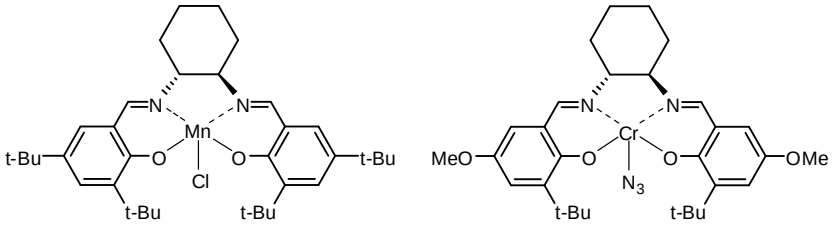


FIGURE 3.4. Jacobsen's Mn(salen)Cl complex, efficient catalyst for the asymmetric ring opening of epoxides.(left), and the most efficient Cr(salen)N_3 catalyst for the copolymerization of cyclohexene oxide and CO_2 up to date (right).

3.1.3 - Some important aspects of the M(salen)X catalyzed copolymerization of epoxides and CO_2

The elementary steps involved in the M(salen)X catalyzed reaction have been studied adequately. The process needs the presence of a cocatalyst. If no cocatalyst is added, TOFs are low (10 h^{-1}) and a significant inactivity period is observed, in which it is presumed to form endogenously a species that can act as a cocatalyst.

The catalysts employed have the general structure depicted in figure 3.5.

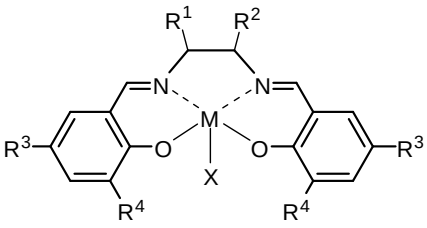


FIGURE 3.5. Generic representation of an M(salen)X catalyst. M = Cr, Co, Al; X =N_3, Cl, Br, I, OAc, HCO_3; R^1, R^2 = H, Me, tBu, -C_4H_{10}-; R^3, R^4 = OMe, *t*Bu.

The nature of the metal has effect on the reaction products. (salen)CoX derivatives are more effective for copolymerizing propylene oxide/CO_2, whereas (salen)CrX derivatives were more efficient at copolymerizing cyclohexene oxide and carbon dioxide[23-27].

Cocatalysts employed range from neutral nucleophiles such as amines (DMAP, pyridine, DBU etc, aliphatic and aromatic phosphines, to anionic ones such as the anions deriving from ammonium or bis(triphenylphosphoranylidene) ammonium (PPN^+) salts (figure 3.6) with the same anions utilized in the complex (N_3, Cl, Br, I, OAc, HCO_3).

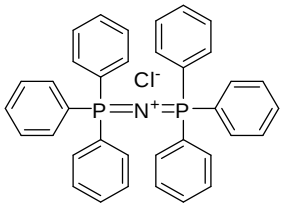


FIGURE 3.6. bis(triphenylphosphoranylidene) ammonium (PPN^+) chloride, one of the most active cocatalysts up to date.

The nature and the amount of cocatalyst added have a dramatic effect on the results of the reaction. In particular, anionic cocatalyst such as PPN salts are more active than neutral nucleophiles.

In this work the most active and investigated metal centre, chromium, will be considered, alongside with the most stable anion, chloride. The cocatalyst chosen is PPNCl. A comprehensive study of the different catalysts and

cocatalysts employed can be found in a recent review by Darensbourg[9]. In the same paper, several other aspects of the reaction are discussed in detail. Hence, here information will be limited to aspects functional to the understanding of the work.

The initiation step of the process makes reason for the importance of the cocatalyst. The five coordinated Cr(III) complex in fact reacts immediately with the nucleophile forming a six-coordinate complex. Both the five coordinated and the six-coordinated complexes have been crystallized and their structures have been determined via X-ray crystallography. These structures are reported in figure 3.7. In both cases, the salen ligand shows a quasi-planar coordination for the N_2O_2 core and the nucleophile is found in an axial position, thus leaving space for the coordination of another nucleophilic species and the formation of the six-coordinated complex.

Subsequently, the epoxide can coordinate to the metal center undergoing activation by the cocatalyst. The next step is the epoxide ring opening in which the nucleophile binds to the forming chain constituting an end-group. MALDI-TOF-MS analyses confirmed the presence of the anions as end groups in the polymer chain. The next step consists in the insertion of carbon dioxide in the metal-oxygen bond forming a carbonate. This step involves the behavior of the carbon of CO_2 as an electrophile; thus, more nucleophilic and less sterically encumbered metal-oxygen centers are more reactive. Scheme 3.1 depicts these initiation steps.

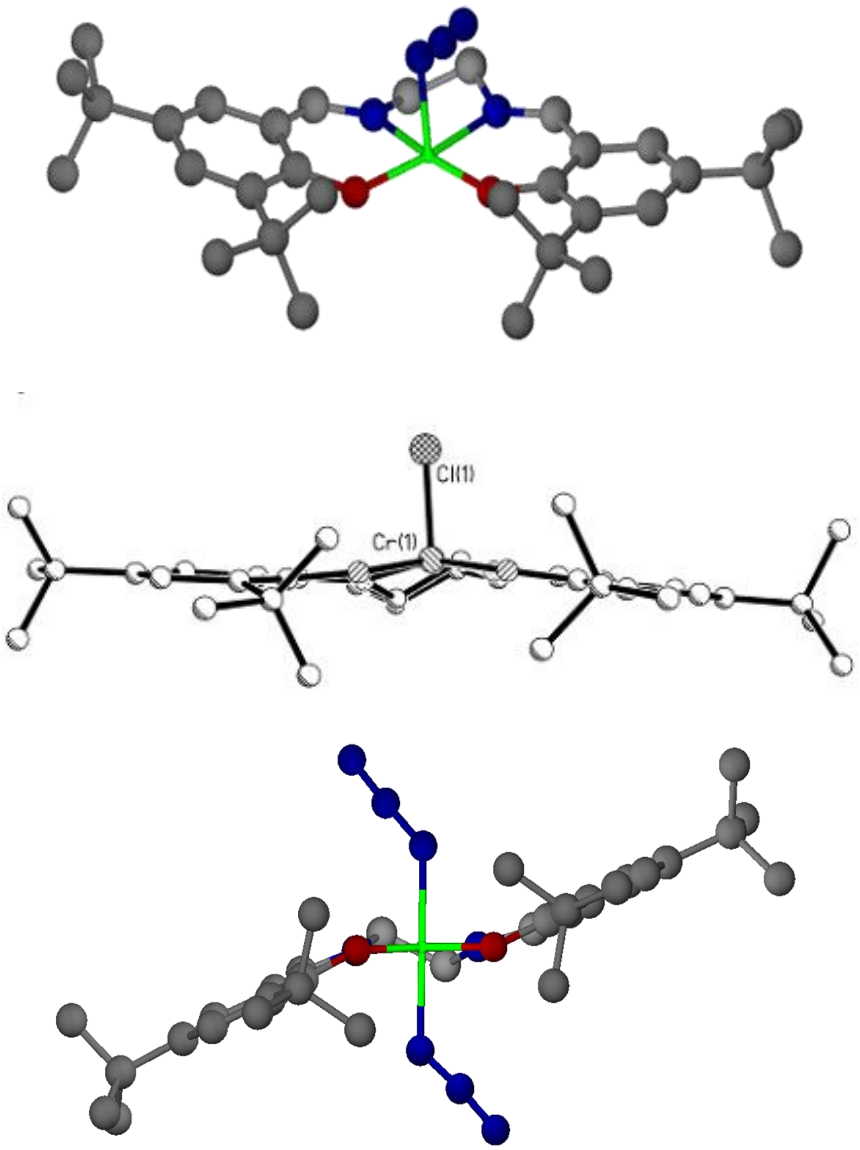
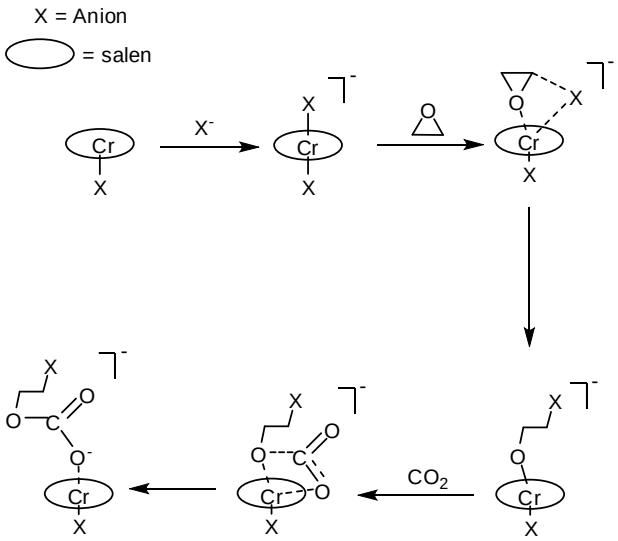


FIGURE 3.7. X-ray structures[28-30] of Cr(salen)N_3, of Cr(salen)Cl and $[Cr(salen)(N_3)_2]^-$. According to nomenclature consistent with figure 3.5, in these complex the ligand has R^1=R^2=H and R^3=R^4=tBu. The latter complex is fastly formed upon dissolution of the former in cyclohexene epoxide in presence of 1 equivalent $PPNN_3$.



SCHEME 3.1. Activation and first chain growth steps in the copolymerization of epoxides and CO_2 catalyzed by Cr(salen)X and PPNX. Substituents on the epoxide are omitted for clarity.

The carbonate formed acts now as a nucleophile for the consequent insertion of a new molecule of epoxide, and the reaction proceeds with new monomers enchainment. (scheme 3.2).

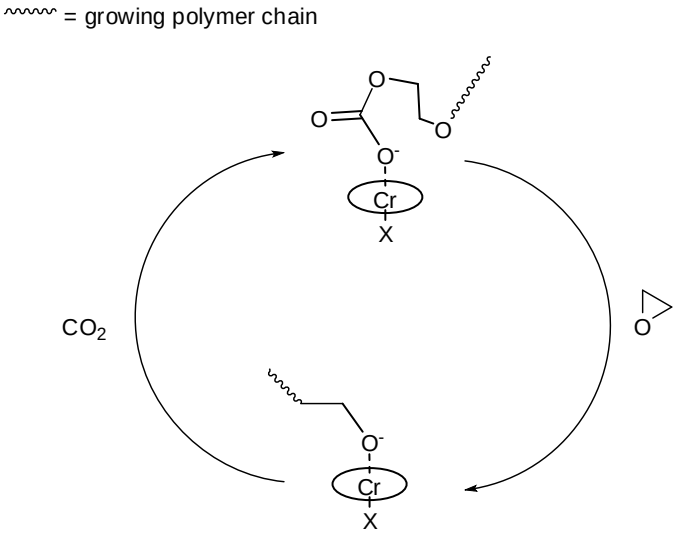


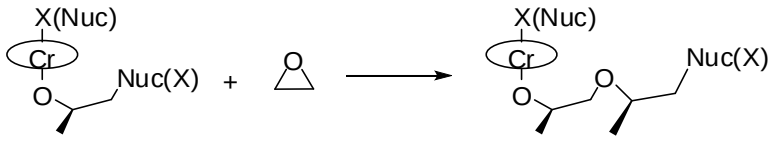
FIGURE 3.2. Chain propagation.

The reaction thus affords living polymers. Usually termination is operated by quenching the reaction with an acid, usually 0.1 M HCl in MeOH, after venting the CO_2 from the reactor.

It is worth noticing that the reaction is prone to chain-transfer phenomena which lead to average molecular weights lower than the theoretical ones. Chain transfers are started primarily by the presence of traces of water, impossible to completely avoid by standard laboratory operation.

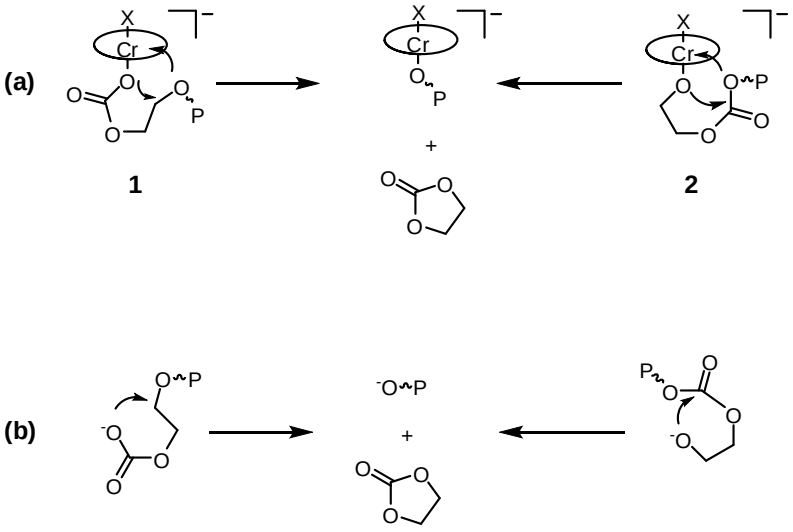
The process produces two undesired byproducts, whose amount can vary dependently on the reaction conditions and on the epoxide utilized: cyclic carbonates and polyether.

The latter is believed to be formed via consecutive epoxide ring opening (scheme 3.4). This pathway is not terribly important for (salen)MX catalytic systems; that is, the afforded copolymers are generally completely alternating. However, for the stronger Lewis acid catalysts, such as Zn(II) complexes, this can be a significant occurrence.



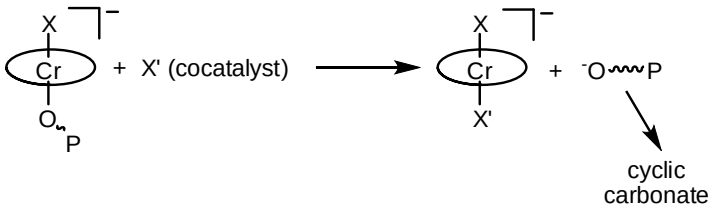
SCHEME 3.3. Side reaction of polyether chain formation.

The formation of cyclic carbonate is thought to occur *via* two concurrent backbiting mechanisms(scheme 3.5), one aided by the metal (a) and one taking place on the free anionic polymer chain (b)



SCHEME 3.5. Formation of cyclic carbonate via on-metal mechanism(a) and free chain mechanism (b).

The latter process is believed to have a lower activation barrier and to be assisted in the presence of an excess of neutral and ionic Lewis bases (cocatalysts) which serve to displace the growing polymer chain from the metal center [31-32] (scheme 3.6).



SCHEME 3.6. Displacement of the polymer chain from the metal center in excess of cocatalyst.

The products obtained by this reaction can be analyzed with the aid of several instrumental techniques. Peak integration in ^{1}H NMR is used for determining the amount of polycarbonate, polyether, cyclic carbonate and unreacted epoxide in the product mixture. Figure 3.8 shows a typical spectrum and the peaks related to each species.

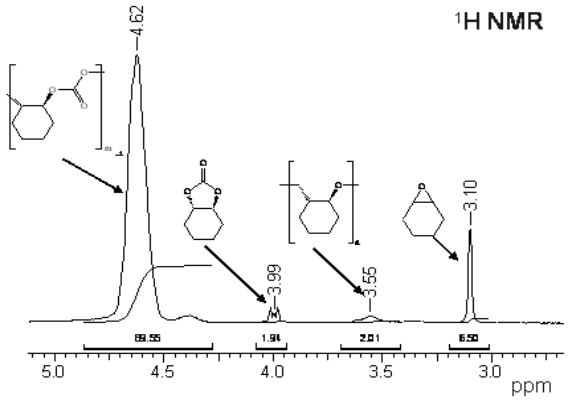


FIGURE 3.8. Representative ^{1}H NMR spectrum of a product. The peaks considered are due to the hydrogens in α to the oxygens.

Average molecular weight and PDIs can be determined via GPC chromatography. Integration of peaks in ^{13}C-NMR can give information about the stereoregularity of the polymer, and the reaction mechanism can be followed via in situ IR spectroscopy. Being less common than others, this technique will be briefly introduced in the next paragraph.

3.1.4 - In situ ATR-IR spectroscopy

In situ ATR-IR spectroscopy is a powerful tool for understanding the kinetics and mechanism of reactions. In this work the experiments have been performed using a stainless steel Parr autoclave modified with a silicon crystal, which allows for FT attenuated total reflectance (ATR) infrared spectroscopy[21]. The ATR crystal is permanently fixed to the bottom of the reactor, and the infrared beam, after passing through several connecting arms reflected by mirrors at each junction, enters the crystal. Signal enhancement is achieved by repetitive reflections (30) along the length of the ATR crystal prior to returning to the detector via the connection arms (see Figure 3.9), each time penetrating the reaction medium about 1 micrometer.

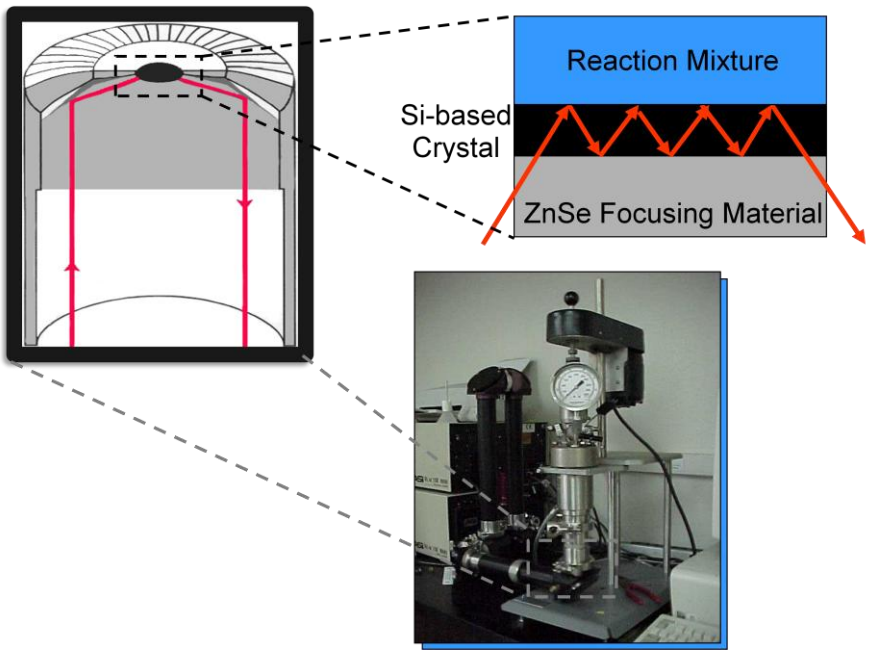


FIGURE 3.9. ASI ReactIR 1000 reaction analysis system with a stainless steel Parr-modified autoclave.

Figure 3.10 illustrates a typical reaction profile obtained while monitoring the coupling reaction of CO_2 and cyclohexene oxide, where the infrared absorbance at 1750 cm^{-1} corresponds to the asymmetric ν_{CO2} vibrational mode and the bands at 1810 and 1802 cm^{-1} correspond to the *trans* cyclic carbonate.

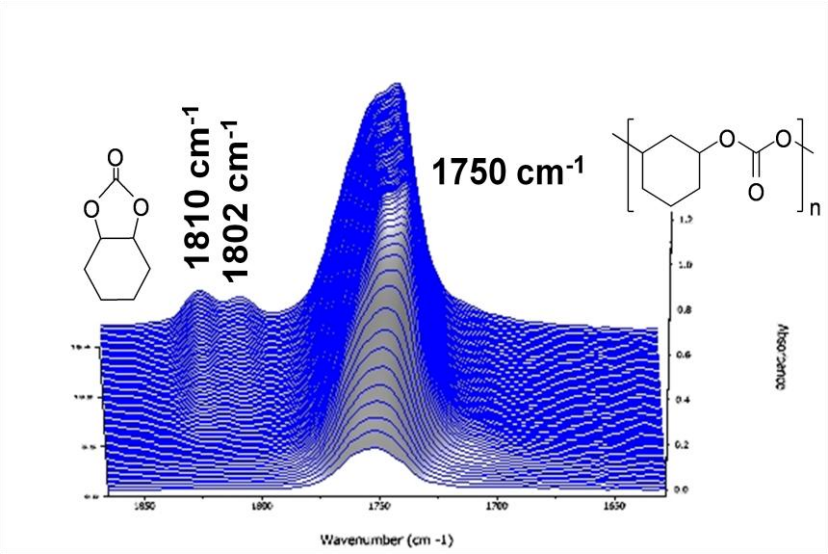


FIGURE 3.10. Typical three-dimensional stack plot of the infrared spectra collected every 3 min during the coupling reaction of cyclohexene oxide and CO_2 (80 °C and 55 bar pressure).

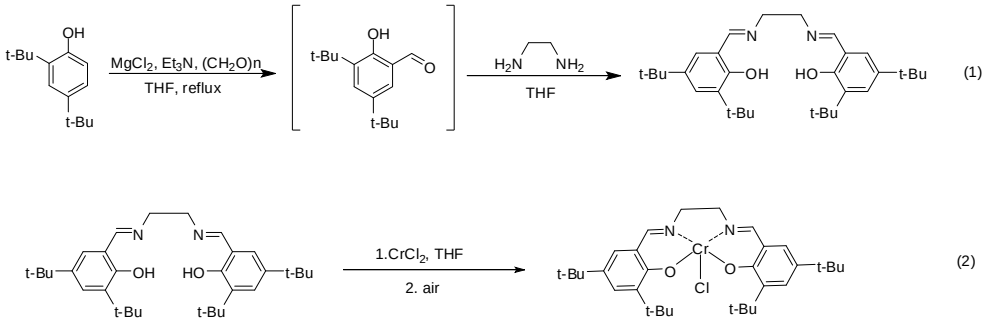
3.2 - Aim of the work

In this work studies to examine the activation barriers for cyclic carbonate formation from metal bound polymer chains in *isolated* (salen)Cr intermediates are reported. Importantly, the effect of excess, i.e., beyond one equivalent, of ionic cocatalyst on the rate of cyclic carbonate production has been investigated.

In an independent part of the project, the synthesis of a potentially CO_2-soluble fluorinated (salen)CrCl complex is reported and its results in the catalysis of the copolymerization process are investigated and compared to those obtained with a known catalyst.

3.3 - Results and discussion(part I)

The investigation was started by synthesizing a well known catalyst, Cr(salen)Cl, (H_2salen = *N,N'-bis*(3,5-di-*tert*-butylsalicylidene)-ethylenediimine). The complex was synthesized following previously published[33-34] procedures (scheme 3.7).



SCHEME 3.7. Synthesis of (salen)CrCl, H_2salen = *N,N'-bis*(3,5-di-*tert*-butylsalicylidene)-ethylenediimine

In order to ascertain that the specific catalytic system under study displayed behavior typical for these processes, a control experiment was carried out under the normally practiced conditions. Characteristic of these copolymerization processes, a reaction performed at 80°C for 4 hr at 500 psi with a monomer/catalyst/PPNCl loading of 2300:1:1 afforded a copolymer with 1% polyether linkages, a M_n of 12,000 (PDI = 1.09), and a TOF (mol epoxide consumed)/(mol catalyst•h) of 211. These observations are representative of previously reported data[35].

To investigate the degradation step of the metal bound polymer chain in the absence of other concurrent chemical processes it is desirous to carry out the copolymerization reaction to completion, i.e., to consume all of the epoxide monomer. Under the typical solventless copolymerization conditions, the reaction mixture becomes too viscous to achieve 100% conversion. Hence, for the purpose of this study the copolymerization process was carried out at a low monomer/catalyst/PPNCl ratio of 100:1:1 and with a methylene chloride

cosolvent. In a prototypical experiment performed in a stainless steel Parr reactor modified to accommodate an ASI ReactIR SiCOMP probe, the reaction was monitored in the ν_{CO_3} region *in situ* for copolymer and cyclic carbonate production (Figure 3.11). The isolated, purified copolymer obtained by this protocol exhibited 0-2% polyether linkages with a M_n value of 3500-4200 and a PDI of 1.2-1.4. Furthermore, there was only a trace of cyclic carbonate formed and cyclohexene oxide was completely consumed.

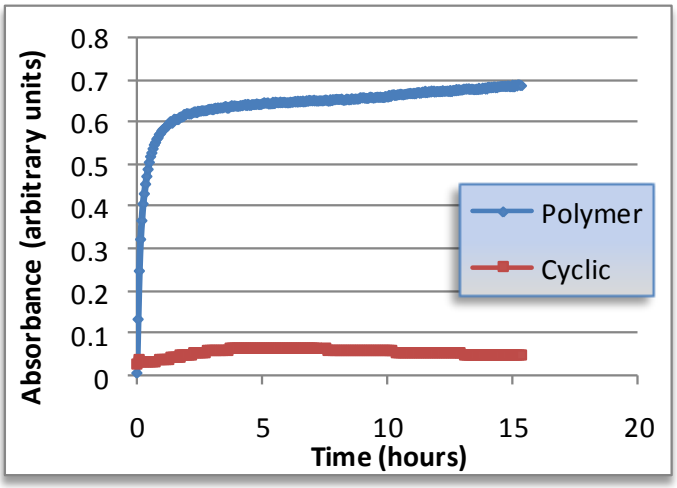


FIGURE 3.11. Reaction profile for formation of poly(cyclohexylene carbonate) and cyclohexylene carbonate as a function of time. Reaction carried out at 80°C in 500 psi CO_2 with a monomer/catalyst/PPNCl loading of 100:1:1 in methylene chloride.

The depolymerization reaction *via* the production of cyclic carbonate was similarly monitored by *in situ* infrared spectroscopy. This was accomplished utilizing a low molecular weight metal bound copolymer chain produced as described above and accompanied by the prior slow release of CO_2 from the reaction solution. Under these reaction conditions of 80°C and a minimal quantity of CO_2, the resting state of the metal bound copolymer chain is most likely species **2** in scheme 3.5. Hence, the backbiting reaction would proceed by way of a metal alkoxide intermediate. Figure 3.12 depicts the traces of the infrared absorptions in the ν_{CO_3} region for the copolymer chain decomposition with concomitant cyclic carbonate production at 80°C in methylene chloride. Initial rate data for the disappearance of poly(cyclohexylene carbonate) *via* formation of cyclohexylene carbonate as a function of temperature are

provided in Table 3.1, along with the calculated Arrhenius activation energy obtained from the corresponding plot in Figure 3.13.

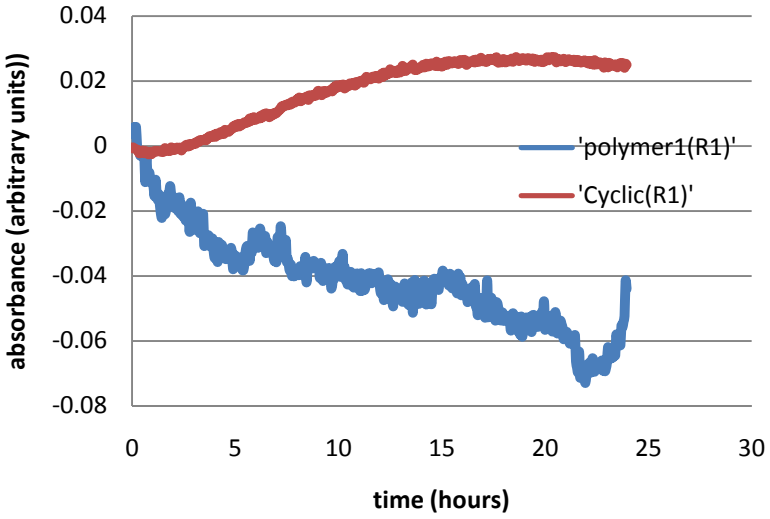


FIGURE 3.12. Depolymerization of metal bound copolymer chain with accompanying formation of cyclic carbonate at 80°C in CH_2Cl_2. — copolymer disappearance — cyclic appearance.

T(K)	Rate (abs/time)	$\Delta E^{\neq}$ activation
343.15	0.0058	
353.15	0.0135	**105 ± 7 kJ/mol**
363.15	0.0359	
373.15	0.1149	

TABLE 3.1. **Initial Rate Data for the Formation of Cyclohexylene Carbonate from Copolymer Degradation**

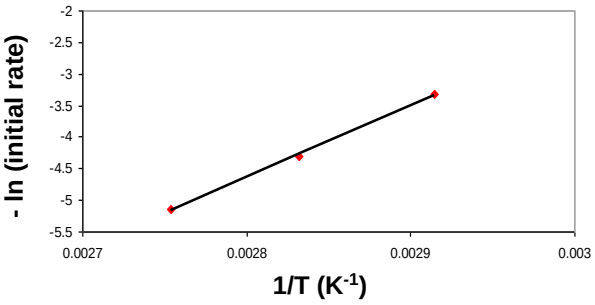


FIGURE 3.13. Arrhenius plot of rate data for copolymer → cyclic carbonate.

The rate of trans-cyclohexylene carbonate production during the copolymerization reaction performed in the traditional solventless manner was determined to have an $E^{\neq}act$ of 133 kJ/mol. Because of the high CO_2 pressure (55 bar), in this instance the backbiting process undoubtedly proceeds via the metal bound carbonate species **1** in Scheme 3.5. The lower activation barrier for the backbiting reaction of 105 kJ/mol determined herein in the absence of CO_2 suggests the pathway to cyclic carbonate *via* species **2** is lower than that of species **1** by about 28 kJ/mol. This is consistent with the observations that the selectivity for copolymer *vs.* cyclic carbonate production is greater at higher pressure of carbon dioxide. Figure 3.14 depicts the decrease in cyclic carbonate production with an increase in CO_2 pressure previously observed during the solventless copolymerization reaction[36].

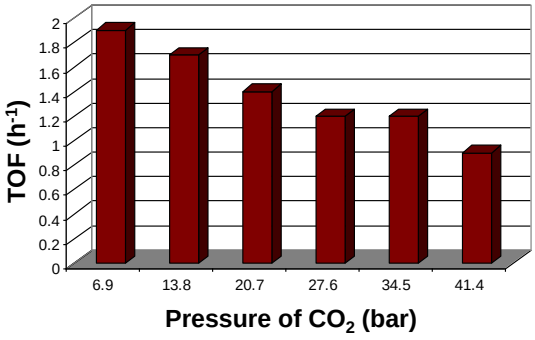


FIGURE 3.14. Production of cyclic carbonate as a function of CO_2 pressure. Data taken from ref. 36.

With an increase in reaction temperature the thus formed cyclic carbonate was found to undergo ring-opening polymerization to polyether and carbon dioxide. For example, see the reaction profile at 90°C in Figure 3.15, where the initially produced cyclohexylene carbonate shown in boxed area rapidly decomposes. For a temperature rise of 10°C (90°→100°) the polyether linkages in the remaining polymeric material increased from 15% to 27%.

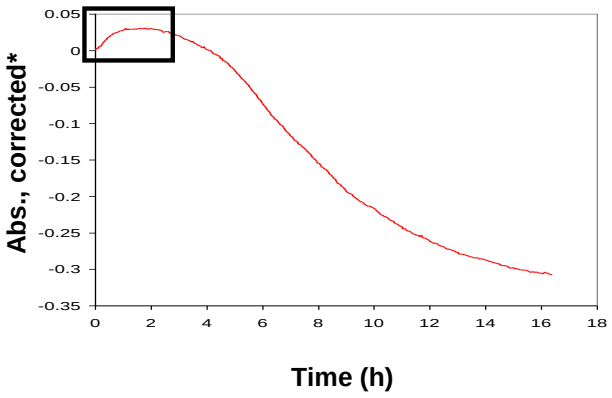
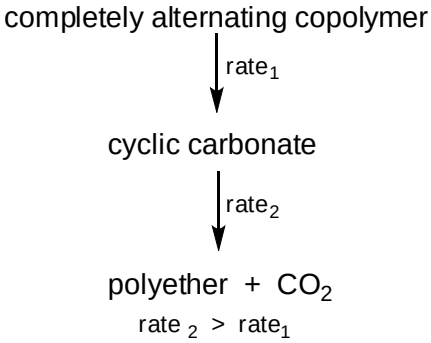


FIGURE 3.15. Depolymerization of poly(cyclohexylene carbonate) in CH_2Cl_2 at 90ºC followed by rapid ring-opening of cyclic carbonate to polyether and CO_2.

We anticipate, based on both experimental and theoretical studies[31-32], that in the presence of an excess of the anionic initiator (cocatalyst) the activation barrier for the "free copolymer chain" depolymerization *via* the backbiting mechanism (Scheme 3.5, step **b**) would be less than that found for pathway **a**. Upon augmenting the cocatalyst loading to two equivalents, it was readily apparent that this leads to faster cyclic carbonate production both during the polymerization and depolymerization steps. Unfortunately for the aims of this study upon increasing the anionic cocatalyst the ring-opening of the cyclic carbonate leading to polyether and CO_2 was enhanced to a greater extent than the copolymer depolymerization to cyclic carbonate (scheme 3.8). Nevertheless, it was apparent that the rate of copolymer degradation to cyclic carbonate was increased as the cocatalyst loading increased. Figure 3.16 depicts the 25% increase in copolymer depolymerization to cyclic carbonate upon increasing the concentration of PPNCl by a factor of 2.



SCHEME 3.8: Products of polymer degradation

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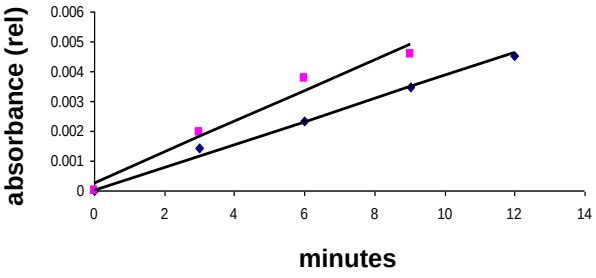


FIGURE 3.16. Rate of copolymer depolymerization *via* initial formation of cyclic carbonate

◆ 1 eq PPNCl ■ 2 eq PPNCl.

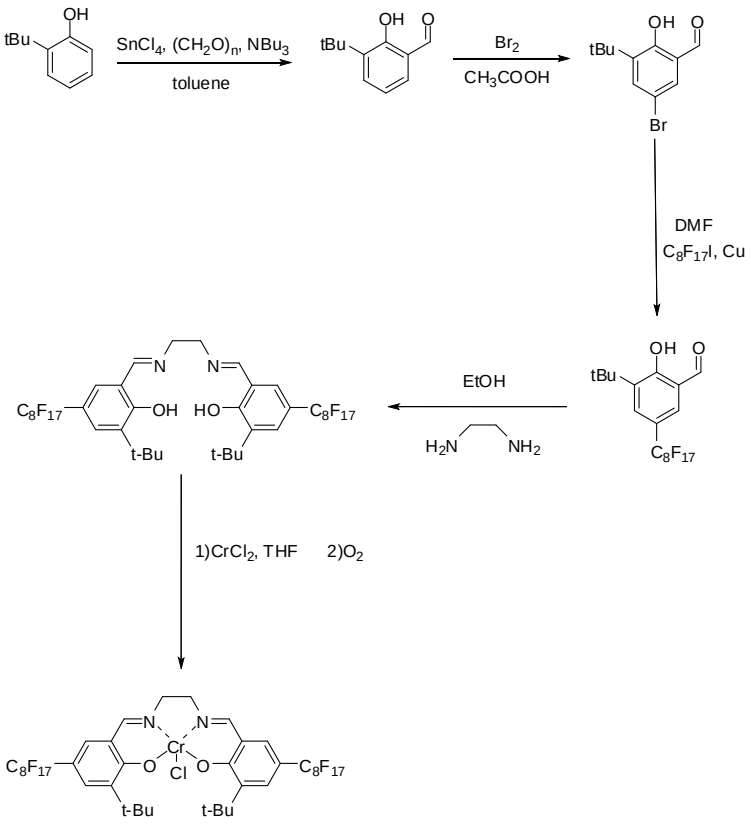
3.4 - Part II: Synthesis and application of a potentially CO_2-soluble Cr(salen)Cl catalyst

In a second part of the work, the synthesis of a potentially CO_2-soluble catalyst for the copolymerization of epoxides and CO_2 was carried out.

The developing of such a catalytic system would allow achieving two important goals: the production of colorless and completely metal free polymers, and the recycle of the catalyst. The strategy followed was to add to the salen ligand some perfluoroalkyl "ponytails" in order to enhance its affinity for carbon dioxide. In fact, it is well known in literature that perfluorocarbons generally have a great affinity for the supercritical carbon dioxide phase[37]. Scheme 3.8 depicts the synthetic pathway followed.

The ligand synthesis was accomplished following a literature procedure[38]. The complex was then obtained by causing the ligand to react with Cr(II) chloride as in the "standard" (salen)CrCl synthesis. Attempts of obtaining crystals of the complex suitable for X-ray spectroscopy were unsuccessful; however, the complex structure can be deduced by comparison of the IR spectra of the complex obtained with that of its analogue (salen)CrCl, that shows the same bands, except for a strong absorption at 1201 cm^{-1} due to ν_{C-F} vibration. (figure 3.17)

The catalyst obtained was then tested in a standard cyclohexene oxide – CO_2 copolymerization reaction and the results were compared with the performance of its non-fluorinated analogue (salen)CrCl under the same reaction conditions (T = 80°C, pCO_2 = 500 psi, t = 16 hours, catalyst and cocatalyst loading = 0.086 mmol per 20 ml of cyclohexene epoxide). Table 3.2 reports the results of both catalysts. The F-salen complex showed a significantly lower catalytic activity (about 50% decrease in TOF), but yielded a very good quality polymer. A lower activity is an acceptable drawback if it is possible to recover and recycle the catalyst.



SCHEME 3.8. Synthesis of the (F-salen)CrCl catalyst.

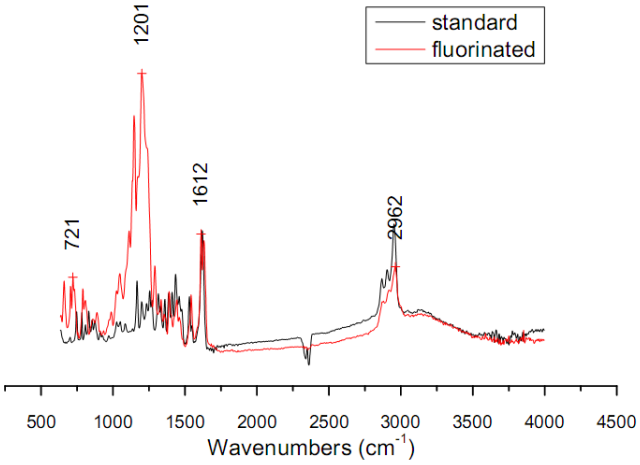


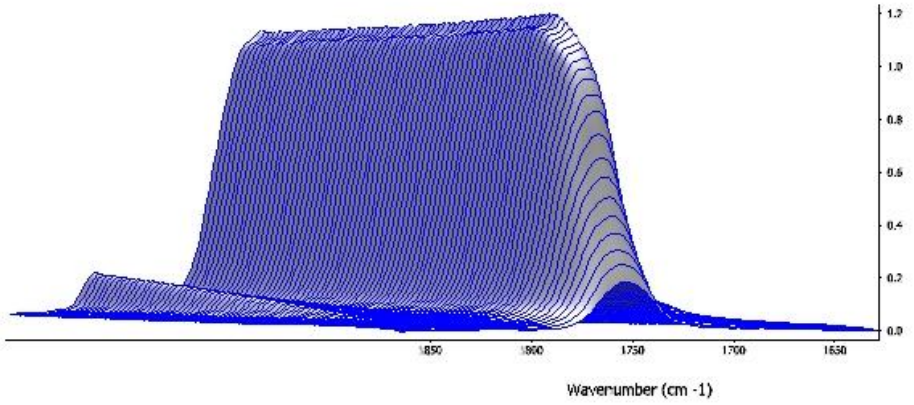
FIGURE 3.17. Comparison between (salen)CrCl (black) and (F-salen)CrCl (red) IR spectra.

	Standard Cr(salen)Cl catalyst	Cr(F-salen)Cl catalyst
Catalyst amount needed per run	50 mg	111 mg
Polymer yield	10 g	5.5 g
TOF (mol CHO consumed / (mol catalyst * time))	212 h-1	111 h-1
Polyether content(NMR)	1%	<1%
Mn	12000	11300
PDI	1.09	1.07

TABLE 3.2. Comparison between complex X and its fluorinated analogue X as catalysts for the copolymerization of cyclohexene oxide and CO_2.

Interestingly, a reaction monitored via ATR-IR in situ spectroscopy (figure 3.18) showed that the production of cyclic byproduct starts after the polymer production has ended; thus, it would possible to stop the reaction at the proper time (5 hours in the case under study) and completely avoid the production of cyclic carbonate.

The solubility of this complex in dense CO_2 is challenging. As for as now, the catalyst has not been solubilized in dense or supercritical CO_2 under any condition. Currently new strategies are being followed in order to obtain a more CO_2-philic catalyst, including the synthesis of a more fluorinated analogue of X[39].



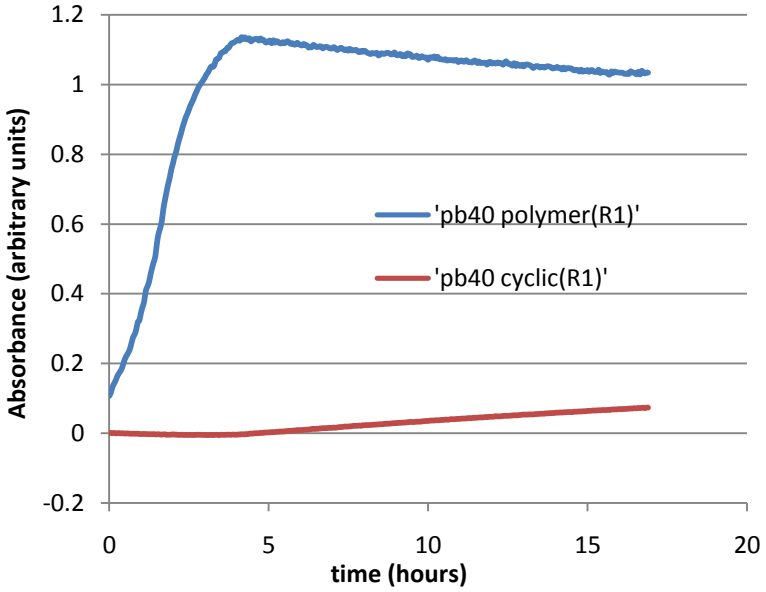


FIGURE 3.18. 3D and 2D reaction profiles for copolymer (blue) and cyclic carbonate (red) for the (F-salen)CrCl catalyzed copolymerization.

3.5 - Conclusions

The (salen)CrCl copolymerization of epoxides and carbon dioxide constitutes a green and efficient protocol for the synthesis of various polycarbonates. Two of the main issues that still affect this process are the coproduction of cyclic carbonates and the difficult separation of the catalyst.

In the first part of this work an investigation on the mechanism and kinetics of the formation of cyclic carbonate has been presented. We have shown from a model system, designed to produce a low molecular weight bound copolymer chain from the completely alternating copolymerization of cyclohexene oxide and CO_2, that in the absence of these comonomers in methylene chloride, cyclic carbonate is produced *via* the backbiting mechanism with an activation energy of 105 ± 7 kJ/mol. This process is assumed to take place *via* a metal alkoxide (polymer chain) intermediate. This activation barrier is significantly lower than that previously reported for formation of cyclic carbonate during the copolymerization of cyclohexene oxide and CO_2 at 55 bar, a process presumably occurring by way of a metal-carbonate (polymer chain) intermediate. Additionally, this study revealed that the depolymerization reaction leading initially to cyclic carbonate was demonstrated to be enhanced in the presence of excess anionic cocatalyst, presumably by way of a metal displaced anionic copolymer chain. Unfortunately, subsequent ring-opening of the cyclic carbonate with concomitant formation of polyether and CO_2 was fast at these reaction temperatures (80-100ºC) such that it was not possible to adequately access the effect of increasing anion initiator concentrations on cyclic carbonate production.

In the second part of the work, a new complex, (F-salen)CrCl, was synthesized with the intent of utilizing it as a potentially CO_2 – soluble catalyst. Separation of the catalyst from the reaction mixture via supercritical extraction would constitute a powerful way of obtaining metal-free products and eventually recycling the catalyst. The complex shown appreciable catalytic activity (TOF of 111 moles converted per mole of catalyst per hour); however, it was not possible to separate it from the reaction mixture due to its low solubility in

liquid and supercritical CO_2. Further developments will include the synthesis of a second generation fluorinated catalysts.

3.6 - Experimental

3.6.1 - Materials and Methods.

Unless otherwise stated all synthesis and manipulations discussed were carried out on a double-manifold Schlenk vacuum line under an argon atmosphere or in an argon filled glove box. Methanol and dichloromethane were freshly purified by a MBraun Manuel Solvent Purification System packed with Alcoa F200 activated alumina desiccant.
Cyclohexene oxide was purchased from TCI America and freshly distilled from CaH_2.
Bone dry carbon dioxide was purchased from Scott Specialty Gases equipped with a liquid dip-tube. ^{1}H and ^{13}C NMR spectra were acquired using Unity+ 300 MHz and VXR 300 MHz superconducting spectrometers. Infrared spectra were recorded on a Mattson 6021 FT-IR spectrometer.

3.6.2 – Procedures and characterizations

N,N'-bis(3,5-di-tert-butylsalicylidene)-ethylenediimine. The synthesis was partially based on a literature procedure[33]. To a stirred suspension of 2,4-di-tert-butylphenol (4.12 g, 20 mmol), anhydrous $MgCl_2$ (3.81 g, 40 mmol) and dry paraformaldehyde (1.32 g, 44 mmol) in dry THF (80 ml), kept at ambient temperature, was added dropwise dry Et_3N (4.05 g, 40 mmol). The green-colored reaction mixture was then heated to gentle reflux for 2 h. A solution of diethyleneamine (600 mg, 10 mmol) in THF was added dropwise at ambient temperature. After addition was complete, the reaction mixture was heated for 4 h at 80 C. The yellow-colored reaction mixture was cooled and added to water. The product was extracted with CH_2Cl_2 (3 · 100 ml), the combined organic fractions were washed with water (50 ml), brine (2 · 50 ml), and dried ($MgSO_4$). Removal of solvents afforded N,N'-bis(3,5-di-tert-butylsalicylidene)-ethylenediimine) as a yellow powder. (80% yield).
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 11.64 (s, 2H), 8.39 (s, 2 H), 7.36 (d, J=2.6 Hz, 2H), 7.06(d, J=2.6 Hz, 2H), 3,92(s, 4H), 1.43 (s, 18H), 1.28 (s, 18H).

(salen)CrCl (H_2salen = *N,N'-bis*(3,5-di-*tert*-butylsalicylidene)-ethylenediimine) was synthesized according to the previously published procedure[34].
The H_2salen ligand (1.0 equiv) and chromium(II) chloride (1.1 equiv) were dissolved in THF and stirred under argon at ambient temperature for 24 h. The reaction mixture

then was exposed to air and stirred for an additional 24 h. After the reaction mixture was poured into diethyl ether, the organic layer was washed with aqueous saturated NH_4Cl (3 100 ml) and brine (3 • 100 ml) followed by drying with Na_2SO_4. After filtration to remove solid impurities and drying agent, solvent was removed in vacuo, yielding a dark brown powder.

General Procedures for Cyclohexene Oxide/CO2 Copolymerization. Fifty milligrams (0.086 mmol) of (salen)CrCl and one equivalent of PPNCl (PPN^+ = *bis*-triphenyl-phosphoranylidene)ammonium) were dissolved in a one-to-one mixture of CH_3OH/benzene and the solution was taken to dryness under vacuum over a 3 hour period. 20 ml of freshly distilled cyclohexene oxide were added and the solution was cannulated into a stainless steel reactor which had been dried under vacuum at 80ºC for over six hours. The reactor was loaded with 500 psi of CO_2 and set to the desired temperature for 4 hours. Subsequently, the reactor was vented in a fume hood and the product was recovered with the minimum quantity of methylene chloride. The copolymer was precipitated from methanol in the presence of HCl. The copolymer was isolated and dried at 100ºC under vacuum overnight, weighed and analyzed by ^1H NMR spectroscopy.

Fluorinated (salen)CrCl synthesis. The ligand was prepared according to a literature procedure[38]. The complex was prepared utilizing the procedure reported above for the synthesis of Cr(salen)Cl. The complex was isolated as a brown powder in a 75% yield.

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Chapter 4

Project III:

Catalysis in biphasic or aqueous systems: synthesis and reactions of heptadienoates

Water is the less expensive and less hazardous solvent available. Its use in organic syntheses has traditionally been neglected mainly because of solubility problems. Nevertheless, in some cases it is possible not only to accomplish in water reactions that were traditionally carried out in conventional organic solvents, but also to exploit its properties to improve the performance of the process. In this chapter a detailed account of the use of biphasic or aqueous systems for the synthesis of heptadienoic acids and derivatives either from allyl-3-butenoate or from 3-butenoic acid and an allyl derivative is presented. The relationships between reaction conditions and yields and selectivities are studied and the results discussed. In the last part of the work, the reactivity of heptadienoates in a Pd-catalyzed oxidative cyclization-acyloxylation reaction is investigated.

Part of this work has been published as:

Bottarelli P., Costa M., Gabriele B., Salerno G., Yebeutchou M., "Catalysis in water: Highly efficient synthesis of heptadienoic acids by rearrangement of allyl but-3-enoate promoted by Rh(I) complexes", *J. Mol. Cat. A, Chem.*, 274 (1)(**2007**), 87-94.

4.1 - Background

4.1.1 - General synthesis methods for heptadienoic acids

Heptadienoic acids and their derivatives are an important class of compounds, which have found application as useful intermediates for the synthesis of compounds of biological and pharmaceutical interest. Heptadienoic acid and its alkyl esters have in fact found extensive use as reported in the literature[1-11].

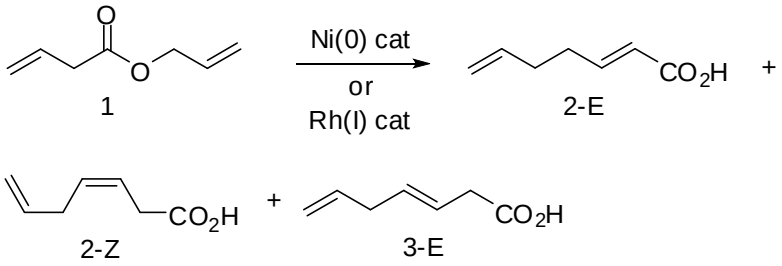
Unsaturated α-amino acids, key components in the synthesis of a class of biologically active peptides, were obtained in enantiomerically pure form starting from heptadienoic acid derivatives[12]. They are also useful chiral synthons and their synthetic interest has recently increased with the advent of ring closing metathesis (RCM) methodologies.

Several approaches to the synthesis of dienoic acids have been reported in the literature. A general organic procedure is based on the reaction of lithium dienenolates (obtained from unsaturated carboxylic acids, in particular but-3-enoic acids) with allylic halides[14]. However, their synthesis is characterized by poor γ-regioselectivity. An indirect way to achieve a γ-regioselective alkylation consists of a tandem process, in which the mixture of the α- and γ-alkylated products obtained from allylation of the lithium dienolate of an unsaturated carboxylic acid is subjected to Cope-rearrangement[15]. In the case of allylic halides as electrophiles, regioselective alkylation at the γ-carbon has also been attained[16-17] by changing the counterion of the dienolate from lithium to Cu^{+}. An alternative approach to the stereospecific generation of 1,4- and 1,5-dienes developed by Corey et al.[18] is based on the addition of vinyl-copper and methallylcopper reagents to 2,4-pentadienoic esters to give (*E*)-3,6-heptadienoate and (*E*)-3,7-(7-methyl)octadienoate ester derivatives in good yields. Another protocol is based on the reaction of 1,5-hexadiene with a solution of cesium metal in THF, in the presence of 18-crown-6 at -75 °C, to afford a hexadienyl anion that can then undergo carbonatation to give a mixture of the cesium salts of 2-vinyl-4-pentenoic acid and (*E*) and (*Z*)-3,6-heptadienoic acid[19].

4.1.2 - Heptadienoates by catalytic rearrangement of allyl but-3-enoate

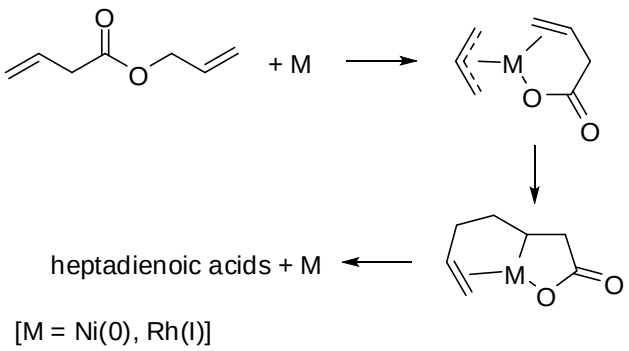
All the above-described procedures are suitable for small scale preparations. For larger scale syntheses, it is more convenient to follow an alternative way, based on the Wittig reaction, which makes use of unsaturated aldehydes and organic phosphorous compounds[7]. Nevertheless, techniques of this type require the preliminary preparation of the suitable aldehyde, as well as the stoichiometric use of a phosphorous reagent, which causes problems in connection with the present environmental requirements. This approach is therefore substantially not attractive for an industrial application. There are also known catalytic processes for the preparation of dienoic acids by reacting vinyl or allyl halides with acetylene and carbon monoxide in hydroxylated solvents in the presence of nickel carbonyl or precursor thereof[20]. Even these methods are not suitable for industrial applications, owing to the high toxicity of nickel carbonyl derivatives.

Several years ago it was reported that some phosphorous-containing Ni(0) and Rh(I) complexes were able to catalyze, in aprotic organic solvents and under mild conditions, the rearrangement of allyl but-3-enoate to a mixture of 2,6- and 3,6-heptadienoic acids (Scheme 4.1)[21].



SCHEME 4.1. Rearrangement of allyl but-3-enoate in presence of Rh or Ni based catalysts.

This approach took advantage of the chelating effect for achieving the formation of a new C-C bond[22-23]. In fact, the formation of a chelate complex can assist the oxidative addition to the metal center of the but-3-enoato group, which is thus held in the appropriate position for the double bond insertion (Scheme 4.2). A final β-H elimination step then leads to heptadienoic acids with regeneration of the metal catalyst.



SCHEME 4.2. Chelation effect and mechanism of the Rh-catalyzed rearrangement of allyl but-3-enoate. Ligands are not shown for clarity.

Good yields were obtained with both nickel(0) and rhodium(I) catalytic systems. Reactions occurred between 20 and 80° C under nitrogen. The $Rh(PPh_3)_3Cl$ complex in MeCN or THF at room temperature gave a 90% yield of 3,6-heptadienoic acids, predominantly the *E* one. The complex deriving from one molecule of $Ni(COD)_2$ + $P(OiPr)_3$ in anisole at room temperature gave a 66% yield of 2,6- and 3,6-heptadienoic acids in a ca. 1:9 molar ratio. The main byproducts were the allyl esters of the heptadienoic acids. Catalytic efficiencies ranged from 180 TON for the Ni-catalyzed reactions to 255 TON for the Rh-catalyzed ones.

The two types of complexes exhibited a different catalytic activity depending on the environments provided by the nature of the phosphorus-containing ligands, which also affected the 2,6-/3,6-heptadienoic acid molar ratio. The $Rh(PPh_3)_3Cl$ complex reacted much more rapidly at room temperature than $Ni(COD)_2$ + $P(OiPr)_3$ and its activity was strongly influenced by solvents. Aprotic solvents, such as MeCN, $CHCl_3$, and THF, gave good results, while strongly coordinating solvents (like DMSO or DMF) were not effective. Interestingly, the reaction rates for both the rhodium and nickel-catalyzed processes were reduced in the presence of an excess of products, owing to the competition for the active sites on the metal.

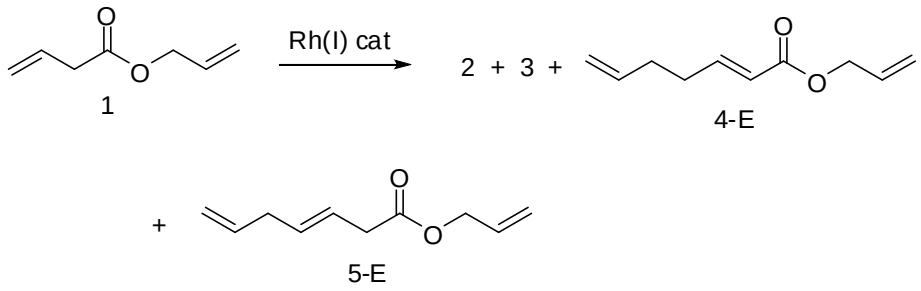
4.2 - Aim of the work

This work consists of three parts. In the beginning, we investigated the possibility of carrying out the rearrangement of allyl but-3-enoate in a green reaction medium such as water or in biphasic organic-water systems. Since the results were satisfactory, in the second part of this work we further extended our reaction system to the direct combination in water or aqueous/organic medium of but-3-enoic acids and allyl derivatives. Different products were found to be formed in the reaction; thus, a more extensive investigation on the effects of the reaction conditions on the selectivity was carried out. Substituted butenoic acids and allyl bromides were tested in the reaction in order to ascertain the generality of the protocol. In the last part of the work, a possible subsequent reaction of heptadienoic derivatives, such as an acyloxylation-cyclization reaction in water, was investigated.

4.3 – Part I: heptadienoic acids by rearrangement of allyl but-3-enoate in water. Results and discussion

4.3.1 - Preliminary tests: reactions in organic solvent

With the aim of developing a more efficient and practical version of Chiusoli's interesting approach to heptadienoic acids, we have investigated the possibility to improve the catalyst performance and carry out the reaction in aqueous media. We have first investigated the catalytic activity of rhodium(I) complexes containing triphenylphosphine, ethylene, 1,5-hexadiene and cyclooctadiene (COD) ligands in the rearrangement reaction of allyl but-3-enoate in different organic solvents. Thus, $Rh(PPh_3)_3Cl$, $[Rh(C_2H_4)_2Cl]_2$, $[Rh(C_6H_{10})_2Cl]_2$, $[Rh(COD)Cl]_2$ and $[Rh(COD)_2]BF_4$ complexes were caused to react with allyl but-3-enoate in aprotic solvents at 100° C for 18 h. The reaction led to a mixture of heptadienoic acids **2** and **3**, together with smaller amounts of their corresponding allyl esters **4** and **5** (formed by partial transesterification of **2** and **3** with **1**, scheme 4.3). The yields and selectivities obtained are reported in Table 4.1.



SCHEME 4.3. General scheme representing the main products of the reaction.

Entry	Rh Complex	Solvent (5 ml)	Conversion of 1 %[b]	Yield %[b]	Selectivity %		Yield %[b]
				(**2**+**3**)	2,6-(E) **2**/(**2**+**3**)	3,6-[(E)+(Z)] **3**/(**2**+**3**) [c]	(**4**+**5**)
1	$Rh(PPh_3)_3Cl$	MeCN	≥ 99	84	3	97	7
2	$Rh(PPh_3)_3Cl$	C_3H_7CN	≥ 99[d]	82	7	93	7
3	$Rh(PPh_3)_3Cl$	CH_2Cl_2	79[d]	63	2	98	6
4	$Rh(PPh_3)_3Cl$	THF	96[d]	87	1	99	3
5	$Rh_2(C_2H_4)_4Cl_2$	MeCN	95[d]	75	8	92	8
6	$Rh_2(C_2H_4)_4Cl_2$	C_3H_7CN	≥ 99	86	6	94	6
7	$Rh_2(C_6H_{10})_2Cl_2$	MeCN	95	76	8	92	8
8	$Rh_2(C_6H_{10})_2Cl_2$	C_3H_7CN	≥ 99	86	5	95	6

TABLE 4.1. Catalytic rearrangement reaction of allyl but-3-enoate **1** to heptadienoic acids **2**-**3** and esters **4**-**5** in organic solvents at 100° C for 18 h.[a]

[a]) All reactions were carried out under the following conditions: **1**(2.6 mmol), $Rh(PPh_3)_3Cl$ ($2.6\cdot10^{-2}$ mmol), $[Rh(C_2H_4)_2Cl]_2$, $[Rh(C_6H_{10})_2Cl]_2$, ($1.3\cdot10^{-2}$ mmol), solvent (5 ml). [b]) Based on GLC analyses (after methylation of the products) referred to $C_6H_4Cl_2$ as an internal standard. [c]) (*E*/*Z*) molar ratios ranged from 3.7 to 5.6. [d]) 4-allylhepta-2,6-dienoioc acid **6** (3-5%) was also formed.

The reaction practically did not occur in hydrocarbon solvents such as methylcyclohexane or toluene in the presence of the complexes listed in Table 4.1. $Rh(PPh_3)_3$ showed a satisfactory activity in aprotic solvents, such as MeCN, C_3H_7CN, THF, and CH_2Cl_2 at 100° C (entries 1-4). Rhodium(I) complexes containing olefin or diolefin ligands (with the exception of the $[Rh(COD)Cl]_2$ and $[Rh(COD)_2]BF_4$ complexes, which were practically ineffective in all the above mentioned solvents) showed an activity similar to that of $Rh(PPh_3)_3$ only in nitrile solvents (entries 5-8), which likely act as electron donor ligands in the crucial oxidative addition step without interfering with the formation of the chelating ring. Rhodium complexes containing olefinic ligands showed a more marked decrease of activity at T < 100 °C with respect to that containing

triphenylphosphine, which in its turn showed a stronger activity decrease in CH_2Cl_2 and THF in comparison with nitrile solvents.

Reaction selectivities did not vary significantly. The product distribution, using either ethylene or 1,5-hexadiene rhodium complexes under the same reaction conditions, were similar, as shown by the results reported in entries 5, 7 and 6, 8 of Table 4.1. This behavior may be ascribed to the fact that as soon as the formation of heptadienoic acids, particularly 2,6-heptadienoic acid, occurs, the rhodium coordinated olefinic ligands are replaced by the acid giving a new catalytic species. To confirm this hypothesis, $[Rh(C_2H_4)_2Cl]_2$ was caused to react with 2,6- and 3,6-heptadienoic acids in CH_2Cl_2 at room temperature to give yellow and red-brown powders respectively. Elemental analyses agreed with a formula corresponding to $Rh(C_7H_{10}O_2)Cl$ for both solids, even though dinuclear species may be formed and different isomers may be present. These powders, scarcely soluble in organic solvents, were soluble in aqueous $NaHCO_3$. The ^1H NMR spectra in this medium did not allow a straightforward spectroscopic structure determination, however, since the signals were too broad. In any case, when these solids were used as catalysts in butyronitrile under the same experimental conditions similar results to the ones of entries 6 and 8 in Table 1 were obtained. On the other hand, a large excess of 3,6- and 2,6-heptadienoic acids in the reaction mixture (1:1 molar ratio with respect to allyl but-3-enoate) tended to prevent the coordination of allyl but-3-enoate to the metal center, thus causing a marked decrease of conversion. Clearly, the negative effect exerted by an excess of products on catalyst activity did not allow the achievement of high TON (Turn Over Numbers) in these reactions (TON were typically around 100 mol of product obtained per mol of catalyst used). However, the acidic nature of the products prompted out to investigate the possibility to carry out the reaction in a biphasic system, consisting of an organic solvent and an alkaline aqueous solution, in order to favor the transfer the products, as soon as they are formed, into the aqueous phase as carboxylates.

4.3.2 - Reactions in biphasic media

The results obtained by using a biphasic system with a saturated $NaHCO_3$ solution as the aqueous phase are shown in Table 4.2. As it can be seen from

the Table, good yields of heptadienoates were indeed obtained under the biphasic conditions working with a substrate to rhodium molar ratio of ca. 400, thus confirming the validity of our hypothesis. Similar results were achieved when the substrate/catalytic complex molar ratio was raised to 800.

Entry	Rhodium Complex	Solvent (3 ml)	Conversion%[b]	Acids Yield %[b]	Selectivity %		Allylic esters Yield %[b]	
					2,6 (*E*)	3,6 (*E*	2,6	3,6
				(**2**+**3**)	**2**/(**2**+**3**)	**3**/(**2**+**3**)	**4**	**5**
9	$Rh(PPh_3)_3Cl$	C_3H_7CN	91[d,e]	48	100	-	8	3
10	$[Rh(COD)\ Cl]_2$	C_3H_7CN	96[d,f]	67	72	28	3	2
11	$[Rh(COD)_2]BF_4$	C_3H_7CN	99[d,g]	78	86	14	4	0
12	$[Rh(C_6H_{10})\ Cl]_2$	C_3H_7CN	96[d,g]	77	82	18	5	1
13	$[Rh(C_2H_4)_2Cl]_2$	C_3H_7CN	$\geq$99[g]	86	96	4	4	1
14	$[Rh(C_2H_4)_2Cl]_2$	CH_2Cl_2	89[d,g]	74	92	8	4	1
15	$[Rh(C_2H_4)_2Cl]_2$	DEE[c]	92[d,g]	78	93	7	3	1
16	$[Rh(C_2H_4)_2Cl]_2$	Toluene	90[d]	81	96	4	2	0
17	$[Rh(C_2H_4)_2Cl]_2$	C_6H_5Cl	93	83	96	4	3	1

TABLE 4.2. Catalytic rearrangement reaction of allyl but-3-enoate **1** to heptadienoic acids 2-3 and esters 4-5 in the biphasic system organic solvent / satd $NaHCO_3$ at 100° C for 12 h.[a]

[a]) All reactions were carried out under the following conditions: **1** (16.43 mmol), $Rh(PPh_3)_3Cl$, $[Rh(COD)_2]BF_4$ ($4.0\cdot10^{-2}$ mmol), $[Rh(C_2H_4)_2Cl]_2$, $[Rh(C_6H_{10})_2Cl]_2$, $[Rh(COD)Cl]_2$ ($2.0\cdot10^{-2}$ mmol), $NaHCO_3$ saturated water solution (5 ml), organic solvent (3 ml). [b]) Based on GLC analysis (after acidification and methylation of the products) referred to $C_6H_4Cl_2$ as an internal standard. [c]) DEE = diethoxyethane. [d]) Butenoic acid recovered from reaction mixture completes the molar balance. [e]) 4-allylhepta-2,6-dienoioc acid **6** (3%) was also formed. [f]) Compound **6** (2%) was also formed. [g]) Compound **6** (1%) was also formed.

The use of $Rh(PPh_3)_3Cl$ or $[Rh(COD)Cl]_2$ led to a lower yield in heptadienoic acids **2** and **3** (entries 9 and 10) compared with the other olefin rhodium(I) complexes tested (entries 11-17). However, it is worth noting that the $[Rh(COD)Cl]_2$ complex was now able to promote the rearrangement process in biphasic media, in contrast with its inactivity in organic solvents (see above). Moreover, a reversed selectivity in favor of the 2,6-heptadienoic derivative instead of 3,6- isomer (the most abundant isomer formed in organic solvents) was observed in all cases.

4.3.3 - Catalytic reaction in aqueous basic media

Very interestingly, a quantitative ICP determination of the rhodium dissolved in the organic phase and in the basic aqueous phase after reagent mixing as well as at the end of the reaction showed that more than 90% of the metal was actually in the aqueous phase. In a similar way, when the reagents were mixed in satd $NaHCO_3$, without additional organic solvent, the ICP analysis of the mixture showed that more than 95% of the metal was in aqueous phase, with the remaining 5 % lying into allyl but-3-enoate. We therefore expected that the reaction could also be carried out in the absence of added organic solvents. Indeed, the reaction carried out in satd $NaHCO_3$, without any organic solvent, proceeded nicely and afforded the heptadienoates in high yield (Table 4.3). Both the substrate conversion rate and product yields were actually higher compared to the reactions carried out in the biphasic system.

The basic aqueous phase then helps to speed up the reaction, since the heptadienoates, stabilized by ionic interaction with water, cannot interfere with the substrate for coordination to rhodium. The next experiments, aimed at optimizing catalytic efficiency and product yield, were therefore carried out in satd. $NaHCO_3$ at 100° C in the presence of different rhodium (I) complexes, in some cases containing different molar ratios of TPPTS (3,3',3''-phosphinidynetris(benzenesulfonic acid), trisodium salt) and with a substrate/rhodium molar ratio up to 4000 (Table 4.3).

Very good yields (73-90%) were obtained with rhodium(I) complexes containing olefin or diolefin ligands (entries 19-21 and 25-27). Thus, the TON in the reaction carried out in the absence of organic solvents reached 3600. On the other hand, $Rh(PPh_3)_3Cl$ and $Rh(C_2H_4)_2Cl]_2$ in presence of TPPTS led to less

satisfactory results (entry 22-24, 28). Thus, the TON in the reaction carried out in the absence of organic solvents reached 3600.

As in the case of the reactions carried out in biphasic media, the most abundant isomer formed in satd. $NaHCO_3$ turned out to be the 2,6-heptadienoate (**2**) rather than the 3,6-unsaturated one (**3**).

The presence of a water soluble phosphine like TPPTS as an additional ligand (entries 22-24) decreased the reactivity of the system. This effect was more enhanced at higher TPPTS/Rh molar ratios. In addition, the selectivity of the reaction turned towards the 3,6- unsaturated isomer. The decreased reactivity can be attributed to a strong coordination of the phosphinic ligand to the metal that prevents the coordination of the substrates. On the other hand, the increase of the amount of TPPTS enhances the electronic density on the metal, disfavoring the elimination of a proton from the β-carbon, thus shifting the selectivity towards the 3,6-unsaturated product.

In order to investigate the possible effect on selectivity , an organic base (diisopropylethylamine) was also tested under the conditions described in Table 4.1. Actually, the selectivity of the reaction did not vary significantly, while the conversion was strongly decreased to 47% if $Rh(PPh_3)Cl$ was used as a catalyst and to 23% if $[Rh(C_2H_4)_2Cl]_2$ was used. This effect confirms that the active metal needs to be as free as possible from additional ligands to favor the coordination of the reagents and obtain the best performance.

Chelate effect brought about by bidentate phosphine ligands, such as ethylenebis(diphenylphosphine) completely inhibited the rearrangement process. Actually, bidentate ligands could prevent the right coordination of but-3-enoate double bond on rhodium(III) intermediate species.

Entry	Rhodium Complex	Substr. / Rh Molar ratio	Sat. $NaHCO_3$ ml	Time h	Conv. %[b] 1	Yield %[b] 2+3	Selectivity % 2,6-(*E*) **2**/(**2**+**3**)	Selectivity % 3,6-(*E*) **3**/(**2**+**3**)	Yield %[b] 4+5
18	$[Rh(C_6H_{10})Cl]_2$	200	5	1	65	63	≥ 99	-	-
19	$[Rh(COD)Cl]_2$	2000	10	16	99	82	79	21	7
20	$[Rh(COD)_2]BF_4$	2000	10	16	88	73	84	16	6
21	$[Rh(C_2H_4)_2Cl]_2$	2000	10	16	97	88	93	7	3
22	$[Rh(C_2H_4)_2Cl]_2$, 2 equiv. TPPTS	2000	10	16	89	62	87	13	-
23	$[Rh(C_2H_4)_2Cl]_2$, 4 equiv. TPPTS	2000	10	16	91	56	73	27	5
24	$[Rh(C_2H_4)_2Cl]_2$, 6 equiv. TPPTS	2000	10	16	94	28	60	40	-
25	$[Rh(C_6H_{10})Cl]_2$	2000	10	16	93	85	96	4	3
26	$[Rh(C_2H_4)_2Cl]_2$	4000	10	36	≥99[c]	90	89	11	3
27	$[Rh(C_6H_{10})Cl]_2$	4000	10	36	95[c]	83	96	4	4
28	$Rh(PPh_3)_3Cl$	2000	7.5	36	95[c]	53	66	34	4

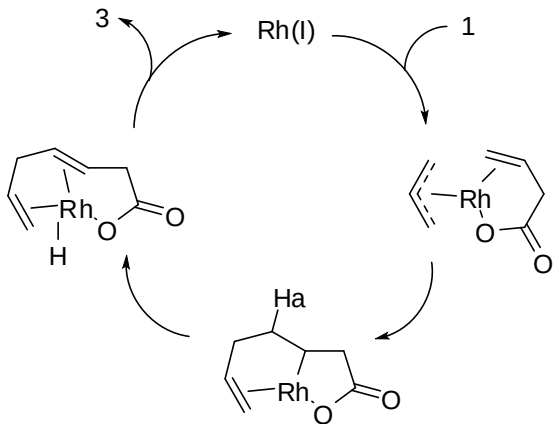
TABLE 4.3. Catalytic rearrangement reaction of allyl but-3-enoate **1** to heptadienoic acids **2**-**3** and esters **4**-**5** in satd. $NaHCO_3$.[a]

[a]) The reactions were carried out under the following conditions: Entry 20: **1** (5.0 mmol), $[Rh(C_6H_{10})_2Cl]_2$ ($1.2\cdot10^{-2}$ mmol), in satd. $NaHCO_3$; entries 21 and 30: **1** (24.65 mmol), $Rh(PPh_3)_3Cl$, $[Rh(COD)_2]BF_4$ ($1.2\cdot10^{-2}$ mmol); entries 23-27-29: **1** (24.65 mmol), $[Rh(COD)Cl]_2$, $[Rh(C_2H_4)_2Cl]_2$, $[Rh(C_6H_{10})_2Cl]_2$ ($3.1\cdot10^{-3}$ mmol), in satd. $NaHCO_3$; entry 24: **1** (24.65 mmol), $[Rh(C_2H_4)_2Cl]_2$ ($3.1\cdot10^{-3}$ mmol), TPPTS ($6.2\cdot10^{-3}$ mmol) in satd. $NaHCO_3$; entry 25: **1** (24.65 mmol), $[Rh(C_2H_4)_2Cl]_2$ ($3.1\cdot10^{-3}$ mmol), TPPTS ($1.24\cdot10^{-2}$ mmol) in satd. $NaHCO_3$ entry 26: **1** (24.65 mmol), $[Rh(C_2H_4)_2Cl]_2$ ($3.1\cdot10^{-3}$ mmol), TPPTS ($1.86\cdot10^{-3}$ mmol) in satd. $NaHCO_3$ [b]) Based on GLC analysis (after acidification and methylation of the products) referred to $C_6H_4Cl_2$ as an internal standard. [c]) Butenoic acid recovered from reaction mixture completes the molar balance.

Attempts to give a more general application of the rearrangement reaction were experienced extending the investigation to differently substituted allyl esters of but-3-enoic acid. Thus crotyl or cyclohex-2-enyl or 1-methylallyl but-3-enoate (2.6 mmol) was added to a solution of $[Rh(C_2H_4)_2Cl]_2$ ($2.6\cdot10^{-2}$ mmol) in CH_3CN (5 ml) and heated at 100° C under stirring for 24 h. Alternatively, the same esters (4 mmol) were caused to react in biphasic solution of C_3H_7CN (3 ml) and $NaHCO_3$ saturated H_2O (3 ml) or in H_2O (5 ml) in the presence of $[Rh(C_2H_4)_2Cl]_2$ ($2.0\cdot10^{-2}$ mmol) under the same conditions. Only crotyl ester led to rearrangement products: 77% of 3,6- and 2,6-octadienoic acids (**9** and **8**) (7:1 molar ratio) at 90% conversion in homogeneous CH_3CN solution and 41% and 51% of 3,6- and 2,6-octadienoic acids (1:3 molar ratio) at 85% and 90% conversion in biphasic medium (41% of but-3-enoic acid **10** from hydrolysis of the ester) and in water respectively; whereas cyclohex-2-enyl and 1-methylallyl esters did not react yielding only hydrolysis products in biphasic medium or water.

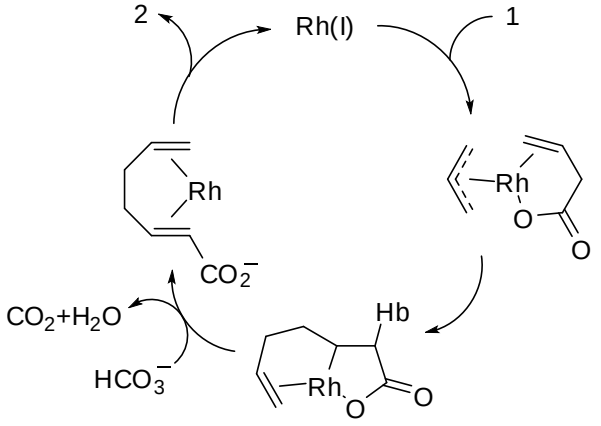
We have ascertained that no significant isomerization occurred when *E*-2,6-heptadienoic acid or the mixture of *E*-3,6- and *Z*-3,6-heptadienoic acids was heated at 100° C for 16 h in butyronitrile in the presence of $Rh(PPh_3)_3Cl$ or in a mixture of basic water and butyronitrile in the presence of $[Rh(C_2H_4)_2Cl]_2$. These results demonstrate that isomeric heptadienoates **2** and **3** do not interconvert under the reaction conditions and therefore must derive from different catalytic steps.

Schemes 4.4 and 4.5 show the likely mechanistic pathways followed in organic solvent and in water, respectively. The first step is an oxidative addition of allyl but-3-enoate rhodium(I), assisted by double bond chelation, then double bond insertion occurs followed by β-hydrogen elimination with formation of a rhodium hydride intermediate, which eventually undergoes reductive elimination. In organic solvents, the β-hydrogen elimination takes place regioselectively from the less acidic hydrogen bonded to the γ-carbon (indicated in Scheme 4.4 as H_a) to afford 3,6-heptadienoic acid **3** as the main reaction product.



SCHEME 4.4. Proposed reaction mechanism in organic solvents. Unreactive ligands are omitted for clarity.

On the other hand, in basic water solution, the β-elimination preferentially occurs from the hydrogen bonded to the α-carbon atom of the chain (indicated in Scheme 4.5 as H_b), through proton abstraction by the base, eventually leading to 2,6-heptadienoic acid **2** as the main reaction product.



SCHEME 4.5.. Proposed reaction mechanism in aqueous media. Unreactive ligands are omitted for clarity.

4.4 - Part I:conclusions

Summing up, we have showed that the use of an aqueous basic medium allows the rearrangement of allyl 3-butenoate to (*E*)-2,6-heptadienoate using Rh(I) complexes as catalysts with excellent yields and very high catalytic efficiencies (up to ca 3600 mol of product per mol of catalyst). This process resulted rather sensitive to the reagent structure pointing out that good results were obtained mainly with allyl but-3-enoate. This eco-friendly procedure may offer additional and practical usefulness and potentiality for the preparation of heptadienoic acids whose application in the synthesis of organic, bioorganic, pharmaceutical and natural products is more and more increasing.

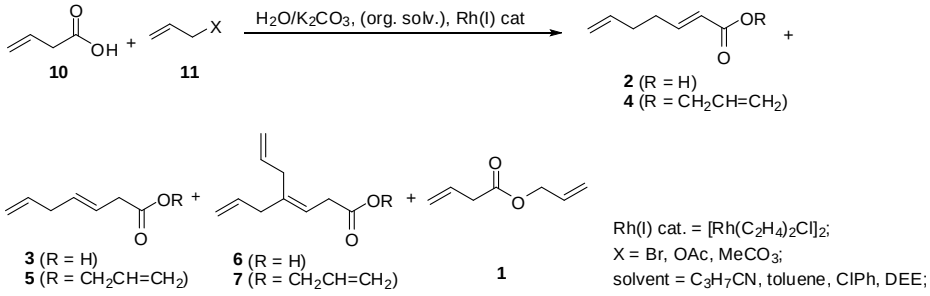
4.5 - Part II: heptadienoic acids by direct combination of but-3-enoic acid and allyl derivatives. Results and discussion

In the previous chapter an efficient and environmentally compatible protocol for the preparation of heptadienoic acids and esters, based on the rearrangement of allyl but-3-enoate in alkaline aqueous media in the presence of a catalytic amount of a Rh(I) complex containing olefinic ligands has been described. With the aim of developing a more practical approach to the synthesis of heptadienoic acids or esters, we have then considered the accomplishment of the rhodium-catalyzed reaction in an alkaline water solution or in an alkaline aqueous-organic two-phase system, starting directly from commercially available but-3-enoic acid and an allylic derivative, thus avoiding the previous preparation of allyl but-3-enoate. Proofs about the chemoselectivity of the reaction with regard to heptadienoic acid or allyl ester formation have been pursued. Combinations of different allyl substrates with various solvents and the presence of phosphine ligands have been examined with regard to the regioselectivity of the reaction. On the basis of the ligand coordinating ability for the rhodium species and the solvent properties, the formation of 2-6- or 3,6-heptadienoic acids and their respective allyl esters may be selectively influenced.

4.5.1 - Preliminary results

Three different allylic substrates have been used: allyl bromide, allyl acetate and allyl methyl carbonate. We first caused the three allyl derivatives to react with but-3-enoic acid in the presence of a catalytic amount of $[Rh(C_2H_4)_2Cl]_2$ in a K_2CO_3/water-organic two-phase system or in a K_2CO_3 aqueous solution. Different solvents such as toluene, chlorobenzene, butyronitrile and diethoxyethane (DEE) were considered when employing biphasic systems. The mixture was stirred at 75° C for 23 h. At the end of the reaction the allyl esters of but-3-enoic, 3,6-, 2,6-heptadienoic and 4-allyl-3,6-heptadienoic acids were recovered from the organic phase. The respective acids were recovered from the aqueous phase containing their potassium salts through acidification with

HCl solution. Scheme 4.6 shows the products formed after HCl treatment. For simplicity, in the following part of this work, the above mentioned products will be referred to as “acids”; it must however always be kept in mind that in the reaction mixture they are always present as potassium salts, due to the alkaline water conditions, and are recovered as acids after reaction workup.



SCHEME 4.6. General equation for the coupling reaction of but-3-enoic acid and allyl derivatives.

Conversions and selectivities are summarized in Table 4.4 along with the selectivity of 2,6-heptadienoic derivatives (acid + ester, **2** + **4**), selectivity ratios of 2,6-/3,6-derivatives (**2** + **4**) / (**3** + **5** + **6** + **7**) and the acid selectivities (**2** + **3** + **6**).

Data reported in Table 4.4 provide significant results. In alkaline water solution conversions were slightly lower than the ones in biphasic systems, whichever allyl derivative was used (entries 29, 34 and 39). Four main products were observed: 2,6- and 3,6-heptadienoic acids **2** and **3**, and their respective allyl esters **4** and **5**; two by-products were also found in lower amounts: 4-allyl-3,6-heptadienoic acid **6**, and its allyl ester **7**.

XCH_2CHCH_2			CONV. %	SELECTIVITY %							Total selectivity to 2,6 derivatives %	Selectivity ratio of 2,6- / 3,6-derivatives	Total selectivity to acids %
				acids			esters						
Entry	**, X =**	**Solvent**	**10**	(3,6) **3**	(2,6) **2**	4-all-(3,6) **6**	all-3-but **1**	(3,6) **4**	(2,6) **5**	4-all-(3,6) **7**	(**2**+**4**)	(**3**+**5**+**6**+**7**)	(**2**+**4**) / (**3**+**5**+**6**+**7**)
29		H_2O	80	7	92				1		93	14.17	99
30		toluene/H_2O	99	1	3		6	11	75	4	78	4.83	4
31	**Br**	ClPh/H_2O	99	3	7	1	4	10	68	6	75	3.71	12
32		DEE/H_2O	100	1	4	1	7	10	74	3	79	5.53	6
33		C_3H_7CN/H_2O	93	9	4		2	22	61	2	65	1.94	13
34		H_2O	83	8	90						90	10.71	99
35		toluene/H_2O	99	15	82				3		85	5.60	97
36	**$MeCO_3$**	ClPh/H_2O	100	4	79	10			5	1	85	5.52	94
37		DEE/H_2O	97	3	75	6	5	1	8	1	83	7.45	84
38		C_3H_7CN/H_2O	100	5	81	8			6		87	6.61	94
39		H_2O	93	12	88						88	7.45	100
40		toluene/H_2O	92	13	77	4		1	5		82	4.63	94
41	**OAc**	ClPh/H_2O	93	13	85	1			1		86	6.20	99
42		DEE/H_2O	91	12	85	1			1		86	6.26	99
43		C_3H_7CN/H_2O	90	11	64		2	2	20		84	6.51	75

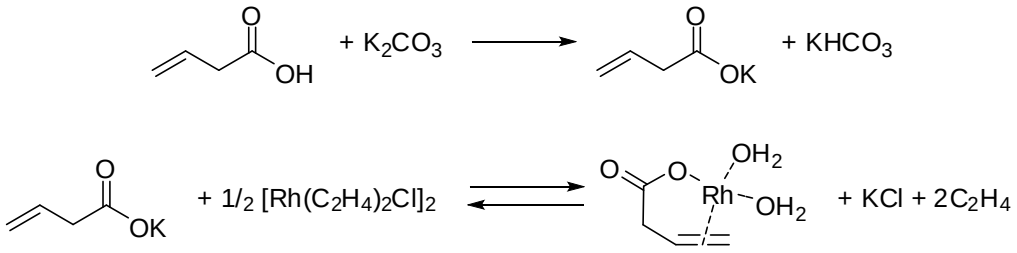
TABLE 4.4. **Reactions of allyl derivatives $XCH_2CH=CH_2$ (8.5 mmol) with but-3-enoic acid (4.1 mmol) in the presence of $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol) in K_2CO_3 water solution (5 ml, K_2CO_3 concentration = 5 mmol / ml) or in alkaline water (1 ml, K_2CO_3 concentration = 5 mmol / ml) organic solvent (4 ml) biphasic system. Organic solvents: toluene, chlorobenzene (ClPh),1,2-diethoxyethane (DEE), butyronitrile (C_3H_7CN). Reaction carried out for 23h at 75°C under stirring (1000 rpm).**

The results (Table 4.4) show that in all cases the selectivity of 2,6-heptadienoate derivatives (acids and esters) was considerably higher than the one of 3,6-isomers independently of the allyl substrate. In alkaline water solution a significant increase of 2,6-heptadienoic acid was observed for all allyl derivatives under the used conditions (entries 1, 6 and 11). Allyl acetate and allyl methyl carbonate yielded acids as predominant products in all reaction media (entries 7-10 and 12-15), whereas the allyl esters were the main products with allyl bromide in all water-organic solvent media (entries 2-5).

4.5.2 - Regio- and chemoselectivities..

The reaction conditions seemed to have a remarkable effect on regioselectivity (i.e. C=C double bond position) and chemoselectivity (i.e. production of acids or esters) of the reaction; we thus planned a series of experiments in order to ascertain the effects of different parameters on yields and selectivities of the different products.

Two alternative steps in the reaction course account for the regioselectivity of the process. In our specific case, K_2CO_3 contained in the aqueous phase reacts with but-3-enoic acid forming a water-soluble potassium salt . In the same phase, a rhodium complex free of water soluble ligands -$Rh(C_2H_4)_2Cl]_2$-, first is solvated by H_2O , then interacts with the organic salt forming a Rh(I) complex according to scheme 4.7.



SCHEME 4.7. Initial steps of the reaction mechanism. Formation of potassium but-3-enoate and its coordination to the active metal.

The Rh complex has not yet been isolated, but an analogue ruthenium compound has been crystallized and characterized by X-ray diffraction analysis (figure 4.1)[24]

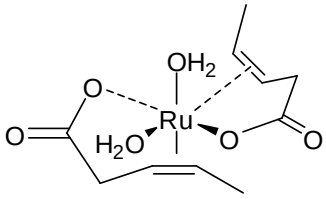
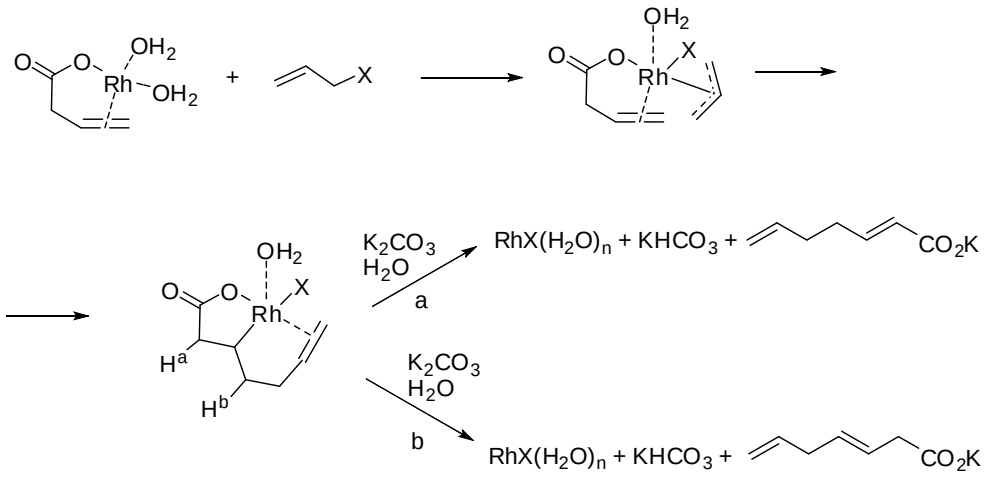


FIGURE 4.1. Ruthenium analogue of the rhodium complex assumed to be the first intermediate of the reaction.

The Rh complex thus formed can distribute between the aqueous and organic phase, undergoing oxidative addition of the allylic derivative. Subsequent formation of a C-C bond and reductive β-hydrogen elimination provides 2,6- and 3,6- heptadienoic acids (scheme 4.8, path a and b). Previously we proposed that the latter two steps are preferentially followed in organic solvents or in aqueous alkaline solution respectively. In organic solvents β-hydrogen elimination involves the less acidic hydrogen H^b as indicated in path b ,Scheme 3 to afford 3,6-heptadienoates as the main reaction products. On the other hand, in alkaline water solution, β-hydrogen elimination preferentially occurs from the hydrogen H^a bonded to the α-carbon atom of the chain (path a in Scheme 4.8) through proton abstraction by the base, eventually leading to 2,6 heptadienoic acid as the main reaction product.



SCHEME 4.8. Proposed reaction mechanism. Path a is preferred in aqueous phase, path b in organic solvent.

The allyl esters **4** and **5** of the two heptadienoic acids **2** and **3** are formed via consecutive one-pot base-catalyzed esterification with the excess of allyl bromide present in the reaction mixture. This was verified by monitoring the course of the reactions versus time, as described in paragraph 4.5.6.

4.5.3 - Effect of the base concentration on the selectivity forwards 2,6- vs. 3,6- derivatives.

Aqueous systems.

Experiments carried out at variable concentrations of base in water showed considerable effects on the regioselectivity of the reaction; 2,6 derivatives were favored at higher K_2CO_3 concentration. A set of reactions was carried out in water (5 ml) containing K_2CO_3 in a concentration ranging from 0 to 5 mmol/ml under the same conditions previously reported and with the same amounts of reagents and catalyst. The results are reported in the figures 4.2, 4.3 and 4.4.

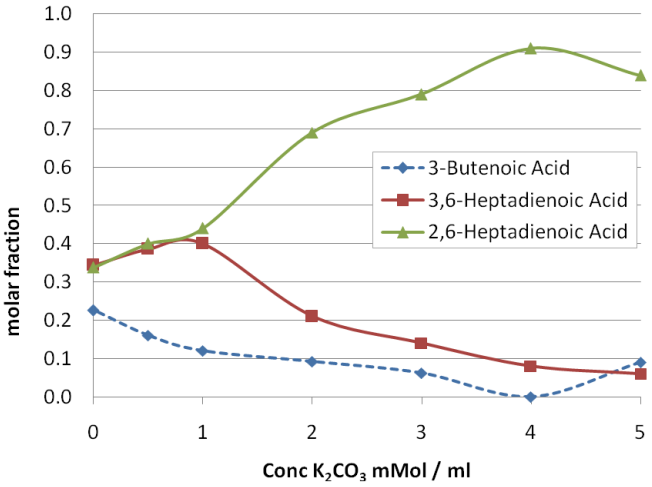


FIGURE 4.2. Molar fractions in the mixture of the reaction of allyl bromide (8.5 mmol) and but-3-enoic acid (4.1 mmol) in water (5 ml) at variable K_2CO_3 concentrations after 23 h at 75°C. Catalyst $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol). Compounds present in less than 3% amounts are not reported for clarity.

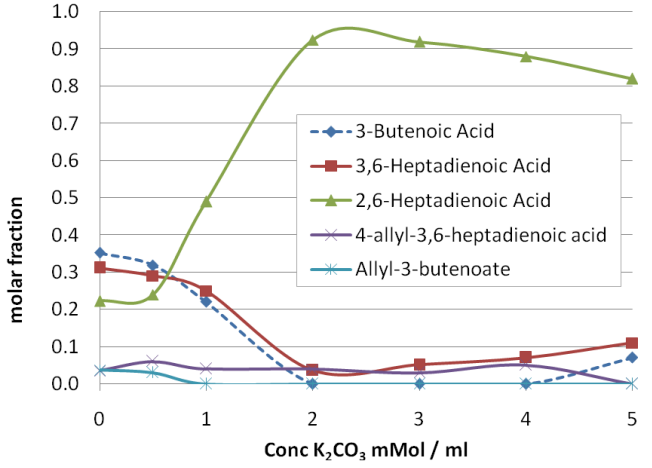


FIGURE 4.3. Molar fractions in the mixture of the reaction of allyl acetate (8.5 mmol) and but-3-enoic acid (4.1 mmol) in water (5 ml) at variable K_2CO_3 concentrations after 23 h at 75°C. Catalyst $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol). Compounds present in less than 3% amounts are not reported for clarity.

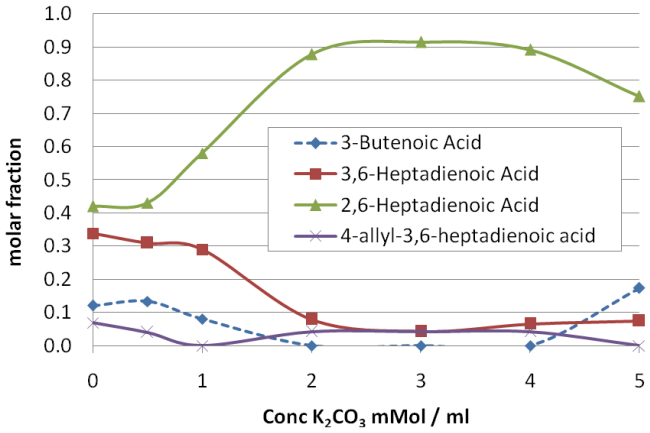


FIGURE 4.4. Molar fractions in the mixture of the reaction of allyl methyl carbonate (8.5 mmol) and but-3-enoic acid (4.1 mmol) in water (5 ml) at variable K_2CO_3 concentrations after 23 h at 75°C. Catalyst $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol). Compounds present in less than 3% amounts are not reported for clarity.

The conversions rise as the concentration of K_2CO_3 increases, likewise the yields and selectivities of 2,6-heptadienoic acid reach a maximum value that is kept up or decreases slowly with further increase of K_2CO_3 concentration owing to a drop of conversion. Opposite is the course of 3,6-heptadienoic acid yields and selectivities.

The relation between the yields and the concentrations of K_2CO_3 in H_2O as reported in figures 4.2-4.4 can be explained on the base of the proposed assumptions. In the absence of a base conversions are lower. 2,6- and 3,6-heptadienoic acids are formed in similar amounts regardless of the allyl derivative used. Addition of increasing amounts of K_2CO_3 leads to an improvement of conversion with all the allyl derivatives until complete disappearance of residual but-3-enoic acid is achieved. At the same time a rapid increase of the production of 2,6-heptadienoic acids is noticed in conjunction with a decrease of that of 3,6-acid. As anticipated, this is likely due to a more favored β-hydrogen elimination step of the acid proton H^a (scheme 3, path a) when an excess of base is present. The maximum value is reached at a concentration of about 2 mmol / ml with allyl acetate and allyl methyl carbonate, while only at 4 mmol / ml with allyl bromide. This can be due to the

higher stability of possible micellar structures formed by allyl bromide in basic water in comparison with those of the more easily water-transferable acetate and methyl carbonate through hydrogen bonds. At higher (>4 mmol / ml) K_2CO_3 concentrations both conversions and selectivities to 2,6-heptadienoic acid decrease again.

Biphasic systems.

The investigation was extended to different biphasic media but limited to allyl bromide owing to its different behavior in comparison with the other two allyl substrates (Table 4.4). Thus but-3-enoic acid and allyl bromide were caused to react in presence of different organic solvents and at variable concentrations of K_2CO_3 in water. Under these conditions the increase of K_2CO_3 concentration gives rise to a steady increase of 2,6-/3,6- derivative yield ratio with toluene, DEE and ClPh whereas it is approximately constant with butyronitrile (figure 4.5). An analogous trend, but with a more marked slope, obtained for the aqueous system under analogue conditions is shown for comparison. In aqueous systems, however, the products were almost exclusively acids while in biphasic systems mostly esters. No 2,6- to 3,6- isomerization occurred under these conditions (see chapter 4.3.3). Thus, the 2,6- / 3,6- yield ratio shown in figure 4.5 may be a measure of the relative reaction rate for the two competitive β-hydrogen elimination steps depicted in scheme 4.8. The linear dependence (in the examined range of base concentrations) of the relative rate of formation of 2,6- derivatives on the K_2CO_3 concentration can be taken as a proof that the base is directly involved in their formation.

The different behavior of butyronitrile may be ascribed to a competitive effect due to the coordinating ability of this solvent for rhodium complex. The presence of butyronitrile helps the rhodium transfer in organic solvent promoting the formation of 3,6- derivatives against the preferred formation of 2,6- derivatives in water, where K_2CO_3 concentration is growing.

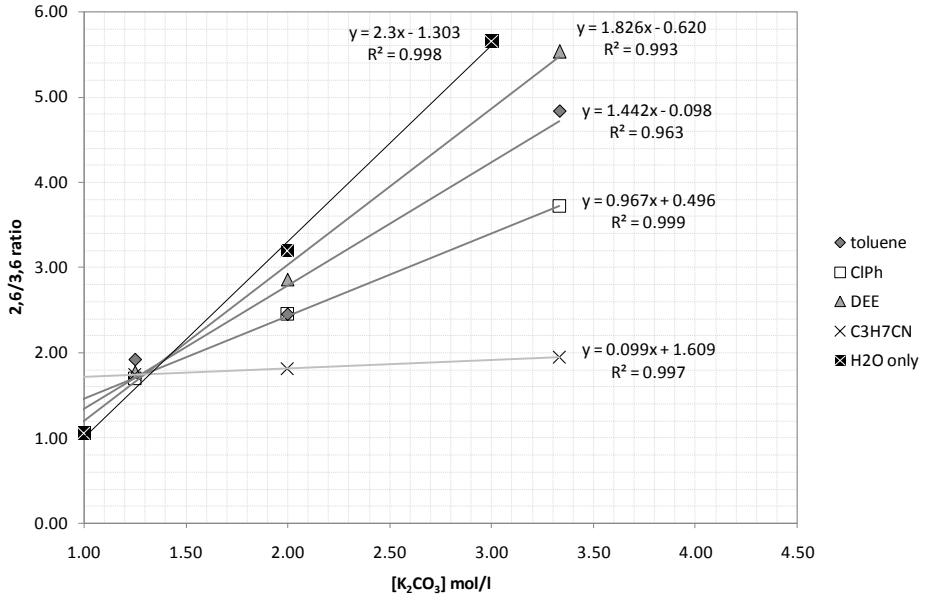


FIGURE 4.5. Linear dependence of the 2,6- / 3,6- derivative yield ratio versus the base concentration for aqueous or biphasic systems (total volume 5 ml). Other conditions as reported in figures 4.2-4.4.

4.5.4 - Effect of triphenylphosphine as ligand on regioselectivity.

The addition of a ligand such as TPP, able to bind to the metal and very soluble in the organic phase, can affect the distribution of the intermediate rhodium complex into the biphasic system producing consequences on the regioselectivity. Thus the reaction of but-3-enoic acid and allyl bromide in the presence of $[Rh(C_2H_4)_2Cl]_2$ and different amounts of TPP were carried out under the conditions described in Table 2. Yields and selectivities are summarized in Table 4.5. The selectivity ratio of 2,6- / 3,6- derivatives is reported in figure 4.6. A manifest decrease of the 2,6- / 3,6- derivative selectivity ratio consistent with the rise of 3,6- derivatives owing to the addition of TPP equivalents is shown. The highest effect was obtained in toluene and ClPh biphasic system followed by DEE and C_3H_7CN, whereas in alkaline water the effect is negligible showing no appreciable variation of the ratio upon addition of TPP.

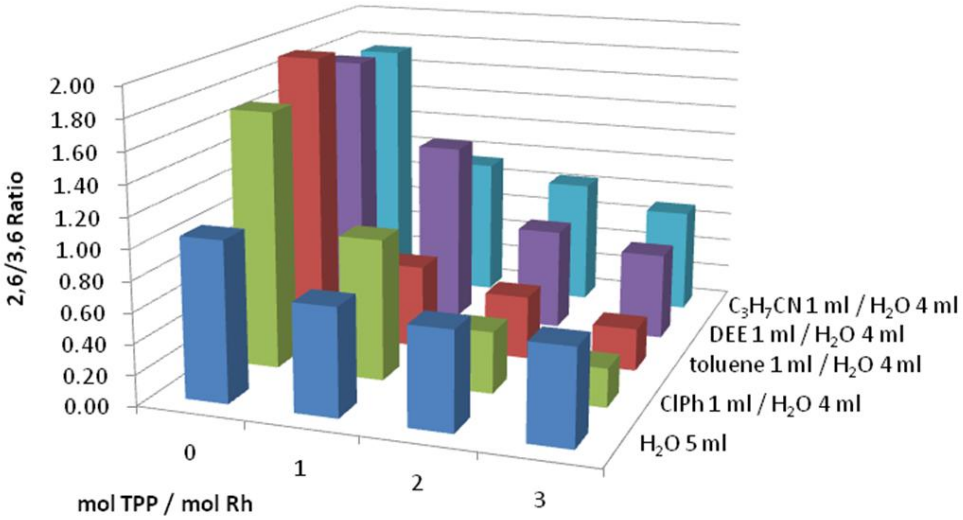


FIGURE 4.6. Comparison of the 2,6- / 3,6- selectivity ratios for different solvent systems in presence of variable amounts of triphenylphosphine (TPP). Conditions as indicated in table 4.5.

Entry	Solvent	TPP/Rh mol/mol	CONV. %	SELECTIVITY %							Total selectivity to 2,6 derivatives	Total selectivity to 3,6 derivatives	Selectivity ratio of 2,6- / 3,6-derivatives
				acids			esters						
			10	(3,6) **3**	(2,6) **2**	4-all-(3,6) **6**	all-3-but **1**	(3,6) **4**	(2,6) **5**	4-all-(3,6) **7**	(**2**+**4**)	(**3**+**5**+**6**+**7**)	(**2**+**4**)/ (**3**+**5**+**6**+**7**)
44	H_2O 5 ml	0	88	45	50	1	-	1	1	1	51	48	1.05
45		1	83	29	29	7	4	16	10	4	40	56	0.71
46		2	86	25	27	12	2	19	11	3	38	59	0.65
47		3	84	29	23	-	6	26	13	4	36	58	0.63
48	Toluene 1 ml / H_2O 4 ml	0	97	12	34	3	-	7	32	12	66	34	1.92
49		1	91	29	21	7	1	21	14	6	35	64	0.54
50		2	98	22	19	23	-	14	10	10	29	70	0.42
51		3	96	41	19	18	-	13	3	7	22	78	0.28
52	ClPh 1 ml / H_2O 4 ml	0	100	6	12	3	1	17	50	11	62	37	1.69
53		1	98	17	22	3	2	23	25	8	47	51	0.93
54		2	100	15	11	1	3	38	17	15	28	69	0.40
55		3	100	15	7	7	6	35	12	18	19	75	0.25
56	DEE 1 ml / H_2O 4 ml	0	98	10	19	4	9	14	39	5	58	33	1.77
57		1	91	22	29	-	2	12	24	10	53	44	1.21
58		2	80	28	25	-	4	24	14	6	39	57	0.68
59		3	91	39	22	1	-	19	14	4	37	63	0.58
60	C_3H_7CN 1 ml / H_2O 4 ml	0	99	6	14	4	1	21	48	5	63	36	1.74
61		1	91	36	40	4	-	8	9	3	48	52	0.94
62		2	98	7	9	-	9	38	32	3	41	49	0.84
63		3	87	22	21	-	5	29	18	5	39	56	0.70

Table 4.5 - Reactions of allyl bromide (8.5 mmol) with but-3-enoic acid (4.1 mmol) in the presence of [Rh(C2H4)2Cl]2 (0.021 mmol) and triphenylphosphine. in water or biphasic systems. K2CO3 5 mmol.. Solvent amounts as indicated. Reaction carried out for 23h at 75°C under stirring (1000 rpm).

4.5.5 - Effect of rhodium distribution between the two phases on regioselectivity.

In order to better demonstrate the correlation between the rhodium distribution between the two phases and the regioselectivity of the reaction, quantitative determinations of the rhodium dissolved in the organic phase and in the aqueous phase after reagent mixing as well as at the end of the reaction were carried out by ICP technique. Data of Rh ICP analyses and yields and selectivities of reactions carried out in water-toluene or water-butyronitrile systems are reported in table 4.6 and in figure 4.7. The results show that the higher is the amount of rhodium dissolved in the aqueous phase, the higher is the selectivity to 2,6-derivatives. The addition of one equivalent of TPP causes a decrease of the amount of rhodium dissolved in water and simultaneously an increase of the 3,6-derivatives selectivity.

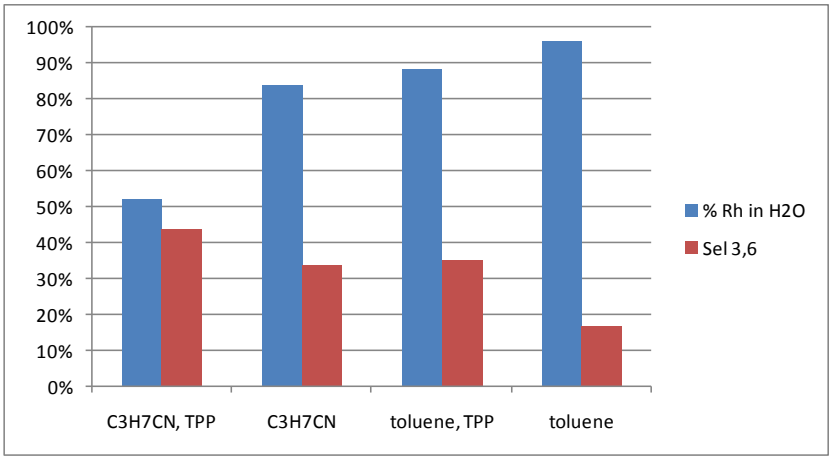


FIGURE 4.7. Relation between the Rh content of the water phase in different solvent/ligand systems and reaction selectivity to 3,6- heptadienoic acid and allyl ester. Rh amount determined by ICP analyses at the beginning of the reaction. Conditions as indicated in table 3.

	% Rh in H_2O (beginning)	% Rh in H_2O (end)	% selectivity to 3,6 isomers
C_3H_7CN / H_2O, TPP (1 mmol / mmol Rh)	52	39	44
C_3H_7CN / H_2O	84	76	34
toluene / H_2O, TPP (1 mmol / mmol Rh)	88	87	15
toluene / H_2O	96	83	11

TABLE 4.6. Relation between the Rh content of the water phase in different solvent/ligand systems and reaction selectivity to 3,6- heptadienoic acid and allyl ester. Rh amount determined by ICP analyses at the beginning and at the end of the reaction. Conditions: allyl bromide 8.5 mmol, but-3-enoic acid 4.1 mmol, $[Rh(C_2H_4)_2Cl]_2$ 0.021 mmol, K_2CO_3 5 mmol, organic solvent 3 ml, H_2O 2 ml, reaction time 23 h, reaction temperature 75°C.

Since in all biphasic conditions a significant fraction of rhodium tends to be dissolved in water, as the results reported in table 4.6 show, yielding mainly 2,6-heptadienoic acid derivatives, thus we investigated the possibility of carrying out the reactions in absence of water and base, in order to force the β-elimination step to take place according to path b as described in Scheme 3 Under these conditions, allyl bromide gave no reaction (likely because of catalyst deactivation due to the formation of HBr). The reactions of allyl acetate and allyl methyl carbonate with but-3-enoic acid in the presence of $[Rh(C_2H_4)_2Cl]_2$, provided low conversions (15-30%) except for allyl acetate in C_3H_7CN which, as expected, gave 3,6-derivatives as the main products (43% selectivity against 33% of 2,6-derivatives at 84% conversion). Allyl acetate and allyl methyl carbonate were also caused to react in absence of water K_2CO_3 solution in the four organic solvents utilizing $Rh(PPh_3)_3Cl$ as a catalyst. In this case the best results were obtained in toluene with high yields and selectivity of 3,6-derivatives (74% yield of **3** at 95% conversion for allyl methyl carbonate and 69% of **3** at 93% conversion for allyl acetate). Lower conversions (54-83%) and yields of **3** (38-61%) were obtained in DEE, ClPh and C_3H_7CN.

4.5.6 - Formation of allyl heptadienoates vs. heptadienoic acids.

Different allyl substrates gave different results with regard to chemoselectivity. Thus, we followed the reaction course versus time using a toluene-water mixture as reaction medium, employing all three reagents. The results are plotted in the figures 4.8, 4.9 and 4.10.

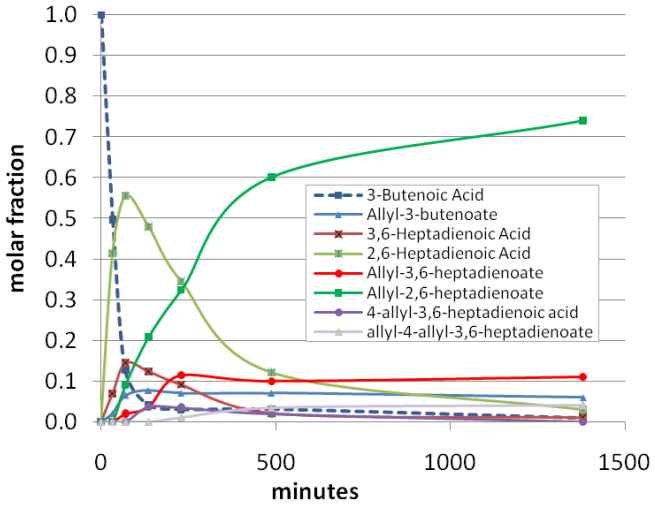


FIGURE 4.8 – Molar fractions in the mixture of the reaction of allyl bromide (8.5 mmol) and but-3-enoic acid (4.1 mmol) in toluene(4ml) / water(1ml) biphasic system at different times. K_2CO_3 5 mmol, $[Rh(C_2H_4)_2Cl]_2$ 0.021 mmol., Reaction temperature 75°C. Compounds present in less than 3% amounts are not reported for clarity.

The three allyl substrates showed a common initial behavior that is the formation of 2,6- and 3,6-heptadienoic acids, with a slower rate for the latter one. Allyl bromide only was found to react with the potassium salts of heptadienoic acids in alkaline biphasic medium leading to allyl ester formation; in addition the 3,6-heptadienoate anion reacted with allyl bromide to yield 4-allyl-3,6-heptadienoate derivative which subsequently was transformed into allyl ester. At the end of the reaction the main product was allyl 2,6-heptadienoate along with lower amounts of allyl 3,6-heptadienoate, allyl 4-allyl-3,6-heptadienoate and, in very small amount, the respective acids (figure 4.8). By contrast, the reactions of allyl acetate and allyl methyl carbonate led to the formation of 2,6- and 3,6-heptadienoate potassium salts with negligible amounts of their allyl esters (figure 4.9 and 4.10).

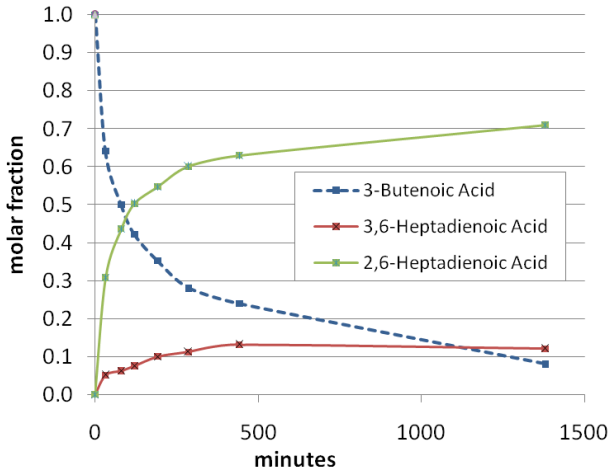


FIGURE 4.9 – Molar fractions in the mixture of the reaction of allyl acetate (8.5 mmol) and but-3-enoic acid (4.1 mmol) in toluene(4ml) / water(1ml) biphasic system at different times. K_2CO_3 5 mmol, $[Rh(C_2H_4)_2Cl]_2$ 0.021 mmol., Reaction temperature 75°C. Compounds present in less than 3% amounts are not reported for clarity.

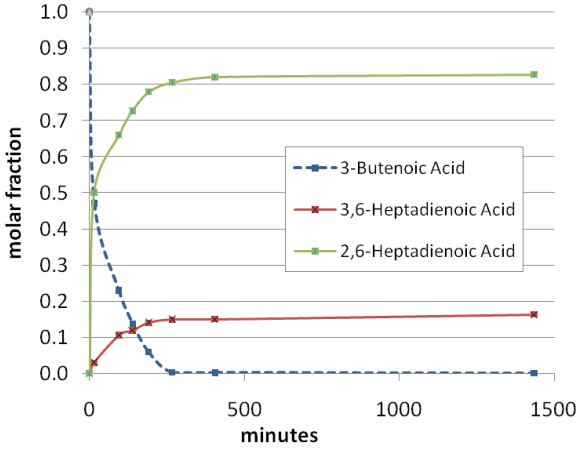


Figure 4.10. Molar fractions in the mixture of the reaction of allyl methyl carbonate (8.5 mmol) and but-3-enoic acid (4.1 mmol) in toluene(4ml) / water(1ml) biphasic system at different times. K_2CO_3 5 mmol, $[Rh(C_2H_4)_2Cl]_2$ 0.021 mmol., Reaction temperature 75°C. Compounds present in less than 3% amounts are not reported for clarity.

Furthermore, we found that the amount of organic solvent present in the biphasic system affects the chemoselectivity of the reaction with allyl bromide. Thus working at constant concentration of base, and leaving inalterate all the other reaction parameters, addition of increasing amounts of organic solvent promoted the cascade reaction of formation of the allyl esters from potassium heptadienoates as shown in figure 4.11. Thus, the selectivity to acids or esters can be controlled through the organic solvent / water (vol/vol) ratio and global selectivity to esters can rise to almost 95% in the case of diethoxyethane.

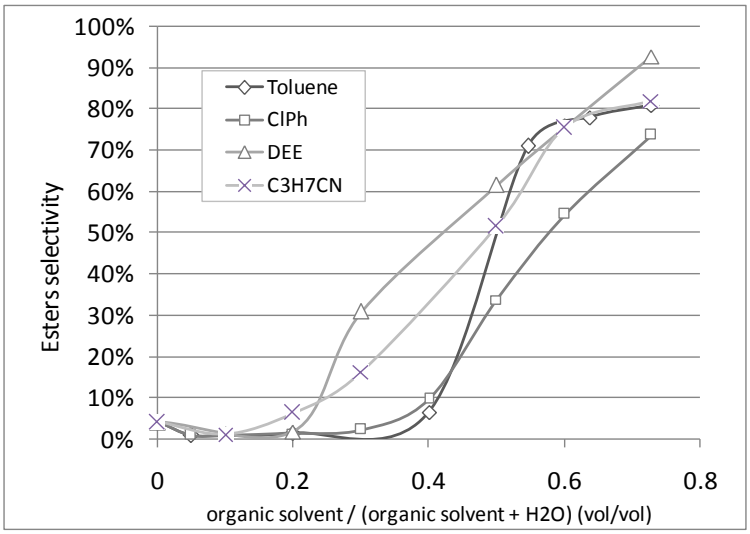


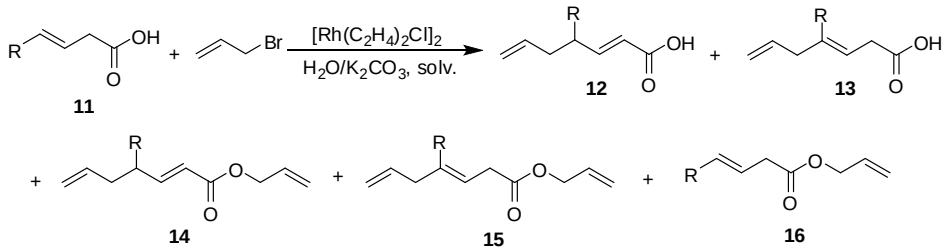
FIGURE 4.11. Ester selectivity for different organic solvent / water systems in the reaction of allyl bromide (8.5 mmol) and but-3-enoic acid (4.1 mmol) after 23h at 75°C. Total volume of the mixture 5 ml. Constant concentration of K_2CO_3 (5 mmol/ml water). Catalyst $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol).

Once again, it is to be remarked that the allyl ester formation is a reaction unrelated to the rhodium presence, as demonstrated conducting reactions of heptadienoate potassium salt and allyl bromide in absence of rhodium.

It is also to be remarked that, whereas different solvents behave similarly with respect to the formation of acids or esters, noticeable differences exist with respect to the composition (i.e. 2,6- or 3,6- isomers) of the acids or esters obtained, as already pointed out in the previous paragraphs.

4.5.7 - Reactions of substituted butenoic acids and allyl derivatives.

The work has been further extended by exploring the possibility of reacting substituted but-3-enoic acids and allyl bromides. The reactions of 4-substituted but-3-enoic acids **11** take place according to scheme 4.9, yielding 4-substituted 2,6- and 3,6-heptadienoic acids **12** and **13** and the respective allyl esters **14** and **15** along with some amounts of products **16** resulting from direct esterification of the starting acid **11.** The results of these experiments are reported in table 4.7.



SCHEME 4.9. General reaction scheme for the coupling of substituted but-3-enoic acids and allyl bromide.

The results show that different organic solvents cause slight differences in the reaction course, as already pointed out in the first part of this work. Lower conversions of pent-3-enoic acid (**11**, R = CH_3) were obtained in comparison to 3-butenoic acid at the same temperature, indicating that steric hindrance on γ-carbon decreases the reactivity of the substrate (entries 65-67-69); however, this problem was mitigated by rising the reaction temperature to 100°C (entry 66). Electronic and statistical factors might be involved in the lower selectivity to 3,6-derivatives.

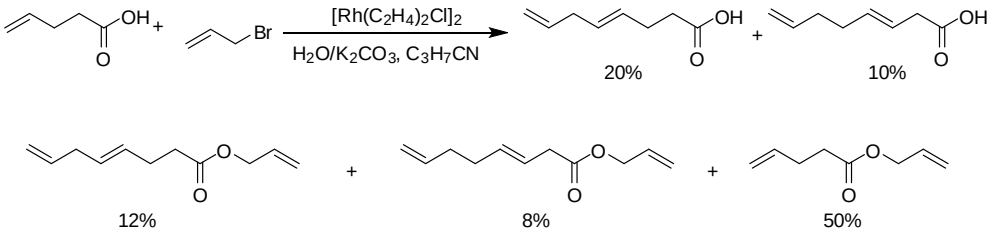
In most cases the predominant products were acids, but significant amounts of the corresponding allyl esters were formed (entries 67-70). It can thus be predicted that, in presence of a higher excess of allyl bromide, the main products would be esters **14** and **15**.

Entry	R	T(°C)	Solvent	% Conv.	% Yield				
				11	**12**	**13**[a]	**14**	**15**[a]	**16**
64	CH_3 (trans)	75	C_3H_7CN	58	50	-	5	-	-
65	CH_3 (trans)	75	toluene	54	38	-	10	-	-
66	CH_3 (trans)	100	C_3H_7CN	98	77	-	5	-	13
67	C_2H_5 (trans)	100	toluene	82	24	4	27	1	22
68	C_2H_5 (trans)	100	C_3H_7CN	98	50	9	3	5	29
69	C_2H_5 (cis)	100	toluene	98	30	10	25	7	23
70	C_2H_5 (cis)	100	C_3H_7CN	98	60	8	5	2	22-

TABLE 4.7. Reactions of allyl bromide (8.5 mmol) with substituted but-3-enoic acids (4.1 mmol) in presence of $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol) in alkaline water (2 ml), (K_2CO_3 = 5 mmol) - organic solvent (3 ml) biphasic system. Reaction carried out for 23h under stirring (1000 rpm).

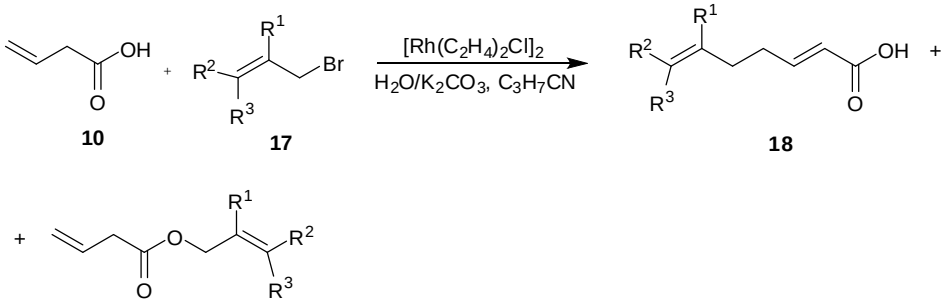
[a]The double bond geometry of products **13** and **15** was not determined.

The reaction of 4-pentenoic acid was carried out under the conditions reported in table 4.7 according to scheme 4.10. This substrate presents a different position of the C=C double bond (in γ to the carbonyl moiety instead of β). In this case, the chelation effect is less favored due to the formation of a 6-terms metallacycle instead of a 5-terms one. This fact reflects on the yields, that were significantly lower than those obtained with 3-butenoic or 3-pentenoic acid. The main product obtained is allyl 4-pentenoate that derives from direct esterification of the substrate without catalyst intervention.



SCHEME 4.10. Coupling reaction of 4-pentenoic acid and allyl bromide.

Variously substituted allyl bromides **17** were also tested according to scheme 4.11. The results of this set of experiments are reported in table 4.8. In this case the potential products are 6- and 7-substituted heptadienoic acids **18**.



SCHEME 4.11. Coupling reaction of but-3-enoic acid and variously substituted allyl bromides.

Entry	R^1	R^2	R^3	Solvent	% Conv.	% Yield	
					10	**18**	**19**
71	CH_3	H	H	C_3H_7CN	80	55	0
72	H	C_6H_5	H	C_3H_7CN	52	18	0
73	H	H	$-(CH_2)_3-$[a]	C_3H_7CN	85	0	58

Table 4.8. Reactions of substituted allyl bromides 11 **(8.5 mmol) with but-3-enoic acid (4.1 mmol) in presence of $[Rh(C_2H_4)_2Cl]_2$ (0.021 mmol) in alkaline water (2 ml) (K_2CO_3 = 5 mmol) - organic solvent (3 ml) biphasic system. Reaction carried out for 23h under stirring (1000 rpm).**

[a] reagent was 3-bromocyclohexene.

The conversions obtained are significantly lower than those obtained with the parent allyl bromide, meaning that the oxidative addition of the allyl derivative and the C-C coupling stage are significantly influenced by the presence of sterically hindered substituents. Only 2-methylallyl bromide (entry 71) gave satisfactory yields of 6-methylhepta-(2,6)dienoic acid. 3-bromocyclohexene (entry 73) gave only the direct esterification product, while other bromides afforded no conversion at all.

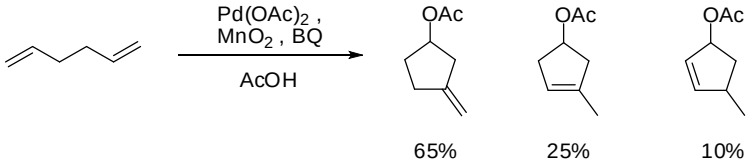
4.6 - Part II: conclusions

In conclusion this work reports a procedure for the synthesis of 2,6- and 3,6-heptadienoic acids and allyl esters consisting of Rh-catalyzed coupling reaction of but-3-enoic acid and allyl derivatives such as allyl bromide, allyl acetate and allyl methyl carbonate in alkaline water or in alkaline water / organic solvent two-phase systems. 2,6-Heptadienoate derivatives are always prevalent in water as acids and in biphasic systems as acids or allyl esters. It is possible to selectively obtain allyl esters via one-pot cascade esterification reaction using allyl bromide in biphasic systems with high amounts of organic solvent. The presence and the concentration of K_2CO_3, the nature of organic solvent or addition of TPP in biphasic media allow tuning the regioselectivity of the reaction towards 3,6-derivatives or 2,6-derivatives. Experimental evidences have been brought to explain the stages controlling the regio- and chemoselectivity of the reaction. Substituted but-3-enoic acids, substituted allyl substrates and pent-4-enoic acid lead to moderate or poor results under similar reaction conditions.

4.7 - Part III: Oxidative Pd-catalyzed cyclization of heptadienoates. Results and discussion

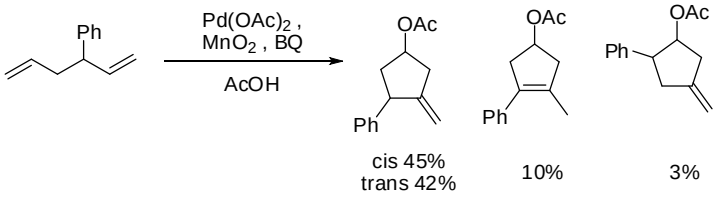
4.7.1 - Background: Oxidative cyclization of 1,5-dienes

1,5-Dienes have been shown to be good substrates for the Pd-catalyzed oxidative cyclization according to the general scheme 4.12. The reaction was carried out in neat acetic acid and products were a mixture of unsaturated cyclic acetates. A stoichiometric amount of Pd(II) was required as reported in the initial works[25] until a suitable reoxidation system was developed by Moberg and coworkers consisting of benzoquinone (BQ) / MnO_2 able to reoxidize the actual catalyst, palladium acetate[26].



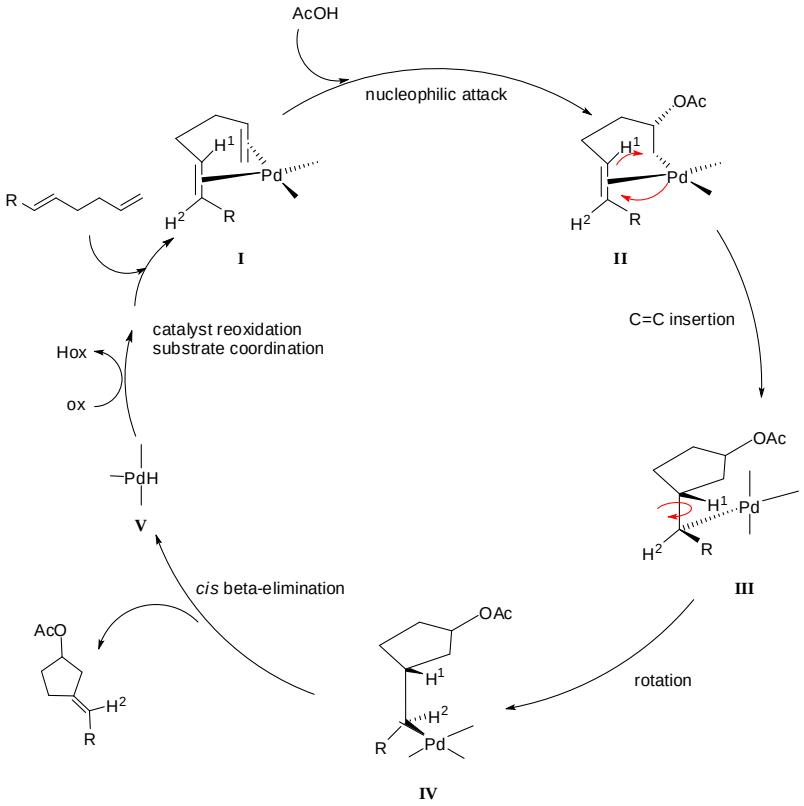
SCHEME 4.12. Pd-catalyzed oxidative cyclization of 1,5-diene.

If the substrate is a substituted 1,5-diene, as the one represented in scheme 4.13, the reaction selectivity is generally enhanced or modified[27].



SCHEME 4.13. Pd-catalyzed oxidative cyclization of hexa-1,5-dien-3-ylbenzene.

The reaction mechanism has been explained in detail[27] (scheme 4.14). 1,5-dienes are able to coordinate palladium forming a pseudo-square planar di-π complex (**I**). The structure of this intermediate affects the subsequent reactivity and thus the selectivity of the reaction; in presence of a nucleophile, a nucleophilic attack takes place on the complex according to Markovnikov rule, making the reaction chemoselective. This step leads to a σ-π –Pd complex (**II**). Subsequently cyclization takes place, due to the insertion of the second olefinic moiety of the substrate in the σ Pd-C bond (**III**). Rotation of the σ C-C bond provides the suitable intermediate (**IV**) for the final elimination of palladium hydride. This step has been proved to happen via cis-mechanism and provides the final product along with the reduced form of the catalyst (**V**), which undergoes a reoxidation step.



SCHEME 4.14. Reaction mechanism for the Pd-catalyzed oxidative cyclization of a substituted 1,5-diene. Ligands are omitted for clarity.

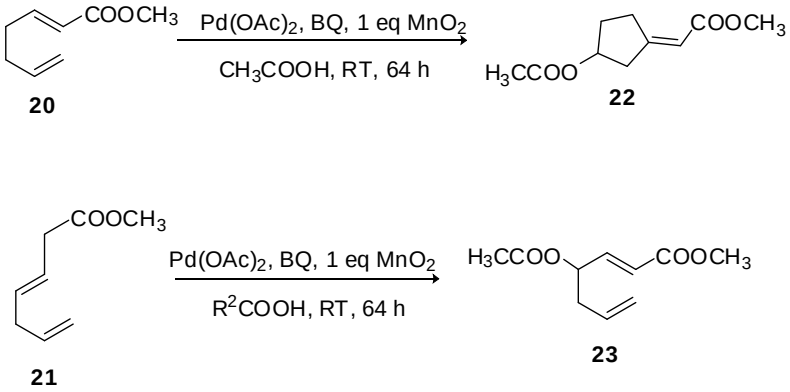
4.7.2 - Pd-catalyzed cyclization of heptadienoates

Preliminary tests

In parts I and II of this work, efficient protocols for the synthesis of 2,6- and 3,6- heptadienoic acids and their esters have been described. In this part of the work these compounds are considered as substrates for the above mentioned Pd-catalyzed cyclization. In fact, 2,6-heptadienoates can be regarded as substituted 1,5-dienes, while 3,6-heptadienoates, being substituted 1,4-dienes would be expected not to be reactive in this case. However, we tested both isomers under Moberg's conditions, obtaining interesting results in both cases; furthermore, we investigated the possibility of carrying out the same reactions in water, in order to avoid the use of neat acetic acid. An account of the results we obtained is given in the next paragraphs.

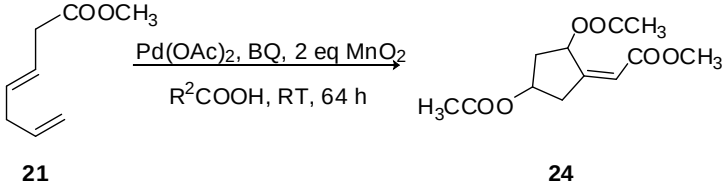
In the beginning we tested the methyl esters of 2,6-and 3,6-heptadienoic acid under the same reaction conditions reported by Moberg and coworkers. The reactions were carried out at room temperature for 64 hours, using acetic acid as both solvent and reagent and the Pd/BQ/MnO_2 catalytic system.

As it could be anticipated, methyl 2,6-heptadienoate **20** behaved as a normal 1,5-diene and gave the expected disubstituted cyclopentylidene **22** (scheme 4.15) in good yields. A different behavior was noticed when methyl 3,6-heptadienoate **21** was reacted under the same conditions: the addition of acetic acid was obtained at the expected position, but no cyclization occurred and the main product was linear 4-acetoxy-2,6-heptadienoate **23**. Interestingly, the position of the double bond shifted to the thermodynamically stabilized conjugated position. The results of both processes are reported in scheme 4.15.



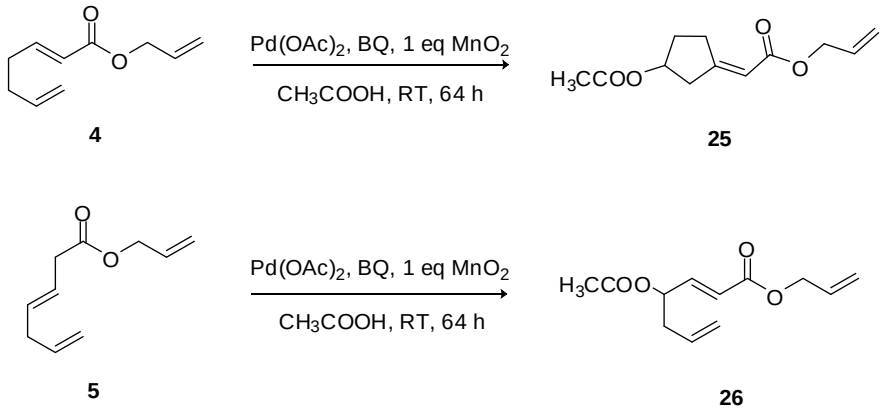
SCHEME 4.15. Reaction of methyl 2,6-heptadienoate and methyl 3,6 heptadienoate in presence of Pd(II) acetate and a BQ/MnO_2 reoxidation system in acetic acid.

It can be noticed that product **23** is on its turn a disubstituted 1,5-diene; thus, it is a good substrate for a further reaction in the same system. Subsequent tests demonstrated that, upon reacting methyl 3,6 heptadienoate **21** under the same conditions, but in presence of a twofold excess of the terminal oxidant (MnO_2), it is possible to obtain the cyclic diacetate **24** as shown in scheme 4.16 in good yields. The product consists of a mixture of two diastereoisomers (relative ratio ca. 1.5:1).



SCHEME 4.16. Cascade reaction of 3,6-heptadienoate in presence of a doubled amount of manganese oxide.

The allyl esters of 2,6- and 3,6- heptadienoate (**4** and **5**) were also tested under the same conditions, yielding the respective products **25** and **26** in good yields according to scheme 4.17. The results of these reactions are reported in table 4.9.



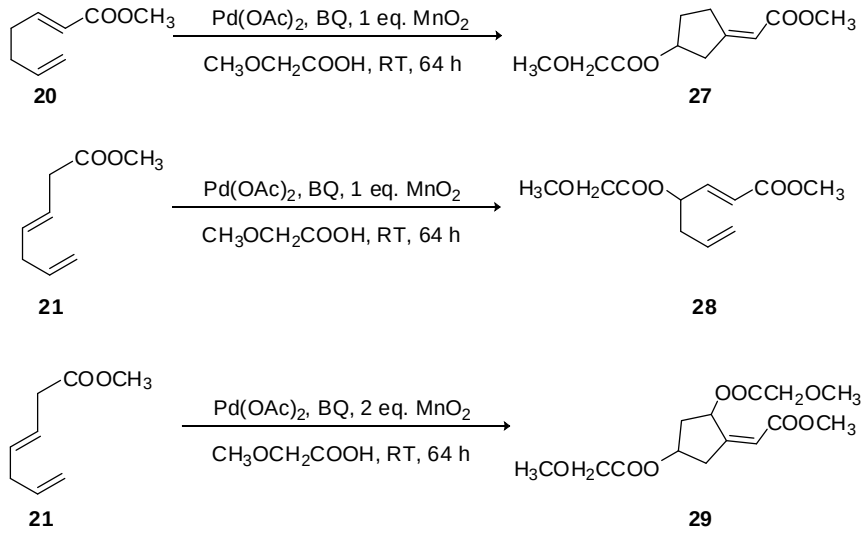
SCHEME 4.17. Reaction of allyl 2,6-heptadienoate and allyl 3,6 heptadienoate in presence of Pd(II) acetate and a BQ/MnO_2 reoxidation system in acetic acid.

Entry	Reagent	Pd/BQ/MnO_2 mmol	Conversion %	Product	Yield %
74	**20**	0.1/0.4/2	86	**22**	64
75	**21**	0.1/0.4/2	99	**23**	78
76	**21**	0.1/0.4/4	99	**24**	75
77	**4**	0.1/0.4/2	96	**25**	76
78	**5**	0.1/0.4/2	92	**26**	67

TABLE 4.9**. Results of the reaction of 2,6- and 3,6-heptadienoates (**4, 5, 20 **and** 21**, 2 mmol) in acetic acid (10 ml) in presence of a $Pd(OAc)_2$/benzoquinone/MnO_2 catalytic system at room temperature for 64h.**

Reactions with methoxyacetic acid

We then investigated possibilities of extending the reaction protocol to different organic acids, in order to achieve a more versatile reaction protocol. The use of methoxyacetic acid was tested for the reaction of the methyl esters **20** and **21** of the heptadienoic acids. The expected products **27** and **28** according to scheme 4.18 were obtained in satisfactory yields as reported in table 4.10.



SCHEME 4.18. Reaction of methyl 2,6-heptadienoate and methyl 3,6 heptadienoate in presence of Pd(II) acetate and a BQ/MnO_2 reoxidation system in methoxyacetic acid.

In this case a few experiments were dedicated to better understand the conditions that yield the maximum amounts of the disubstituted product **29**. As it comes out from entries 81 and 82 in table 4.10, increased temperatures and reaction times lead to the highest yields of **29**. Product **29**, similarly to product **24** obtained from acetic acid, was found to consist in a mixture of two diastereomeric forms, in relative ratio about 2:1.

Entry	Reagent	Pd/BQ/MnO_2 mmol	T	t (h)	Conversion %	Product	Yield %
79	**20**	0.1/0.4/2	RT	64	67	**27**	50
80	**21**	0.1/0.4/2	RT	64	50	**28** **29**	40 5
81	**21**	0.1/0.4/4	40°C	40	55	**28** **29**	8 45
82	**21**	0.1/0.4/4	RT	100	84	**29**	78

TABLE 4.10**. Results of the reaction of 2,6- and 3,6-heptadienoates (**20 **and** 21**, 2 mmol) in methoxyacetic acid (10 ml) in presence of a $Pd(OAc)_2$/benzoquinone/MnO_2 catalytic system.**

Reactions in water

We also explored the possibility of carrying out the reaction in aqueous media. This would allow, along with the positive effect on the environmental impact of the reaction, the use of different organic acids, including the ones that are solid at room temperature. At first we tested acetic and methoxyacetic acids in water obtaining good results. In most cases conversions were sensibly improved (table 4.11). In the case of methyl 3,6-heptadienoate reacted with methoxyacetic acid in water, the yield of the desired product was decreased because of the formation of several minor byproducts (entry 84). Methyl 2,6-heptadienoate gave the expected product in quantitative yield (entry 83).

Entry	Reagent	Acid	Conversion %	Product	Yield %
83	**20**	CH_3COOH	>99	**22**	98
84	**21**	CH_3COOH	>99	**23**	77
85	**5**	CH_3COOH	73	**26**	51
86	**20**	CH_3OCH_2COOH	>99	**27**	60
87	**21**	CH_3OCH_2COOH	>99	**28**	40

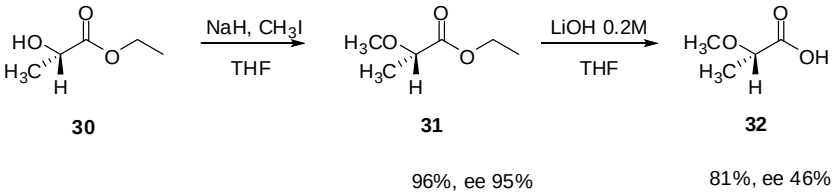
TABLE 4.11**. Results of the reaction of 2,6- and 3,6-heptadienoates (**5, 16 **and** 17**, 2 mmol) in a mixture of organic acid (5 ml) and water (5 ml) in presence of a $Pd(OAc)_2$/benzoquinone/MnO_2 (0.1/0.4/2 mmol) catalytic system at room temperature for 64h.**

Reaction of different organic acids

The possibility of carrying out the reaction in water allows the use of organic acids solid at room temperature, such as glycolic and chloroacetic acid. . Unluckily, the reactions led to mixtures of different addition, cyclization, and in some case degradation products and our attempts of isolating the desired products failed. Weaker organic acids such as 2-methylbutanoic or 2-ethylhexanoic acid, on the other hand, showed no or very low conversion.

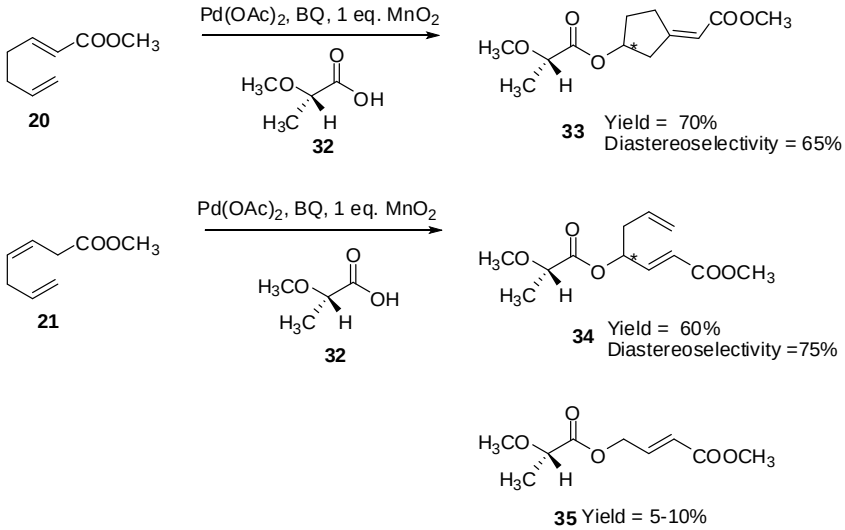
Asymmetric induction

The nucleophilic addition of the organic acid on the heptadienoic esters leads to the formation of a chiral center. As a further development, we investigated the possibility of obtaining a stereoselective addition with the preferential formation of one enantiomer on the newly formed chiral center. The strategy we followed was to induce asymmetry *via* introduction of one enantiomer of a chiral organic acid. The model molecule we chose was 2-methoxypropionic acid **32**, for its similarity to the highly reactive methoxyacetic acid. (S)-2-methoxypropionic acid was synthesized in two steps starting from ethyl-(S)-lactate **30** according to scheme 4.19[28-29]. A 46% enantiomeric excess was found for the (S) enantiomer of product **32**.



SCHEME 4.19. Synthesis of (S)-methoxypropanoic acid from ethyl (S)-lactate.

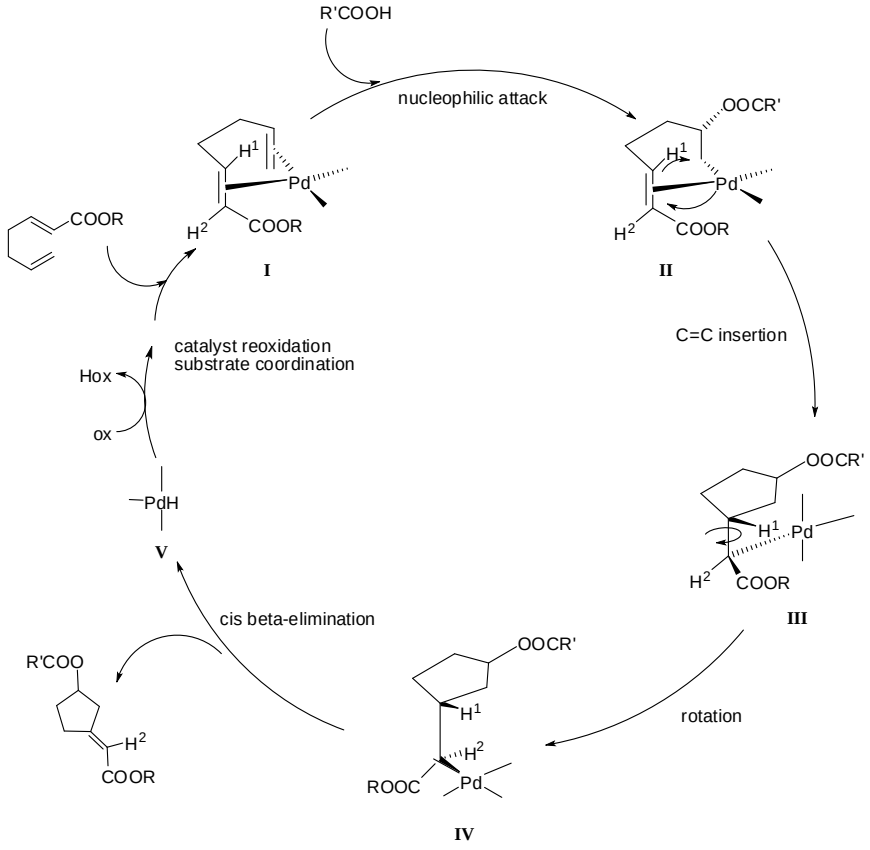
The reaction of **32** with both 2,6- and 3,6-heptadienoate methyl esters was performed in the neat acid and proceeded smoothly affording the desired products **33** and **34** (scheme 4.20) in good yields and with good diastereomeric excess. A degradation product (**35**) was also found to be produced in minor amounts.



SCHEME 4.20. Asymmetric induction in the reaction of 2,6- and 3,6- methyl heptadienoate with (S)-methoxypropanoic acid. Reactions carried out at RT for 64 hours.

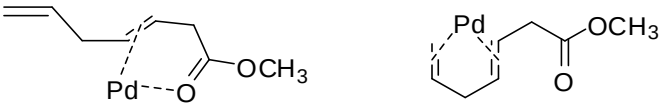
Mechanistic aspects

The catalytic mechanism of reaction for 2,6-heptadienoates is likely closely related to that of monosubstituted 1,5-dienes as reported in literature[27]. Scheme 4.21 reports its application to our substrates. The *trans* geometry for the C=C double bond has been confirmed by 2D NOESY NMR spectroscopy.



SCHEME 4.21. Catalytic mechanism for the oxidative cyclization of 2,6-heptadienoates.

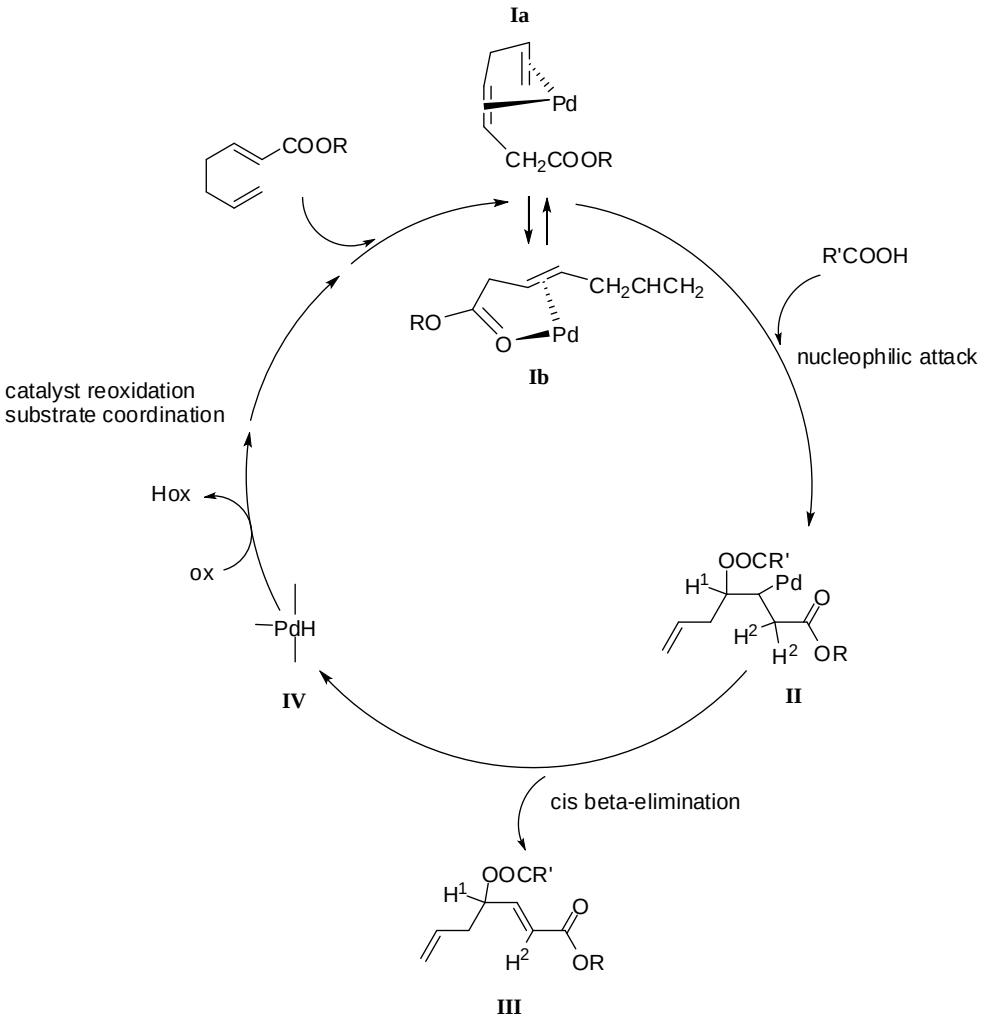
A different behavior should be proposed for the reaction of 3,6 heptadienoic esters that in contrast selectively afford a linear addition product. In order to explain the different reactivity of the two types of substrate, different intermediates should be postulated. The different position of the two C=C double bonds can lead to two different coordination modes for 3,6-heptadienoates on palladium. Coordination may occur on both insaturations (scheme 4.22, (a)) or between the C=C double bond in γ position and the carbonylic oxygen (scheme 4.22, (b)).



(a) (b)

SCHEME 4.22. Possible coordinations of 3,6-heptadienoates to palladium.

The proposed reaction mechanism is depicted in scheme 4.23. Considering the two possible coordinations of palladium in the initial complex (**I a**-**b**), in both cases the nucleophilic attack takes place on the γ-carbon, the same involved in the reaction of 2,6-derivatives. Only traces of products bearing the acetate group in different positions were found in the reaction mixtures. The product of this step is a σ-bonded palladium linear adduct (**II** in scheme 4.23). This compound can undergo cis-β elimination of palladium hydride at two positions. The candidate hydrogens for extraction are indicated as H^1 and H^2. The elimination of H^2 is favored by the higher stability of the final product, due to the conjugation of the C=C and C=O double bonds. Consistently, the conjugate product was the only one found in the reaction mixture. The *trans* geometry for the C=C double bond was confirmed by coupling constants in NMR experiments.



SCHEME 4.23. Proposed reaction mechanism for 3,6-heptadienoates.

4.8 - Part III: conclusions

Esters of 2,6- and 3,6- heptadienoic acids have been reacted in presence of an organic acid to yield monosubstituted or disubstituted cyclopentylidenes or linear addition products in good yields. The choice of substrate and reaction conditions allows to easily tune the selectivity of the reaction. The use of water as solvent has been demonstrated to be useful in this case too; moreover, it has been shown that a stereoselectivity in the nucleophilic attack can be achieved by asymmetric induction due to the use of a single enantiomer o an organic acid as a nucleophile.

4.9 - Experimental

4.9.1 - Materials and methods

The manipulations were performed under an atmosphere of dry nitrogen or argon using standard vacuum-line and Schlenk techniques. Solvents were dried and distilled under nitrogen before use. Triphenylphosphine was recristallyzed from n-hexane and used immediately. All other reagents, ligands and rhodium complexes were obtained from commercial suppliers and used without further purification.
All yields were determined by GC according to the internal standard method. To obtain improved chromatographic peaks, organic acids were transformed in their respective methyl esters by treating with a CH_2N_2 solution in diethyl ether. GC analyses were carried out using a HRGC Mega 2 series Fisons Instruments equipped with a polymethylsilicone + 5% phenylsilicone as a stationary phase (HP-5) capillary column (30 m $\times$ 0.25 mm).
Thin-layer chromatography (TLC) was performed on silica gel on silica gel 60 F_{254} coated aluminum plates. Gravity-flow liquid chromatography was carried out on silica gel 60 (Merck, 0.063-0.200 mm), solvent mixtures were prepared by volume.
Elemental analyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106. ^{1}H NMR and ^{13}C NMR spectra were taken in $CDCl_3$, unless otherwise specified, at room temperature and recorded at 300 (or 600) and 75 MHz, respectively. IR spectra were taken on a NICOLET 5700 FT-IR spectrometer. Mass spectra were obtained using a GC system HP6890 Series coupled with a HP 5973 Mass Selective Detector at 70 eV ionization voltage.

4.9.2 - Procedures

Preparation of Substrates. Allyl but-3-enoate **1** was prepared according to a literature procedure[30]. Substituted allyl esters of but-3-enoic acid **7**, **8** and **9** were prepared according to the following procedure: but-3-enoic acid (1.377 g, 16.0 mmol), crotyl alcohol (1.168 g, 16.2 mmol), or 2-cyclohexen-1-ol (1.590 g, 16.2 mmol), or 3-buten-2-ol (1.169 g,16.2 mmol) and p-toluenesulfonic acid monohydrate (0.030 g, 0.16 mmol) were dissolved in dry THF (30 ml). The mixture was refluxed for 16 h in a flask equipped with a reverse Dean-Stark apparatus containing molecular sieves 4A for water absorption. The solvent was distilled under vacuum and the resulting ester was purified by flash chromatography (SiO_2).

General procedure for the catalytic rearrangement of allyl but-3-enoate. An example of experimental procedure is reported here. Reagent amounts, solvent amounts and other parameters may vary as specified in the tables**.** The reactions were carried out in a Schlenk flask under N_2 or Ar atmosphere. Allyl but-3-enoate (2.6 mmol), the chosen catalyst ($2.6 \cdot 10^{-2}$ mmol of rhodium mononuclear complexes, or $1.3 \cdot 10^{-2}$ mmol of dinuclear complexes) and, if required, (di-isopropylethyl)amine (235.2 mg, 2.8 mmol) were loaded in the flask. The desired amount of organic solvent and / or $NaHCO_3$-saturated water was added and the mixture was placed in a pre-heated (100°C) oil bath and stirred at 1000 rpm for 18 hours. The reaction mixture was recovered from the flask using 3x5 ml of K_2CO_3- saturated water and 3x5 ml of dichloromethane. The mixture was then placed in a separatory funnel and the two phases were separated. The organic phase was analyzed via GC using the internal standard method, then the solvent was removed under vacuum. Flash chromatography (silica gel) of the residue using a mixture of hexane/ EtOAc (10/1) as eluent afforded ester products. The aqueous phase was acidified to pH 1 with 2M HCl and extracted with dichloromethane (3 x 10 ml). GC analyses, using the internal standard method, were performed on the organic extract. After removal of the solvent under vacuum, flash chromatography (silica gel) of the residue using a mixture of hexane/ EtOAc (1/1) as eluent afforded acid products.
All yields were determined by GC according to the internal standard method. To obtain improved chromatographic peaks, organic acids were transformed in their respective methyl esters by treating with a CH_2N_2 solution in diethyl ether.

Procedure for the catalytic isomerization of 2,6- and 3,6-heptadienoic acids. Under an inert atmosphere the complex $Rh(PPh_3)_3Cl$ (0.012 g, $1.3 \cdot 10^{-2}$ mmol), E-2,6-heptadienoic acid or the mixture of E-3,6- and E-2,6-heptadienoic acids (93/7 molar ratio) (0.164 g, 1.3 mmol) and butyronitrile (3.0 ml) were introduced into a Schlenk flask. Then the mixture was heated at 100 °C for 16 h.
Under the same conditions the complex $[Rh(C_2H_4)_2Cl]_2$ (0.002 g, $5 \cdot 10^{-3}$ mmol), E-2,6-heptadienoic acid or the mixture of E-3,6- and Z-3,6-heptadienoic acids (93/7 molar ratio) (0.126 g, 1.0 mmol) and a mixture of NaHCO3 saturated water solution (2.0 ml) and butyronitrile (1.5 ml) were heated at 100 °C for 16 h. The isomerization of heptadienoic acids was monitored by gas chromatography.

Synthesis of rhodium complexes of 2,6- and 3,6-heptadienoic acids. $[Rh(C_2H_4)_2Cl]_2$ (0.078 g 0.2 mmol), *E*-2,6-heptadienoic acid (0.051 g 0.4 mmol) and CH_2Cl_2 (4.0 ml) were introduced into a Schlenk flask under nitrogen. The mixture was stirred at room temperature for 6 h to give a lemon yellow precipitate. n-Pentane (5.0 ml) was added,

and the mixture was cooled to –20 °C overnight. The yellow powder was collected by filtration under nitrogen (0.055 g).
In a similar way, $[Rh(C_2H_4)_2Cl]_2$ (0.078 g 0.2 mmol), a mixture of *E*-3,6- and *E*-2,6-heptadienoic acids (93/7 molar ratio) (0.052 g, 0.4 mmol) and CH_2Cl_2 (3.0 ml) were introduced into a Schlenk tube under nitrogen. The mixture was stirred at room temperature for 6 h to give a scanty amount of a yellow-brown precipitate. n-Pentane (5.0 ml) was added and the mixture was cooled –20 °C overnight. The yellow-brown precipitate was collected by filtration under nitrogen (0.036 g).

General procedure for the reaction of but-3-enoic acid and allyl derivatives. An example of experimental procedure is reported here. Reagent amounts, solvent amounts and other parameters may vary as specified in the tables. The reactions were carried out in a Schlenk flask under N_2 or Ar atmosphere. But-3-enoic acid (4.1 mmol), the allyl derivative (8.5 mmol). $[Rh_2(C_2H_4)_2Cl]_2$ (0.021 mmol) or $Rh(PPh_3)_3Cl$ (0.041 mmol), , K_2CO_3 (amount specified in the tables),organic solvent and water (amounts specified in the tables) and, if required PPh_3 (1, 2 or 3 mmol per mmol of Rh atoms) were loaded. The flask was placed in a pre-heated at the desired temperature oil bath for 23 hours under stirring at 1000 rpm. The reaction mixture was recovered from the flask using 3x5 ml of K_2CO_3- saturated water and 3x5 ml of dichloromethane. The mixture was then placed in a separatory funnel and the two phases were separated. The organic phase was analyzed via GC using the internal standard method, then the solvent was removed under vacuum. Flash chromatography (silica gel) of the residue using a mixture of hexane/ EtOAc (10/1) as eluent afforded ester products. The aqueous phase was acidified to pH 1 with 2M HCl and extracted with dichloromethane (3 x 10 ml). GC analyses, using the internal standard method, were performed on the organic extract. After removal of the solvent under vacuum, flash chromatography (silica gel) of the residue using a mixture of hexane/ EtOAc (1/1) as eluent afforded acid products.
All yields were determined by GC according to the internal standard method. To obtain improved chromatographic peaks, organic acids were transformed in their respective methyl esters by treating with a CH_2N_2 solution in diethyl ether.

ICP analyses of rhodium. Quantitative determinations of rhodium by ICP technique were carried out at Chimica Generale ed Inorganica, Chimica Fisica, and Chimica Analitica Department of Parma University. The samples were prepared according to a procedure reported in the literature[31].

General procedure for the oxidative addition – cyclization reaction of heptadienoates. An example of experimental procedure is reported here. Reagent

amounts, solvent amounts and other parameters may vary as specified in the tables. The reactions were carried out in a Schlenk flask under N_2 atmosphere. The reagent (2.1 mmol), $Pd(OAc)_2$ (0.1 mmol, 25.0 mg) benzoquinone (0.4 mmol, 45.0 mg) and MnO_2 (2.1 mmol, 185.0 mg) were loaded and then 7 ml of neat organic acid, or a mixture of organic acid and water as specified in the tables, were added. The mixture was stirred (1000 rpm) at room temperature for 72 hours. The reaction was quenched with brine (5 ml) and filtered on a Buchner funnel. The solid residual was washed with 10 ml n-hexane/diethyl ether (7/3 vol/vol). The liquid phase was extracted (3 x 10 ml) with n-hexane/diethyl ether (7/3 vol/vol). The organic phases were combined and washed with dist. water (10 ml) and then with $NaHCO_3$ saturated water (3 x 10 ml), then dried over Na_2SO_4. Solvent evaporation under vacuum yielded the crude product. Separation of products was carried out by liquid chromatography (eluent hexane-ethyl acetate, 8/1 to 5/1 vol/vol).

4.9.3 - Characterizations

All products were characterized by IR, ^1H and ^{13}C NMR spectroscopies, MS spectrometry, and elemental analysis. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300 MHz and 75 MHz, respectively with Me_4Si as internal standard. Chemical shifts and coupling constants (J) are given in ppm (δ) and in Hz, respectively.

But-3-enoic acid allyl ester 1. Distillation (b.p. 78 °C/16 mbar) gave (10.710 g, 85 %) of the ester as a colorless liquid; IR (film) ν_{max} cm^{-1} 3085 (w), 2986 (w), 1734 (s), 1646 (m), 1424 (m), 1363 (m), 1170 (s), 992 (m), 921 (m). ^1H NMR (300 MHz) δ_H 3.13 (dt, J = 6.9, J = 1.3, 2H, CH_2COO), 4.60 (dt, J = 5.6, J = 1.3, 2H, OCH_2), 5.14–5.22 (m, 4H, C*H*$_2$=CHCH$_2$COOCH$_2$CH=C*H*$_2$), 5.32 (ddt, J = 17.2, 2J = 1.3, 1H, =CH*H*), 5.88–5.98 (m, 2H, CH_2=C*H*CH$_2$COOCH$_2$C*H*=CH_2). ^{13}C NMR (75 MHz) δ_C 38.9, 65.1, 118.1, 118.3, 130.1, 132.0, 170.9. MS *m/z* 126(M^+, 8), 69(100), 81(53), 84(33), 57(17), 97(10), 111(7), 51(3**).** Anal. Calcd for $C_7H_{10}O_2$: C, 66.55; H, 7.99. Found C, 66.48; H, 7.96.

Hepta-2(*E*),6-dienoic acid 2. Colorless oil**.** IR (film) ν_{max} cm^{-1} 2926 (m), 1697 (s), 1651 (w), 1418 (m), 1288 (m), 1227 (w), 986 (w), 914 (w). ^1H NMR (300 MHz) δ_H 2.20–2.37 (m, 4H, CH_2CH_2), 5.00-5.09 (m, 2H, H_2C=), 5.73–5.87 (m, 2H, H_2C=C*H*CH$_2$CH$_2$CH=C*H*), 7.08 (dt, J = 15.6, J = 6.8 Hz, 1H, C*H*=CHCO$_2$H), 11.23 (s, 1H, OH). ^{13}C NMR (75 MHz) δ_C 31.5, 31.8, 115.6, 120.9, 136.8, 151.2, 171.6. MS *m/z* 126(M^+, 1), 81(100), 68(52), 54(38), 97(23), 51(13), 77(11), 57(9), 65(8), 85(7), 111(5), 108(5), 60(3), 125(3), 71(2), 74(2). Anal. Calcd for $C_7H_{10}O_2$: C, 66.63; H, 7.99. Found C, 66.58; H, 7.95.

Hepta-3(*E*),6-dienoic acid 3. Colorless oil**.** IR (film) ν_{max} cm^{-1} 2920 (m), 1709 (s), 1414 (m), 1289 (w), 990 (w), 970.1 (w), 914 (w). ^{1}H NMR (300 MHz) δ_H 2.79 (2H, dd, J = 6.1 Hz, J = 6.4 Hz, CH_2=CHC*H*$_2$), 3.09 (2H, d, J = 5.4 Hz, C*H*$_2$CO$_2$H), 4.98-5.08 (m, 2H, H_2C=), 5.55 (1H, dt, J = 14.0 Hz, J = 6.1 Hz, *H*C=CHCH$_2$CO$_2$H), 5.63 (1H, dt, J = 14.0 Hz, J = 5.4 Hz, HC=C*H*CH$_2$CO$_2$H), 5.80 (1H, ddt, J = 17.1 Hz, J = 10.1 Hz, J = 6.4 Hz CH_2=C*H*CH$_2$), 9.35 (s, 1H, OH). ^{13}C NMR (75 MHz) δ_C 36.4, 37.5, 115.2, 122.0, 131.0, 132.1, 177.3. MS *m/z* 126(M^+, 15), 81(100), 79(80), 41(50), 67(45), 53(35), 84(35), 97(10), 45(10). Anal. Calcd for $C_7H_{10}O_2$: C, 66.63; H, 7.99. Found C, 66.55; H, 7.96.

Allyl hepta-3(*E*),6-dienoate 4. Colorless oil**.** IR (film) ν_{max} cm^{-1} 2926 (m),1697(s),1651(w),1418 (m), 1288 (m), 1227 (w), 986 (w), 914 (w). ^{1}H NMR (300 MHz) δ_H 2.78–2.84 (m, 2H, H_2C=CHC*H*$_2$CH=CH$_2$), 3.07–3.14 (m, 2H, CH_2COO), 4.57-4.60 (m, 2H, CO$_2$C*H*$_2$), 5.00–5.08 (m, 2H, *H*$_2$C=CHCH$_2$CH=), 5.21-5.28 (m, 2H, OCH$_2$CH=C*H*$_2$), 5.60-5.65 (m, 2H, *H*C=C*H*CH$_2$COO), 5.77–5.93 (m, 2H, H_2C=C*H*CH$_2$CH=CH + OCH$_2$C*H*=CH$_2$). Noesy 1D experiments confirmed 3(*E*) geometry. ^{13}C NMR (75 MHz) δ_C 36.4, 37.9, 65.1, 115.4, 117.9, 122.6, 132.1, 132.0, 136.3, 171.5. MS *m/z* 166(M+, 1), 151(1), 137(3), 125(25), 107(35), 83(40), 81(60), 79(100), 67(10), 53(30). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49. Found C, 72.20; H, 8.45.

Allyl hepta-2(*E*),6-dienoate 5. Colorless oil**.** IR (film) ν_{max} cm^{-1} 3080(m), 2932 (m), 1724(s), 1653(m), 1446(w), 1270(w), 1170(m), 990(w), 971(w). ^{1}H NMR (300 MHz) δ_H 2.16-2.33 (m, 4H, =CHC*H*$_2$C*H*$_2$CH=), 4.61 (ddd, J = 5.5 Hz, J = 1.3 Hz, J = 1.4 Hz, 2H, CO$_2$C*H*$_2$), 4.99-5.05 (m, 2H, C*H*$_2$=CHCH$_2$CH$_2$), 5.21 (ddt, J = 10.4 Hz, J = 1.1 Hz, , J = 1.3 Hz, 1H, OCH$_2$CH=C*H*H), 5.30 (ddt, J= 17.1 Hz, J = 1.1 Hz, J = 1.4 Hz, 1H, OCH$_2$CH=CH*H*), 5.85 (dt, J = 15.6 Hz, J = 1.4 Hz, 1H, C*H*COO), 5.71-5.97 (m, 2H, H_2C=C*H*CH$_2$CH$_2$ + OCH$_2$C*H*=CH$_2$), 6.98 (dt, J = 15.6 Hz, J = 6.6 Hz, 1H, *H*C=CHCOO). MS *m/z* 166(M+, 1), 151(3), 137(3), 125(20), 109(60), 81(100), 79(80), 68(25), 55(40). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49. Found C, 72.20; H, 8.44.

Allyl 4-allyl-hepta-3,6-dienoate 7. Colorless oil**.** ^{1}H NMR (300 MHz) δ_H 2.76–2.79 [m, (4H, H_2C=CHC*H*$_2$)$_2$C=], 3.11 (d, J = 7.1 Hz, 2H, CH_2COO), 4.59 (dt, J = 5.7 Hz, J = 1.4 Hz, 2H, CO$_2$C*H*$_2$), 5.00–5.08 [m, 4H, (*H*$_2$C=CHCH$_2$)$_2$C=], 5.23 (ddd, J = 10.3, Hz, J = 1.3 Hz, J = 1.2 Hz, 1H, CO$_2$CH$_2$CH=C*H*H), 5.31(ddd, J = 15.7, Hz, J = 1.6 Hz, J = 1.3 Hz, 1H, CO$_2$CH$_2$CH=CH*H*), 5.47 (t, J = 7.1 Hz, 1H, =*CH*CH$_2$), 5.70–5.96 [m, 3H, (H_2C=C*H*CH$_2$)$_2$C= + CO$_2$CH$_2$C*H*=CH$_2$]. MS *m/z* 206(M^+, 8), 187(5), 163(12), 145(30), 119(65), 105(45), 91(95), 79(100), 67(40), 55(30). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.68; H, 8.80. Found C, 75.61; H, 8.72

Octa-2(*E*),6(E)-dienoic acid 8. Colorless oil**.** ^{1}H NMR (300 MHz) δ_H 1.65 (dd, J = 6.7, J = 1.4 Hz, 3H), 2.13-2.32 (m, 4H), 5.28-5.64 (m, 2H), 5.83 (d, J = 15.9 Hz, 1H), 7.08 (dt, J = 15.9, J = 6.9 Hz, 1H), 9.80 (bs, 1H). ^{13}C NMR (75 MHz) δ_C 17.8, 30.4, 32.2, 120.5, 129.3, 131.8, 151.8, 172.0. MS *m/z* 140(5), 122(1), 111(2), 95(5), 86(40), 79(5), 68(10), 55(100), 41(15). Anal. Calcd for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found C, 68.46; H, 8.61.

Octa-3(*E*),6(E)-dienoic acid 9. Colorless oil**.** ^{1}H NMR (300 MHz) δ_H 1.66 (d, J = 6.6 Hz, 3H, CH_3), 2.68-2.76 (m, 2H), 3.04 (d, J = 6.2 Hz, 2H), 5.33-5.46 (m, 2H), 5.48-5.84(m, 2H), 9.80 (bs, 1H). ^{13}C NMR (75 MHz) δ_C 17.8, 35.4, 37.7, 120.7, 126.2, 128.2, 133.7, 178.4.]. MS *m/z* 140(30), 122(5), 95(35), 81(80), 79(100), 67(50), 55(45), 41(50). Anal. Calcd for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found C, 68.47; H, 8.62.

But-3-enoic acid but-2(*E*)-enyl ester. Chromatography with *n*-hexane/EtOAc (8/2) gave (1.455 g, 65 %) the ester as a colorless liquid; IR (film) ν_{max} cm^{-1} 3045 (w), 2983 (w), 1733 (s), 1635 (m), 1414 (m), 1210 (s), 990 (m), 910 (m); ^{1}H NMR (300 MHz) δ_H 1.69(d, J = 6.0 Hz, 3H), 3.06(ddd, J = 7.2 Hz, J = 1.5 Hz, J = 1.5 Hz, 2H), 4.50(dd, J = 7.8 Hz, J = 1.5 Hz, 2H), 5.13-5.17(m, 2H), 5.52-5.94 (m syst., 3H); ^{13}C NMR (75 MHz) δ_C 26.8, 48.2, 74.9, 127.9, 134.1, 139.4, 141.3, 180.4; MS *m/z* 140(1), 126(1), 111(2), 94(5), 80(10), 69(15), 55(100), 41(35). Anal. Calcd for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found C, 68.44; H, 8.60.

But-3-enoic acid cyclohex-2-enyl ester. Chromatography with *n*-hexane/EtOAc (8/2) gave (2.390 g, 80 %) the ester as a colorless liquid; IR (film) ν_{max} cm^{-1} 3020 (w), 2925 (w), 2853(s), 1737 (s), 1644 (m), 1447 (m), 1262(w), 1176 (s), 920 (m). ^{1}H NMR (300 MHz) δ_H 1.61-2.06 (m syst., 6H), 3.07(dt, J = 6.8 Hz, J = 1.3 Hz, 2H), 5.12-5.18 (m, 2H), 5.25-5.27(m, 1H), 5.66-5.99(m syst., 3H); ^{13}C NMR (75 MHz) δ_C 15.6, 21.6, 26.4, 36.3, 65.0, 115.1, 122.3, 127.0, 129.5, 167.9. MS *m/z* 166(2), 147(5), 125(10), 104(10), 81(100), 79(70), 69(20), 53(20), 41(35). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.24; H, 8.49. Found C, 72.18; H, 8.46.

But-3-enoic acid 1-methylallyl ester. Chromatography with *n*-hexane/EtOAc (8/2) gave (1.120 g, 50 %) the ester as a colorless liquid; IR (film) ν_{max} cm^{-1} 3044 (w), 2983 (w), 1734 (s), 1635 (m), 1415 (m), 1212 (s), 990 (m), 911 (m); ^{1}H NMR (300 MHz) δ_H 1.28(d, J = 6.6 Hz, 3H), 3.06(dt, J = 6.8 Hz, J = 1.4 Hz, 2H) 4.25(dq, J =7.2 Hz, J = 6.6 Hz, 1H), 4.99-5.11 (m, 2H),5.12-5.23 (m syst., 2H), 5.74-5.98 (m syst., 2H); ^{13}C NMR (75 MHz) δ_C 140(1), 125(1), 111(5), 82(30), 71(25), 55(100), 43(25). Anal. Calcd for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found C, 68.45; H, 8.61.

4-Methylhepta-2(E),6-dienoic acid 12 (R=CH_3). Colorless oil. IR (film) ν_{max} cm^{-1} 2968(s), 2928(s), 1698(s), 1652(s), 1418(m), 1287(m), 1236(w), 987(w), 917(m). ^{1}H NMR (300 MHz) δ_H 1.08 (d, J = 6.7 Hz, 3H), 2.04-2.19 (m, 2H), 2.21-2.45 (m, 1H), 5.01-5.06 (m, 2H), 5.67-5.81 (m, 1H) 5.79(dd, J_1 = 15.5 Hz, J_2 = 0.8 Hz, 1H), 7.00(dd, J_1 = 15.5 Hz, J_2 = 7.4 Hz, 1H), 10.65 (bs, 1H). ^{13}C NMR (75 MHz) δ_C 18.5, 36.2, 39.9, 116.8, 119.1, 135.5, 156.4, 172.2. MS *m/z* 140(M^+, 5), 125(15), 111(10), 100(10), 99 (100), 96(90), 86(5), 81(20), 71(15), 53(20).

4-Ethylhepta-2(E),6-dienoic acid 12 (R=C_2H_5). Colorless oil. IR (film) ν_{max} cm^{-1} 2966(s), 1701(s), 1690(m), 1654(s), 1418(m), 1304(m), 1221(w), 991(m), 915(m). ^{1}H NMR (300 MHz) δ_H 0.88 (t, J = 7.4 Hz, 3H), 2.01-2.22 (m. syst., 5H), 5.00-5.09 (m, 2H), 5.66-5.83 (m, 1H), 5.79(dd, J_1 = 15.3 Hz, J_2 = 0.8 Hz, 1H), 6.89(dd, J_1 = 15.3 Hz, J_2 = 8.2 Hz, 1H), 9.50(bs, 1H). ^{13}C NMR (75 MHz) δ_C 11.4, 26.3, 40.8, 43.9, 115.5, 116.2, 135.6, 155.4, 171.7. MS *m/z* 154(M^+, 10), 125(15), 113(40), 109(40), 95(45), 91(15), 79(75), 71(15), 67(85), 55(45), 51(15), 45(30), 41 (100)

4-Ethylhepta-3(E),6-dienoic acid 13 (R=C_2H_5). Colorless oil. IR (film) ν_{max} cm^{-1} 2945(s), 1720(s), 1690(m), 1636(s), 1420(m), 1306(m), 1221(w), 971(m), 915(m). ^{1}H NMR (300 MHz) δ_H 0.98 (t, J = 7.6 Hz, 3H), 2.13-2.24 (m, 2H), 2.79 (d, J = 6.8 Hz, 2H), 3.09 (d, J = 7.1 Hz, 2H), 5.00-5.09 (m, 2H), 5.32(t, J = 7.1 Hz, 1H), 5.66-5.83 (m, 1H), 9.50(bs, 1H). ^{13}C NMR (75 MHz) δ_C 12.6, 23.3, 33.1, 38.1, 116.6, 120.5, 136.3, 143.9, 178.4. MS *m/z* 154(M^+, 10), 125(15), 113(40), 109(40), 95(45), 91(15), 79(75), 71(15), 67(85), 55(45), 51(15), 45(30), 41 (100).

Allyl 4-Methylhepta-2(E),6-dienoate 14 (R=CH_3). Colorless oil. IR (film) ν_{max} cm^{-1} 3079(w), 2930(w), 1724(s), 1649(s), 1457(m), 1274(m), 991(m), 918(w). ^{1}H NMR (300 MHz) δ_H 1.04(d, J = 6.6 Hz, 3H), 2.03-2.24(m, 2H) 2.35-2.44(m, 1H), 4.61(d, J = 5.7 Hz, 2H), 4.99-5.05(m, 2H), 5.19-5.38(m, 2H), 5.64-5.98(m. syst., 3H), 6.92(dd, J_1 = 15.6 Hz, J_2 = 7.8 Hz, 1H). ^{13}C NMR (75 MHz) δ_C 16.3, 40.1, 43.8, 64.9, 116.1, 118.0, 119.4, 132.3, 135.7, 154.2, 166.4. MS *m/z* 180(M+, 1), 139(40), 123(15), 111(15), 95(50), 79(35), 73(5), 67(45), 55(55), 41(100)

Allyl 4-Ethylhepta-2(E),6-dienoate (14, R=C_2H_5). Colorless oil. IR (film) ν_{max} cm^{-1} 3079(w), 2933(m), 1715(s), 1652(s), 1457(m), 1257(m), 1174(m), 991(m), 917(w). ^{1}H NMR (300 MHz) δ_H 10.86 (t, J = 7.4 Hz, 3H), 2.01-2.21 (m. syst., 5H), 4.63(d, J = 5.7 Hz, 2H), 4.99-5.08 (m, 2H), 5.21-5.36 (m, 2H) 5.66-5.98(m. syst., 2H), 5.80(d, J = 15.7 Hz, 1H), 6.78(dd, J_1 = 15.7 Hz, J_2 = 8.3 Hz, 1H). ^{13}C NMR (75 MHz) δ_C 11.4, 26.4, 40.9, 43.9, 64.9, 116.1, 118.0, 120.9, 132.1, 135.7, 153.0, 166.7. MS *m/z* 154(M^+, 10), 125(15),

113(40), 109(40), 95(45), 91(15), 79(75), 71(15), 67(85), 55(45), 51(15), 45(30), 41 (100)

Allyl 4-Ethylhepta-3(E),6-dienoate 15 (R=C_2H_5). Colorless oil. IR (film) ν_{max} cm^{-1} 2965(s), 2877(m), 1733(s), 1652(s), 1364(m), 1257(m), 991(m), 917(w)**.** ^{1}H NMR (300 MHz) δ_H 0.97(t, J = 7.3 Hz, 3H), 2.19(q, J = 7.3 Hz, 2H), 2.78(d, J = 6.5 Hz, 2H), 3.09(d, J = 7.2 Hz, 2H), 4.58(d, J = 5.6 Hz, 2H), 4.98-5.08(m, 2H), 5.21-5.36(m. syst., 3H), 5.67-5.98(m. syst., 2H). ^{13}C NMR (75 MHz) δ_C 12.6, 23.3, 37.3, 38.2, 65.1, 116.5, 118.0, 120.9, 131.8, 135.5, 136.2, 166.7. MS *m/z* 194(M+, 1), 165(1), 153(5), 135(20), 125(10), 107(30), 93(100), 79(45), 67(95), 55(45), 41(100)

Octa-3(*E*),7-dienoic acid. Colorless oil**.** ^{1}H NMR (300 MHz) δ_H 2.28-2.44(m, 2H), 2.46-2.54(m, 4H), 2.78(d, J = 6.4 Hz, 2H), 4.79-4.83(m, 2H), 5.00-5.11(m, 2H), 5.73-5.87(m, 1H), 11.67 (bs, 1H). ^{13}C NMR (75 MHz) δ_C 30.3, 32.3, 40.9, 110.7, 115.7, 116.5, 146.0, 179.0. MS *m/z* 166(M+, 1), 151(3), 137(3), 125(20), 109(60), 81(100), 79(80), 68(25), 55(40). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49. Found C, 72.20; H, 8.44

Octa-4(*E*),7-dienoic acid. Colorless oil**.** ^{1}H NMR (300 MHz) δ_H 2.28-2.44(m, 2H), 2.46-2.54(m. syst., 4H), 4.79-4.83(m, 2H), 5.00-5.11(m, 2H), 5.73-5.87(m, 1H), 11.79 (bs., 1H). ^{13}C NMR (75 MHz) δ_C 3028.4, 33.2, 40.9, 110.6, 115.7,116.5, 135.8, 179.4. MS *m/z* 139(M^+, 10), 125(10), 121(20), 97(30), 93(85), 79(100), 67(40), 55(45), 51(10), 45(5), 41(90).

Allyl octa-3(*E*),7-dienoate. Colorless oil**.** IR (film) ν_{max} cm^{-1} 2930(s), 1735(s), 1678(s), 1356(m), 1272(m), 1173(m),990(m), 926(w). ^{1}H NMR (300 MHz) δ_H 2.08-2.43 (m. syst., 4H), 2.50(d, J = 7.4 Hz, 2H), 4.57(d, J = 5.3 Hz, 2H), 4.97-5.08(m, 2H), 5.21-5.35(m, 2H), 5.55-5.58(m, 2H), 5.74-5.94(m. syst., 2H). ^{13}C NMR (75 MHz) δ_C 30.0, 32.8, 42,9, 65.3, 110.8, 118.2, 121.1, 122.5, 132.0, 132.8, 177.6. MS *m/z* 180(M^+, 1), 141(50), 100(5), 95(5), 83(65), 67(10), 55(100), 43(50).

Allyl octa-4(*E*),7-dienoate. Colorless oil**.** IR (film) ν_{max} cm^{-1} 2932(s), 1732(s), 1648(s), 1366(m), 1173(m),990(m), 926(w). ^{1}H NMR (300 MHz) δ_H 2.08-2.42 (m, 6H), 4.57(d, J = 5.3 Hz, 2H), 4.97-5.08(m, 2H), 5.21-5.35(m, 2H), 5.55-5.58(m, 2H), 5.74-5.94(m, 1H). ^{13}C NMR (75 MHz) δ_C 29.9, 32.8, 37.8, 65.2, 110.8, 118.2, 121.1, 122.5,132.0, 132.8, 177.6. MS *m/z* 180(M^+, 1), 133(20), 119(10), 105(10), 93(25), 79(25), 71(5), 67(35), 55(30), 51(5), 41(100).

6-Methylhepta-2(E),6-dienoic acid 18 (R^1=CH_3). Colorless oil. IR (film) ν_{max} cm^{-1} 2932(br), 1699(s), 1651(s), 1418(m), 1287(m), 971(w), 890(m)**.** ^{1}H NMR (300 MHz) δ_H 1.72(s, 3H), 2.16(t, J = 7.7 Hz, 2H), 2.37(dt, J_d = 6.8 Hz, J_t = 7.7 Hz, 2H), 4.69-4.75(m, 2H), 5.83(dt, J_d = 15.7 Hz, J_t = 1.4 Hz, 1H), 7.07(dt, J_d = 15.7 Hz, J_t = 6.8 Hz, 1H), 11.70 (bs., 1H). ^{13}C NMR (75 MHz) δ_C 22.3, 30.2, 35.6, 110.8, 120.8, 143.9, 151.6, 172.2. MS *m/z* 140(M+, 5), 125(25), 111(10), 107(10), 95(50), 91(5), 83(5), 79(50), 67(30), 55(100), 51(20), 45(25), 41(45)

7-Phenylhepta-2(E),6-dienoic acid 18 (R^2=C_6H_5). Colorless oil. ^{1}H NMR (300 MHz) δ_H 2.40-2.50(m. syst, 4H), 5.63-5.69(m. syst., 2H), 6.43(d, J = 15.9 Hz, 1H), 7.21-7.37, (m, 6H), 11.70(bs., 1H). ^{13}C NMR (75 MHz) δ_C 30.7, 31.1, 117.9, 121.1, 126.0, 126.4, 127.0, 127.3, 128.5, 137.4, 171.4. MS *m/z* 202(M^+, 25), 155(20), 142(90), 128(80), 115(100), 91(85), 77(40), 65(25), 51(25), 45(25), 40(50).

But-3-enoic acid cyclohex-2-enyl ester 19. Colorless liquid. IR (film) ν_{max} cm^{-1} 3020 (w), 2925 (w), 2853(s), 1737 (s), 1644 (m), 1447 (m), 1262(w), 1176 (s), 920 (m). ^{1}H NMR (300 MHz) δ_H 1.61-2.06 (m syst., 6H), 3.07(dt, J = 6.8 Hz, J = 1.3 Hz, 2H), 5.12-5.18 (m, 2H), 5.25-5.27(m, 1H), 5.66-5.99(m syst., 3H); ^{13}C NMR (75 MHz) δ_C 15.6, 21.6, 26.4, 36.3, 65.0, 115.1, 122.3, 127.0, 129.5, 167.9. MS *m/z* 166(2), 147(5), 125(10), 104(10), 81(100), 79(70), 69(20), 53(20), 41(35). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.24; H, 8.49. Found C, 72.18; H, 8.46.

Rhodium complexes of 3,6-heptedienoic acids. Red-brown powder, decomposition 208 °C. Elemental analysis calculated for [$Rh(C_7H_{10}O_2)Cl$] molecular mass 264.51: C: 31.79, H: 3.81; found, C: 31.76, H: 3.85. IR (KBr): υ_{max}(cm^{-1}): 3433 (s), 2923 (w), 1726 (s), 1550 (s), 1384 (w), 1254 (w), 1156 (w), 1024 (w), 904 (w).

Rhodium complexes of 3,6-heptedienoic acids. Yellow powder. Decomposition 209 °C. Elemental analysis calculated for [$Rh(C_7H_{10}O_2)Cl$], molecular mass 264.51: C: 31.79, H: 3.81; found, C: 31.77, H: 3.84. IR (KBr): υ_{max}(cm^{-1}): 3432 (m), 2930 (w), 1684 (s), 1505 (w), 1296 (w), 1220 (w), 1039 (w), 696 (w).

Methyl hepta-2(*E*),6-dienoate 20. Colorless oil**.** IR (film) ν_{max} cm^{-1} 2950 (m), 1724 (s), 1656 (w), 1436 (m), 1271 (w), 1170 (w), 990 (w), 915 (w). ^{1}H NMR (300 MHz) δ_H 2.20–2.32 (m, 4H), 3.63 (s, 3H), 4.98-5.07 (m, 2H), 5.74–5.87 (m, 2H), 6.95 (dt, J = 15.6 Hz, J = 6.8 Hz, 1H). ^{13}C NMR (75 MHz) δ_C 36.4, 37.7, 51.6, 115.4, 122.0, 130.1, 138.9, 172.2. MS *m/z* 140(M^+, 10), 125(3), 109(13), 98(35), 81(100), 67(25), 59(24), 53(30), 41(30). Anal. Calcd for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found C, 68.48; H, 8.57.

Methyl hepta-3(*E*),6-dienoate 21. Colorless oil**.** IR (film) ν_{max} cm^{-1} 2977 (m), 1738 (s), 1638 (w), 1437 (m), 1255 (w), 1165 (m), 995 (w), 971(w), 914 (m). ^{1}H NMR (300 MHz) δ_H 2.76-2.80 (m, 2H), 2.78 (dd, J = 6.4 Hz, J = 1.6 Hz, 2H), 3.66 (s, 3H), 4.99-5.08 (m, 2H), 5.59 (dt, 1H, J = 14.4 Hz, J = 5.0 Hz) 5.73–5.87 (m, 2H). ^{13}C NMR (75 MHz) δ_C 34.6, 37.7, 51.6, 115.3, 122.7, 131.4, 136.2, 172.2. MS *m/z* 140(M+, 10), 125 (5), 111(10), 98 (45), 81(100), 67(20), 59(25), 53(25), 41(25). Anal. Calcd for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found C, 68.48; H, 8.59.

Methyl-(E)-2-(3-acetoxy-cyclopentilidene)acetate 22. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H), 1.94 - 2.05 (m, 2H), 2.57 (d, J = 18.0 Hz, 1H), 2.75 (dt, J_d = 18.0 Hz, J_t = 2.5 Hz), 2.87 - 2.94 (m, 2H), 3.68 (s, 3H), 5.20 – 5.34 (m, 1H), 5.83 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 21.1, 29.7, 31.8 , 41.5, 50.8, 74.5, 113.0, 164.4, 166.8, 170.7. MS, m/z 198(M^+, 1), 166(2), 156(5), 138(100), 123(15), 107(60), 95(30), 79(50), 67(10), 43(45).

Methyl-(4-acetoxy)-hepta-2(E),6-dienoate 23. ^{1}H NMR (300 MHz, $CDCl_3$); δ 2.07 (s, 3H), 2.43 (dd, J_1= 8.0 Hz, J_2 = 6.7 Hz, 2H), 3.74 (s, 3H),5.09 – 5.11 (m, 1H), 5.14 – 5,17 (m, 1H), 5.46 – 5.48 (m, 1H), 5.72 (ddt, J_{d1} = 17.6 Hz, J_{d2} = 9.9 Hz, J_t = 7.0 Hz, 1H), 5.96 (dd, J_{d1} = 15.7 Hz, J_{d2} = 1.7 Hz, 1H), 6.85 (dd, J_{d1} = 15.7 Hz, J_{d2} = 5.1 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$); δ 20.8, 38.1, 51.4, 71.4, 118.8, 121.4, 132.0, 144.8, 166.3, 169.9. MS, m/z 198 (M^+, 1), 166 (2), 157 (15), 138 (5), 125 (10), 115 (8), 87 (5), 79 (30), 55 (5), 43 (100).

Methyl-(E)-2-(2,4-di-(acetyloxy)-cyclopentilidene)acetate 24. ^{1}H NMR (300 MHz, $CDCl_3$), δ 2.06 (s, 6H), 2.04 – 2.12 (m, 1H), 2.36 (ddd, J_1 = 15.5 Hz, J_2 = 7.0 Hz, J_3 = 5.7 Hz, 1H), 2.80 – 2.82 (m, 2H), 3.69 (s, 3H), 5.14 – 5.18 (m, 1H), 5.99 (dd, J_1 = 4.0 Hz, J_2 = 2.0 Hz, 1H), 6.14 (b-d, J = 7.0 Hz, 1H). MS m/z 183 (10), 164 (20), 154 (40), 136 (45), 128 (7), 122 (55), 111 (18), 105 (20), 100 (5), 95 (30), 82 (5), 77 (10), 67 (20), 59 (15), 53 (10),43 (100).

Allyl-(E)-2-(3-acetoxy-cyclopentilidene)acetate 25. ^{1}H NMR (300 Mhz, $CDCl_3$): δ 1.94-2.00 (m, 2H), 2.00 (s, 3H), 2.57 (d, J = 18 Hz, 1H), 2.75 (dt, J_d = 18 Hz, J_t = 2.4 Hz), 2.87 - 2.98 (m, 2H), 4.59 (dt, Jd = 5.7 Hz, Jt = 1.4 Hz, 2H), 5.23 - 5.28 (m, 2H), 5.84 - 5.97 (m, 1H), 5.84 (s, 1H,). ^{13}C NMR (75 MHz, $CDCl_3$); δ 20.6, 29.8, 31.8, 41.5, 64.5, 74.5, 113.1, 117.8, 132.5, 164.7, 165.9, 170.7. MS, m/z 198 (M+, 1), 166 (2), 156 (5), 138 (100), 123 (15), 107 (60), 95 (30), 79 (50), 67 (10), 43 (45).

Allyl-4-acetoxy-hepta-2(E),6-dienoate 26. ^{1}H NMR(300 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.04 - 2.17 (m, 2H), 4.55 - 4.66 (m, 3H), 5.21 -5.36 (m, 2H), 5.74 - 6.05 (m, 3H), 6.87 (

dd, J_{d1} = 15.7 Hz, J_{d2} = 5.2 Hz, 1H). MS m/z 223 (M^+, 5), 210 (4), 198 (3), 180 (60), 152 (25), 139 (65), 123 (70), 111 (35), 95 (100), 79 (40), 67 (50), 55 (30).

Methyl-(E)-2-(3-(2-methoxy)acetoyloxy-cyclopentilidene)acetate 27. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 - 2.03 (m, 2H), 2.63 (d, J = 19.3 Hz, 1H), 2.79 (dm, J_d = 19.3 Hz, H^8), 2.87 - 2.97 (m, 2H), 3.44 (s, 3H), 3.68 (s,3H), 3.98 (s, 2H), 5.31 - 5.34 (m, 1H), 5.81 - 5.84 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 29.7, 31.8, 41.5, 50.8, 59.3, 69.9, 75.2, 113.2, 163.9, 66.8, 169.9. MS, m / z 155 (1), 138 (100), 123 (10), 107 (80), 95 (8), 85 (1), 79 (40), 67 (8), 59 (5), 53 (4), 45 (60).

Methyl 4-(2-methoxy)acetoyloxy-hepta-2(E),6-dienoate 28. ^{1}H NMR (300 MHz, $CDCl_3$); δ 2.46 (t, J = 6.7 Hz, 2H), 3.44 (s, 3H), 3.78 (s, 3H), 4.05 (s, 2H), 5.11 – 5.13 (m, 2H), 5.56 (dd, J_1 = 11.8 Hz, J_2 = 5.8 Hz, 1H), 5.70 – 5.73 (m, 1H), 5.96 (d, J = 15.7 Hz, , 1H), 6.85 (dd, J_{d1} = 15.7 Hz, J_{d2} = 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 38.1, 51.7, 59.5, 69.5, 76.5, 119.0, 128.4, 131.7, 144.1, 166.1, 169.2. MS m / z 213 (1), 198 (1), 187 (4), 169 (10), 159 (85), 139 (75), 123 (10), 107 (30), 79 (100), 59 (25), 55 (15).

Methyl-(E)-2-(2,4-di-((2-methoxy)acetyloxy)-cyclopentilidene)acetate 29. ^{1}H NMR (300 MHz, $CDCl_3$); δ 2.10 - 2.17 (m, 2H), 2.58 (dm, 1H), 3.03 (dm, 1H), 3.24 (s, 6H), 3.66 (s, 3H), 3.97 (s, 2H), 3.98 (s, 2H), 5.26 - 5.39 (m, 1H), 5.99 – 5.61(m,1H), 6.28 – 6.31 (m, 1H). MS m / z 286 (1), 257 (2), 227 (10), 194 (10), 180 (1), 166 (2), 153 (15), 137 (40), 121 (15), 106 (35), 95 (2), 85 (1), 77 (10), 67 (3), 59 (2), 45 (100).

(S)-ethyl-2-methoxypropanoate 31. ^{1}H NMR(300 MHz, $CDCl_3$); δ 1.23(t, J=7.1 Hz, 3H), 1.34(d, J= 6.8 Hz, 3H), 3.34(s, 1H,), 3.81(q; J=6.8 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 18.4, 57.6, 60.8, 76.4, 173.1. MS m / z 132 (M^+, 1), 117 (1), 102 (20), 89 (10), 73 (5), 59 (100), 43(15). $[\alpha]^{20}_D$ (EtOH, c = 0.1) = -50.89°.

(S)-2-methoxypropionic acid 32. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.48 (d, J = 6.9 Hz, 3H), 3.47 (s, 3H), 3.95 (q, J = 6.9 Hz, 1H), 10.11 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 18.0, 57.8, 76.0, 178.1. MS m / z 104 (M^+, 2), 91 (60), 81 (40), 73 (10), 67 (20), 57 (100), 51 (5), 41 (15). $[\alpha]^{20}_D$ (EtOH, c = 0.1) = -32.3°.

(2S)-((E)-3-(2-methoxy-2-oxoethylidene)cyclopentyl)2-methoxypropanoate 33. ^{1}H NMR(300 MHz, CDCl3); most abundant diastereoisomer: δ 1.35 (d, J = 7.1 Hz, 3H), 2.02-2.06 (m, 2H), 2.60-2.66 (m, 1H), 2.78-2.83 (m, 1H), 2.86-2.95 (m, 1H), 2.97-3.02(m, 1H), 3.368 (s, 3H), 3.704 (s, 3H), 3.822 (q, J= 7.1 Hz, 1H), 5.30-5.33 (m, 1H), 5.84-5.86 (m; 1H); less abundant diastereoisomer: δ 1.37 (d, J = 6.9 Hz, 3H), 2.02-2.06

(m, 2H), 2.60-2.66 (m, 1H), 2.78-2.83 (m, 1H), 2.86-2.95 (m, 1H), 2.97-3.02(m, 1H,), 3.371 (s, 3H), 3.705 (s, 3H), 3.8205 (q, J = 6.9 Hz, 1H), 5.30-5.33 (m, 1H), 5.84-5.86 (m; 1H). ^{13}C NMR (75 MHz, CDCl3); most abundant diastereoisomer: δ 18.29, 29.7, 31.9, 41.5, 50.9, 57.6, 75.1, 76.1, 113.1, 164.0, 166.7, 172.8; less abundant diastereoisomer: δ 18.29, 29.72, 32.0, 41.4, 50.9, 57.6, 75.1, 76.1, 113.1, 164.0, 166.7, 172.8. MS m/z 242 (M^+, 1), 187 (10), 139 (10), 127 (10), 116 (10), 99 (20), 85 (15), 75 (5), 68 (25), 59 (100), 53 (5), 43 (20). Diastereoselectivity of the reaction was determined according to the relative values for the ^{1}H NMR integration in the raw mixture.

(E)-methyl 4-((S)-2-methoxypropanoyloxy)hepta-2,6-dienoate 34. ^{1}H NMR(300 MHz, $CDCl_3$); most abundant diastereoisomer: δ 1.43 (d, J = 6.8 Hz, 3H), 2.44-2.53 (m, 2H), 3.401 (s, 3H), 3.759 (s, 3H), 3.91 (q, J= 6.8 Hz, 1H), 5.13-5.16 (m, 2H), 5.56-5.59 (m; 1H), 5.70-5.77(m, 1H), 5.99 (d, J = 15.7 Hz, 1H), 6.89 (dd, J = 15.7 Hz, J = 5.1 Hz, 1H); less abundant diastereoisomer: δ 1.42 (d, J = 6.8 Hz, 3H), 2.44-2.53 (m, 2H), 3.403 (s, 3H), 3.759 (s, 3H), 3.91 (q, J= 6.8 Hz, 1H), 5.13-5.16 (m, 2H), 5.55-5.59 (m; 1H), 5.69-5.76(m, 1H), 6.00 (d, J = 15.7 Hz, 1H), 6.90 (dd, J = 15.7 Hz, J = 5.1 Hz, 1H). ^{13}C NMR (75 MHz, CDCl3); most abundant diastereoisomer: δ 18.5, 38.3, 51.8, 57.8, 71.8, 76.4, 119.1, 121.7, 131.9, 144.5, 166.2, 172.05; less abundant diastereoisomer: δ 18.6, 38.2, 51.8, 57.7, 71.8, 76.3, 119.1, 121.75, 131.9, 144.4, 166.2, 172.1. MS m/z 242 (M +, 1), 187 (10), 139 (10), 127 (10), 116 (10), 99 (20), 85 (15), 75 (5), 68 (25), 59 (100), 53 (5), 43 (20). Diastereoselectivity of the reaction was determined according to the relative values for the ^{1}H NMR integration in the raw mixture.

(S,E)-methyl 4-(2-methoxypropanoyloxy)but-2-enoate 35. ^{1}H NMR(300 MHz, $CDCl_3$); δ 1.41 (d, J = 7.0 Hz, 3H), 3.39(s, 3H), 3.74(s, 3H), 3.91(q; J = 7.0Hz, 1H), 4.80(dd, J = 4.7 Hz, J = 2.0 Hz, 2H), 6.02 (dt, Jd = 15.7 Hz, Jt = 2.0 Hz, 1H), 6.94(dt, Jd =15.8 Hz, Jt =4.7 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$); δ 18.4, 51.7, 57.7, 62.7, 76.2, 122.1, 140.8, 166.0, 172.3 MS, m / z 202 (M^+, 1), 99 (8), 68 (10), 59 (100), 43 (10).

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About the author

Paolo Bottarelli was born in Parma, Italy, on September 24th, 1979. In July 1998 he obtained his diploma from the Liceo Scientifico "Guglielmo Marconi" in Parma.

In July 2004 he received his degree in Industrial Chemistry with full marks from the Università di Parma, with an experimental thesis, carried out under the supervision of Prof. Pietro Moggi, about the preparation of Co/SiO_2 catalytic systems via sol-gel techniques and their characterization and catalytic activity in the Fischer-Tropsch process.

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In January 2005 he was awarded of a grant to start his PhD at the Department of Organic and Industrial Chemistry of the Università di Parma, under the supervision of Professor Mirco Costa. During this period he spent six months as a visiting scholar at the Department of Chemistry of Texas A&M University, College Station, TX, USA, under the supervision of prof. Donald J. Darensbourg. The results of the research carried out from January 2005 to December 2007 are reported in this thesis.

Since January 2008 he is holder of a grant for research in the field of oxidative carbonylation in supercritical carbon dioxide at the University of Parma under supervision of prof. Mirco Costa.

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