NEW REACTIONS UNDER HOMOGENEOUS CONDITIONS

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New reactions under homogeneous conditions

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DECLARATION

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"I have a dream that one day
this nation will rise up and live
out the true meaning of its creed:
'We hold these truths to be self-evident,
that all men are created equal.'"

Martin Luther King,
28 August 1963,
at the Lincoln Memorial,
Washington D.C.

"Sé que nunca más recuperaré
a mi hijo pero dame, al menos,
el consuelo de la verdad"

General González Arribas,
Carta al Cuartel General del
Ejército del Aire sobre
el accidente del Yak-42.

A mis padres, las mejores
personas que hay en este mundo

A los invisibles…

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Alea jacta est…….

Abstract

BDTBPMB has been proven to be an essential ligand in carbonylation chemistry. Its two *tert*-butyl groups and wide bite angle give it the ideal characteristics for this kind of chemistry, and leads to high activity and selectivity with use of its complexes. During this work the group of reactions where this ligand has been proven to be active has been extended with two new protocols for hydroxycarbonylation and aminocarbonylation. In the hydroxycarbonylation process, a large variety of unsaturated compounds were studied. Dioxane was found to be the ideal solvent, due to its properties in terms of coordinability, and miscibility with water. Using this solvent as the medium, a BDTBPMB complex of palladium was found to be highly active and selective under mild conditions.

Initial attempts to address the aminocarbonylation of alkenes catalysed by the Pd/BDTBPMB system did not give high activity. This problem was overcome by the addition of an arylalcohol. Under those conditions, high selectivity and conversion was obtained in a wide variety of amides. However, attempts to address the aminocarbonylation of alkenes with ammonia gas to generate primary amides did not result in any conversion. The generation of these primary amides was obtained with transamidation of *N*-phenylnonamides which can be prepared by aminocarbonylation.

Amides have been successfully hydrogenated to amines catalysed by a Ru/Triphos system. This system has been proven to be highly active in this reaction. High selectivities have been obtained in the generation of secondary amine. However, initial results of the hydrogenation of primary amides resulted in no formation of primary amines. A careful analysis of the mechanism of the formation of various products from the hydrogenation of primary amides allows the selective formation of primary amines by the ruthenium/Triphos system in the presence of ammonia. The possibility of the generation of primary amides *in situ* from acids under hydrogenation conditions, giving primary amines was explored with high conversion and moderate selectivities.

To complete this work, a system based on a palladium complex for the decarboxylation of benzoic acids was developed. Usually, the decarboxylation reactions catalysed by copper require high temperatures. However, palladium complexes of highly electron donating ligands such as BDTBPMB or $P(^tBu)_3$ were found to be highly active under milder conditions. This catalytic system was proven to be active in desulfonation reactions giving high conversion.

Abbreviation

ACAC	*acetylacetonate*
ACH	*Acetone cyanohydrin*
ACOEt	*Ethyl acetate*
AIBN	*2,2'-Azobis(2-methylpropionitrile)*
BCPE	*1,2-P,P'-bis(9-phosphabicyclo[3,3,1]nonyl)ethane*
BDPPMB	*1,2-bis(diphenylphosphinomethyl)benzene*
BDPPMP	*2,6-bis(diphenylphosphinomethyl)pyridine*
BDTBPMB	*1,2-bis(ditertbutylphosphinomethyl)benzene*
BDTBPMN	*bis(ditertbutylphosphinomethylnaphtalene*
BDTBPMP	*2,6-bis((di-tert-butylphosphino)methyl)pyridine*
BDTBPP	*1,3 bis(ditertbutylphosphino)propane*
BINAP	*2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene*
BNPPA	*(S)-(+)-binaphyl-2,2-diyl Hydrogen Phosphate*
BQ	*Benzoquinone*
DBA	*dibenzilydenacetone*
DIOP	*(−)-2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane*
DCPB	*dicyclohexylphosphinobutane*
DME	*1,2-dimethoxyethane*
DMSO	*Dimethylsulfoxide*
DPPB	*Diphenylphosphinobutane*
DPPE	*Diphenylphosphinoethane*
DPPF	*Diphenylphosphinoferrocene*
DPPM	*Diphenylphosphinomethane*
DPPP	*Diphenylphosphinopropane*
GDP	*Gross domestic product*
GC	*Gas chromatography*
HEX	*Hexane*
HPIR	*High pressure infrared*

HPNMR	*High pressure NMR*
KBDTBPMBS	*Potassium 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonate*
MEP	*Methyl propanoate*
MMA	*Methyl metracrylate*
MSA	*Methanesulfonic acid*
NMP	N-*methyl-2-pyrolidinone*
PMMA	*Poly(methyl metracrylate)*
TDTBPMB	*1,3,5-tris((di-*tert*-butylphosphino)methyl)benzene*
TFO	*Trifluoroacetate*
THF	*tetrahydrofuran*
TMEDA	*N,N,N',N'-tetramethylethylenediamine*
TOF	*Turnover frequency (mol product/(mol catalyst·h)*
TON	*Turnover number (mol product/(mol catalyst)*
TPPDS	*Triphenylphosphine bissulfonated sodium*
TPPMS	*Triphenylphosphine monosulfonated sodium*
TPPTS	*Triphenylphosphine trisulfonated sodium*
TRIPHOS	*1,1,1-Tris(diphenylphosphinomethyl)ethane*
XANPHOS	*4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene*

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Chapter 1: Introduction

1.- Introduction.

1.1.- Chemistry in the World

Chemistry is defined as the science of transformation. Usually simple feedstocks can be transformed into manufactured products by chemical processes. These products such as plastics, medicines, clothes, etc, are consumed daily by us all. Chemistry drives our cars and makes our lives easier and more comfortable.

We have been investigating and producing manufactured products since the origin of humanity. However, we could see a turning point with Antoine-Laurent de Lavoisier (26^{th} of August, 1743 –8^{th} of May, 1794) named "*the father of modern chemistry*". He, with the discovery of oxygen and hydrogen, and the law of conservation of mass, started this new science and set basis for the new concept of science. Since Lavoisier, excellent chemists, such as Perkin, Dalton, and Berzelius, discovered the fundamental principles of this science. In these two centuries chemistry has been studied deeply, and has become the driving force of our economy and something common to our everyday lives.

This knowledge elevated chemistry to the top of business markets. Nowadays, chemical markets generate approximately £1500 billon per year. The European Union is the leading chemical-producing area in the world with the production of 31% of the world's chemicals (the USA and Japan produce 22% and 20% respectively), and an average growth of 3 % per year.[1]

Although a variety of different feedstocks are used in chemical industry, this economy is primarily fed by fossils based resources such as petroleum. Petroleum is a mixture of saturated hydrocarbons and is very abundant. This makes petroleum a cheap feedstock for the chemical industry, and a wide range of processes has been developed in the last century for its transformation into interesting products. Nowadays hundreds of millions of tons of petroleum are required every year in developed countries. This is the same order of magnitude as the food produced in these countries.[2]

1.2.- Catalysts

The word "*catalyst*" is complex in its origin. It comes from two greek words: *kata* (below) and *lyein* (facilitate, help). The first time that this concept was used, was by Berzilius in 1835 when he was working in fermentation processes and noticed the positive effect of some substances in the process. However, the more specific definition of what a catalyst is was determined many years later in 1895, by Ostwald. He is quoted as saying "*a catalyst is a substance that changes the rate of a chemical reaction without itself appearing in the product.*" [3] This concept does not exclude the case where the added substrate may interfere in the process. Therefore, nowadays this definition has been redefined as *"A catalyst is a substance which increases the rate at which a chemical reaction approaches equilibrium without itself permanently involved."*[3]

In essence a catalyst is a material which makes the process more viable. The concept of viability implies that the reaction can be carried out under milder conditions, with a lower amount of waste and/or better selectivity. Although the role of these material in making the process more viable has not been fully determined, the generally accepted proposal is the reduction of the activation energy of the rate determining step in the formation of the product (Fig 1.1). The decrease in energy in this step makes the reaction easier and leads to the formation of the desired product.

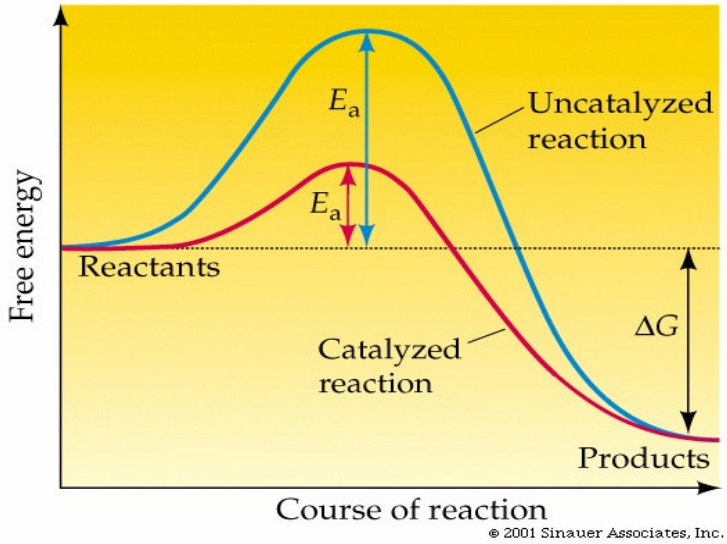


Fig 1.1. *Decrease of activation energy by a catalyst (Adapted from reference 4)*

These beneficial effects of catalysts results in their widespread use in the chemical industry. Chris Adams, writing for The North American Catalyst Society, stated that "*35% of global GDP depends on catalysts although this excludes the emergent genetic business. Confining the analysis to the chemicals industry, with global sales of perhaps* $\$1.5 \cdot 10^{12}$ *the proportion of processes using catalyst costs are much less than 1 % of the sales revenue from the products which they help create. Small wonder that the catalyst market is increasing at 5 % per annum*".[5]

The decision to choose a catalyst is one of the most important stages in the preparation of a process. In essence the aspects which contribute to making a good catalyst, are as follows:

- Required conditions
- Selectivity
- Atom economy and generation of waste
- Cost
- Time stability and recyclability
- Air stability
- Operate under continuous flow conditions

The essential conditions required by a process must be taken into consideration. The temperature, pressure and time of a reaction are variable which may influence the cost of the process, and therefore the cost of the product and any profits arising. A lower temperature results in a less expensive heating process and a lower pressure process requires equipment which is less material intensive, and therefore, requires a less expensive installation. For these three reasons, it is desirable for a process to be carried out under as mild conditions as possible – preferably ambient pressure and temperature – to increase the profit obtained.

A more selective process produces less waste. The generation of waste lowers the profit due to the fact that a part of the reactant is lost in the process. Likewise, the produced waste must subsequently be treated to minimize the environmental impact. Three kinds of selectivity are as follows:

- Chemoselectivity: The generation of one of the possible product types, such as alcohols or aldehydes.
- Regioselectivity: The generation of one regioisomer such as the formation of branched or linear aldehyde in the oxo process (Fig 1.2).
- Stereoselectivity. The generation of one of the stereomers: diastereomers or enantiomers.

Very often the selectivity is dependent on the conditions of the process. Harsh conditions in a reaction may lead to a decrease in selectivity while mild conditions, although giving better selectivity, tend to yield low conversion. Therefore a compromise between conversion and selectivity must be made.

The generation of by-products and waste is undesirable, but may be inherent in the reaction, such as the formation of calcium chloride in the Solvay process.[6] By-products may also arise from a loss in selectivity, such as the generation of a branched product in the carbonylation process. The production of by-products must be minimized in the industrial applications of these processes.

Two factors have been established to quantify the generation of these by-products and waste – the atom economy factor and the *E* factor.

Atom economy is a concept described by Trost.[7] Atom economy is defined as "*The formula weights of the desired products divided by the stoichiometric weight of the all reactants*". Therefore the incorporation of all the reactants into the final molecule should be maximised in the process.

Fortunately, in modern chemistry there are many good examples of high atom economic processes such as the carbonylation of unsaturated compounds, dimerization of alkenes, or the Pauson-Khand reaction (Fig 1.2). Carbonylation of unsaturated compounds consists of the generation of a carbonyl compound from a double (or triple) bond by reaction with a nucleophile in the presence of carbon monoxide.[8] In the dimerization of alkenes, two molecules of unsaturated esters react to give a diester which is a precursor of adipic acid[9] (one of the most important monomers in polyester production). Cyclopentenones are easily obtained by the Pauson-Khand reaction.[10] All of these processes have been widely studied and are used frequently in modern chemistry.

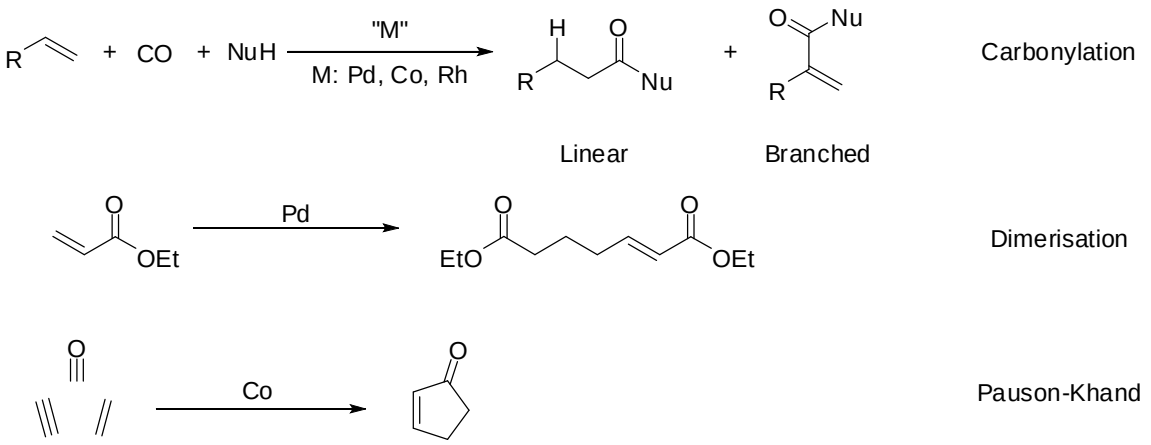


Fig 1.2. *Examples of 100% atom economic processes*

The second parameter for the quantification, the *E* Factor, was introduced by Sheldon[11] and defined as the mass (kg) ratio of waste to desired product.

Table 1.1. The *E* Factor of different chemical sectors.[5]

Industrial segment	Product tonnage (kg)	*E* factor
Oil refining	10^6-10^8	Approx. 1
Bulk Chemicals	10^4-10^6	<1-5
Fine Chemicals	10^2-10^4	5-50+
Pharmaceuticals	10-10^3	25-100+

Large scale industry, such as oil refining or bulk chemistry, has an *E* factor significantly lower than that of the fine chemicals or pharmaceutical segments (Table 1.1). To understand the imbalance in the *E* factor, the value of the manufactured product should be considered. Both fine chemicals and the pharmaceutical industry produce highly valuable products while the bulk chemistry sector has a high scale of production, but at lower prices. Therefore, considering the *E* factor affects the final cost of a product, and therefore the profit, the fine chemicals and pharmaceutical sectors have a bigger margin to work within. However the generation of waste, and the high *E* factor of these two areas of chemistry is basically unacceptable nowadays.

Another factor which must be taken into account is the cost of the catalyst. A catalyst is often formed from precious metals or expensive enzymes. Therefore the cost of the catalyst can result in the rejection of a process. This cost should not exceed one per cent of the value of the final product. Along with cost, the availability of the catalyst has to be considered. Due to supply and demand, when a cheap catalyst is overexploited, its price will increase, therefore converting an acceptable process into an unacceptable one.

One example is the recent price of palladium. The new processes developed based around this metal have resulted in its price increasing (Fig 1.3)[12]. Therefore a process based on palladium which was viable in the 1960's may not be valid nowadays.

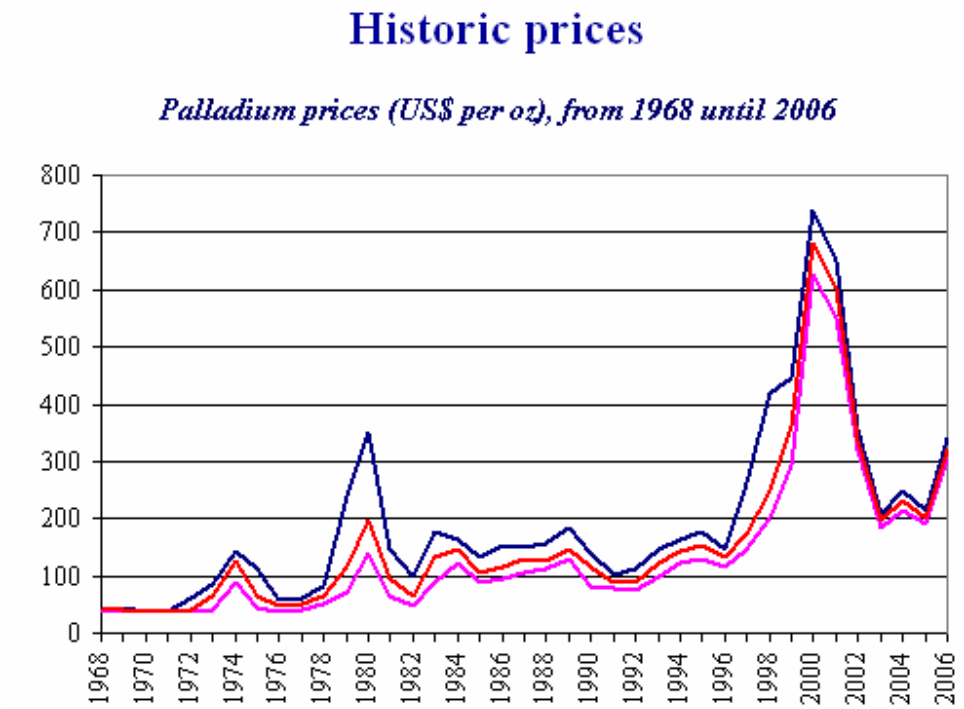


Fig 1.3. *Fluctuation of palladium price in the last four decades*[12]

The cost is affected by the period of time for which a catalyst can be used and its recycling properties. In practice, no catalyst is active indefinitely and it is possible that deactivation can take place during the catalytic process. However the catalyst must be able to be used for as long as possible to increase the profit and decrease the amount of waste generated. The possibility of recycling catalysts is an interesting option to consider. An

expensive catalyst with high regeneration possibilities may be considered an excellent choice of reagent for a process.

An interesting example of catalyst regeneration was discovered by Crabtree in the hydrogenation of carboxylic acids to give alcohols using a 1,1,1-tris(diphenylphosphino-methyl)ethane (Triphos)/ruthenium catalyst under hydrogen atmosphere[13] (see Section 3.1.2)**.** In this system, the release of CO from the forming alcohol poisons the catalyst (**1**) by generating the carbonyl species (**2**)**.** However, at high temperature and in the presence of water, this CO is converted to CO_2 by the water shift process, regenerating the catalyst (Fig 1.4). This reactivation may take place *in situ* by addition of water to the reaction.

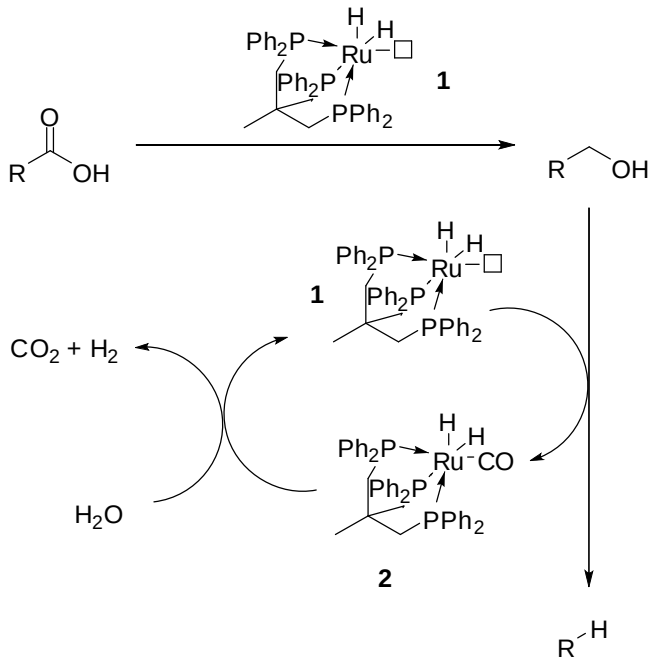


Fig 1.4. *Mechanism of catalyst reactivation in the hydrogenation of carboxylic acids.*

A final point is the possibility to operate the process under continuous conditions. Some processes in fine chemistry and a large part of bulk chemistry are continuous processes. Therefore the ideal catalyst must work under these conditions. The catalyst

must therefore be able to be recovered at the separation stage without loss of activity, and be pumped back into the reaction within a short time.

1.2.1.- Homogeneous and Heterogeneous Catalysts.

In general, a catalyst can be distinguished as either homogeneous or heterogeneous. A catalyst can be considered homogeneous when it can be dissolved in the medium in which the reaction will be carried out. Heterogeneous catalysts however, are insoluble in the reaction medium.

This difference makes the behaviour of the catalyst change substantially (Table 1.2). While the process of diffusion between solid and liquid (or gas) phases is a determining factor in heterogeneous catalysis, in homogeneous this factor is not present. Heterogeneous processes therefore generally require harsher conditions and a higher concentration of catalyst compared to homogeneous ones.

Table 1.2. Comparison of homogeneous and heterogeneous systems (*adapted from references 5, 14 and 15*).

	Homogeneous	**Heterogeneous**
Diffusion problems	Not present	Present
Concentration	Small	High
Reaction condition	Mild	Severe
Catalyst structure	Known	Unknown
Stoichiometry	Known	Unknown
Catalyst separation	Difficult	Easy
Stability	May be poor	High
Application	Limited	Wide

The understanding of the reaction mechanism is far from an easy task. However, the vast number of techniques to analyse a solution afford the possibility of understanding the homogeneous catalytic process well. The use of high pressure infrared spectroscopy (HPIR) and NMR (HPNMR) spectroscopy can give some information about the

coordination sphere around the metal in the catalyst and how this catalyst progresses.[16, 17] These useful techniques normally do not have a homologue in the solid state. Therefore, while the homogeneous catalytic cycles and stoichiometry can be understood fully in most cases, details of the heterogeneous catalysts are less well know.

The bottle-neck of homogeneous catalysis is the stability of the catalyst and subsequent separation. While heterogeneous catalysts can endure unusually high temperatures for the duration of a reaction, the upper temperature limit of homogeneous catalysts is approximately 250ºC.[18] Likewise, the catalyst under homogeneous conditions does not present the same stability as under heterogeneous conditions. This results in the catalyst requiring to be recycled frequently and more often than heterogeneous catalysts. This subsequently results in a significant loss of interest for industrial applications.

These two effects limit the range of applications of homogeneous catalysts. Only processes under mild conditions (usually below 100ºC) and in which volatile products easily separated from the medium are produced can be applied under homogeneous conditions, unless special properties of the catalyst and products allow special separation methods to be used.

1.2.2.- Homogeneous Catalysts.

Both heterogeneous and homogeneous catalysis have important roles in catalytic chemistry, with approximately 85% of the processes being catalysed by heterogeneous catalysts. To understand this imbalance, historical aspects should be considered. The first synthesis of an organometalloid compound (an arsenic compound) was developed by Cadet de Gassicourt in 1760.[15] However, a century and a half passed without any processes catalysed by an organometallic reagent being described. The birth of the concept of homogeneous catalysis was on the 26th of July 1936 when Roelen, a highly skilled researcher working on the Fischer-Tropsch process in the laboratories of Ruhrchemie AG at Oberhausen, detected and isolated a small amount of propanal produced in the process.[19] Roelen discovered that the formation of propanal occurs by the addition of a formyl group to a double bond, catalysed by $[Co_2(CO)_8]$ (Fig 1.5). This discovery, named the Oxo Process, or hydroformylation, is a highly atom economic process, and produces highly

demanded oxygenated products. This has become the most important reaction catalysed by homogeneous catalysis,[8] with the production of six million of tonnes of alcohols and aldehydes per year.[3,18]

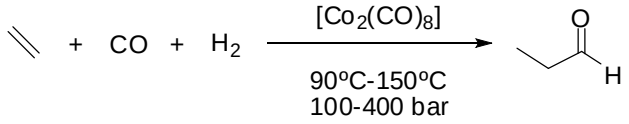


Fig 1.5. *Oxo process developed by Roelen*[19]

Hydroformylation was the first homogeneous process developed which involved the addition of a molecule of carbon monoxide. Carbonylation reactions have been developed such as hydroxycarbonylation and alcoxycarbonylation, as described by Reppe.[15] In this carbonylation, the acid and the ester can be produced from alkenes under a carbon monoxide atmosphere in the presence of either water or an alcohol (Fig 1.6).

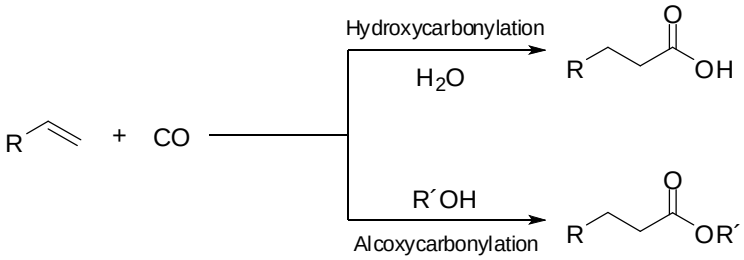


Fig 1.6. *Hydroxycarbonylation and alcoxycarbonylation*

In addition, other processes such as the Wacker process,[20] metathesis, polymerisation, isomerisation or hydrogenation (Fig 1.7), constitute the basis of modern homogeneous catalysis.[15]

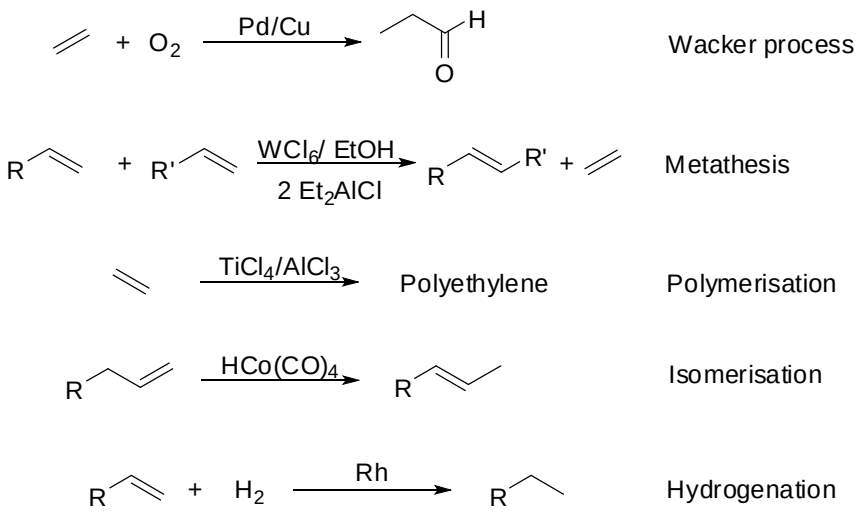


Fig 1.7. *Homogeneous processes*

These systems have been improved since the 1960's with the replacement of iron, nickel, cobalt and tungsten with phosphine complexes of rhodium, palladium and ruthenium. One of these systems was developed by the Wilkinson group. This system is formed by a rhodium complex of triaryl phosphine and is extremely efficient in the hydroformylation of alkenes.[21] The use of certain diphosphines lead to better selectivities.[22]

New processes based on these new phosphine catalysts have been developed in the last thirty years, such as the carbonylation of methanol to generate acetic acid from methanol described by Pringle or Van Leeuwen,[23] or the coupling reactions of Heck[24], Stille[25] and Suzuki.[25,26] These processes convert homogeneous catalysts, with better selectivity under milder conditions, into significantly important systems for the production of plastics, fine chemicals, pharmaceuticals, etc.

1.2.2.1.- Use of Phosphines in Homogeneous Catalysis.

Phosphines are trisubstituted phosphorous (III) compounds with a pair of electrons which are able to coordinate to a metal atom. The electronic and steric effects of these compounds can be altered by modification of the substituents. This converts phosphines into what is a tuneable ligand in homogeneous catalysis. The use of electron withdrawing

or electron donating groups or a *tert*-butyl group instead of a methyl group can drastically change the coordination ability of phosphines and, therefore, the effectiveness of the catalyst.

The first example of the use of phosphines was described by Reppe. A complex of nickel with triphenylphosphine [$NiBr_2(PPh_3)_2$] was found to be more efficient than $NiBr_2$ in the reaction of an alkyne, an alcohol and carbon monoxide (alcoxycarbonylation).[27] This, with other important contributions, provided an excellent base for this new chemistry. These contributions include the hydrogenation of alkenes catalyzed by a triphenylphosphine-platinium tin complex,[28] the Shell process of hydroformylation based on a trialkylphosphine cobalt catalyst,[29] and the advances in the use of the rhodium complex [$RhCl(PPh_3)_3$] in hydroformylation[30] and hydrogenation[31] as reported by Wilkinson.

Since these origins, some reasoning about the influence of electronic and steric effects of this kind of ligand has been determined. Prior to the 1970's, only the electronic effects of these ligands were taken into consideration. In that decade, studies confirmed that the combination of both effects gives the characteristics of the phosphine ligand. Therefore in view of improving the activity of catalysts formed by phosphines, a rational design of the phosphine ligand must be done. Tools for this rational design are a measurement of both the electronic and the steric effects.

1.2.2.1.1.- Electronic Effects.

The electron donating properties of the ligand depend on its electronic effect. This electronic effect was defined by Tolman. By *effect* he meant "*changes in molecular properties as a result of changing part of a molecule*" and by *electronic* he meant "*a result of transmission along chemical bonds, for example, changing from* $P(p\text{-}C_6H_4OMe)_3$ *to* $P(p\text{-}C_6H_4Cl)_3$*.*"[32]

Tolman developed an easy method for the measurement of this effect based on Strohmeier's studies about the variability of the CO frequencies in complexes of several metals, when a phosphine was placed *trans* to the carbonyl group.[33] The presence of a highly electron donating ligand affects the strength of the bond trans to this (the *trans*

influence). Tolman prepared a series of phosphinetricarbonylnickel [$Ni(CO)_3L$] compounds by reaction at room temperature of [$Ni(CO)_4$] with the corresponding phosphine.[32] Measurement of the IR frequency of the carbonyl group of different phosphines (Table 1.3) and referencing this to P^tBu_3 allowed Tolman to create a formula for the quantification of the electronic effect of phosphines. This was done simply by the sum of χ parameter of each substituents (Fig 1.8).

Table 1.3. CO Frequencies of [$Ni(CO)_3L$] (Adapted from reference 33).

L	**υ**
P(*p*-Tol)$_3$	2066.7
P(*o*-Tol)$_3$	2066.6
PMe_3	2064.1
PEt_3	2061.7
$P(^iPr)_3$	2059.2
$P(^tBu)_3$	2056.1

$$PX_1X_2X_3 \qquad \upsilon = 2056.1 + \sum_{i=3}^{3} \chi_i$$

Fig 1.8. *Equation for the measurement of electronic effects in phosphines*

1.2.2.1.2.- Steric Effects.

Complementary to the electronic effect is the steric effect. The first attempt to measure this effect was also carried out by Tolman.[32] He proposed the use of molecular models to measure what was defined as the *cone angle.* This cone angle (θ) was described as the hypothetical angle formed by the three substituents of monophosphines in a cone with the origin 2.28Å from the phosphorus atom, where in theory the metal atom of the complex will be (Fig 1.9 (a)).

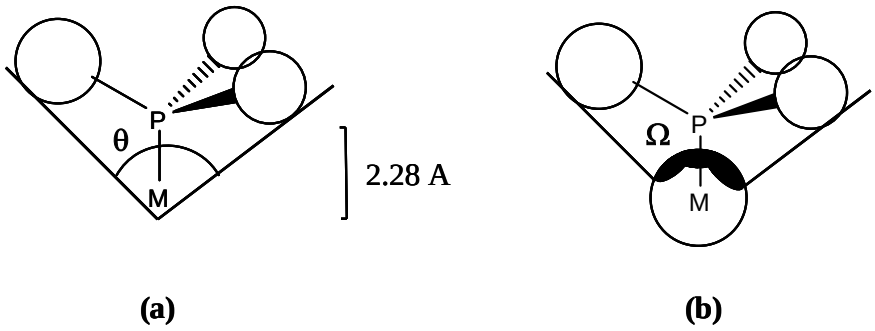


Fig 1.9. *Cone angle (a) and White's definition of solid angle (b)*

The Tolman cone angle is an excellent approximation. However, the substituent in the ligand rarely presents a perfect cone, and therefore there is a difference between the real steric effect (measured by X-ray) and the steric effect predicted by Tolman. A modification of this cone angle was described recently by White and co-workers.[34] This measurement consists of the projected area of the hypothetical shadow (solid angle, Ω) of the substituents on the phosphine (Fig 1.9 (b)) giving a more realistic result (Fig 1.10).

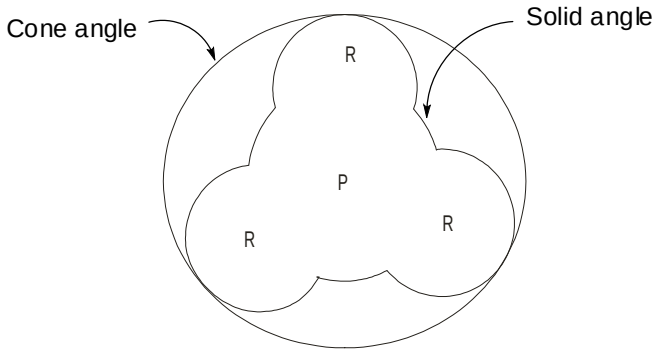


Fig 1.10. *A comparison of solid angle and cone angle (adapted from 34a)*

When diphosphines were established as a good alternative to monophosphines in catalysis, the first approach to be applied for the measurement of their steric effects was a sum of the Tolman cone angles of both phosphines.[35] This was a good approximation. Since this first attempt, other procedures such as solid angle or pocket angles,[36] have been reported. Of these, the most usual is the bite angle (β)[37] which refers to the angle between the two P-Metal bonds. Recently it has been found that the bite angle of the diphosphine not only affects the steric properties of the complex, but also the orbitals of the complex.

Therefore the electronic properties may be affected by the new geometry.[37b,37c] For instance, the energies of the orbitals in platinum change slightly if the conformation is linear or square planar (Fig 1.11).[38] Therefore, although the natural conformation for platinum (0) is linear, it may be modified by coordination with a phosphine which forces the platinum to adopt another conformation, therefore changing both its electronic and steric properties.

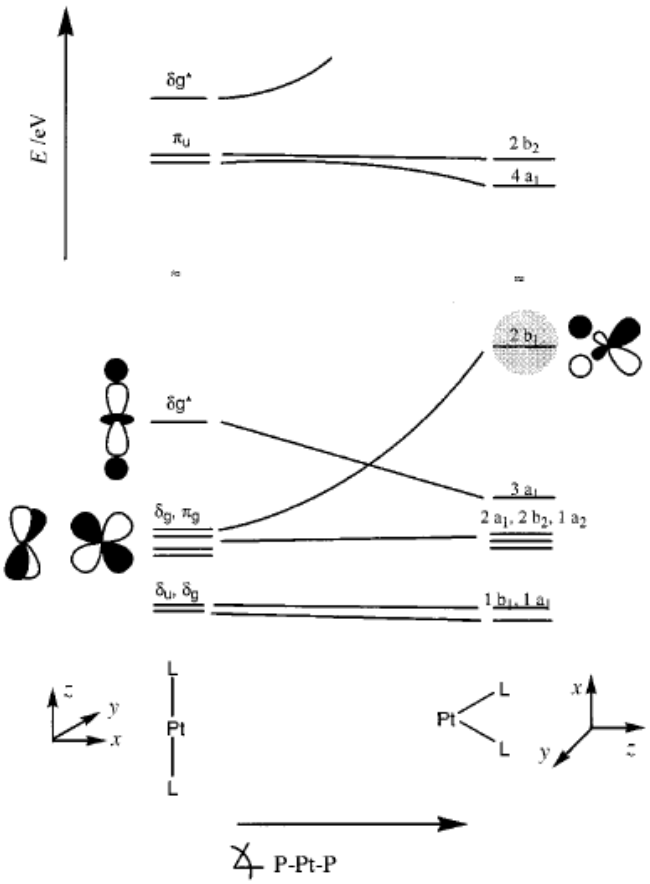


Fig 1.11. *Variation of orbitals depending on geometry of platinum complex*[38]

The choice of a diphosphine for a certain process depends greatly on the bite angle. It is well known that a large bite angle facilitates processes such as reductive elimination[39] while transmetallation processes require a less sterically demanding diphosphine.[40] Therefore, simplifying the choice of diphosphine, such as supposing that a diphosphine which presents a bite angle of 90º is the best option for a process catalysed by square planar

complex, such as palladium or platinium, is basically a serious error. Several variables must be considered in this choice and often the choice of the best ligand for a process can not be predicted *a priori*, and only an experimental study of the possible ligand can confirm the hypothesis.

1.2.2.2.- Phosphines and Homogeneous Catalysis in the Real World.

Homogeneous catalysts, especially those which are formed by a phosphine and a metal, are an important advance in chemistry. However, no catalyst has an infinite lifetime. Decomposition processes which may take place in the medium under reaction conditions, lead to the inactivity of the catalyst. The study of these processes and the conclusions made make the system more understandable and therefore easier to improve. However, these studies are far from being a trivial task, because the decomposition of a catalyst may be influenced by the medium, reactants and their impurities, and the conditions of the reaction.

Generally, these processes of inactivation can be divided into two groups:

- Thermal decomposition
- Chemical decomposition
    - Oxidation
    - Alkylation
    - Ligand scrambling

1.2.2.2.1.- Thermal Decomposition.

Homogeneous catalysts are appreciably more sensitive to thermal decomposition than heterogeneous catalysts (see Section 1.2.1). Therefore the thermal limit of this kind of process has to be taken into consideration. This limit is highly dependent on the ligand and the medium. For example, the generation of methyl propanoate from the methoxycarbonylation of ethene (Fig 1.12) by triphenylphosphine palladium catalysis required temperatures higher than 100ºC. Under these conditions the phosphine is quickly alkylated and becomes a phosphonium salt (See Section 1.2.2.2.2.2.).[41] However, the use

of 1,2-*bis*(ditertbutylphosphinomethyl)benzene (BDTBPMB) instead of triphenylphosphine decreased the required temperature to 80ºC.[2] The sum of this fact with the fully protonation of the ligand in acid condition avoid the decomposition the of catalyst by alkylation.[42]

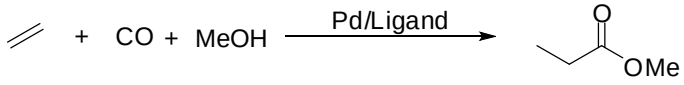


Fig 1.12. *Methoxycarbonylation of ethene*

1.2.2.2.2.- Chemical Decomposition.

Chemical decomposition may be considered as all of the processes which may affect the catalytic activity. Usually a homogeneous catalyst is more sensitive to these processes of deactivation than a heterogeneous catalyst. The system may be affected by impurities in the reactants, intermediates or by the product itself. The quantity of phosphine also affects the activity of the catalyst. Normally the equilibrium of complex formation requires an excess of phosphine to increase the concentration of complex in the medium. However, a high excess of this may lead to the decrease in activity. A classical example of this effect is reported by Oliver and Booth in hydroformylation,[5,43] where a plot of activity versus PPh_3/Rh shows a maximum and a drastic decrease of activity when the PPh_3/Rh is higher than this point in a typical "volcano plot" (Fig 1.13).

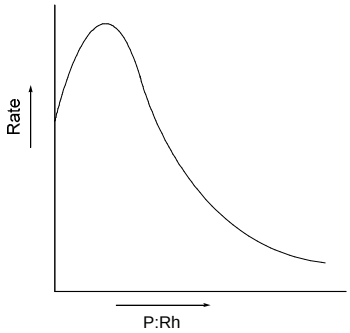


Fig 1.13. *Plot of activity versus PPh_3/Rh in hydroformylation*[5]

1.2.2.2.2.1.- Oxidation.

Phosphines, as phosphorus (III) compounds, are usually air-sensitive and may be oxidised to phosphine oxides under an oxygen atmosphere or in the presence of peroxide (Fig 1.14). This reaction is highly dependent on the subtituents on phosphine. Therefore, while the highly donating phosphines are quickly oxidised under oxidising conditions, arylphosphines are relatively stable in the solid state.

Considering that phosphines oxides are inert, the exclusion of oxygen or other oxidants from the reaction must be a priority in homogeneous catalysis.

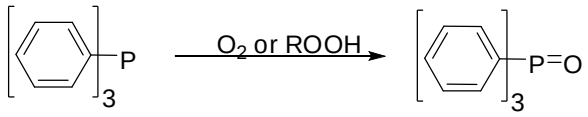


Fig 1.14. *Oxidation of phosphines*

1.2.2.2.2.2.- Alkylation of Phosphines.

Phosphines are highly electron donating ligands, and are therefore plausible nucleophiles to consider in the process. Very often the phosphines are alkylated in the presence of a possible electrophile, generating undesirable phosphonium salts. The generation of these phosphonium salts may be severe in some processes such as the methoxycarbonylation of alkenes catalysed by the PPh_3/Pd system (Fig 1.6). In this system, methanol (used as a nucleophile and solvent in the reaction), may react with the phosphine, generating methyltriphenylphosphonium hydroxide (Fig 1.15a).[41] This generation is appreciably accelerated at high temperatures. At 100ºC, approximately 20% of the initial phosphine is lost per hour.

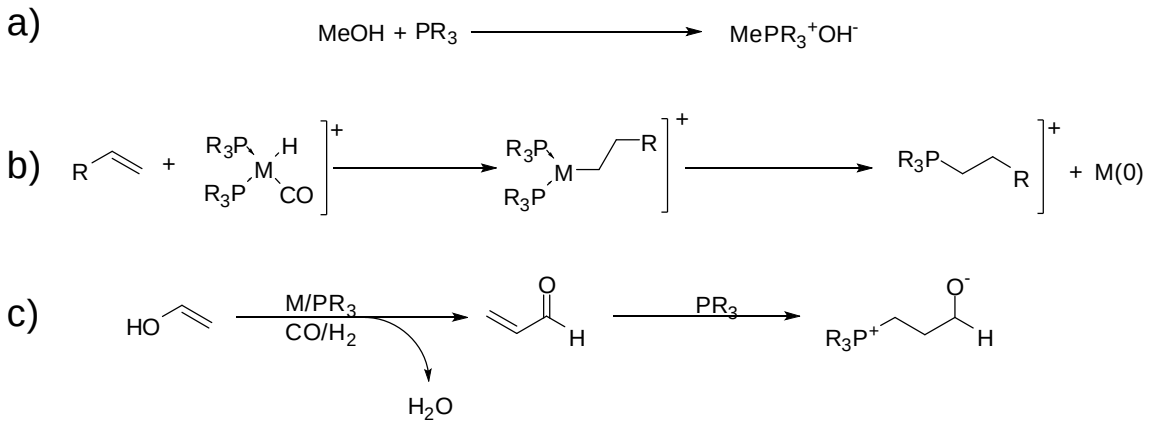


Fig 1.15. *Generation of alkylphosphonium salts by different methods*

Alkylphosphonium salts may also be formed by reductive elimination of an alkylmetal species[41] (Fig 1.15b). These alkylmetal species are quite common in the carbonylation process and are generated initially by insertion of a metalhydride into a double bond. This route is not only undesirable in terms of the ligands, but the reductive elimination leads the production of a metal (0) species, which are usually not active in these kind of processes.

In the case where the product is an α,β-unsaturated compound, such as the generation of acrylic acid by hydroxycarbonylation of acetylene, or the hydroformylation of vinyl alcohol giving acrolein, a Michael addition of the phosphine to the double bond can take place giving the corresponding zwitterion[44] (Fig 1.15c).

1.2.2.2.2.3.- Ligand Scrambling.

Unsymmetrical ligands, especially arylphosphines, can scamble the substituents such as triphenylphosphine monosulfonated sodium salt (TPPMS)[5,45] as Figure 1.16 shows.

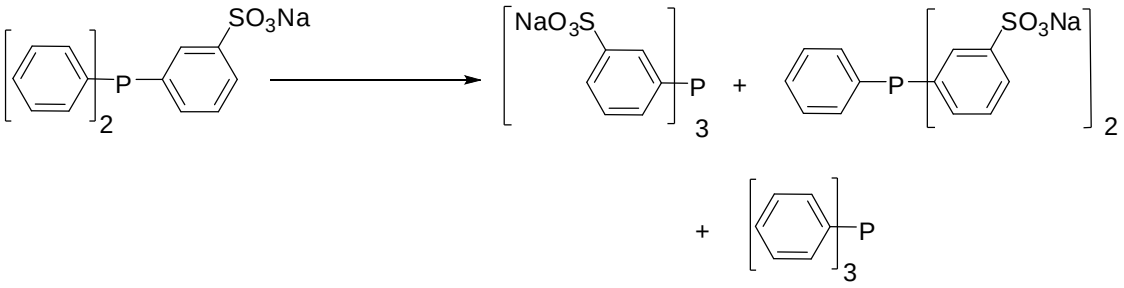


Fig 1.16. *Scrambling of triphenylphosphine monosulfonated sodium salt*[1]

The scrambling of the substituents modifies the reactivity and properties of the ligand. For example, in the particular case shown in Figure 1.16, the generation of a highly sulfonated ligand, such as triphenylphosphine bissulfonated sodium (TPPDS) or triphenylphosphine trisulfonated sodium (TPPTS), drastically changes the solubility of these compounds in polar solvents such as water, in turn affecting the catalytic process.

1.3.- 1,2-bis(ditertbutylphosphinomethyl)benzene as a Ligand.

Diphosphines are reported to give considerably better efficiency than monophosphines in several processes such as carbonylation. 1,2-Bis(ditertbutylphosphinomethyl)benzene (BDTBPMB) (Fig 1.17) contains a large bridge which in turn gives a large natural bite angle (103.9ºC).[42] The presence of a phenyl group gives some rigidity which is essential in the activity of this ligand. This steric effect, in addition to its high electron donating properties given by two *tert*butyl groups in each phosphine, make 1,2-bis(ditertbutylphosphinomethyl)benzene an essential ligand in a large number of systems especially in carbonylation processes.

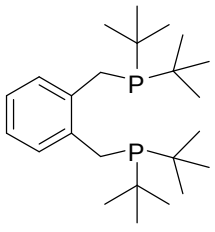


Fig 1.17. *1,2-bis(ditertbutylphosphinomethyl)benzene*

The first synthesis of this ligand was reported by Shaw in (1974) by direct attack of the di*ert*butylphosphine on 1,2-di(bromomethyl)benzene (Fig 1.18).[46] This synthesis requires a deprotonation of the formed phosphonium hydride by base. Although recently this synthesis has been improved with the addition of an acid[47] in the first step, this preparation gives only moderate yields (30%). No by-product has been reported.

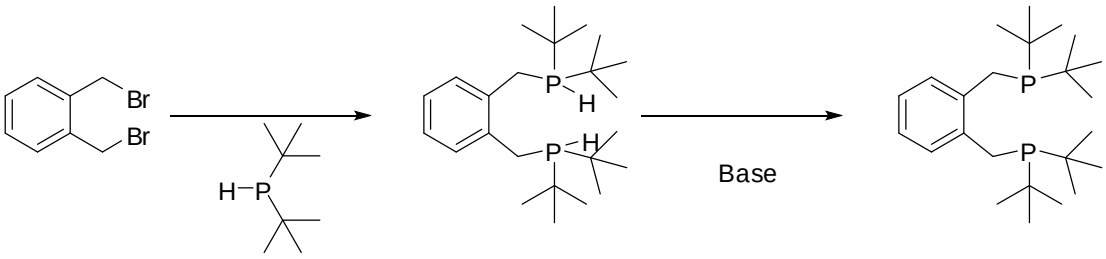


Fig 1.18. *Preparation of BDTBPMB via attack of ditertbutylphosphine*

The generation of LiP^tBu_2 by deprotonation of ditertbutylphoshine with butyl lithium makes the phosphorus more nucleophilic, and therefore easier to react with the dihalide compound (Fig 1.19 Scheme A). This route yielded high conversion, although a cyclic phosphonium salt is formed as by-product (40%).[48] This phosphonium salt is formed by the intramolecular reaction of the monosubstituted phosphine intermediate with the halide in the benzilic position (Fig 1.19 Scheme B). Attempts to cleave this ring have been unsuccessful.

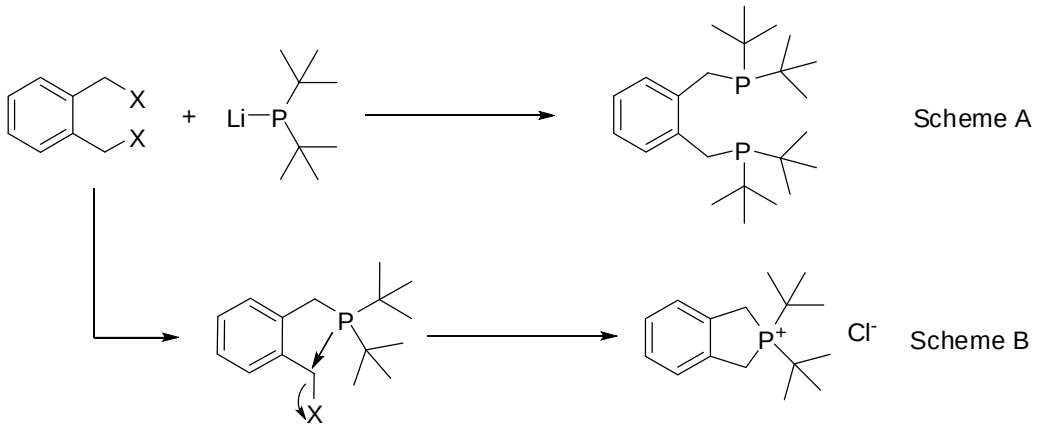


Fig 1.19. *Formation of 5 membered ring phosphonium salt in the synthesis of BDTBPMB*

The modification of this route using $LiP^tBu_2(BH_3)$[49] instead of LiP^tBu_2 blocks the synthesis of the phosphonium salt. This route forms the corresponding BH_3 protected BDTBPMB (Fig 1.20). Easy deprotection developed by Lucite[50] involves treatment with methanesulfonic acid, giving the phosphonium hydride, which is then deprotonated by an ethanolic sodium hydroxide solution giving the corresponding BDTBPMB.

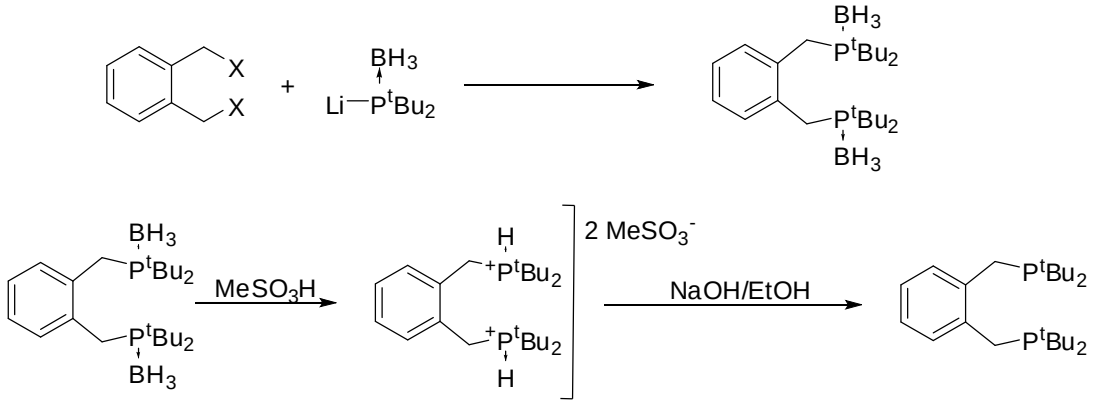


Fig 1.20. *Formation of BDTBPMB via a boron protected secondary phosphine*

Another interesting approach to obtain BDTBPMB involves via deprotonation of orthoxylene with butyl lithium/potassium *tert*butoxide in the presence of an amine, usually TMEDA generating the corresponding potassium salt. This potassium salt gives a highly nucleophilic species, which is able to attack the chloroditertbutylphosphine (Fig 1.21), to obtain the desirable phosphine in yields ranging from 31-69% depending on the conditions used.[51] A variant of this system is the use of the Grignard reagent of 1,2-di(chloromethyl)benzene instead of the potassium salt, to give a yield of 55%.[52]

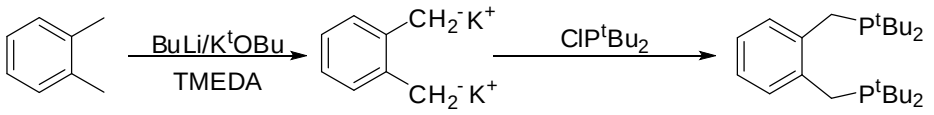


Fig 1.21. *Formation of BDTBPMB via a potassium salt*

1.3.1- 1,2-bis(ditertbutylphosphinomethyl)benzene in Catalysis.

1.3.1.1.- Generation of Methylmetracrylate: From the Old Process (ACH) to the New Alpha Process.

Poly(methyl methacrylate) (PMMA) also known as plexiglax (Rohm and Haas), Lucite (DuPont) or Perspex (ICI) is a highly transparent thermoplastic polymer. Its uses are normally in the substitution of glass in common objects such as tables, glasses, and windows. The sales of this common polymer, discovered by Rohm, came to only $13,000 in its first year. Its importance was raised during the Second World War in the manufacturing of new aircraft – in 1943 alone, 83,000 tonnes of PMMA were produced.[2] Nowadays, 2.4 x 10^6 tonnes are produced annually, of which Lucite International owns 25% of the worldwide production.[53]

The traditional process for the manufacture of methyl methacrylate (MMA), the monomer for PMMA, involves a three-step process: firstly the generation of a cyanohydrin (Fig 1.22), followed by the dehydration of the alcohol/hydration of cyano group, and finally exchange of ammonia and methanol (Fig 1.23).

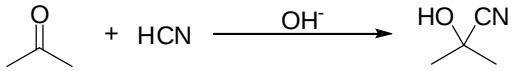


Fig 1.22. *Generation of cyanohydrin*

Cyanohydrin is generated by the addition of hydrogen cyanide to the carbonyl group of acetone in a basic medium (usually an alkali metal hydroxide) at temperatures below 40ºC (Fig 1.22). Under these mild conditions this first step yields high conversion and selectivity (92-99%).[54] The reaction of this cyanohydrin with sulphuric acid at 80-140ºC forms the 1-oxo-2-methylpro-2-enylammonium bisulphate (Fig 1.23). The acidic medium has two roles: the elimination of water to generate the double bond, and the transformation of the cyano group to the amide salt. The reaction of this salt with methanol gives the methyl methacrylate in good selectivity, 77 %.[54]

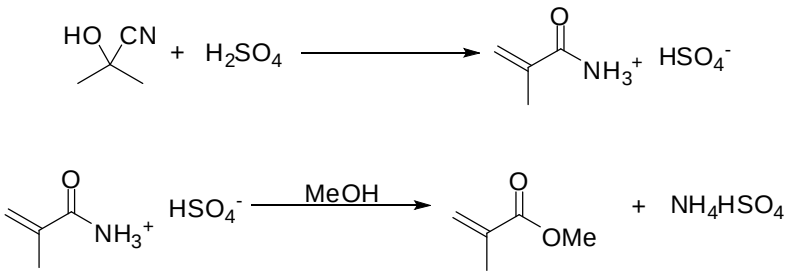


Fig 1.23. *Generation of methyl methacrylate from cyanohydrin*

Although this process is economically competitive, it presents some negative factors. The main negative factor is the use of hydrogen cyanide. This combined with the production of 1.2 tonnes of ammonium bisulphate per tonne of methyl methacrylate results in the ACH process being unacceptable.

Some alternative processes have been developed in the last few years,[54] of which one of the most important is the alpha process developed recently by Lucite which consists of two steps.[53] The first stage consists of the methoxycarbonylation of ethene under a carbon monoxide atmosphere by homogeneous BDTBPMB/palladium catalyst to generate methyl propanoate (MeP). MeP reacts with formaldehyde in the gas phase at 320^{o}C and at 2 bar pressure giving MMA with 97 % selectivity (Fig 1.24). The concentration of water, which is generated *in situ*, must be kept to a minimum in order to decrease the production of methacrylic acid. In this process virtually no waste is generated. Therefore, this fact along with the high efficiency of the new catalyst (See Section 1.3.1.2) makes the process more environmentally friendly. Also, a 20 % cost saving has been estimated for this new process.[53]

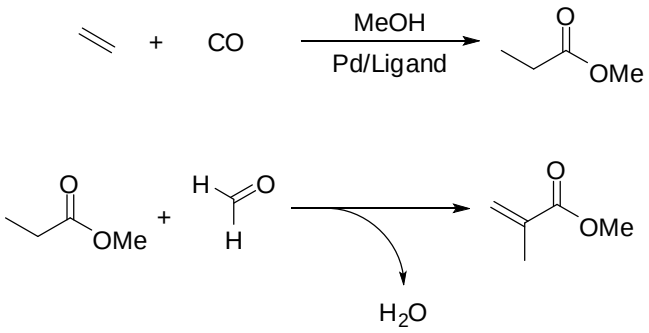


Fig 1.24. *Generation of MMA by the alpha process*

1.3.1.2.- Methoxycarbonylation of Alkenes.

As Section 1.3.1.1 shows, methoxycarbonylation of ethene is an attractive route to prepare MMA. Two processes, methoxycarbonylation and the generation of a polyketone, can take place in the reaction of ethene with carbon monoxide in methanol catalysed by palladium complexes (Fig 1.25). The selectivity of this process exhibits a drastic dependence on the nature of the ligand. Usually monophosphine systems lead to the generation of the methyl ester while diphosphines give the polyketone.[55]

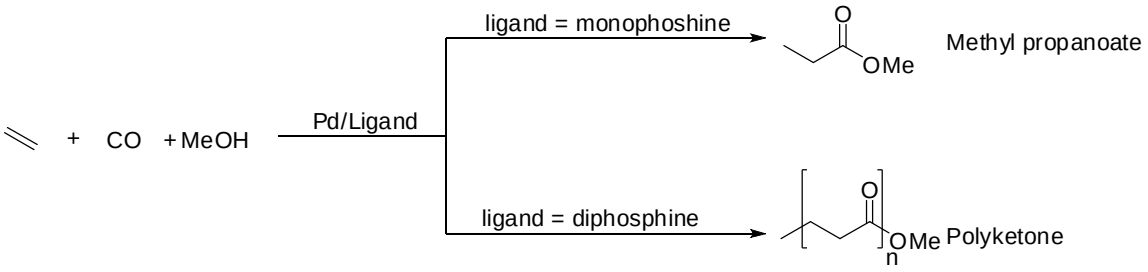


Fig 1.25. *Possible products from ethylene/CO/methanol using a palladium catalyst*

According to the proposed mechanism (See Section 2.1.2), this difference between monophosphines and diphosphines has been explained by considering the possibility of a *cis-trans* isomeration equilibrium of the formed acyl species, which may occur in the medium when monophosphines are used (Fig 1.26). Therefore the *trans* acylpalladium intermediate can progress to the corresponding ester by methanolysis to yield methyl propanoate.

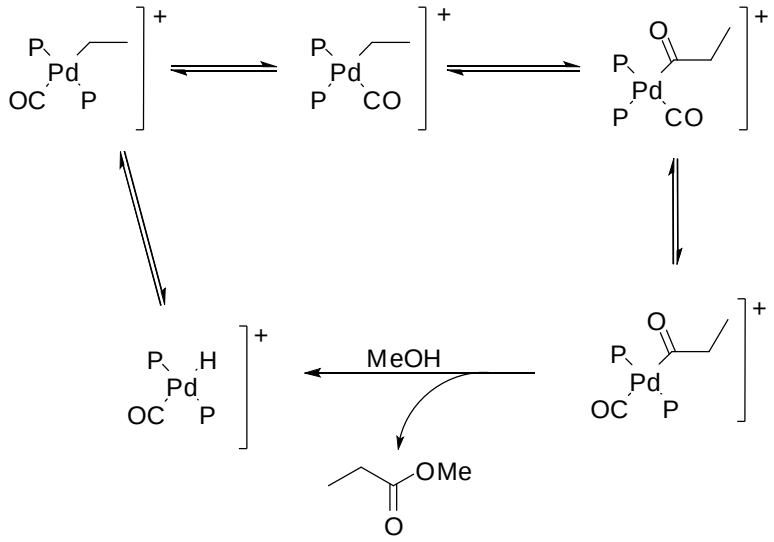


Fig 1.26. *Generation of MeP catalysed by monophosphine palladium complex*

This *cis-trans* isomerisation is forbidden in the case of diphosphines such as dppp.[55a] The decoordination of a molecule of carbon monoxide liberates a coordination site where a new molecule of ethylene can be inserted into the acylpalladium complex. By successive insertion of carbon monoxide and ethylene the chain grows generating the polyketone (Fig 1.27).

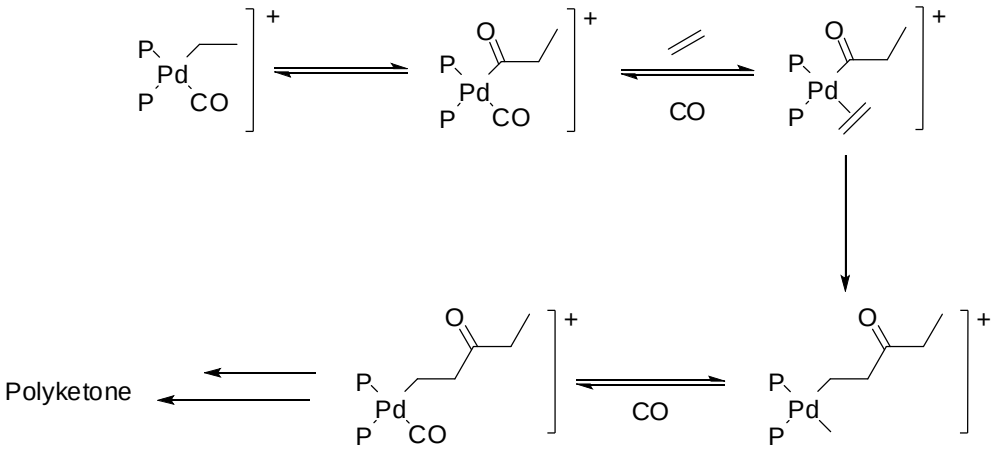


Fig 1.27. *Generation of polyketone*

Shell developed a higlyh efficient system for methoxycarbonylation based on a palladium complex of a bisphosphine, 1,3-bis(ditertbutylphosphino)propane (dtbpp) formed by the combination of $Pd(OAc)_2$ with dtbpp in the presence of methanosulphonic acid.[56] The combination of high steric effects with strong electron donating properties of this phosphine give the system high activity and selectivity (>98%). A few years later, the Tooze group improved this system using BDTBMPB instead of dtbpp. The use of BDTBMPB, which has a larger bite angle than dtbpp and a rigid bridge, increased the selectivity to 99.9% (Table 1.4, entry 1). Palladium acetate as a precatalyst in the Tooze system was replaced by $[Pd_2(dba)_3]$. When palladium acetate is used, the essential diphosphine palladium complex is not formed. However, it is obtained in the case of $[Pd_2(dba)_3]$. Also, C-H activation in the aromatic ring of the phosphine ligand occurs instead of the desired complex formation (Fig 1.28).[42]

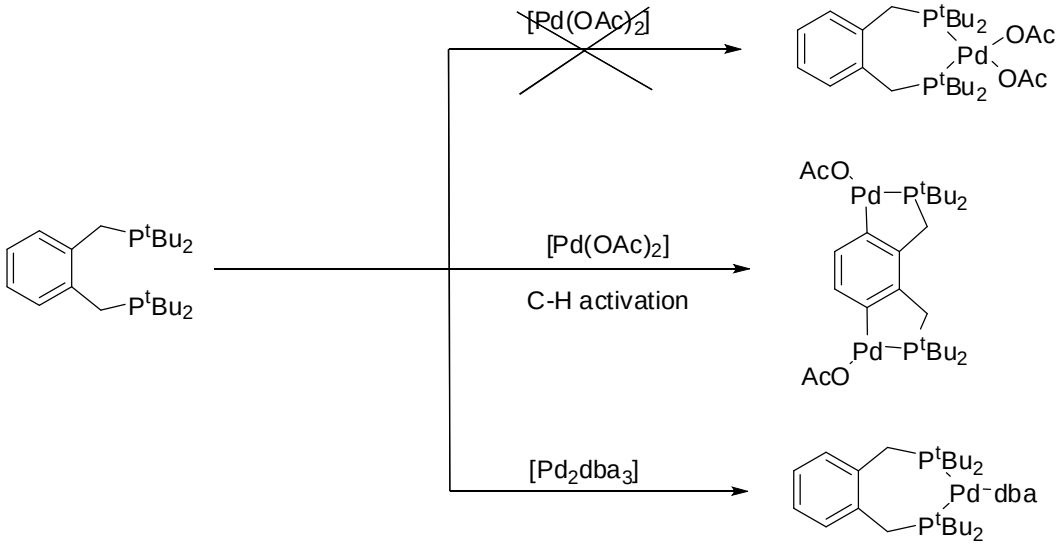
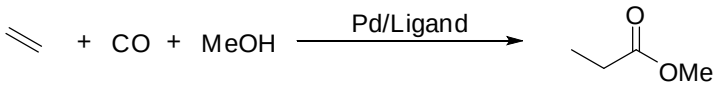


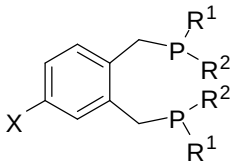
Fig 1.28. *Formation of the BDTBPMB palladium complex*

The *tert*butyl group has been proven to be essential in the activity and selectivity of this process. The combination of its highly donating properties with a high steric effect makes this group very desirable in catalysis. Therefore, in this system, the substitution of one or both *tert*butyl groups on each phosphorus atom for less sterically demanding and donating groups such as cyclohexyl, isopropyl or phenyl has a dramatic effect on the system, dropping the selectivity and yield of the process (Table 1.4, entries 1-5).

The modification of the electronic properties of the aromatic ring using electron donating groups such as methoxy, or electron withdrawing groups such as nitro group, does not have a significant effect on the system (Table 1.4, entries 6 and 7). In the case of other aromatic rings in the bridge, the modification of these drastically changes the activity. For example, the use of the BDTBPMB analogue with a ferrocenyl instead of the benzilidene lowered the activity obtained with BDTBPMB.[57] The use of a naphthylidene bridge, bis(ditertbutylphosphinomethylnaphtalene (BDTBPMN), in the case of carbonylation of vinyl acetate (Fig 1.29) gave signficantly less yield than BDTBPMB.[58]

Table 1.4. Methoxycarbonation of ethylene with BDTBPMB analogues (*adapted from reference 46)*





BDTBMPB analogues

Entry	X	R^1	R^2	Parallel pocket angle	TOF	Selectivity
1	H	^{t}Bu	^{t}Bu	127.7	12000	99.9
2	H	^{i}Pr	^{i}Pr	157.9	200	20
3	H	Cy	Cy	150.5	200	25
4	H	Ph	Ph	145.5	400	20
5	H	^{t}Bu	Cy	a)	500	30
6	OMe	^{t}Bu	^{t}Bu	127.7	11500	99.9
7	NO_2	^{t}Bu	^{t}Bu	127.7	11800	99.9

a) not reported

Efficient methoxycarbonylation of higher alkenes using this system has been reported recently.[59] Although methoxycarbonylation of higher alkenes catalysed by the BDTBPMB/Pd system requires longer reaction times and a higher loading of palladium than the respective methoxycarbonylation of ethene, it yielded high conversion and linear/branched selectivity under mild conditions (1 bar, 20ºC).

Another interesting proof of the effectiveness of BDTBPMB/Pd system in carbonylation was reported by Rucklidge in the synthesis of methyl lactate (Fig 1.29).[58] The polymer of this "green solvent" is an attractive biodegradable and non-toxic alternative to traditional polyethylene and polystyrene. The normal route to obtain this lactate consists of the fermentation of glucose.[60] However, an interesting route is from a cheap feedstock, vinyl acetate. In this reaction the BDTBPMB/Pd catalyst system gave higher conversion and better selectivity than other systems.[61]

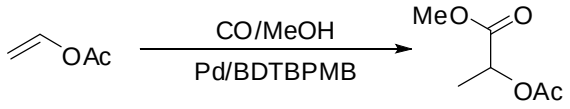


Fig 1.29. *Methoxycarbonylation of vinyl acetate*

The mechanisms of this kind of carbonylation have been thoroughly studied in the last few years, proving that the hydride mechanism takes place in the medium and establishing all the intermediates of this mechanism (See Section 2.1.2)[62] The carbomethoxy mechanism was firstly disproven by NMR[62a] and by deuterium labelling studies using d^1MeOH (MeOD) as solvent.[62b] Considering the carbomethoxy cycle two possible deuterated products, α-deuterated methyl propanoate (**1**) or β- deuterated methyl propanoate (**2**), may be obtained in the methoxycarbonylation of ethene (Fig 1.30). Compound **2** is produced by methanolysis of the alkylpalladium intermediate. **1** is generated by β-elimination of this intermediate, followed by addition of hydride and methanolysis (Fig 1.30).

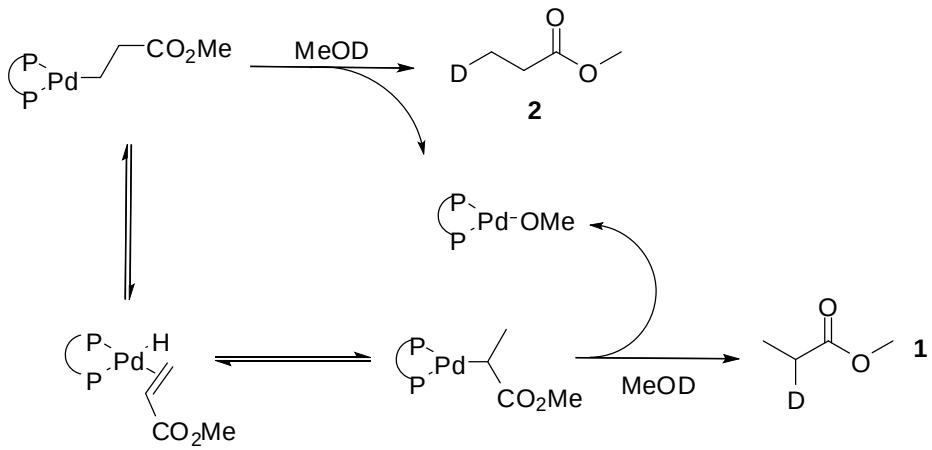


Fig 1.30. *Formation of α-deuratred methyl propanoate (**1**) or β- deuteratred methyl propanoate (**2**) in the carbomethoxy mechanism*

However, in the hydride mechanism, the hydride palladium species is inserted into the double bond to generate the alkylpalladium intermediate (See Section 2.1.2). It is well known that this process is reversible by β-elimination. Therefore, a deuterium/hydride transfer may occur in the MeOD, medium generating the deuteride palladium species. By successive insertion of this species into the double bond a mixture of deuterated methylpropanotate from d^0 to d^5 is produced. The present of d^0 in the final product, which can not be formed from the carbomethoxy cycle, confirmed the hydride mechanism as the correct one (Fig 1.31).[62b]

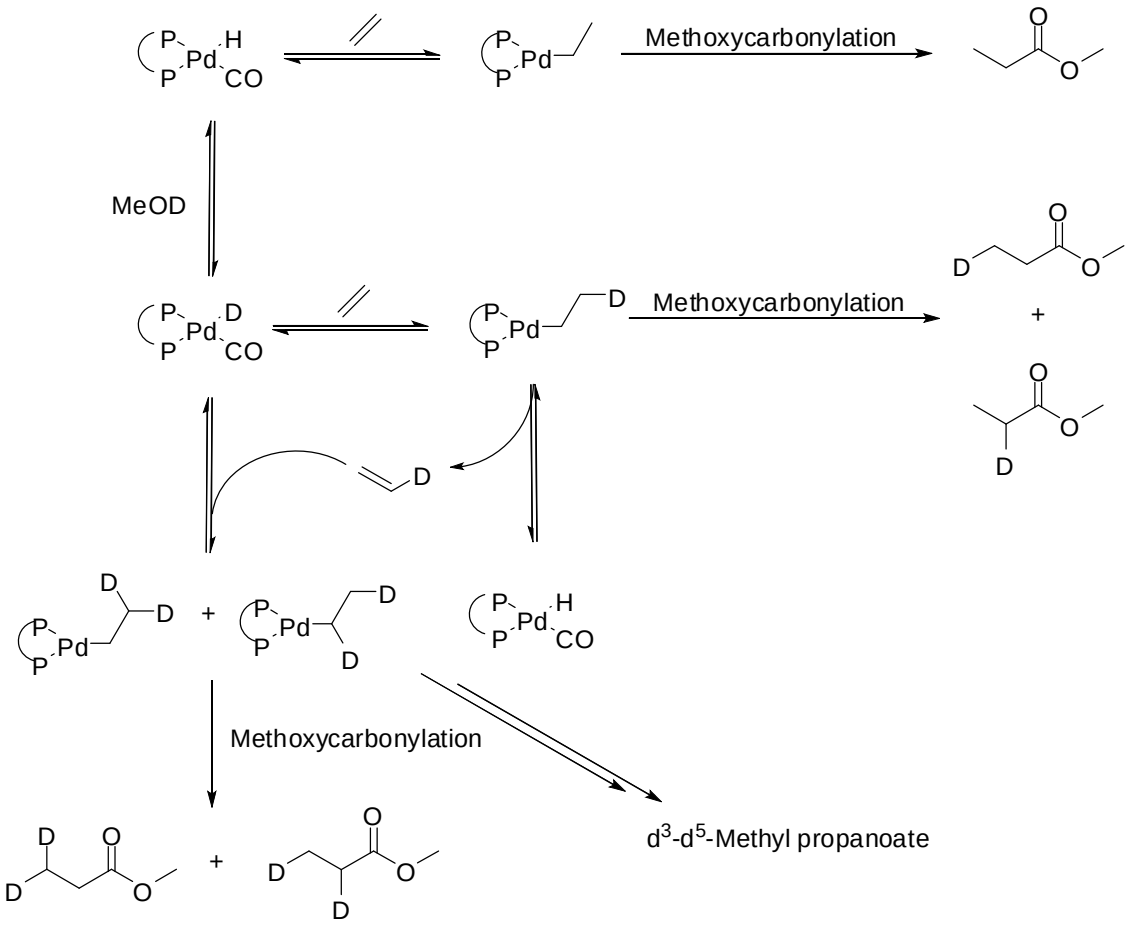


Fig 1.31. *Formation of deuterated methyl propanoate in the hydride mechanism*

Although the hydride mechanism in this kind of methoxycarbonylation has been categorically proven in these studies, there are some paradoxes. For instance, the palladium hydride species (**3**) which is formed *in situ* by the reaction of a palladium precursor, [Pd(BDTBPMB)dba],[62c] a hydride source (usually a non-coordinanting acid such as methanesulphonic acid) in methanol was not formed. Only the protonation of the coordinating dba was obtained. An addition of benzoquinone or molecular oxygen is needed as an intermediate in the hydride (**3**) synthesis (Fig 1.32).[62c,d]

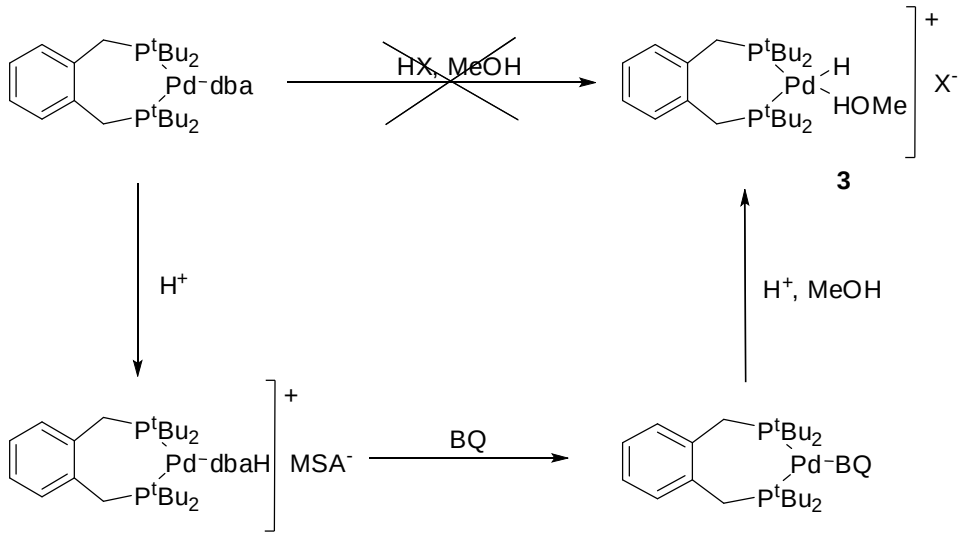


Fig 1.32. *Generation of palladium hydride **3***

The use of higher linear alkenes confirmed that isomerisation of the alkene via the hydride insertion/β-elimination equilibrium (Fig 1.31) is extremely fast. When methoxycarbonylation of 1-octene was carried out in Toluene/CH_3OD a quasi-normal distribution of all the possible deuterated isomers of the product and reactant were obtained.[59] Only in pure MeOD was the d^1 peak appreciably much larger than the other peaks (Fig 1.33). Hence, isomerisation of alkenes under these conditions is a fast process, and considerably faster than methoxycarbonylation.

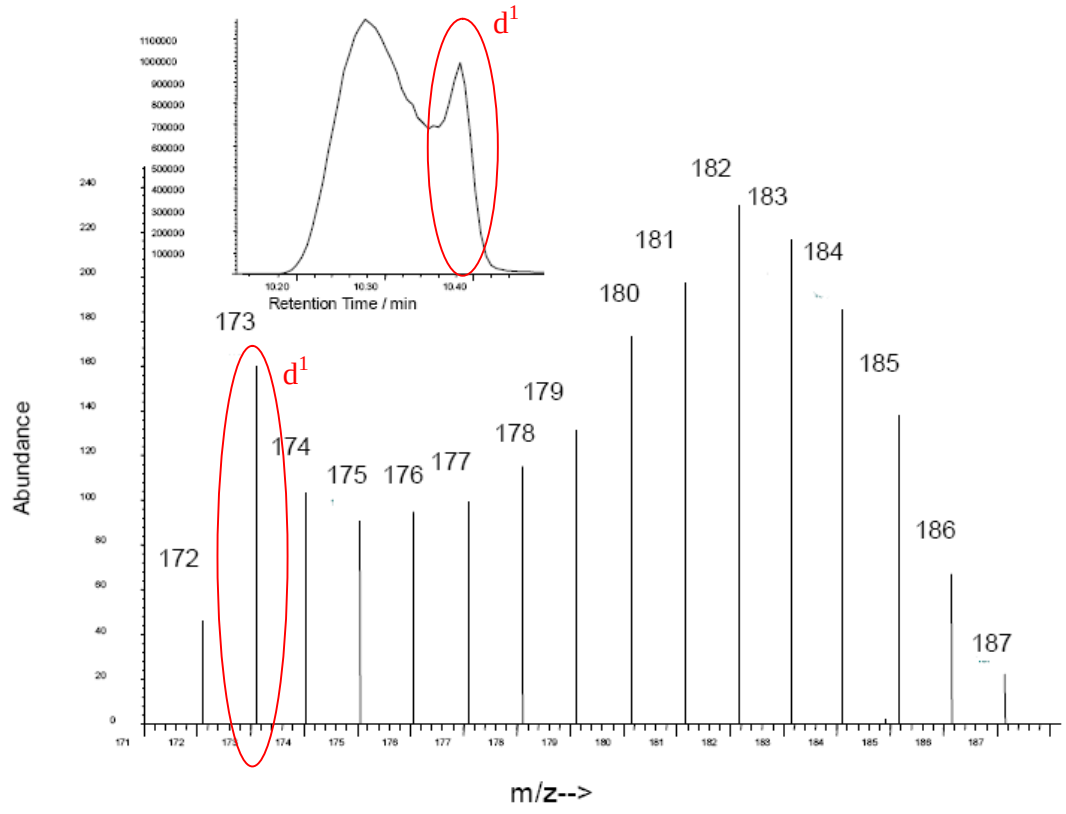


Fig 1.33. *Parent ions from methyl nonanoate formation in deuterated methanol (GC trace insert).*[60]

The ability to generate of all isomers of the alkene via hydride migration under the methoxycarbonylation conditions has been elegantly applied in the synthesis of α,ω-diesters by Cole-Hamilton.[63] These compound used in the synthesis of polyester, polyamides and nylon can be obtained from an unsaturated ester, including from an internal double bond (Fig 1.34). This methoxycarbonylation has been reported before, where a mixture of products was observed, with the added carboxylate group being distributed along the carbon chain.[15] However, the BDTBPMB/Pd system leads the methoxycarbonylation to only the α,ϖ-diester due the quick isomeration equilibrium established in this case and the much faster rate of migration of the linear rather than the branched isomer at the coordinated carbon monoxide ligand.

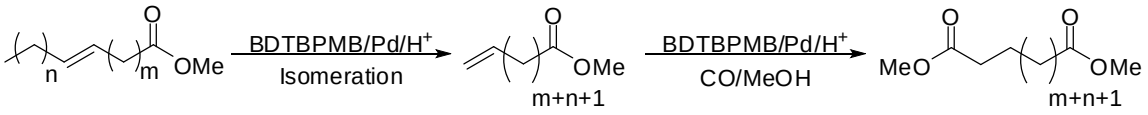


Fig 1.34. *Methoxycarbonylation of unsaturated ester*

Supported by this study, an interesting tandem metathesis/methoxycarbonylation has been reported using renewable sources such as natural oil (Fig 1.35).[64] Metathesis of natural oil with butene, catalysed by a second generation Grubb's catalyst has been reported with excellent yield and selectivity (Fig 1.35. Scheme A).[65] The combination of the Grubb's catalyst/(BDTBPMB/Pd) systems leads to the generation of α,ϖ-diesters and linear esters in one pot (Fig 1.35).

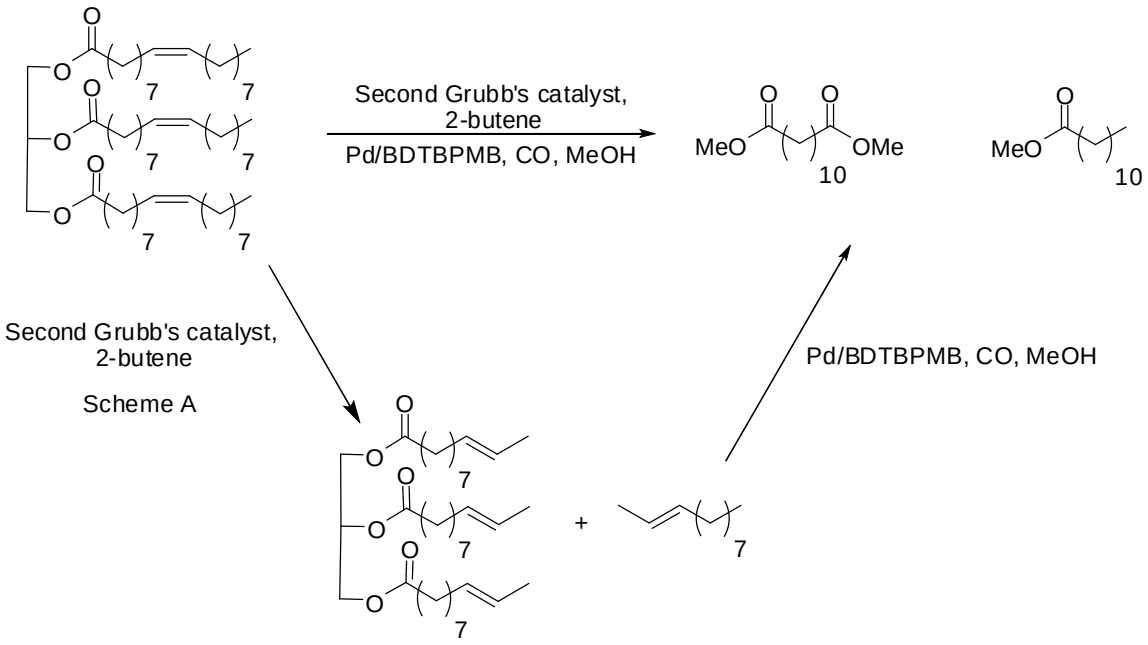


Fig 1.35. *Tandem metathesis/methoxycarbonylation process*

1.3.1.3.- Hydroxycarbonylation of 1,3-Butadiene.

Hexanedioic acid, also known as adipic acid, is one of the monomers used in the preparation of polyester, nylon 6,6 and resin (Fig 1.36).[2] In the USA, 1000 million kilograms are produced every year.[66]

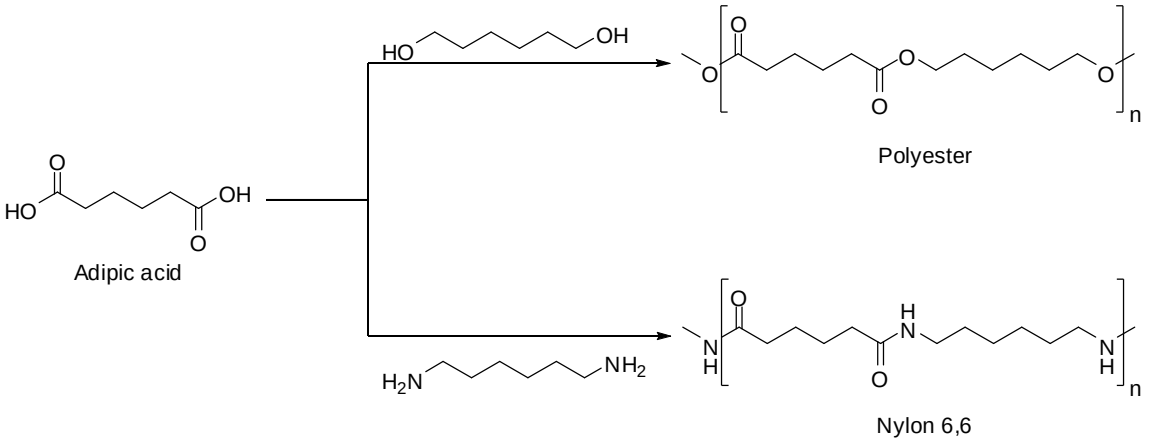


Fig 1.36. *Use of adipic acid*

The traditional process of obtaining adipic acid involves the oxidation of KA oil – a mixture of cyclohexanone and cyclohexanol – by nitric acid. This process requires three steps from benzene, the original feedstock: a hydrogenation followed by two successive oxidation steps (Fig 1.37. Scheme A). Therefore, the synthetic route to this important compound is far from being optimised. Hence, in the last few decades an alternative based on the hydroxycarbonylation of 1,3-butadiene (a cheap available feedstock) has been studied (Fig 1.37. Scheme B). However, the formation of the inactive crotyl-palladium species can block this synthetic route (Fig 1.37. Scheme C).

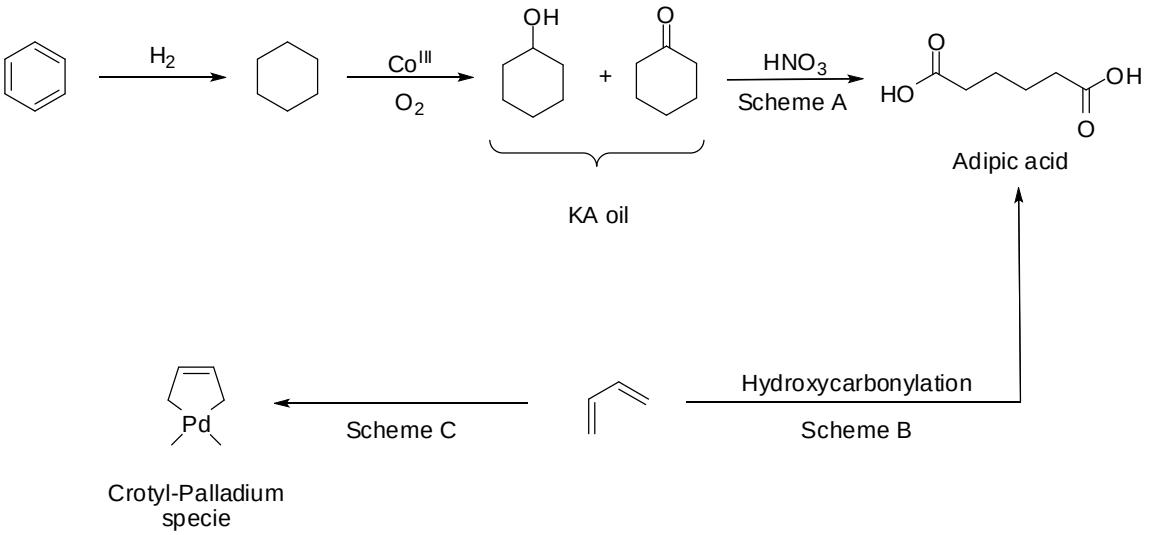
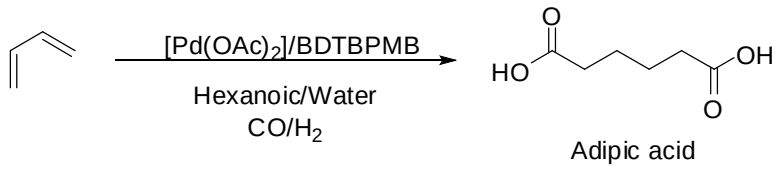


Fig 1.37. *Formation of adipic acid*

Recently this route to adipic acid has been improved by Drent.[67] This process gives high activities (Table 1.5, entry 1)[67a] using a $[Pd(OAc)_2]$/BDTBPMB in an organic acid medium. Apparently in this system the role of the organic acid is far from the just the role of a proton source as described in the plausible mechanism of carbonylation (See Section 2.1.2). The activity was improved with the addition of hydrogen to the medium (Table 1.5, entry 2).[67a]

Table 1.5. Hydroxycarbonylation of butadiene.[67]



Entry	Pressure of CO	Pressure of Hydrogen	TOF
1	60	-	880
2	60	5	1020

1.3.1.4.- Methoxycarbonylation of Chloroarenes.

The methoxycarbonylation of chloroarenes involves the activation of the carbon-chloro bond by oxidative addition generating an arylpalladium species (Fig 1.38). The high stability of the C-Cl bond in comparison to other carbon-halide bonds[68] makes this bond highly inert to oxidative addition, which is usually the first step of cross-coupling reactions and of carbonylation (Fig 1.38). This fact has been attributed to the high bond strength of the C-Cl bond (C-Cl = 96 kcal/mol; C-Br = 81 kcal/mol: C-I = 65 kcal/mol).[69]

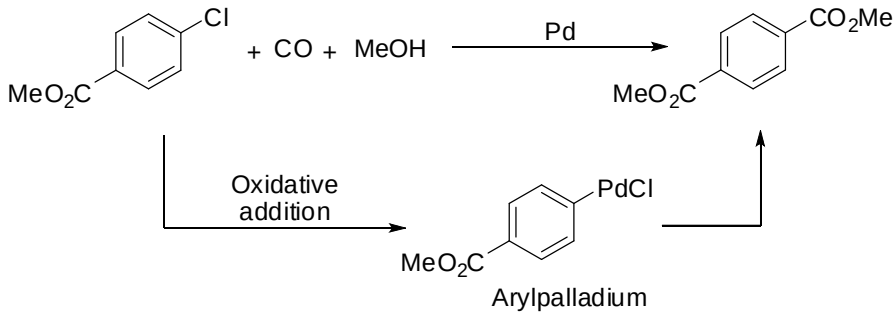


Fig 1.38. *Methoxycarbonylation of chlorobenzene*

Sterically hindered electron-donating ligands are required in the oxidative addition of chloroarenes such as P^tBu_3. BDTBPMB has been proven active in the oxidative addition of chlroroacetophenone in the presence of a highly electron withdrawing alcohol (trifluoroethanol) under carbon monoxide atmosphere, to give the methyl ester in 90% yield.[70]

1.3.2.- Immobilisation of the BDTBPMB/Pd System.

As Section 1.2.1 showed, the need for separation of the homogeneous catalyst from the medium may be difficult and sometimes impossible without destruction of the catalyst. The immobilisation of the catalyst onto a solid support is an interesting approach to resolve this problem (Fig 1.39). Normally, immobilisation processes require the modification of the ligand to attach it to a linker. However this process may involve a tedious route, and very often immobilised systems yield less than a similar system in typical homogeneous media.

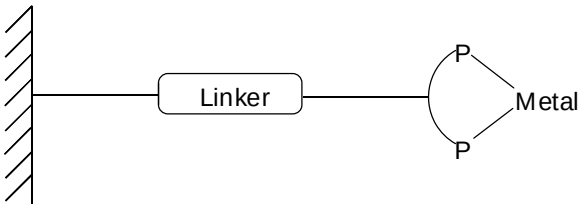


Fig 1.39. *Immobilisation of a diphosphine system*

Recently, the Tanaka group has developed an elegant process for the immobilization of the unmodified BDTBPMB/Pd complex on a sulfonic resin.[71] This is easily obtained from the Wang resin and propanesultone (Fig 1.40). The sulfonic group of the resin plays two roles – firstly in the generation of the necessary hydride palladium complex in the substitution of methanesulfonic acid, and secondly in the bonding of palladium in the BDTBPMB/Pd complex, linking this to the resin (Fig 1.40).

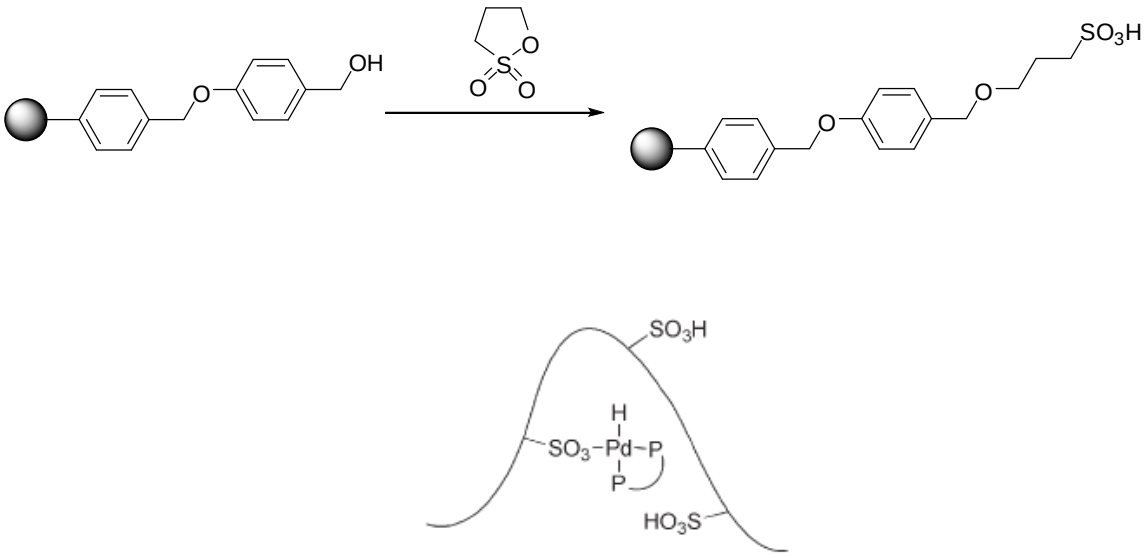
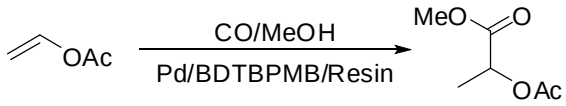


Fig 1.40. *Immobilisation of Pd/BDTBPMB in a modified sulfonic Wang resin. (Adapted from reference 71).*

This system has been proven to be as active and selective as the homogeneous catalytic system in the carbonylation of vinyl acetate (Fig 1.29) and is stable in four successive runs (Table 1.6).

Table 1.6. Carbonylation of vinyl acetate, with catalyst recycling.[71]



Cycle	Ester yield (%)	Selectivity (%)	Branched selectivity (%)
Fresh	82.1	98.9	3.4
1	89.4	98.7	2.7
2	83.5	99.3	3.0
3	84.9	99.1	2.9

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Chapter 2: Carbonylation

2.- Carbonylation

2.1.- Introduction

The ability of carbon monoxide to generate carbonyl complex is well known, as is the insertion of carbon monoxide onto an alkyl in a metal complex.[1] These reactions, along with the fact that carbon monoxide is a cheap feed-stock available from synthesis gas, opened the doors to the development of carbonylation chemistry. Nowadays, this kind of reaction produces a large volume of oxygenated products and chemical intermediates.[2-5] Carbonylation processes are very versatile, and may involve different substrates such as alkenes, allenes, alkynes or aromatic halides and these kinds of reaction need the participation of a nucleophilic compound which have a relatively acidic hydrogen such as waters, alcohols, acids or amines. The combination of different substrates with different nucleophiles can form a wide range of compounds such as acids, esters, anhydrides or amides.

The first process in this kind of chemistry was reported by Reppe in the synthesis of acrylic acid from acetylene catalysed by tetracarbonylnickel(0), $[Ni(CO)_4]$ (Fig 2.1). The reaction proceeded under harsh conditions (~300 bar and 170ºC).[5,6] $[Ni(CO)_4]$ was patented in 1943 as a catalyst for the production of propionic acid from ethylene by hydroxycarbonylation under extreme conditions (100-300 bar and 250-320ºC).[5] Although this process was quickly established in the United States, Germany and Japan, nowadays, due to the drastic conditions and the highly toxicity of $[Ni(CO)_4]$, only a BASF plant in Germany is operative.[2]

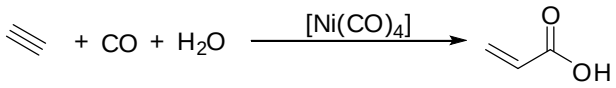


Fig 2.1. *Hydroxycarbonylation of acetylene catalysed by [Ni(CO)4]*

Although a wide range of transition metals such as Fe, Ru, Co, Rh, Ir, Pt or Mo are used in this chemistry, after the first procedure using palladium catalyst was reported by BASF[7] and Toyo Rayon[8], catalysts based on palladium complexes became more important.

2.1.1- Reactivity of Different Substrates and Nucleophiles.

Different substrates may be used in carbonylations, such as alkynes, alkenes or aromatic halides. Thanks to the high availability of unsaturated compounds such as ethene or propene, and the high atom economy of carbonylation of these substrates (*a priori*, no waste is generated), alkynes and alkenes are widely used in this reaction.

Usually alkynes bond more strongly than alkenes. Thus, the reaction of an alkyne is appreciably faster than the corresponding reaction with the alkene. If both an alkyne and an alkene are co-fed, the alkene does not react until all of the alkyne is exhausted.[9] However, the high cost of alkynes in respect to alkenes, and the possibility of formation of a π-allylpalladium species which is not active[10] from a typical impurity of alkyne, the allenes[11] (Fig 2.2) make the alkenes more attractive feedstocks than alkynes in carbonylation.

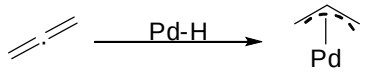


Fig 2.2. *Formation of π-allylpalladium species from allene*

Thus, alkene reactivity has been widely studied. Norbornene and cyclohexene give higher rates of reaction than linear alkene such as octene. Likewise, sterically hindred alkenes and internal alkene react more slowly than the corresponding linear isomer. For example, in the hydroesterification of alkenes with $[Pd(MeCN)_2(PPh_3)_2]$, the reported reactivity is norbornene > cyclohexene > 1-octene > cyclopentene > cyclooctene > 3-methyl-1-pentene > 2- methyl-2-pentene.[12]

Nucleophile reactivity has not been studied systematically. Only some qualitative observations have been reported regarding oxygen reagents. The reactivity of oxygen reagents in carbonylation is as follows: aliphatic alcohol > acid > water > phenols.[13] Increasing the steric hindrance of on alcohol causes a significant decrease in reactivity. Hence primary alcohols are more reactive than secondary alcohols, which are more reactive than tertiary alcohols.[13] No nitrogen nucleophilic reactivity has been described.

2.1.2.- Mechanism of carbonylation

The mechanism is far from being elucidated completely. However a proposed mechanism is shown in figure 2.3.[2]

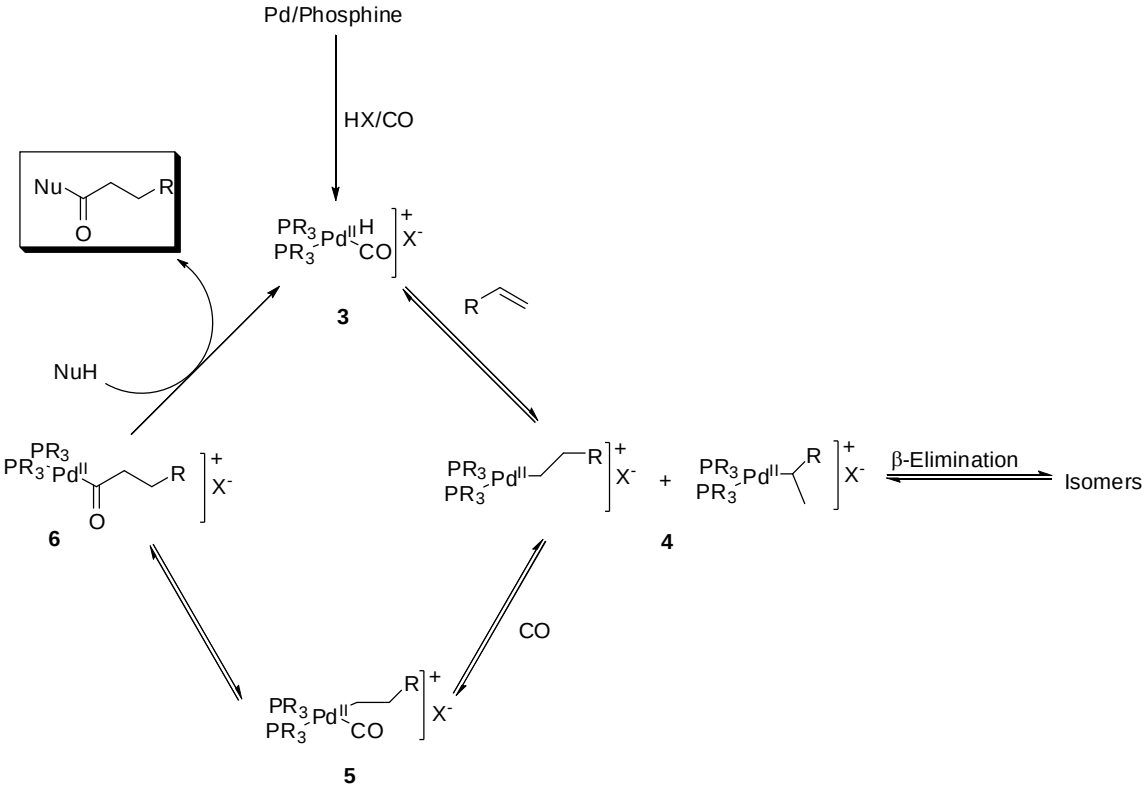


Fig 2.3. *Simplified proposed mechanism for carbonylation*

The formation of the palladium complex from a palladium precursor and a ligand (usually phosphines) and the reaction of this complex with a strong acid (the absence of this gives low conversion (Table 2.1, entry 1)[14]) in the presence of carbon monoxide generate the palladium hydride (**3**) which is the active species in carbonylation. The formation of this palladium hydride **3** is highly dependent on the nature of the acid, especially in its affinity for the metal centre. For example in the carbonylation of propene, the use of a non-coordinanting acid such as trifluoromethanesulfonic acid, or sulphuric acid reported gave a high yield (Table 2.1, entries 2 and 3). However the use of hydrochloric acid lowered the yield (Table 2.1, entry 4). Presumably, the coordination of Cl^- may block the generation of hydride palladium (**3**)[14] or the coordination of carbon monoxide.

Table 2.1. Methoxycarbonylation of propene catalysed by $Pd(OAc)_2/PPh_3$/HA (*Adapted from Reference 14).*

Entry	Acid	Ester (g)	Average rate (g ester/g of Pd·h)
1	None	Traces	N/A
2	H_2SO_4	16.0	3200
3	CF_3SO_2H	17.0	3400
4	HCl	4.8	96

The catalytic cycle begins when palladium hydride coordinates to an alkene, to give the corresponding alkylpalladium species via insertion (**4**). This species can then progress by two routes. β-elimination from the branched alkylpalladium species gives the isomer of the alkene. Alternatively **4** can coordinate to a molecule of CO giving species **5**, which produces acylpalladium (**6**) by insertion of the alkylpalladium onto CO. The acylpalladium complex reacts with water to give the acid and the palladium hydride.

The origin of the selectivity is generated in the insertion step. In this step, there are two possible routes (Figure 2.4). The insertion of hydride in path A is to the less substituted carbon, giving the branched product, while path B gives the linear alkyl intermediate.

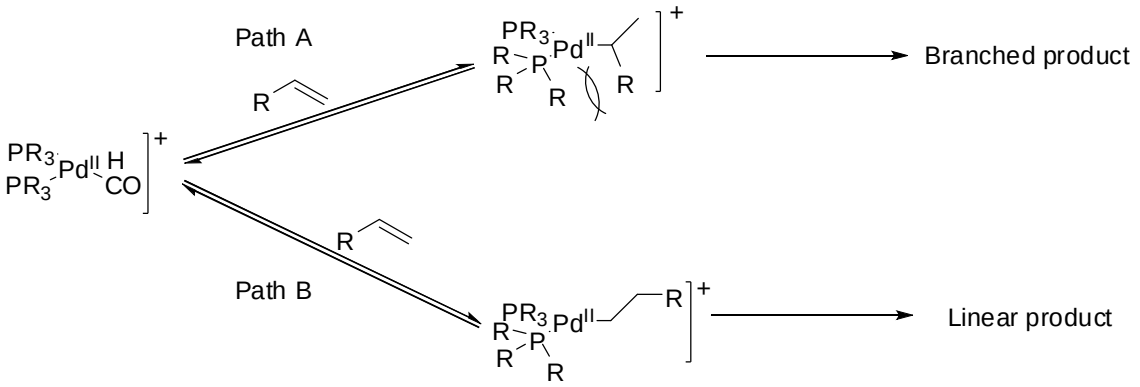


Fig 2.4. *Origin of the selectivity in carbonylation*

In this selectivity, the steric effects of the ligand play an important role, because in the intermediate of the path A there is a steric interaction between the branched alkyl and the substitutents on the ligand. Thus, with bulky ligands, path A is less favourable than path B, which gives the linear acid as the main product.

2.1.3.- Deactivation of the Catalyst

As Section 1.2 shows, the cost of a catalyst affects the viability of a process, as a catalyst must be cheap and stable over a long period of time. Hence the study of the stability of catalysts and their deactivation can provide a powerful tool to improve the catalytic system.

In carbonylation, the deactivation is principally due to the formation of palladium black, which is not active in carbonylation. This inactivation can be produced in several ways:

- Stoichiometric WGSR.[15,16]

$$Pd^{2+} + CO + H_2O \rightarrow Pd(solid) + CO_2 + 2H^+$$

In the presence of water, which is required to decrease the induction time in carbonylation,[2] and as nucleophile in hydroxycarbonylation, carbon monoxide can be oxidized to carbon dioxide (WSGR). This transformation leads the formation of palladium black from the active Pd^{2+} complex, because of the low stability of the dihydrido palladium complex formed.

- Oxidation of alkenes to aldehydes.[17]

$$Pd^{2+} + C_2H_4 + H_2O \rightarrow Pd(solid) + Me\text{-}CHO + 2H^+$$

This reaction is part of the Wacker process to synthesise aldehydes from alkenes. However, in this process an oxidant is required to reoxidize palladium black to

palladium(II). In hydroxycarbonylation or in a wet medium, this reaction leads to loss of catalysis.

- Oxidation of phosphine to phosphine oxide.[17,18].

$Pd^{2+} + PR_3 + H_2O \rightarrow Pd(solid) + O{=}PR_3 + 2H^+$

In this reaction not only is palladium(II) reduced to palladium black, but also, the phosphine, is oxidized to phosphine oxide, which is not strongly coordinating.

- Effect of hydrogen.

Interestingly, a positive role of the addition of hydrogen in alkoxycarbonylation has been reported, specially in alkoxycarbonylation of bulky alcohols.[2,18] As Section 2.1 shows, the reaction rate is highly dependent on the steric effects of the nucleophile. However, in presence of hydrogen, the alkoxycarbonylation with *tert*-butanol yielded similar results as these with n-butanol (Table 2.2)[19]. Also the regioselectivity of the process towards the linear product increased slightly.

Table 2.2. Alkoxycarbonylation of 1-octene in the presence of hydrogen (CO/H_2 = 5:1).[19]

Alcohol	Ester yield (%)	n/i-ester ratio
n-butyl	93	5.1
tert-butyl	87	6.0
iso-propyl	84	5.7
n-propyl	88	5.1

Surprisingly, although hydrogen has no effect on the alkoxycarbonylation of alkynes[11] El Ali has reported the beneficial effect of the use of syngas instead of carbon monoxide in the aminocarbonylation of alkyne (Fig 2.18).[20]

However, although the hydrogen leads to high selectivities and yield, the presence of hydrogen seems to destabilize the catalyst.[2] Drent concluded that the negative role of the use of hydrogen is more important than the positive one.[2]

2.1.4.- Hydroxycarbonylation of Alkenes.

Acids are useful compounds in surfactant chemistry and in non-steroidal anti-inflammatory drugs, such as ibuprofen and naproxen which produced a profit of $2.5 billion in 1992.[21] Generation of acids is possible by hydroxycarbonylation of alkenes (Fig 2.5). However, due to the low reactivity of water which leads to low conversion (see Section 2.1.1.) and low linear/branched selectivity, and the deactivation of the catalyst promoted by water (see Section 2.1.3), this interesting carbonylation has not been studied as much as other carbonylation such as methoxycarbonylation.

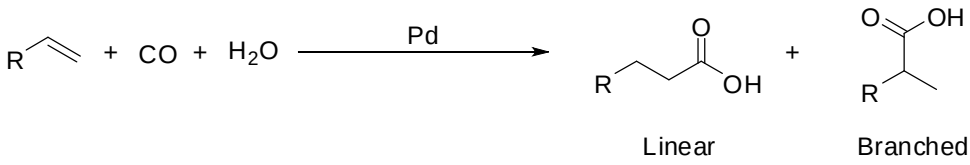
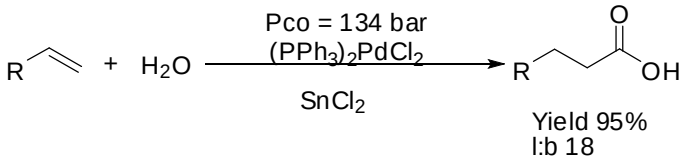


Fig 2.5. *Hydroxycarbonylation of alkenes*

One of the first papers was reported by Fenton in the 1970´s using a medium of acetic acid/water over a short period of time with moderate yield, however, the linear/branched selectivity of the process was low, between 1 and 3.6. [15] Knifton drastically improved the selectivity using tin (II) chloride as a promoter (Fig 2.6).[13] A plausible explanation of this effect involved coordination of the π-acceptor $SnCl_3^-$ to the palladium center. This coordination gives steric hindrance in the active site (hydrogen site) and changes the electronic properties, so that the insertion of the alkene, after the decoordination of a phosphine, gives the least hindered linear product (Fig 2.6).[13,22] $PbCl_2$ and $GeCl_2$ can be used instead of $SnCl_2$ with good results. Without tin(II) chloride, linear and branched acids were obtained in equal amounts



Catalytic system: Cl_3Sn, H, Pd, PPh_3, PPh_3

Fig 2.6. *Hydroxycarbonylation of alkenes as described by Kinfton*

Substituted polybutadienes can also be formed by hydroxycarbonylation. Carboxylic acids can be attached to the terminal double bonds of polybutadienes by hydroxycarbonylation using the Knifton procedure.[23] This process may be particularly interesting for linking groups to a polybutadiene support, and the preparation of more polar polymers (Figure 2.7).

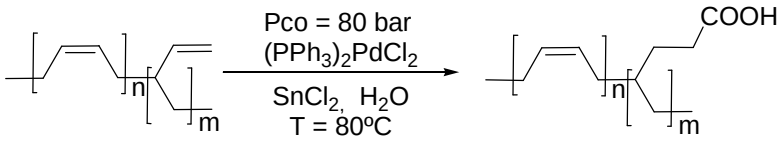


Fig 2.7. *Hydroxycarbonylation of polybutadiene*

The oxidative version of hydroxycarbonylation has been developed by Alper. The catalysis system is based on $PdCl_2$-$CuCl_2$ in presence of HCl and oxygen (Fig 2.8).[24] However, although no high pressure is needed in this system, the main isomer formed is the branched isomer.

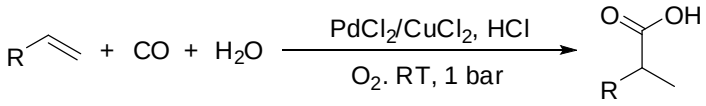


Fig 2.8. *Oxidative carbonylation*

The regioselective hydroxycarbonylation of vinylarenes to branched products is an important synthesis to prepare non-steroidal anti-inflammatories. This synthesis was reported in acidic conditions with high yields (Figure 2.9)[25]. The reaction requires mild

conditions (room temperature and one bar of carbon monoxide). However, a low pH (< 2) is also required so that a strong acid is necessary. The best results are achieved using HCl, although with HI the reaction also gives good results. With HI, a secondary reaction - the water gas shift reaction becomes important. This results in a significantly drop in CO pressure. With non-halide acids, like sulphuric acid, no conversion was obtained. This suggested the need of coordination of halide to generate the acid. This was confirmed when, with $Pd(OAc)_2$ as catalyst, no product was obtained. Using this species as a precatalyst and using a phase transfer agent like $nBu_4N^+Cl^-$, the same results as with $[(PPh_3)_2PdCl_2]$ were obtained.

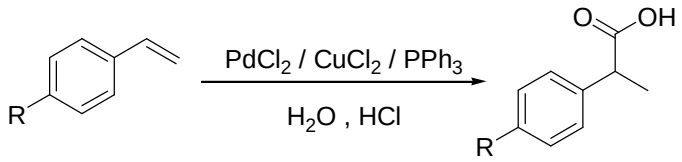


Fig 2.9. *Synthesis of non-steroidal anti-inflammatory drugs by hydroxycarbonylation*

The recovery of the catalyst has also been achieved.[26] Using TPPTS instead of triphenylphosphine and a biphasic system with water, the product is in the organic phase and the catalyst in the aqueous phase when the reaction ends. The reaction is slower than when just one phase is used, due to the mass transport limitations. Hence, a mass transfer agent must be used to increase the solubility of alkenes in water. However, no deactivation of the catalyst was reported after five cycles.

The asymmetric synthesis of ibuprofen has been realized by Alper and co-workers using (S)-(+)-binaphyl-2,2-diyl Hydrogen Phosphate (BNPPA) as the ligand (Figure 2.10),[27] with relatively good enantiomeric excess.

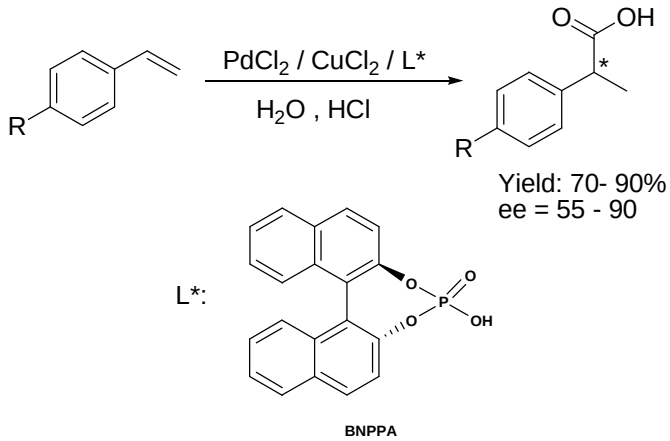


Fig 2.10. *Asymmetric synthesis of ibuprofen*

An alternative to the use of water has been developed by Aratani.[28] This involves the use of formic or oxalic acid to give the linear acid from the alkene. It is catalysed by palladium acetate in the presence of 1,4-bis(diphenylphosphino)butane (dppb) under 6.8 bar of carbon monoxide at 150ºC (Fig 2.11). This synthesis gives the linear acid with good selectivities and yields (80-100%).

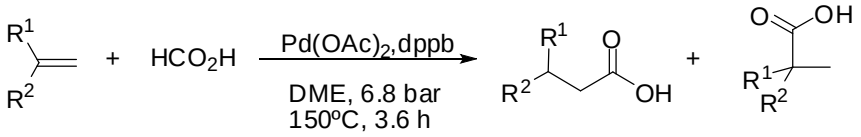


Fig 2.11. *Hydroxycarbonylation of alkenes by $Pd(OAc)_2$-dppb-HCO_2H-CO*

A plausible mechanism involves a double role of formic acid, as both the proton source and the nucleophile (Figure 2.12). The first step of this mechanism is the formation of the active species **8** by two sequential steps: The coordination of both the ligand and a molecule of carbon monoxide forms **7** and the abstraction of a proton from formic acid by the catalyst gives the corresponding hydride (**8**). This hydride produces to the alkyl palladium (**9**) by coordination and insertion of the olefin. By insertion of the carbon monoxide molecule into the Pd-C bond, followed by coordination of the formate gives species **10**. Species **10** reacts with a second molecule of formic acid to regenerate the catalyst and form species **11**, which is unstable, and on heating produces the corresponding acid.

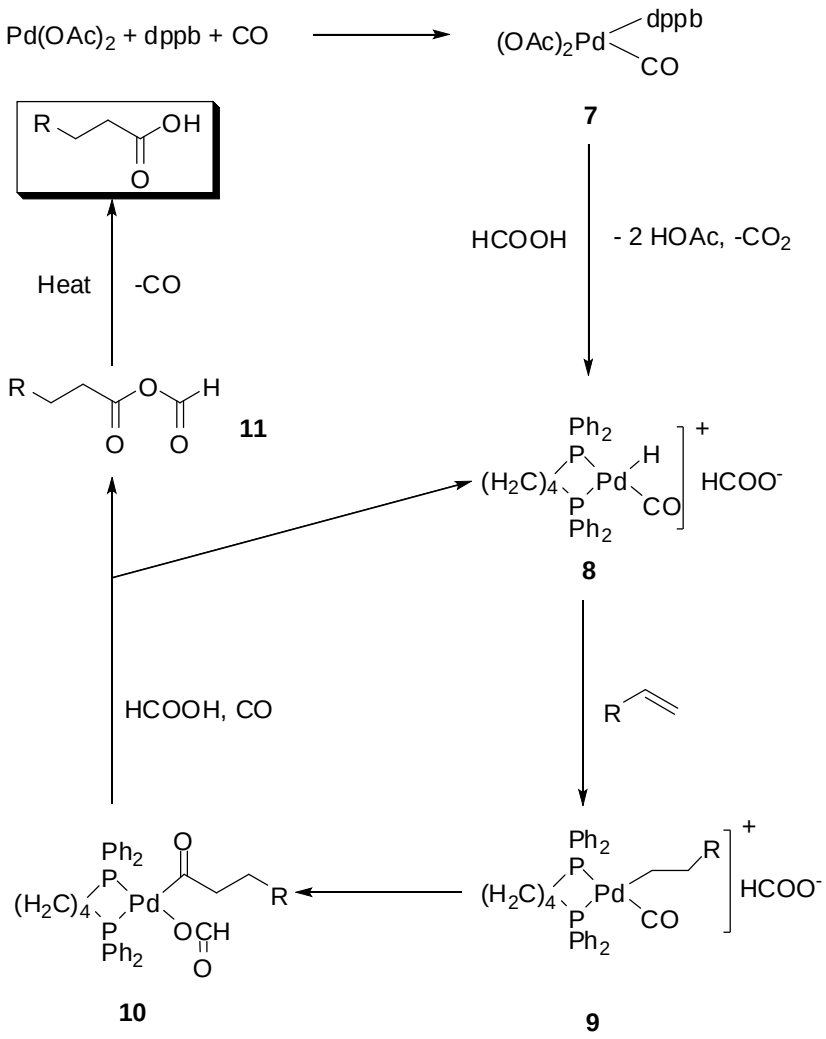


Fig 2.12. *Plausible mechanism of hydroxycarbonylation using formic acid*.

2.1.5.- Aminocarbonylation of Alkenes.

Amides have some interesting properties especially in the concept of polarity and durability. This fact results in the production of amides being one of the most important in bulk chemistry. Their uses cover a wide range of applications, such as additives in detergents and thickeners.

Amides are produced on the laboratory scale by the reaction of an acid chloride and an amine (Fig 2.13 Scheme A).[29] However, this route, although efficient in concept of

yield and selectivity, is not acceptable for industrial application due to the high generation of waste.

The industrial process is far from being optimized. Nowadays, the main route for the generation of amides is the thermal decomposition of the ammonium salt formed by an acid (Fig 2.13 Scheme B).[30] This route involves high temperatures (~180ºC) and the use of highly valuable feedstocks –acids-. Due to these two facts, the aminocarbonylation of alkenes (a cheap and available feedstock) is as good alternative route to generate amides (Fig 2.13 Scheme C).

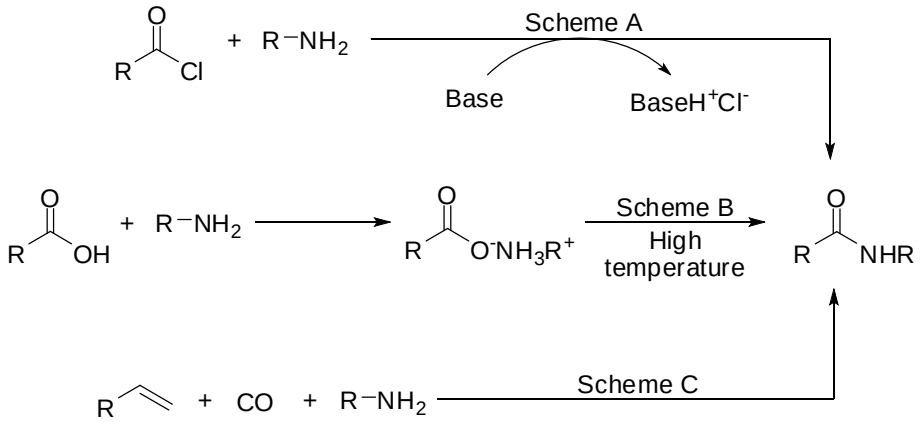


Fig 2.13. *Generation of amides*

Surprisingly, the industrial interest of this kind of carbonylation did not result in a thorough study. The apparent discrepancy was explained by H. M. Colquhoun *et al*: "Yields and selectivities were often good, but the extreme conditions required seems to have inhibited further development in this chemistry".[31] Indeed, the first results in this area using transition metal salts [$RuCl_3$, $Ni(CN)_2$] or metal carbonyls [$Fe(CO)_5$, $Co_2(CO)_8$] as catalyst, gave good results but involve extreme temperatures (up to 350ºC) and pressures (up to 1000 bar).[32]

Recently, some heterogeneous catalysis procedures based on ruthenium[33a], rhodium[33b] or cobalt,[33c] have been developed for aminocarbonylation. However, although the conditions required were milder, they are still relatively harsh.

In homogeneous catalysis, only a few papers have appeared in the aminocarbonylation of alkenes.[34] For example, the synthesis of pentenamide -an important

synthetic intermediate in the chemistry of nylon- has been successfully patented recently by the aminocarbonylation of 1,3-butadiene (Fig 2.14).[34a] In this work, Drent *et al* addressed an important route of synthesis from an interesting feedstock, 1,3-butadiene. 1,3-Butadiene is cheap and readily available, and therefore quite attractive for carbonylation chemistry. *A priori* important synthetic intermediates such as pentenamides, pentenoic acids and adipic acid may be obtained by carbonylation of 1,3-butadiene. However the formation of an inert palladium species such as π-allylpalladium and crotylpalladium species, have blocked this desirable route of synthesis. Apparently, Drent has overcome these difficulties, discovering this synthetic route.

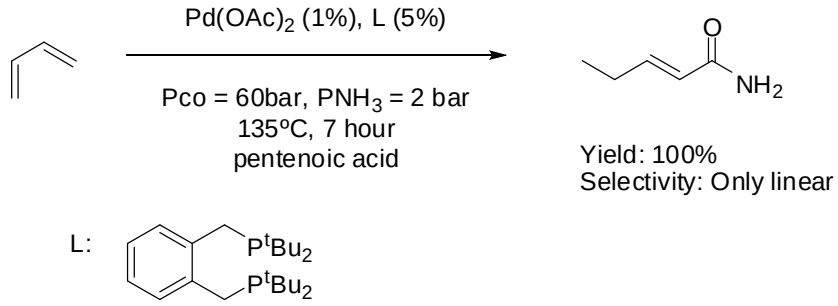


Fig 2.14. *Synthesis of pentenamide from 1,3-butadiene via aminocarbonylation*

The effect of a nucleophilic promoter such as aryl alcohol has been found to be very positive in the aminocarbonylation of alkenes (Fig 2.15).[34b] The combination of an aryl alcohol with a halide salt has reported excellent yields (up to 60 %) and selectivities (up to 92 %), with TOF higher than 300 mol product·(mol cat·h)$^{-1}$.

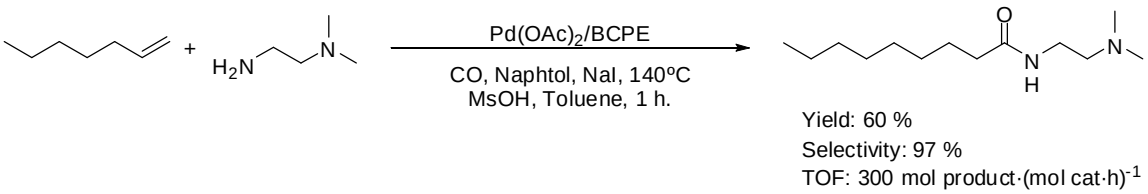


Fig 2.15. *Aminocarbonylation of octene with addition of an arylalcohol*

The surprising role of the aryl alcohol is unexplored so far. However, a proposal of the promoting effect has been made in the aminocarbonylation of arylhalides using another

nucleophilic promoter, imidazole (Fig 2.16).[35] The plausible role of imidazole is as an intermediate nucleophile. Imidazole may attack the acylpalladium species generating an intermediate amide, which can be in turn be attacked by the amine to generate the final amide and liberate the imidazole.

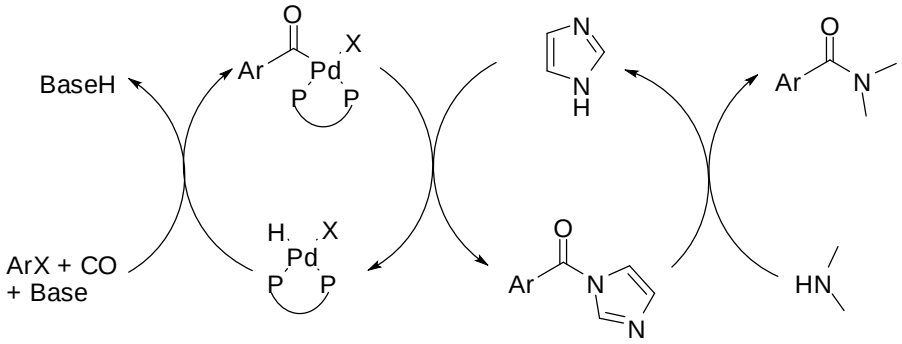


Fig 2.16. *Plausible mechanism of imidazol in Aminocarbonylation of arylhalide (Adapted from reference 35)*

The intramolecular version of aminocarbonylation has been paid special attention. The possibility of the formation of lactames from the substituted anilines is a highly desirable route in fine chemistry. Alper has described the formation of different lactones via intramolecular aminocarbonylation.[36] Several products can be obtained depending upon the orientation of the cyclisation. For example, in the aminocarbonylation of *ortho*-vinylaniline, two products can be formed -β-lactame or γ-lactame- depending of the orientation of cyclation (*5-exo or 6-endo*) (Fig 2.17). Elegantly, Alper addressed the difficulty and described high selectivities in obtaining these two possible products by changing of the conditions of the reaction. The use of (-)-DIOP gave a slight enantiomeric excess (33 % ee) in the aminocarbonylation of 2-(1-methylvinyl)aniline.[37]

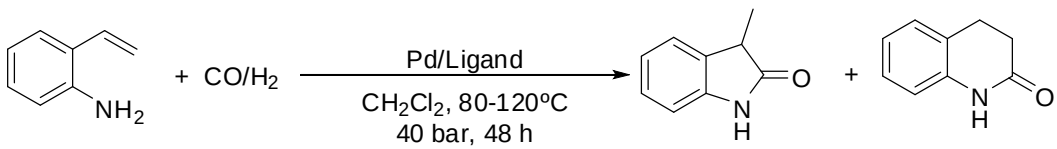


Fig 2.17. *Aminocarbonylation of ortho-vinylaniline (Adapted from reference 36)*

Alkynes are another interesting substrate in aminocarbonylation. Acrylamides, amongst the most important monomers in plastic chemistry, may be elegantly formed via aminocarbonylation of alkynes (Fig 2.18).[38] Three products are obtained in the aminocarbonylation of alkynes: the corresponding linear and branched acrylamides (usually the branched product was the main product), and the product for the double carbonylation, the imide.

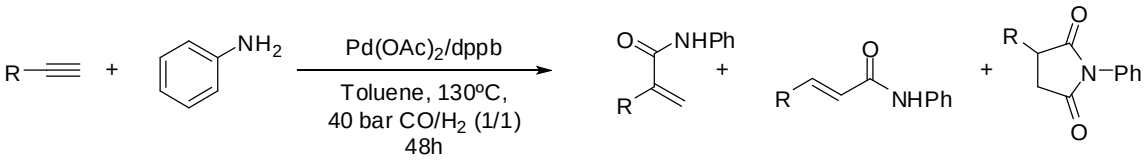


Fig 2.18. *Aminocarbonylation of alkynes (Adapted for reference 38).*

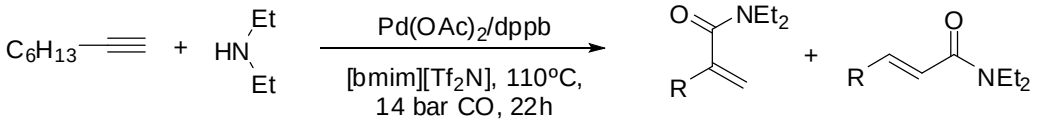
Aromatic amines, such as aniline, have proven to be more reactive than alkyl amines. Usually anilines required milder condition and shorter reaction time than the alkyl amines (Table 2.3, entries 1 and 2).[39] This fact may explain the hypothetical destruction of the palladium hydride **1** (See Fig 2.3), the active catalytic species by the more basic alkyl amine.

Table 2.3. Aminocarbonylation of phenylacetylene (Adapted from reference 39).

Entry	Amine	pKa	Amine (mmol)	Alkyne (mmol)	T (ºC)	t (h)	Amine yield (%)	
							Branched	Linear
1	Butylamine	10.77	15.0	15.0	100	65	34	3
2	Aniline	4.63	9.0	9.0	50	1	14	Traces

Recently the use of ionic liquid has allowed the recycling of catalysts during this important synthetic route.[40] The high stability of the catalyst under these conditions has been observed with five consecutive uses of the catalyst without any loss in the catalyst properties (Table 2.4).

Table 2.4. Aminocarbonylation of heptyne in ionic liquids. Recycling of catalyst (Adapted from reference 40).



Run	Yield (%)
1	66
2	64
3	70
4	70
5	68

Generation of 2-ynamides, an intermediate for biologically active molecules,[41] by oxidative aminocarbonylation has been reported (Fig 2.19).[42] In this kind of aminocarbonylation, oxygen is introduced into the medium and is required for the recycling. It plays a similar role to that in the Wacker process by promoting the oxidation of palladium zero to palladium (II), the active species.

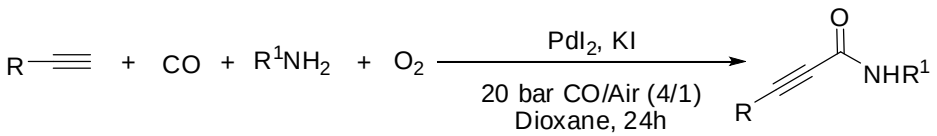


Fig 2.19. *Oxidative aminocarbonylation of alkynes (Adapted from reference 42).*

Bicyclic and tricyclic lactams can be obtained in a single step via an elegant tandem Heck/aminocarbonylation (Fig 2.20).[43] This route, described by Negishi, forms consecutive cycles by zipper reaction.

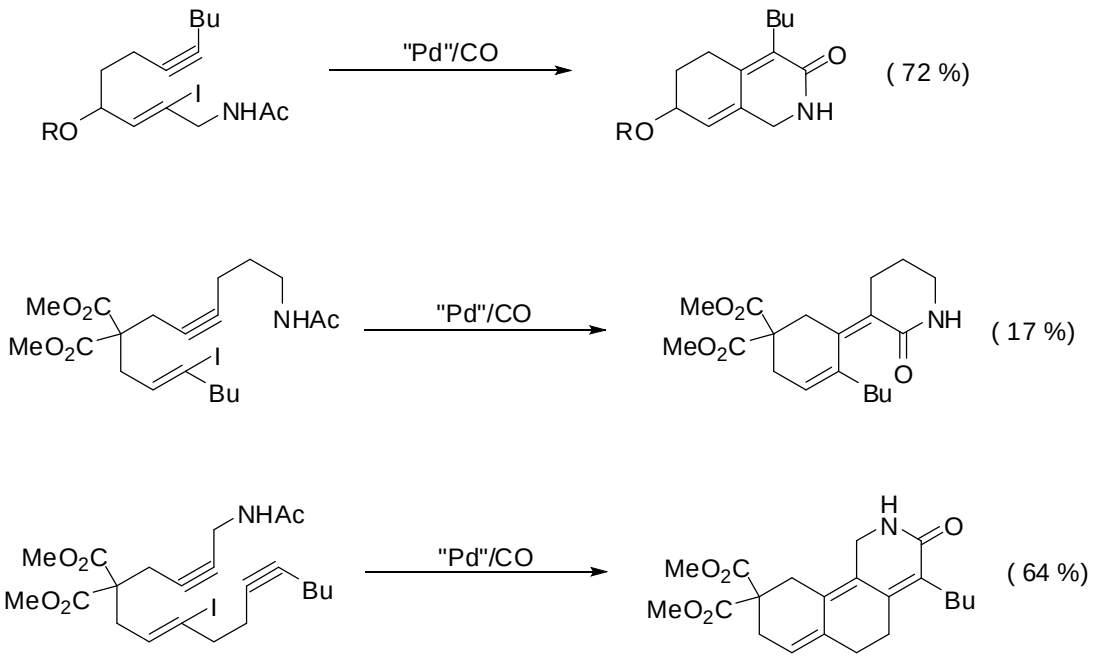


Fig 2.20. *Generation of lactams via tandem Heck/Aminocarbonylation (Adapted from reference 43).*

2.2.- Result and Discussion.

2.2.1- Hydroxycarbonylation of Alkenes Catalysed by the Pd/BDTBPMB System.

As Section 2.1.4 shows, hydroxycarbonylation of alkenes is a highly desirable route to generate acids despite the problems of stability and reactivity, derived from the use of water (See Section 2.1.1 and 2.1.3).

A thorough study of the conditions of hydroxycarbonylation was considered especially interesting in view of optimising the product already reported. 1,2-Bis(ditertbutylphosphinomethylbenzene) (BDTBPMB) was chosen as the ligand for this study. The two *t*-butyl groups per phosphine and a large, rigid bridge make bis(ditertbutylphosphinomethyl)benzene (Fig 2.21) an excellent ligand for homogeneous carbonylation (See Section 1.3).

The choice of solvent is far from trivial. The rate determining step of the carbonylation reactions is the reaction of the nucleophile (in this case, water) with the acylpalladium intermediate. Therefore, the reaction rate depends significantly of the concentration of water. Hence, the chosen solvent must be highly soluble in water to increase its concentration in the medium, containing the substrate and catalyst.

The selected solvent in this case was dioxane. Dioxane has two ideal proprieties which make this solvent quite interesting in hydroxycarbonylation. One is the possibility of having high concentrations of water due to its solubility in dioxane, as previously mentioned. The second is that dioxane is a cyclic ether. Usually these kinds of solvent such as diethyl ether and tetrahydrofuran give excellent results in catalysis.

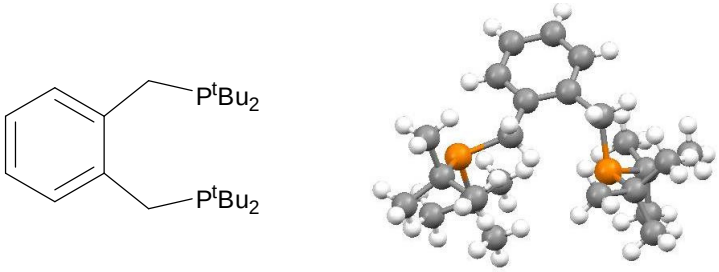


Fig 2.21. *1,2-bis(ditertbutylphosphinomethylbenzene)*

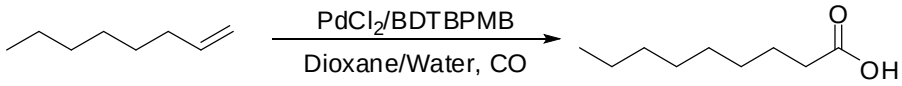
Initial NMR studies showed that, due to the basicity of the palladium complex of highly electron donating ligands such as BDTBPMB, water is acid enough to form the initial hydride which in turn starts the catalytic cycle (see Section 2.1.2). This fact allows the reaction in acid free conditions. Due to corrosion problems in the presence of acid, it forces the use of special materials which are very often expensive. Acid-free procedures are favoured in industry due to these corrosion problems.

2.2.1.1.- Effect of Temperature on the Hydroxycarbonylation of Octene.

Temperature is one of the most important variables in industrial processes, and its effects have to be taken carefully into consideration. For example, it is well known that high temperatures increase the rate of the reaction, making the reaction faster and therefore requiring shorter reaction times. Likewise, high temperatures increase the cost of heating,

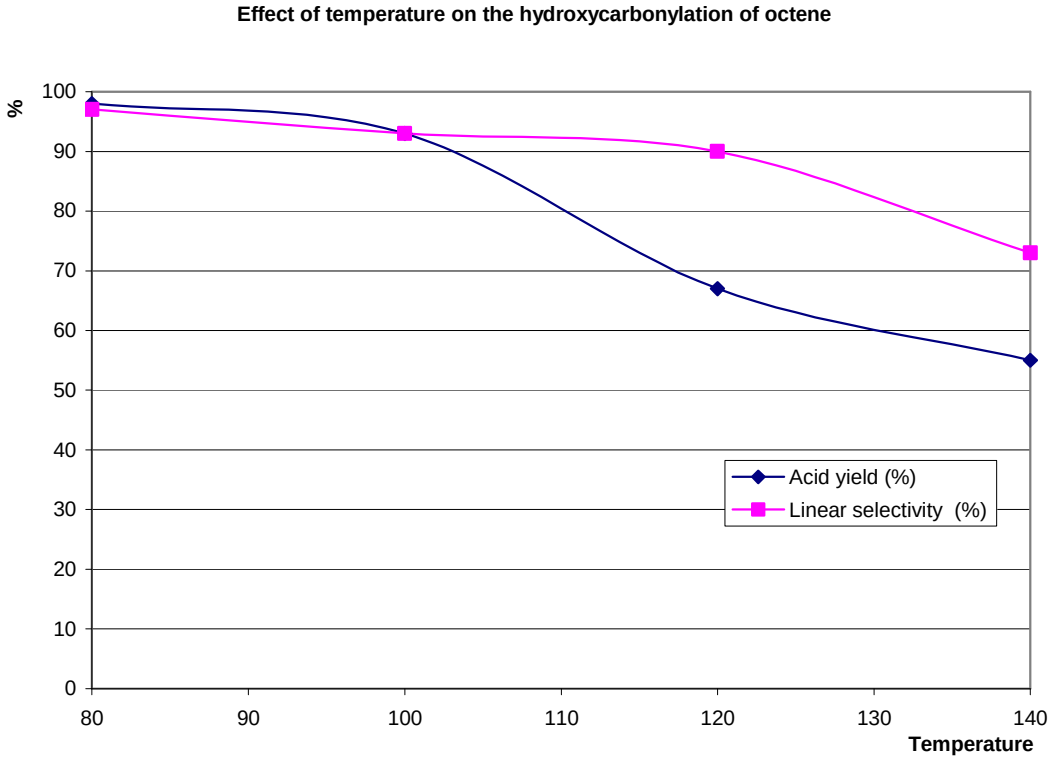
and usually decrease the stability of the catalyst. Hence, the temperature effect has both positive and negative consequences. Therefore, the choice of the ideal temperature is often the most important parameter in industry. Engineering, the process itself and economical aspects have to be taken into consideration during the choice of temperature for the process.

Table 2.5. Effect of temperature on the hydroxycarbonylation of octene.



Entry	Temperature	Acid yield (%)	Linear selectivity (%)
1	20	Traces	-
2	80	98	97
3	100	93	93
4	120	67	90
5	140	55	73

Conditions: Octene (1 mL, 6.37 mmol), $PdCl_2$ (32 mg, 0.19 mmol), BDTBPMB (82 mg, 0.21 mmol), dioxane (10 mL), water (2 mL), P_{CO} (70 bar), 5 h

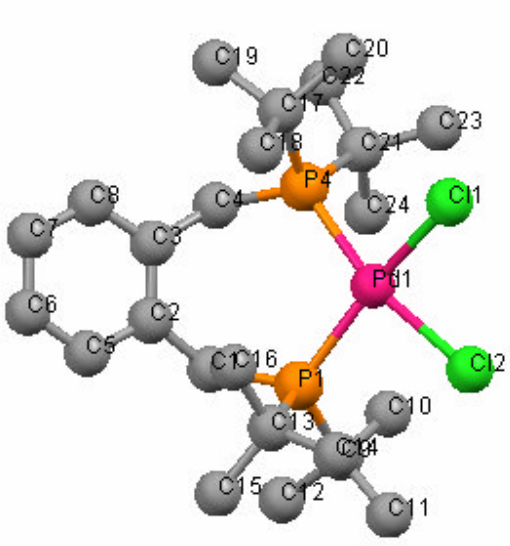


The screening of temperatures was carried out from room temperature (20ºC) to 140ºC. The results obtained are shown in the Table 2.5.

Only traces of product were obtained at room temperature (Table 2.5, entry 1). When the temperature was raised to 80 degrees, excellent conversion and selectivity were obtained (Table 2.5 entry 2). A Slight decrease in yield was obtained when the reaction was carried out at 100 degrees (Table 2.5, entry 3).

Appreciable deactivation of the catalyst was observed at high temperatures (Entry 2.5, entries 4 and 5). This deactivation leads to a dropping in yield and selectivity. This destruction of the catalyst is more evident at 140 degrees where selectivity decreases from excellent results to only moderate results (Table 2.5, entry 5).

Table 2.6. Selection of bond lengths and angles in [Pd(BDTBPMB)Cl_2] *(Hydrogen atoms omitted for clarity)*..[44]



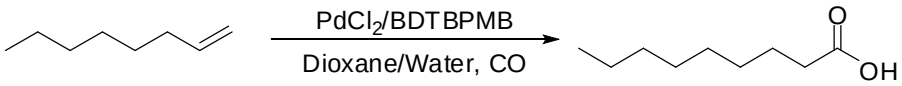
Bond lengths (Aº)	
Pd(1)-P(1)	2.3094 (8)
Pd(1)-P(4)	2.3288 (8)
Pd(1)-Cl(1)	2.3645 (7)
Pd(1)-Cl(2)	2.3602 (8)
Angles(º)	
P(1)-Pd(1)-P(4)	101.88 (3)
P(1)-Pd(1)-Cl(2)	88.38 (3)
P(4)-Pd(1)-Cl(2)	162.26 (3)
P(1)-Pd(1)-Cl(1)	162.72 (3)
P(4)-Pd(1)-Cl(1)	89.97 (3)
Cl(2)-Pd(1)-Cl(1)	83.60 (3)

Yellow crystals were obtained when the reaction was stopped. The structure from these confirms the initial formation of the complex, [Pd(BDTBPMB)Cl_2]. Bond lengths and angles are within the normal range (Table 2.6). Bond lengths are similar to the already reported [Pd(BDPPMB)Cl_2].[45] However, the angles are slightly different, specially the Cl-Pd-Cl angle. This is 7 degrees smaller in the case of [Pd(BDTBPMB)Cl_2] (Cl-Pd-Cl in

[Pd(BDPPMB)Cl_2] is 90.4º).[45] The difference is easily understandable, considering the appreciable difference in regard to steric effects between the substituent of the phosphorus groups in both complexes – the phenyl group in the case of [Pd(BDPPMB)Cl_2] and *tert* butyl in the case of [Pd(BDTBPMB)Cl_2] -.

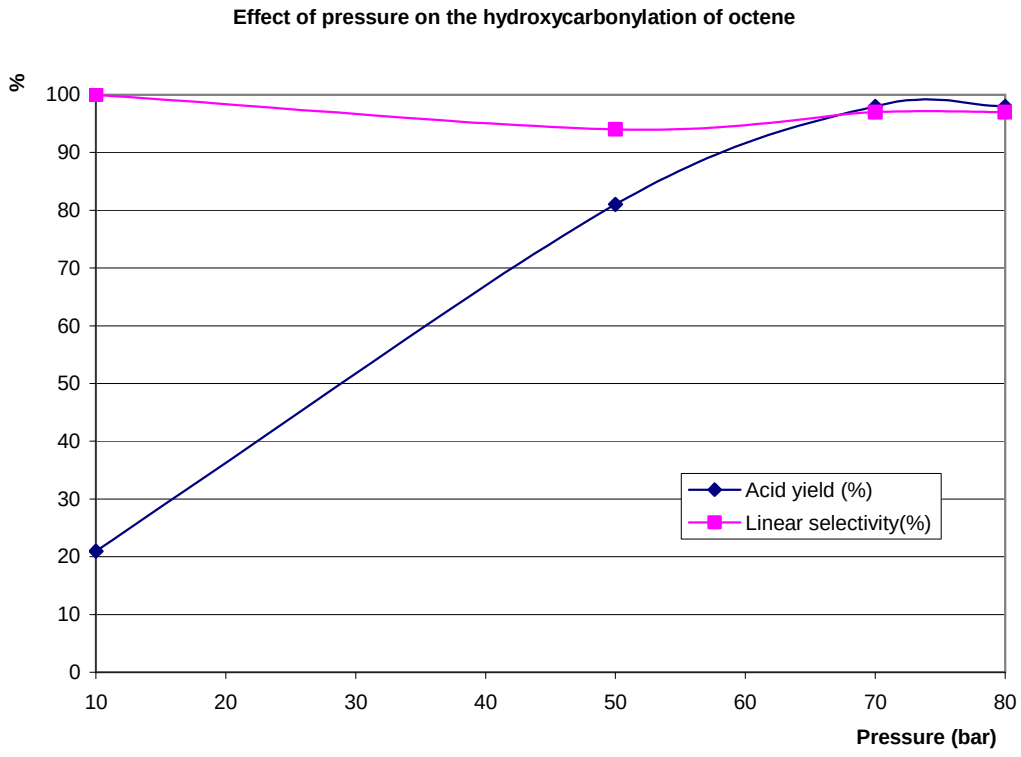
2.2.1.2.- Effect of pressure on the Hydroxycarbonylation of Octene.

Table 2.7. Effect of pressure on the hydroxycarbonylation of octene.



Entry	Pressure	Acid yield (%)	Linear selectivity (%)
1	80	98	97
2	70	98	97
3	50	81	94
4	10	21	>99

Conditions: Octene (1 mL, 6.37 mmol), $PdCl_2$ (32 mg, 0.19 mmol), BDTBPMB (82 mg, 0.21 mmol), dioxane (10 mL), water (2 mL), P_{CO} (as decrived), 80ºC, 5 h.



The pressure required is another important variable in all procedures which involve gases. The total pressure in the system is important in two concepts: The cost of the equipment and an increase of security control. It is evident that high pressures require equipment with thicker walls to carry out the process safely. However, the requirement of a thick wall involves a large increase in cost of the equipment. Elevated pressures involve a risk of explosion, which must be taken into consideration during the planning of the plant. More specific control equipment is needed to keep this explosion risk to a minimum leading to an increase in the cost of the plant. With this explosion risk, the use of CO is important due to its toxicity, and must be taken into consideration as well in the design of the control loops.

For these two reasons, it is evident that the pressure affects the process cost and the profit. Hence, a detailed study of the required pressure should be carried out. This study was carried out from 10 bar to 80 bar. The results obtained are shown in the Table 2.7.

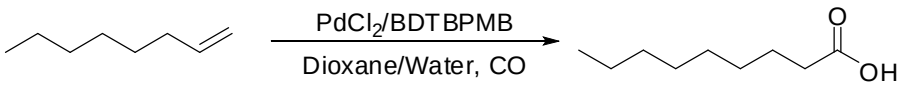
Low pressures yielded low conversion and high selectivity (Table 2.7, entry 1). An increase in pressure to 50 bar drastically increased the conversion of the system (Table 2.8, entry 2). This positive effect in the increase in pressure was more evident when the reaction was carried out under 70 bar of pressure. Under this pressure, excellent conversion and selectivity were obtained (Table 2.7, entry 3). An increase in pressure to 80 bar did not result in significant differences (Table 2.7, entry 4). Hence, hydroxycarbonylation of octene, catalysed by $PdCl_2$/BDTBPMB requires a moderate pressure to obtain high conversion. A positive role in the increase in pressure was found during this study. These results agreed with the kinetic studies described by Noskow and Petrov.[2,22] In these studies Noskow and Petrov proposed a positive order in CO, which agrees with the results found in this study.

2.2.1.3.- Study of the Concentration of Water on the Hydroxycarbonylation of Octene.

The concentration of water in the medium presents both beneficial and detrimental effects in important concepts, such as stability of the catalyst (see Section 2.1.3) and reaction rates. Therefore, a high concentration of water raises reaction rates, but also

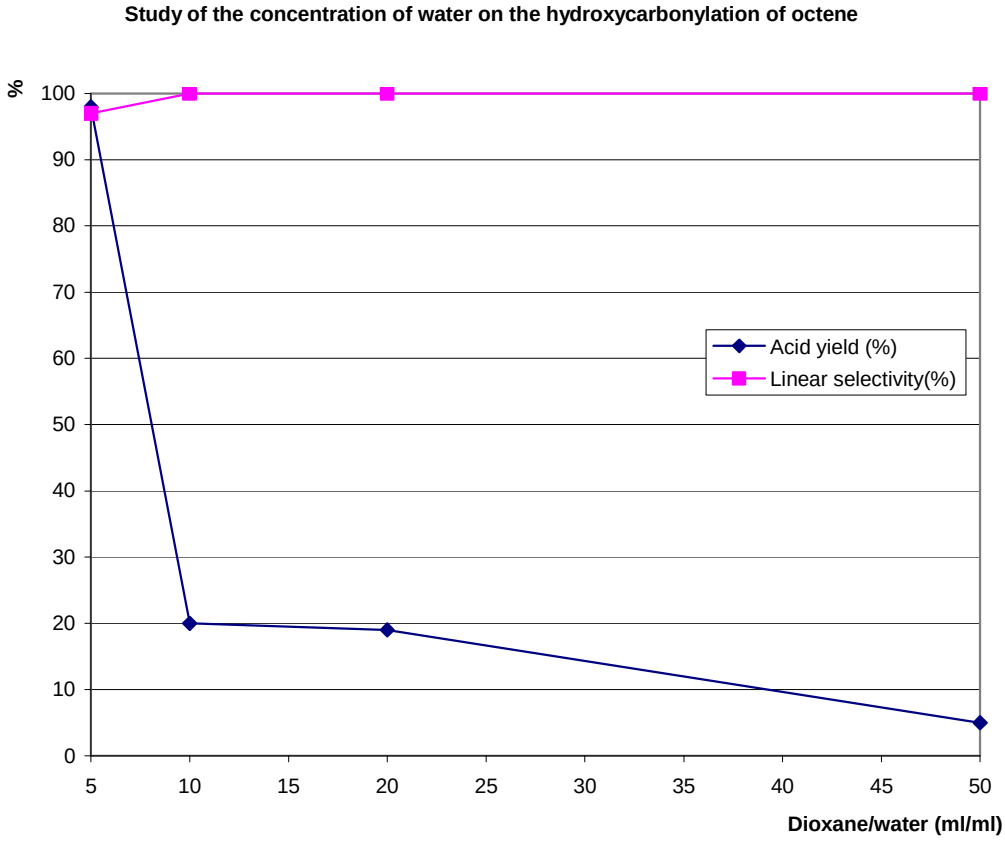
increases the instability of the catalyst. Therefore, a study into the optimum concentration of water in the medium has been carried out.

Table 2.8. Study of the concentration of water on the hydroxycarbonylation of octene.



Entry	Dioxane/water ratio	Acid yield (%)	Linear selectivity (%)
1	5:1	98	97
2	10:1	20	>99
3	20:1	19	>99
4	50:1	5	>99

Conditions: Octene (1 mL, 6.37 mmol), $PdCl_2$ (32 mg, 0.19 mmol), BDTBPMB (82 mg, 0.21 mmol), dioxane (10 mL), water (as descrived), P_{CO} (70 bar), 80ºC, 5 h



Water-miscible dioxane allows the use of high concentrations of watert. So, a large range of ratios, from 5:1 to 50:1, has been studied here. The results are summarised in Table 2.8.

High yield and selectivity have been obtained when the reaction was carried out with a high concentration of water (Table 2.8, entry 1). However, as expected, the instability of the catalyst under these conditions is evident. Some palladium black, which is not active in hydroxycarbonylation, was obtained.

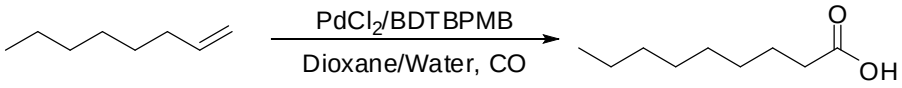
Decreasing the water concentration yielded a significant drop in yield (Table 2.8, entries 2 and 3). No palladium black was formed under these conditions. This fact proved the high dependence on the water concentration of the stability of catalyst. The drop in yield is appreciably more evident when a dilute medium was used (Table 2.8, entry 4).

2.2.1.4.- Hydroxycarbonylation of Octene in Other Solvents.

Dioxane was chosen as the ideal solvent for hydroxycarbonylation due to a variety of its propieties. However, it is interesting to examine the use of other solvents in hydroxycarbonylation. Ethereal solvents such diethyl ether or tetrahydrofuran and acetonitrile have been tested during this study and the results are shown in Table 2.9.

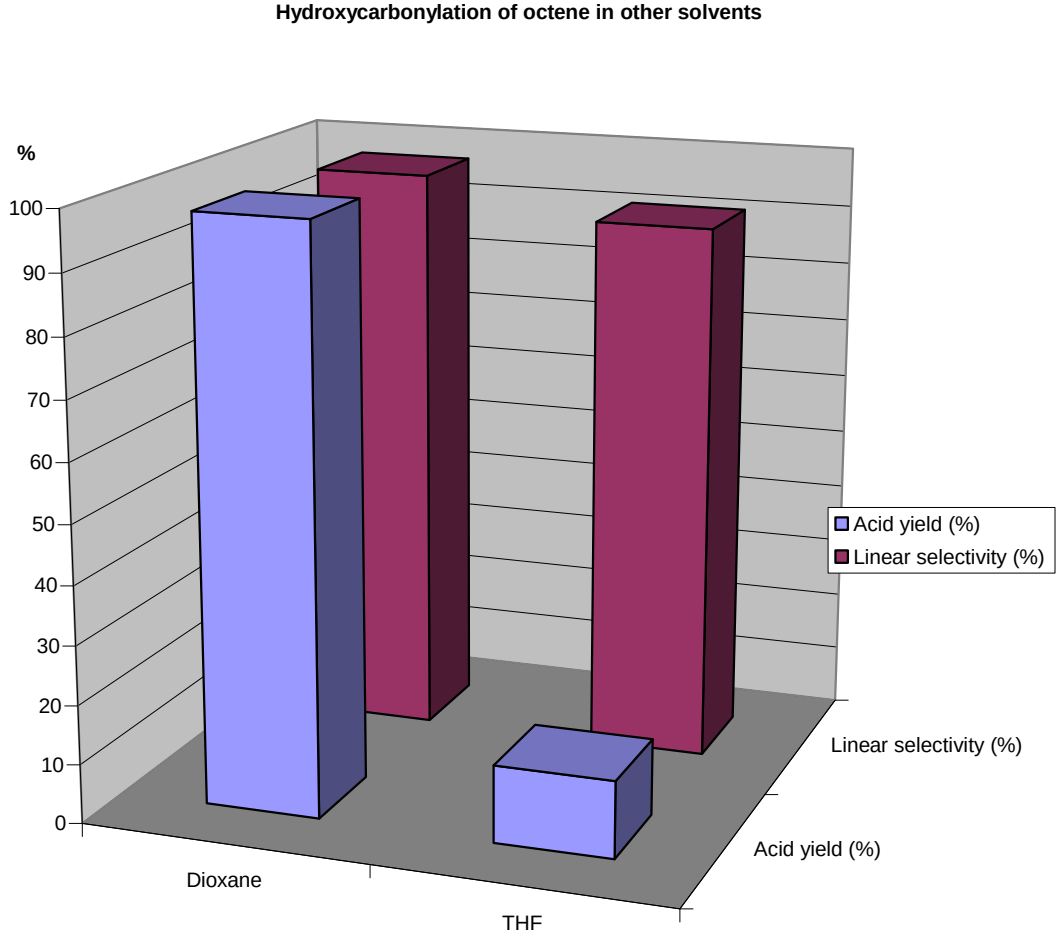
The use of other ethereal solvents which were less miscible with water, such as THF or diethyl ether, yielded lower conversion or no conversion (Table 2.9, entries 2 and 3). Surprisingly, in the more water-soluble acetonitrile, no yield was obtained (Table 2.9, entry 4), possibly because it binds too strongly to palladium. This study confirmed that the initial choice of dioxane was the best option for these reactions.

Table 2.9. Hydroxycarbonylation of octene in other solvents



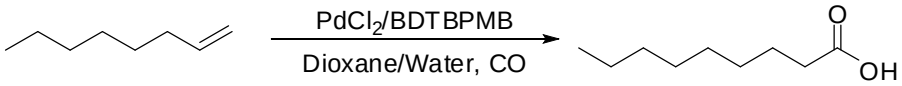
Entry	Solvent	Acid yield (%)	Linear selectivity (%)
1	Dioxane	98	97
2	THF	13	91
3	Et_2O	0	0
4	MeCN	0	-

Conditions: Octene (1 mL, 6.37 mmol), $PdCl_2$ (32 mg, 0.19 mmol), BDTBPMB (82 mg, 0.21 mmol), solvent (10 mL), water (2 mL), P_{CO} (70 bar), 80ºC, 5 h



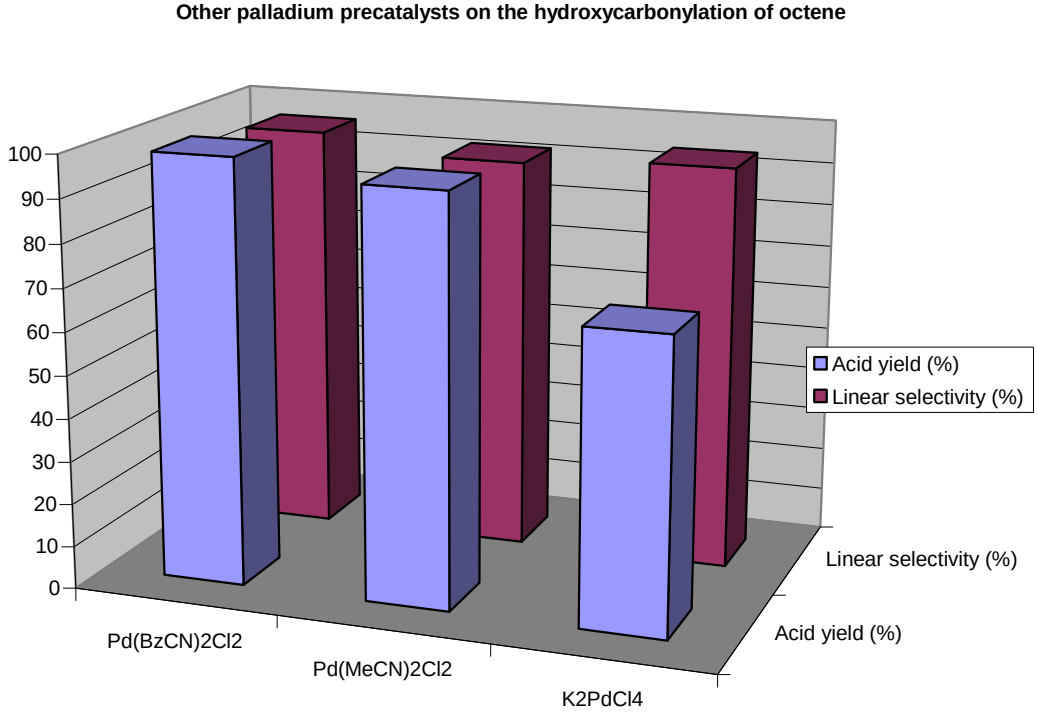
2.2.1.5.- Other Palladium Precatalysts on the Hydroxycarbonylation of Octene.

Table 2.10. Other palladium precatalysts on the hydroxycarbonylation of octene.



Entry	Palladium compound	Acid yield (%)	Linear selectivity (%)
1	$[Pd(PhCN)_2Cl_2]$	>99	96
2	$[Pd(OAc)_2]$	0	-
3	$[Pd(MeCN)_2Cl_2]$	95	92
4	$[Pd_2dba_3]$	0	-
5	$K_2[PdCl_4]$	68	94
6[a)]	$[Pd(OAc)_2]$	0	-
7[a)]	$[Pd_2dba_3]$	0	-

Conditions: Octene (1 mL, 6.37 mmol), palladium precursor (0.19 mmol), BDTBPMB (82 mg, 0.21 mmol), dioxane (10 mL), water (2 mL), P_{CO} (70 bar), 80ºC, 5 h. a) 175 mg (0.63 mmol) of Bu_4NCl was added



Other precatalysts were tested. The results were summarised in Table 2.10. While $[Pd(MeCN)_2Cl_2]$ and $[Pd(PhCN)_2Cl_2]$ yielded similar results (Table 2.10, entries 1 and 3). $K_2[PdCl_4]$ gave lower results than palladium chloride (Table 2.10, entry 5). Other species of palladium(II), such as palladium acetate, produced no conversion (Table 2.10, entry 2). It is presumed that the formation of the palladacycle by C-H activation of the ring, as described by Eastham, Tooze and co-workers,[46] blocked the hydroxycarbonylation route (Fig 2.22). A source of palladium(0) like $[Pd_2dba_3]$ was not effective in this procedure (Table 2.10, entry 4).

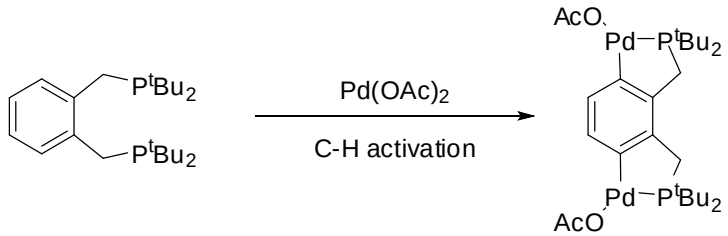


Fig 2.22. *Formation of a palladacycle by C-H activation of aromatic ring of BDTBPMB.*[46]

To discard a hypothetical halide effect from the chlorine atom of $PdCl_2$, two additional experiments were carried out using $[Pd(OAc)_2]$ and $[Pd_2dba_3]$ as precursors, along with chlorine source, Bu_4NCl. No conversion was found in these two reactions (Table 2.10, entries 6 and 7).

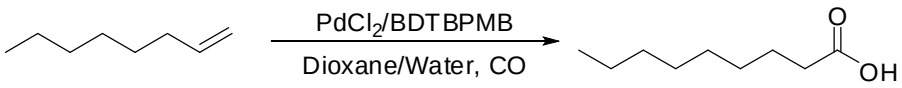
2.2.1.6.- Hydroxycarbonylation of Octene under Other Conditions.

As Section 2.1.3 shows, hydrogen may play opposite effects -a positive effect in the increase in reaction rate and a negative effect in the stabilization of the catalyst-. Hence, hydrogen usually makes the reaction faster despite an increase in catalyst instability. Therefore, it is interesting to know which effect is predominant in the hydroxycarbonylation of octene, and if it is possible to increase the rate without a loss in the stability of the catalyst.

When the reaction was carried out under 100 bar of syngas (CO/H_2 1:1) low conversion was obtained (Table 2.11, entry 1). This fact proved that the negative effect of

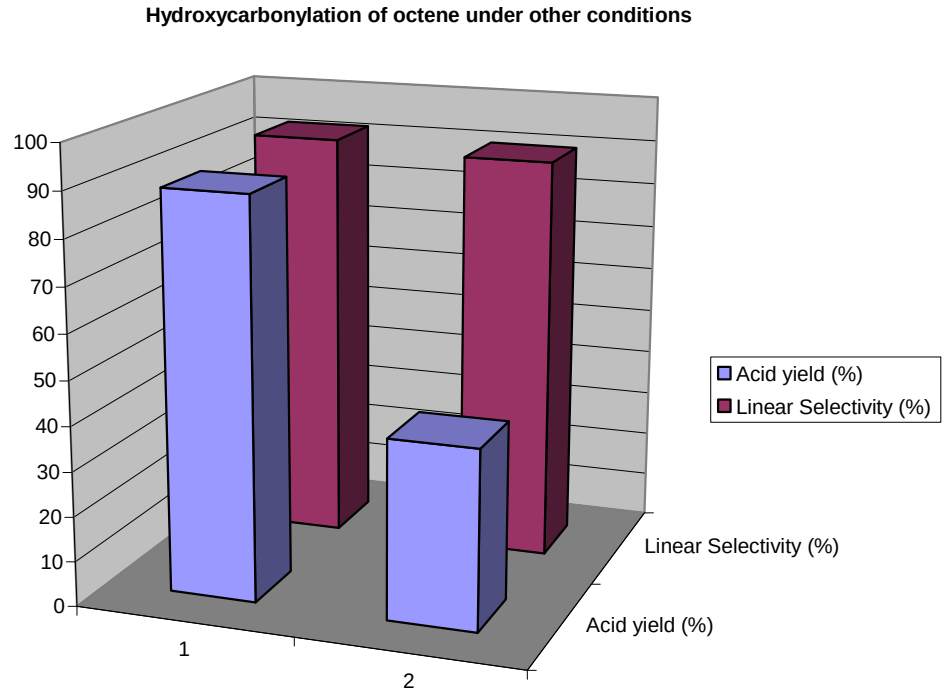
hydrogen is more important than the positive effect, as Drent concluded (see Section 2.1.3).[2]

Table 2.11. Hydroxycarbonylation of octene under other conditions.



Entry	Pressure	Additive	Acid yield (%)	Linear selectivity (%)
1	100[a)]	-	40	90
2	70	MsOH (10 %)	89	92

Conditions: Octene (1 mL, 6.37 mmol), palladium precursor (32 mg, 0.19 mmol), BDTBPMB (82 mg, 0.21 mmol), dioxane (10 mL), water (2 mL), P_{CO} (70 bar), 80ºC, 5 h. a) Syngas (1:1) was used instead of carbon monoxide.



Normally substoichiometric amounts of acid are need in alkoxycarbonylation and hydroxycarbonylation. However, due to the basicity of the palladium complex of BDTBPMB, which can be protonated by water, acid is not required in hydroxycarbonylation under these conditions.

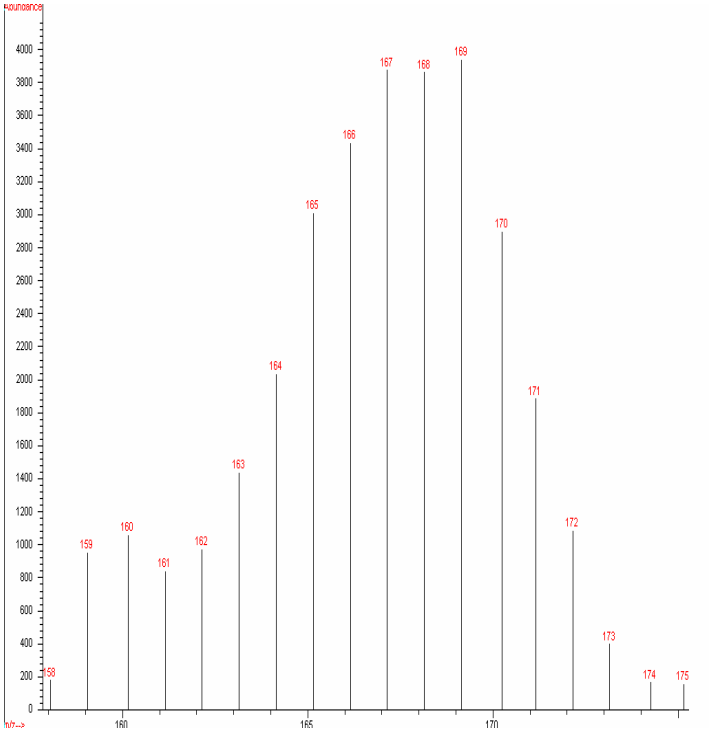
Although hydroxycarbonylation can be carried out under acid-free conditions, the role and effect of acid is interesting. The use of a non-coordinanting strong acid such as methanesulfonic acid, yielded slightly lower conversion. Hence, it may be concluded that the presence of an acid in the solution does not significantly affect the reaction.

2.2.1.7.- Deuteration Study of Hydroxycarbonylation.

It is well known that water reacts slowly in hydroxycarbonylation probably due to its low nucleophilicity. An interesting experiment to prove how fast the isomeration route is relative to the reaction of water with the acylpalladium species is the deuteration study. The use of D_2O in place of water can give a measurement of how slow the nucleophilic attack is compared to the isomerisation route, which has proven to be very fast in methoxycarbonylation (See Sections 2.1.2 and 1.3.1.2).[46]

Table 2.12. Deuterium abundance in the final product, nonanoic acid.

	% abundance
d^0	0.5
d^1	2.9
d^2	3.3
d^3	2.6
d^4	3
d^5	4.5
d^6	6.2
d^7	9.4
d^8	10.7
d^9	12
d^{10}	12
d^{11}	12.2
d^{12}	9
d^{13}	5.8
d^{14}	3.4
d^{15}	1.2
d^{16}	0.5
d^{17}	0.5



When D_2O was used in hydroxycarbonylation in place of water, a near Gaussian distribution of multiply deuterated products was obtained, except the peaks corresponding to d^1 and d^2 which are slighly higher (Table 2.12). This confirms that isomerisation is fast relative to hydroxycarbonylation. The presence of d^0-nonanoic acids confirms that a hydride mechanism must operate,[46] whilst a slightly increased amount of d^1-nonanoic acid – compared with that expected from a random distribution – is similar to that observed when using methanol diluted with toluene (1/4 v/v). This confirms that the carbonylation reaction is considerably slower than isomerisation. If it were fast compared with isomerisation, significantly amount of d^1 product would have been observed.

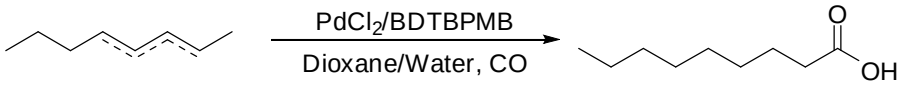
2.2.1.8.- Hydroxycarbonylation of Other Octene Isomers.

Considering that isomerisation is extremely fast (and appreciably faster than the nucleophilic attack) and that usually the internal isomers react slower than the α-isomer (probably due to an increase in steric effects), it is interesting to know if internal isomers reacts as fast as external isomers to generate the linear acid as main product.

To confirm this theory, 2-octene, 3-octene and 4-octene were tested under the conditions proven for 1-octene. The results are summarised in Table 2.13.

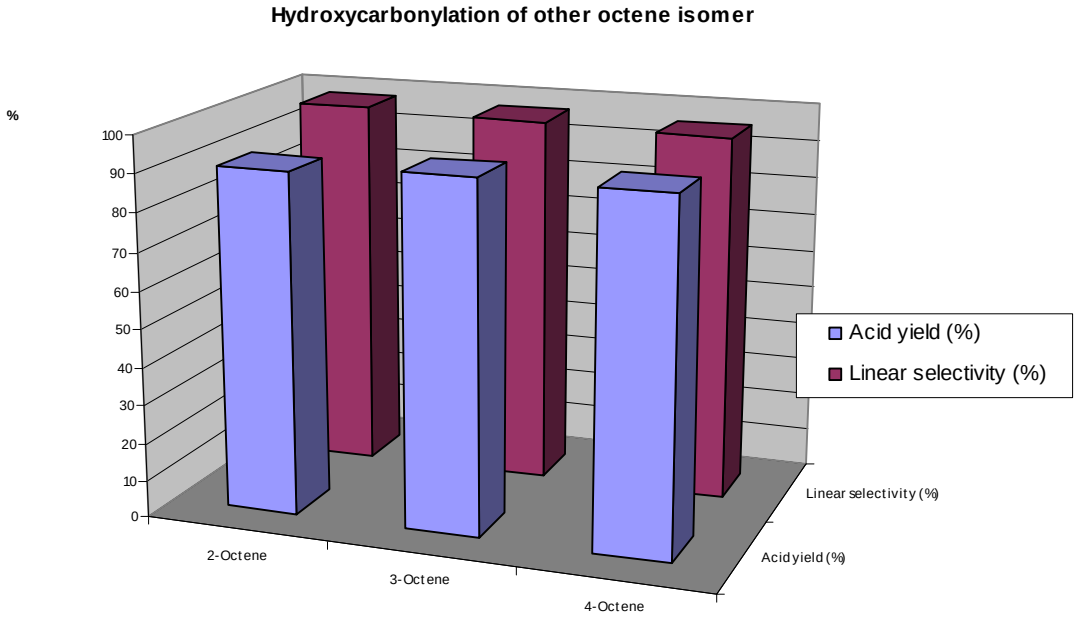
Good result in terms of yield and selectivity have been obtained (Table 2.13, entries 1, 2 and 3), including in the internal 4-octene, which were similar to the results obtained in the case of 1-octene.

Table 2.13. Hydroxycarbonylation of other octene isomers.



Entry	Solvent	Acid yield (%)	Linear selectivity (%)
1	2-Octene	90	98
2	3-Octene	92	97
3	4-Octene	92	96

Conditions: Octene (1 mL, 6.37 mmol), $PdCl_2$ (32 mg, 0.19 mmol), BDTBPMB (82 mg, 0.21 mmol), toluene (10 mL), water (2 mL), P_{CO} (70 bar), 80ºC, 5 h



2.2.1.9.- Hydroxycarbonylation of Other Alkenes.

Two other interesting alkenes, 2-methyl-pent-2-ene and styrene, have been tested under hydroxycarbonylation conditions. The results are shown in Table 2.14.

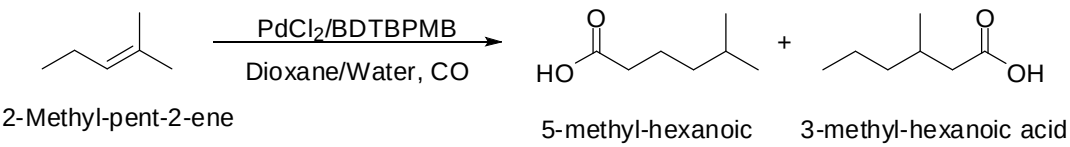
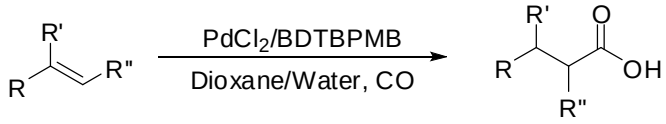


Fig 2.23. *Hydroxycarbonylation of 2-methyl-pent-2-ene*

2-Methyl-pent-2-ene is particularly interesting to examine the limits of the process. This substrate presents a highly hindered internal double bond (Figure 2.23). Hence, the

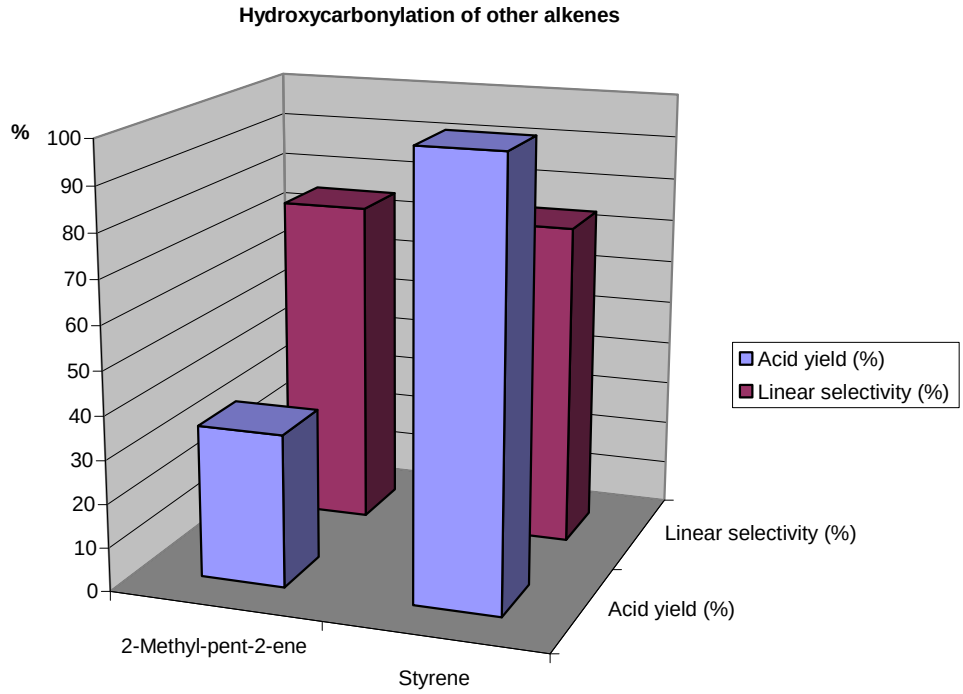
isomeration route is appreciably more difficult than in the case of octene isomers. Likewise, the carbonylation of an external double bond can take place in two positions, one which generates 3-methylhexanoic acid, which is more hindered than the one which generates 5-methylhexanoic acid. Hence, yield and 3-methylhexanoic acid/5-methylhexanoic acid selectivity can give evidence on how difficult the isomerization of internal alkenes is and also the carbonylation preference between the two external positions.

Table 2.14. Hydroxycarbonylation of other alkenes.



Entry	Solvent	Acid yield (%)	Linear selectivity (%)
1	2-Methyl-pent-2-ene	35	75[a)]
2	Styrene	100	74

Conditions: Alkene (6.37 mmol), $PdCl_2$ (32 mg, 0.19 mmol), BDTBPMB (82 mg, 0.21 mmol), toluene (10 mL), water (2 mL), P_{CO} (70 bar), 80ºC, 5 h. a) Selectivity 5-methyl-hexanoic/3-methyl-hexanoic acid.



The reaction yielded moderate conversion (35 %) and 5-methylhexanoic acid/3-methylhexanoic acid selectivity of 3:1 (Table 2.14, entry 1). This result, although understandable considering the high steric effects presented in the substrate, is significantly lower than the results obtained for methoxycarbonylation, where these kinds of substrates yielded high conversion and selectivities.[47]

The synthesis of isoprofen via hydroxycarbonylation is a desirable synthetic route (see Section 2.1.4). However, the electronic effects of the phenyl ring present in styrene plays an important role in the selectivity and reactivity of this substrate. Usually a mixture of the desired branched product and linear product is obtained.[48]

When styrene was tested under normal hydroxycarbonylation conditions, full conversion was obtained. However, the system presented a marked preference for the linear isomer (74 %, Table 2.14, entry 2).

2.2.1.10.- Hydroxycarbonylation of Unsaturated Carbonyl Compounds.

Carbonylation of unsaturated carbonyl compounds is a process in industrial chemistry which is becoming important. The possibility of the preparation of essential difuncionalized monomers for plastic manufacture, such as adipic acid or hexanedioic acid, via carbonylation is generating high hopes in industry.

For example, as Section 1.3.1.3 shows, the generation of adipic acid, (essential for the production of polyester), can be addressed by the hydroxycarbonylation of 1,3-butadiene. This route involves two hydroxycarbonylation steps. The first consists of the preparation of pentenoic acid, which reacts in the second step to generate the adipic acid (Fig 2.24).

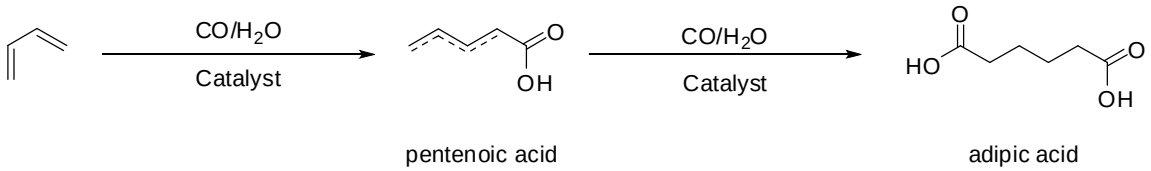


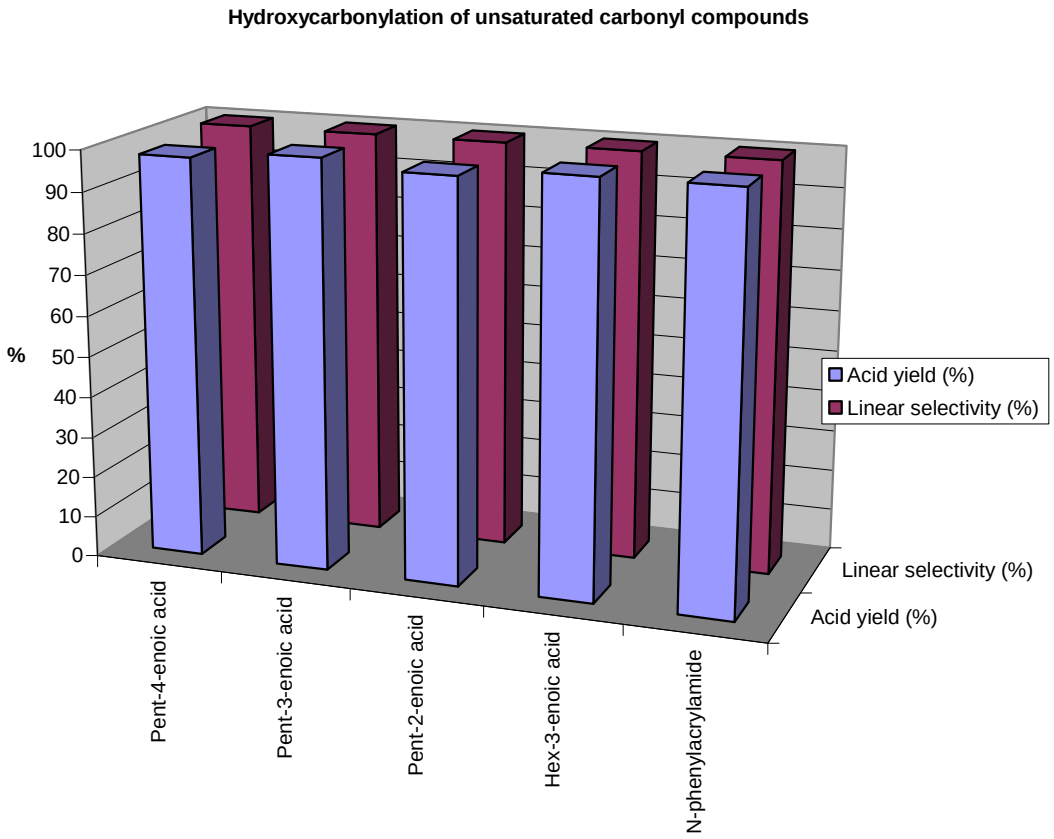
Fig 2.24.*Generation of adipic acid via two hydroxycarbonylation steps.*

Therefore the study of possible routes to the generation of difuncionalized products is highly desirable for industrial applications. Three isomers of pentenoic acid, oleic acid and N-phenylpentamide have been tested under normal hydroxycarbonylation conditions and the results have been summarised in Table 2.15

Table 2.15. Hydroxycarbonylation of unsaturated carbonyl compounds.

Entry	Alkene	Time (h)	Acid yield (%)	Linear selectivity (%)
1	Pent-4-enoic acid	5	98	100
2	Pent-3-enoic acid	5	100	100
3	Pent-2-enoic acid	5	98	100
4	Hex-3-enoic acid	5	100	100
5	Methyl oleate	5	0	-
6	Methyl oleate	24	0	-
7	N-phenylacrylamide	5	100	100

Conditions: Alkene (6.37 mmol), $PdCl_2$ (32 mg, 0.19 mmol), BDTBPMB (82 mg, 0.21 mmol), toluene (10 mL), water (2 mL), P_{CO} (70 bar), 80ºC, 5h.



Pent-4-enoic acid yielded excellent conversion and selectivity to adipic acid (Table 2.15, entry 1). Similar conversions and yields have been obtained for internal isomers of pentenoic acid, such as pent-3-enoic acid (Table 2.15, entry 2).

Certainly the conjugative stabilisation presents in α,β-unsaturated acids, such as pent-2-enoic acid, can affect the reactivity of these substrates. However, under hydroxycarbonylation conditions, pent-2-enoic acid yielded similar results in terms of yield and selectivity, as the other pentenoic isomer. Only adipic acid was obtained (Table 2.15, entry 3). Other saturated acids such as hex-3-enoic acid gave similar yields and selectivities as the pentenoic acid (Table 2.15, entry 4).

Unexpectedly, considering the excellent results obtained in the generation of α,ω-diesters from methyl oleate via methoxycarbonylation (Fig 1.34),[49] methyl oleate seemed to be inert under normal hydroxycarbonylation conditions (Table 2.15, entry 5). A longer reaction time did not give any improvement in the results (Table 2.15, entry 6).

Hydroxycarbonylation of *N*-phenylacrylamide led to the formation of N-phenylsuccinimide with good yield (Table 2.15, entry 7). This result is understandable considering a plausible mechanism in two steps. Initially, hydroxycarbonylation to generates 4-oxo-4-(phenylamino)butanoic acid, which under goes cyclisation to give the final product, *N*-phenylsuccinimide (Fig 2.25).

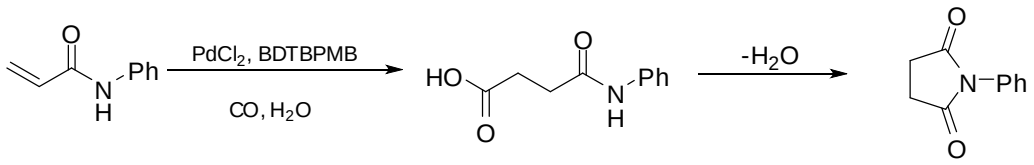


Fig 2.25. *Pausible mechanism for the generation of N-phenylsuccinimide from N-phenylacrylamide.*

2.2.1.11.- [BDTBPMBH$_2$][BF$_4$]$_2$: an Air-stable Alternative to the Use of BDTBPMB.

The manipulation on the laboratory scale of highly air sensitive ligands, such as BDTBPMB, is very often tedious and requires special equipment such as a glove box.

Hence, the use of air stable ligands is highly desirable in laboratories. However, in carbonylation air-sensitive ligands tend to be more active than air-stable ones.

It is, indeed, highly desirable to generate homologues of highly air sensitive ligands which keep their high activity, but are capable of being manipulated in the presence of air. In this area, Fu and co-workers have described $[P^tBu_3H][BF_4]$ as an interesting alternative to the use of P^tBu_3 which is high air sensitive. $[P^tBu_3H][BF_4]$ has proven to be as efficient as P^tBu_3 in cross-coupling and Heck reactions.[50] Fu described the high air stability of $[P^tBu_3H][BF_4]$ which can be stored for a number of months without any sign of oxidation.

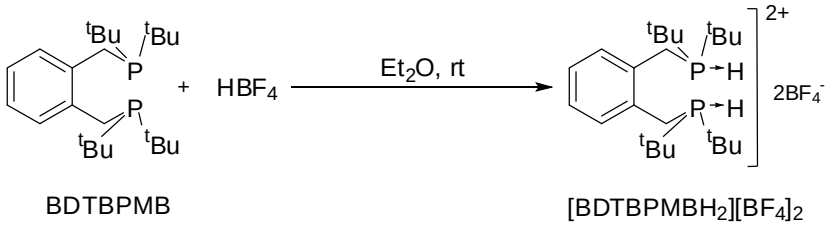


Fig 2.26. *Generation of $[BDTBPMBH_2][BF_4]_2$*

It is assumed that the excellent quality in regards to air stability present in $[P^tBu_3H][BF_4]$ can be extended to other air sensitive ligands such as BDTBPMB.

The addition of tetrafluoroboric acid to a solution of BDTBPMB in diethyl ether instantly gave a white solid, $[BDTBPMBH_2][BF_4]_2$ (Fig 2.26), which was quite insoluble in most common solvents. This made purification easy by washing with diethyl ether and acetone.[51]

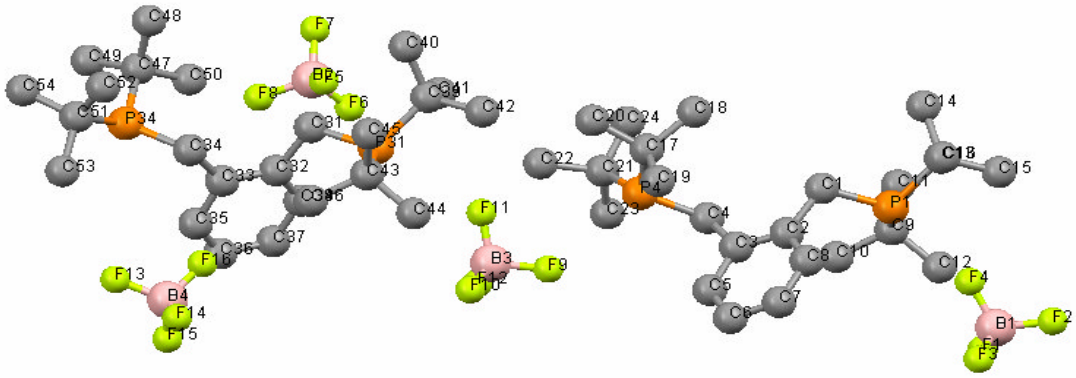


Fig 2.27. *X-Ray structure of $[BDTBPMBH_2][BF_4]_2$ (Hydrogen atoms omitted for clarity).*[44]

$[BDTBPMBH_2][BF_4]_2$ has proven to be stable in the solid state for long periods of time (>3months) however, it is quickly oxidised in solution. $^{31}P-\{^1H\}$-NMR showns a broad peak at 44.7 ppm which may correspond to a P-H bond. This hypothesis was corroborated by X-Ray crystallography (Fig 2.27).

The structure of $[BDTBPMBH_2][BF_4]_2$ contains two independent molecules in the asymmetric unit. The bond lengths and angles are within normal ranges. The phosphorus atoms lie above and below the aryl ring [values for second independent molecule in parentheses] P(1) 1.57(1) [1.52(1)] P(4) -1.66(1) [-1.54(1)] Å, the P..P separation is > 6 Å. The P-H hydrogen atoms interact with the $[BF_4]^-$ anions : H1 - F4 2.40(3), P1 - H1 - F4 140.1; H4 - F9 2.32(2) P4 - H4 - F9 157.0; H31 - F11 2.44(4) P31 - H31 - F11 139.5; H34 - F2' 2.30(3) P34 - H34 - F2' 148.8. This interaction P-H-$[BF_4]^-$ (Fig 2.28) is the cause of the high insolubility of $[BDTBPMBH_2][BF_4]_2$.

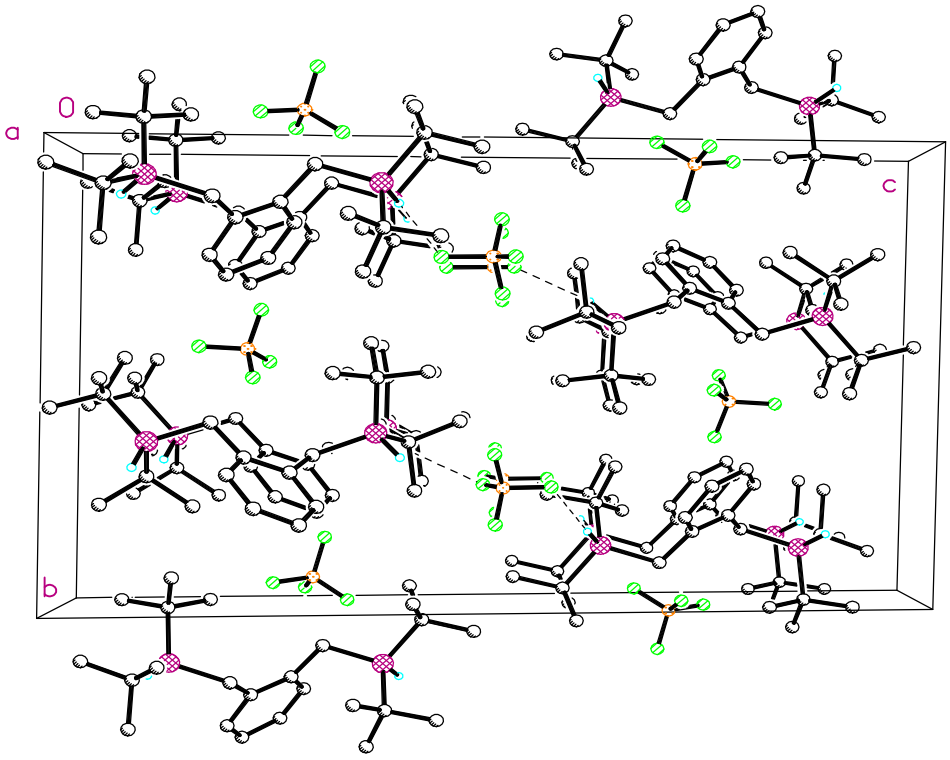


Fig 2.28. *P-H hydrogen atoms interact with the $[BF_4]^-$ anions in the $[BDTBPMBH_2][BF_4]_2$ net.*[44]

This phosphonium salt was active in hydroxycarbonylation giving similar results to BDTBPMB (Fig 2.29).

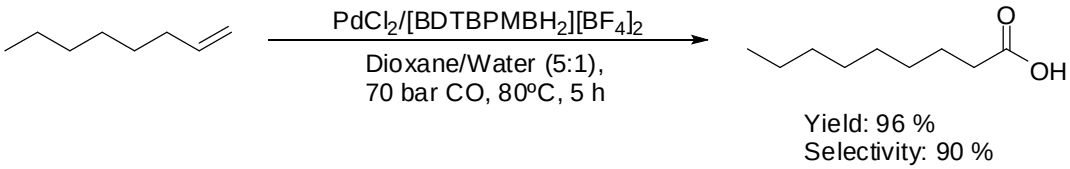


Fig 2.29. *Hydroxycarbonylation of alkene under catatysis of $PdCl_2$/[$BDTBPMBH_2$][BF_4]$_2$*

2.2.2.- Aminocarbonylation of Alkenes.

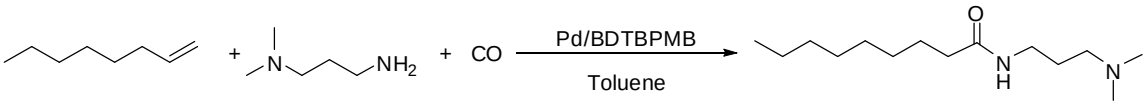
Aminocarbonylation of alkenes is becoming important as a route to generate amides (See Section 2.1.5). Hence, it is interesting to know if the system formed by a palladium complex of BDTBPMB will be active in this kind of reaction.

The preliminary results in this area did not show good activities.[52] High loadings of catalyst and a long reaction time were required to yield high conversions. The use of a promoter was proposed as an option to improve the results.[34b,35] Therefore, the main focus has been the study of promoters in the aminocarbonylation of alkenes. However, it should be noted that the concept of aminocarbonylation as the generation of an amide from an alkene, carbon monoxide, and an amine. However, the behaviours of anilines (arylamines) and alkylamines are evidently different for example, in regard to their basicity (pKas of aniline and butylamine are 4.6 and 10.7 respectively)[39] and nucleophilicity. Hence, this study has been divided into two Sections - aminocarbonylation of alkenes using alkylamines, and the use of anilines.

2.2.2.1.- Aminocarbonylation of Alkenes using Alkylamines.

2.2.2.1.1.- Preliminary Results.

Table 2.16. Preliminary results of the aminocarbonylation of alkenes using alkylamines



Entry	Pd compound	Additive	Additive 2	T	Yield	Linear Selectivity	TON
1	$[Pd(OAc)_2]$	PhOH	NaCl	140	0	-	-
2	$[Pd(MeCN)_2Cl_2]$	PhOH	NaCl	140	0	-	-
3	$[Pd(OAc)_2]$	PhOH	NaI	140	0	-	-
4	$[Pd(MeCN)_2Cl_2]$	PhOH	NaI	140	0	-	-
5	$[Pd(OAc)_2]$	N-methylimidazol	NaI	140	0	-	-
6	$[Pd(MeCN)_2Cl_2]$	N-methylimidazol	NaI	140	0	-	-
7	$[Pd(OAc)_2]$	*p*-cyanophenol	NaI	120	0	-	-
8	$[Pd(OAc)_2]$	2-Naphthol	NaI	120	36	100	180
9	$[Pd(MeCN)_2Cl_2]$	2-Naphthol	NaI	120	0	-	-
10	$[Pd_2dba_3]$	2-Naphthol	NaI	120	0	-	-
11	$[Pd(OAc)_2]$	1-Naphthol	NaI	120	0	-	-
12	$[Pd(OAc)_2]$	Methyl 3-hydroxy-2-naphthoate	NaI	120	0	-	-

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12.74 mmol), Pd (0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), additive (6.37 mmol), additive 2 (0.0637 mmol), P_{CO}=20 bar, toluene (10 mL), 120ºC, 1 h.

As Fig 2.15 and 2.16 show, two nucleophilic promoters, imidazol and arylalcohol, have been reported to be quite active in aminocarbonylation.[34b,35] The use of phenol and sodium chloride as promoters did not yield any conversion in the aminocarbonylation of octene, catalysed by Pd/BDTBPMB (Table 2.16, entries 1 and 2). The replacement of sodium chloride for sodium iodide, or the use of N-methylimidazol or cyanophenol instead of phenol, did not give any significant changes (Table 2.16, entries 3 to 7). However, the use of a combination of 2-naphthol/sodium iodide as promoters yielded a moderate conversion and TON at 120ºC (Table 2.16, entry 8). Replacing of $[Pd(OAc)_2]$ by $[Pd(MeCN)_2Cl_2]$ or $[Pd_2dba_3]$ completely blocked the system, and no conversion was obtained (Table 2.16, entry 9 and 10).[53] Surprisingly, when the promoter was changed and

1-naphthol was used, no conversion was obtained (Table 2.16, entry 11). This result may be explained by a slight increase in steric effects present in 1-naphthol. Electron-withdrawing groups, such as esters, completely blocked the route (Table 2.16, entry 12).

Table 2.17. Blank assays in the aminocarbonylation of octene

Entry	Amine	Naphthol	NaI	MSA	Yield	Linear Selectivity	TON
1	3-dimethylamino-1-propylamine (1 eq)	-	0.5%	1.2 %	0	0	0
2	3-dimethylamino-1-propylamine (1 eq)	1 eq	-	1.2 %	0	0	0
3	3-dimethylamino-1-propylamine (1 eq)	1 eq	0.5 %	-	0	0	0
4	-	1 eq	0.5%	1.2 %	1[a]	100	5

Conditions: Octene (2 mL, 12.74 mmol), amine (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), naphthol (as described), NaI (as described), P_{CO}=20 bar, toluene (10 mL), 140ºC, 1 h. a) Naphthalen-2-yl nonanoate

For a better understanding of the role played by promoters and if they are essential in the activity, a succession of blank assays have been carried out (Table 2.17). In the absence of 2-naphthol or sodium iodide, no conversion was obtained (Table 2.17, entries 1 and 2).[54]

Usually, a non-coordinanting acid, such as methanesulfonic acid (MSA), is added to the solution to generate the initial palladium hydride species (See Section 2.1.2). Therefore, it is plausible to think that in the absence of this *initiator* no conversion will be obtained. An experimental assay confirmed this hypothesis (Table 2.17, entry 3).

When only 2-naphthol was used in the medium (no amine) traces of naphthalen-2-yl nonanoate were obtained (Table 2.17, entry 4). The formation of this product is easily understandable considering that, in absence of amines, the alkoxycarbonylation route to generate naphthalen-2-yl nonanoate is the only possible reaction which can take place (Fig 2.30).

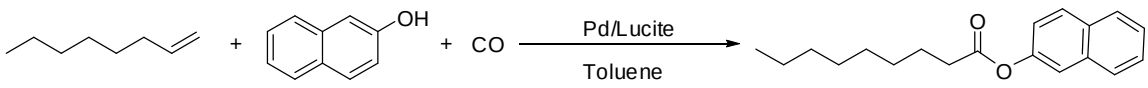


Fig 2.30. *Formation of naphthalen-2-yl nonanoate via alcoxycarbonylation*

This result may confirm the hypothesis of the role of nucleophilic promoters, as proposed by Beller and Hallberg (see Fig 2.17).[35] Hence a possible role of 2-naphthol is as an intermediate in the synthesis of amides. Therefore, the acylpalladium species (**6**) may react with 2-naphthol to generate naphthalen-2-yl nonanoate, along with the hydride palladium species (**3**), which can start another catalytic cycle. Naphthalen-2-yl nonanoate may then react with the amine in an amide/ester exchange to regenerate 2-naphthol and generate the corresponding amide (Fig 2.31).

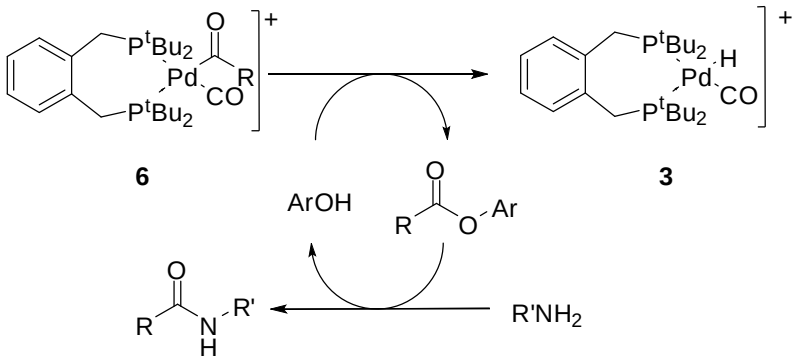


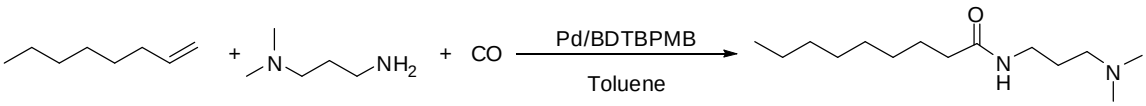
Fig 2.31. *Possible role of 2-naphthol in the amidocarbonylation of 1-octene.*

2.2.2.1.2.- Effect of Temperature on the Aminocarbonylation of Octene.

As Section 2.2.1.1 shows, the temperature may be considered one of the most important variables in an industrial process. This variable can affect aspects such as the cost of production, rates of reaction and the stability of the catalyst. Therefore, this variable should be studied. A study of three temperatures has been carried out and the results are summarised in Table 2.18.

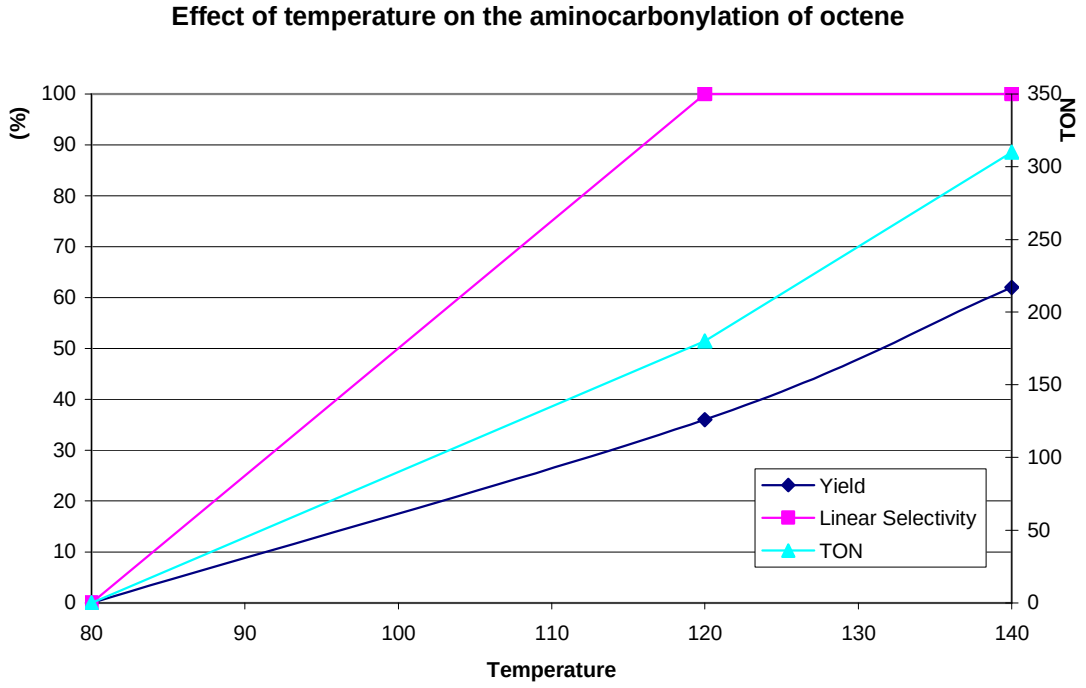
When the reaction was run at low temperatures (80ºC), no conversion was obtained (Table 2.18, entry 1). An increase in temperature to 120ºC raised the TON up to 180 moles product/mole catalyst (Table 2.18, entry 2). This positive effect of temperature was more notable at 140ºC where the reaction yielded high conversion and selectivity (Table 2.18, entry 3). Surprisingly, although the temperature of this last reaction (140ºC) was quite high, no deactivation of the catalyst in the form of palladium black was observed.

Table 2.18. Effect of temperature on the aminocarbonylation of octene.



Entry	T (ºC)	Yield	Linear Selectivity	TON
1	80	0	0	0
2	120	36	100	180
3	140	62	100	310

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (912 mg, 6.37 mmol), NaI (9.5 mg, 0.0637 mmol), P_{CO}=20 bar, toluene (10 mL), 1 h.

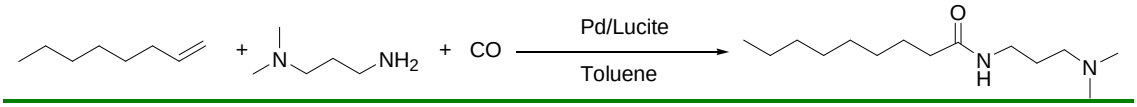


2.2.2.1.3.- Study on the Effects of the Variation of Naphthol Concentration on Aminocarbonylation.

At higher promoter concentration, the positive promoter effect may become a negative role in the reaction.[13] Hence, the promoter concentration is an interesting area to study, especially in this particular case because, according to the plausible mechanism of

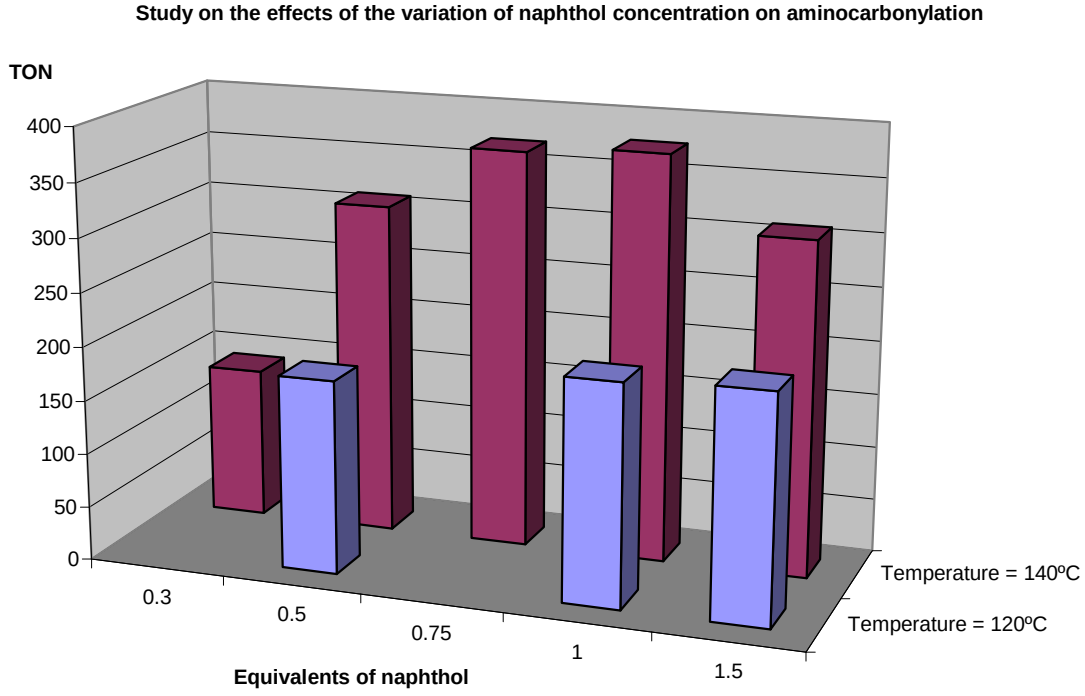
the promoter (Fig 2.31), the promoter may be involved in the rate determining step which is the reaction of the acyl-palladium intermediate with the nucleophile (Fig 2.3).[55]

Table 2.19. Study on the effects of the variation of naphthol concentration on aminocarbonylation.



Entry	Temperature	Naphthol equivalent	Yield	Linear Selectivity	TON
1	120	0.5	36	100	180
2	120	1	41	100	205
3	120	1.5	42	100	210
4	140	0.30	29	100	141
5	140	0.5	65	100	310
6	140	0.75	74	100	370
7	140	1	76	100	377
8	140	1.5	65	100	310

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (as described), NaI (9.5 mg, 0.0637 mmol), P_{CO}=20 bar, toluene (10 mL), 1 h.



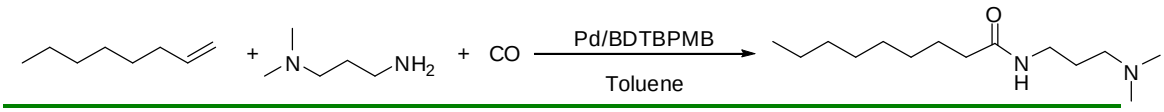
Hence, to find the optimum concentration of naphthol a study has been carried out at two temperatures, 120ºC and 140ºC. The results of these studies are shown in Table 2.19. Moderate conversion was obtained at 120ºC using 0.5 equivalents of naphthol per equivalent of octene (Table 2.19, entry 1).

A slight difference in TON was observed when the concentration of naphthol in the medium was increased (Table 2.19, entries 2 and 3). Surprisingly, although at 120ºC the concentration of naphthol did not have a significant effect, when the reaction was carried out at 140ºC a positive effect was observed in an increase of concentration of naphthol. Hence, the use of 0.3 equivalents of naphthol per equivalent of octene gave moderate conversion (Table 2.19, entry 4), the conversion was increased by the use of 0.5 equivalents of naphthol (Table 2.19, entry 5). This effect is at its highest when the concentration of naphthol was 0.75 or 1.0 equivalents (Table 2.19, entries 6 and 7). A further increase in concentration of naphthol yielded a slight drop in conversion (Table 2.19, entry 8).

2.2.2.1.4.- Study of the Effects of the Variation of Amine Concentration on Aminocarbonylation.

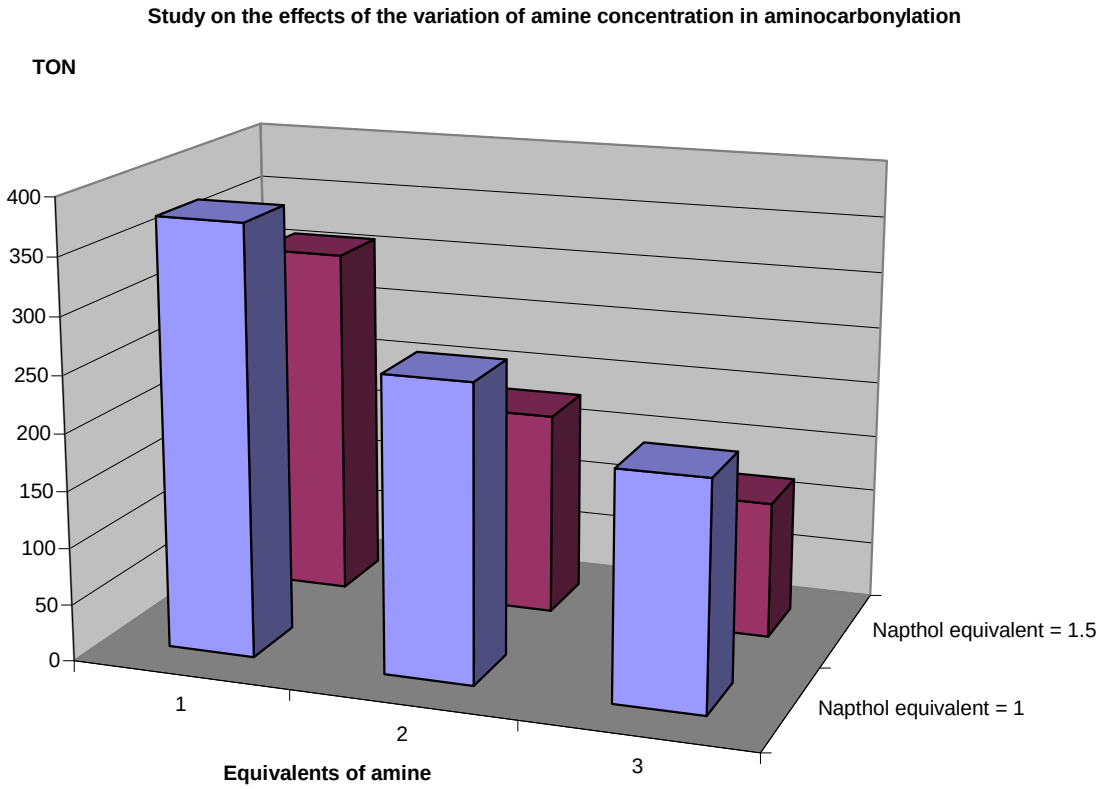
It has been proven that the rate determining step in carbonylation is the reaction of the nucleophile with the acylpalladium species (See Fig 2.3).[55] Therefore, it is acceptable to believe that a higher nucleophile concentration (in this case an amine) would increase the reaction rate. However, according to the plausible role of the promoter (see Fig 2.31), the rate may not be dependent on the nucleophile concentration. Hence, it is interesting to study how the concentration of amine may affect the reaction.

Table 2.20. Study on the effects of the variation of amine concentration in aminocarbonylation.



Entry	Amine equivalent	Naphthol equivalent	Yield	Linear Selectivity	TON
1	1	1	76	100	377
2	2	1	52	100	260
3	3	1	40	100	200
4	1	1.5	65	100	310
5	2	1.5	39	100	180
6	3	1.5	36	100	121

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (as described), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (as described), NaI (9.5 mg, 0.0637 mmol), P_{CO}=20 bar, toluene (10 mL), 140ºC, 1 h.



The effect of the amine concentration on the reaction has been studied. For a better understanding of this effect this study has been carried out at two different concentrations of naphthol, -1 and 1.5 equivalents of naphthol per equivalent of octene-.

Both set of conditions (using 1 or 1.5 equivalent of naphthol) gave the same surprising trend. While high conversion was achieved by the use of one equivalent of amine (Table 2.20, entries 1 and 4), an excess of this amine significantly lowered the activity of catalyst (Table 2.20, entry 2 and 5). This negative role was more evident when 3 equivalents of amine were used (Table 2.20, entry 3 and 6).

To explain this unusual trend the deprotonation of the active hydride species (**1**) by the highly basic amine should be taken into consideration (Fig 2.32). This route is in essence an acid-base equilibrium. Therefore an increase in the concentration of the base may move this equilibrium completely to the right. This fact may explain why an increase in the amine concentration led to a drop in activity.

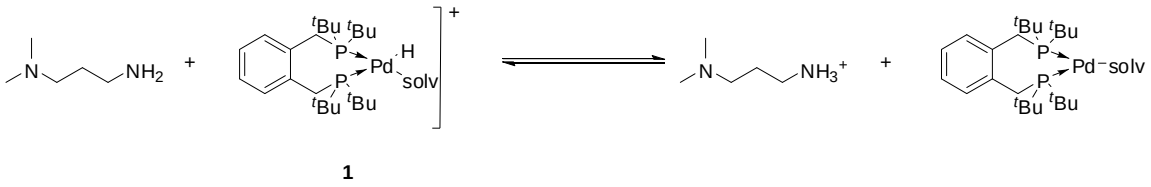


Fig 2.32. *Destruction of the active species for a highly basic amine.*

2.2.2.1.5.- The Effect of Pressure on the Aminocarbonylation of Octene.

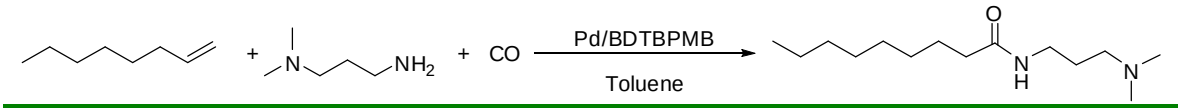
As Section 2.2.1.2 shows, the cost of the equipment, and therefore the cost of the plant is highly dependent on the pressure required in the process. Hence, a study to find the optimum pressure is required.

This study was carried out in a pressure range between 10 bar and 50 bar, and the results are summarised in Table 2.21.

Under low pressure (10 bar) moderate conversion was obtained (Table 2.21, entry 1). The maximum conversion was obtained when the reaction was carried out under 20 bar of carbon monoxide (Table 2.21, entry 2). An increase in pressure to 40 bar gave lower

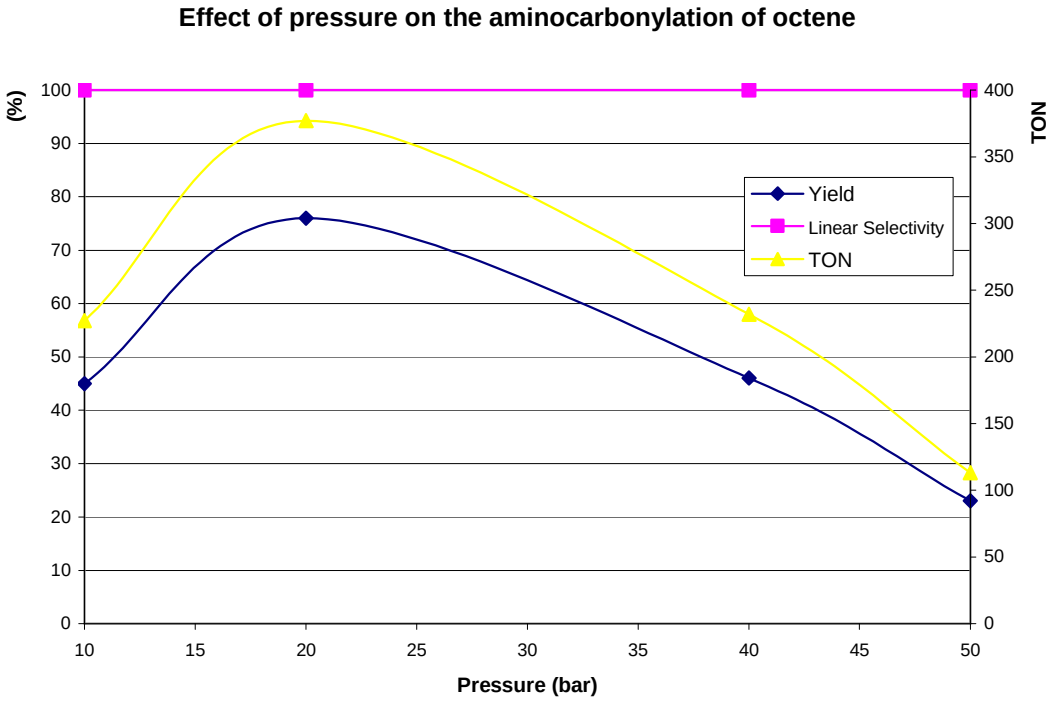
conversion (Table 2.21, entry 3). This negative effect was more marked when 50 bar of carbon monoxide were used (Table 2.21, entry 4).

Table 2.21. Effect of pressure on the aminocarbonylation of octene.



Entry	Pressure	Yield	Linear Selectivity	TON
1	10	45	100	227
2	20	76	100	377
3	40	46	100	232
4	50	23	100	113

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.8 g, 12.74 mmol), NaI (9.5 mg, 0.0637 mmol), toluene (10 mL), 140ºC, 1 h.

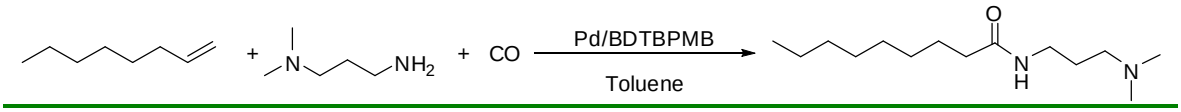


Two trends with different characteristics can be seen -one at low pressures (10 to 20 bar) which presents a positive pressure effect, increasing the conversion when the pressure is increased. This trend is similar to the results reported in alkoxycarbonylation where a positive role of carbon monoxide was observed,[2,22] and also in hydroxycarbonylation (see

Section 2.2.1.2). Above 20 bar, this positive trend changed drastically, giving a negative pressure effect. This trend is very unusual in these kinds of carbonylation, however it is the most commonly described trend in other carbonylation such as hydroformylation.[56]

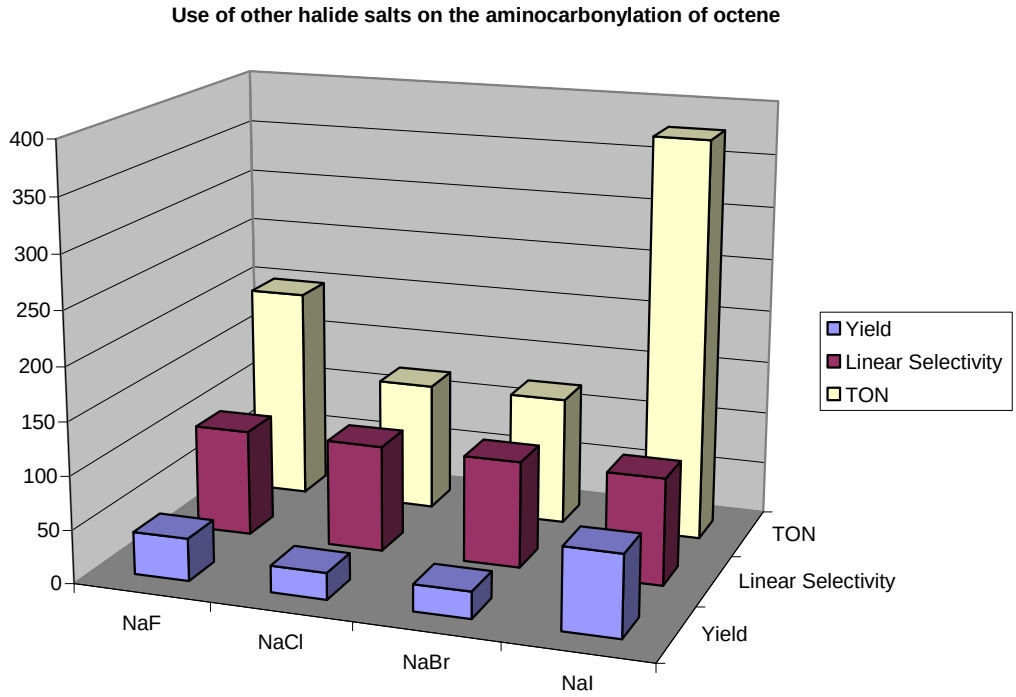
2.2.2.1.6.- Use of Other Halide Salts on the Aminocarbonylation of Octene.

Table 2.22. Use of other halide salts on the aminocarbonylation of octene



Entry	Halide salt	Yield	Linear Selectivity	TON
1	NaF	40	100	200
2	NaCl	25	100	121
3	NaBr	25	100	121
4	NaI	76	100	377

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.8 g, 12.74 mmol), MX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



The combination of naphthol and sodium iodide has proven quite effective in the aminocarbonylation of octene. For a better understanding of the reaction, other halide salts were tested and their results are shown in Table 2.22.

The use of NaCl or NaBr gave a significant decrease in regards to the conversion (Table 2.22, entries 2 and 3). This may be explained by considering a hypothetical Metal-X bond (where X means halide). Metal-I would be expected to be the strongest Metal-X bond and, hence, iodide is the halide which can donate the most electron density via σ-bond donation (Fig 2.33).[54a]

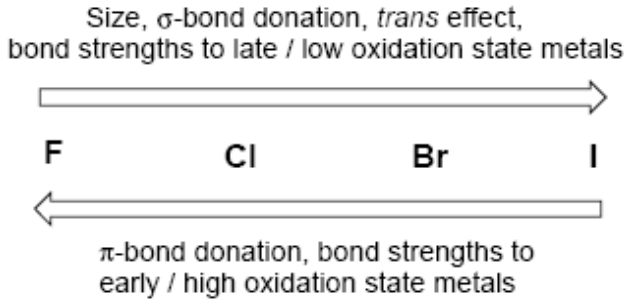


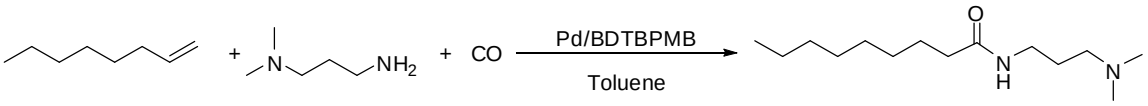
Fig 2.33. *Trends in the halide effect.*[55a]

Surprisingly, when sodium fluoride was used, moderate conversion was obtained (Table 2.22, entry 1). This conversion is significantly higher than the conversion obtained with sodium chloride or bromide. To understand this behaviour in the halide effect, where NaF and NaI present a positive effect while NaBr and NaCl present a negative effect, electronic effects of the Metal-X species must be taken into consideration.

It is well known that fluoride is the smallest halide. So, it is expected that Metal-F presents an important π-bond donation (Fig 2.33).[54] Likewise, iodide is the strongest σ-donating halide. Both, π-donation and σ-donation can affect the electronic density of the metal by increasing it. An increase in the electronic density at the metal may make it more reactive.

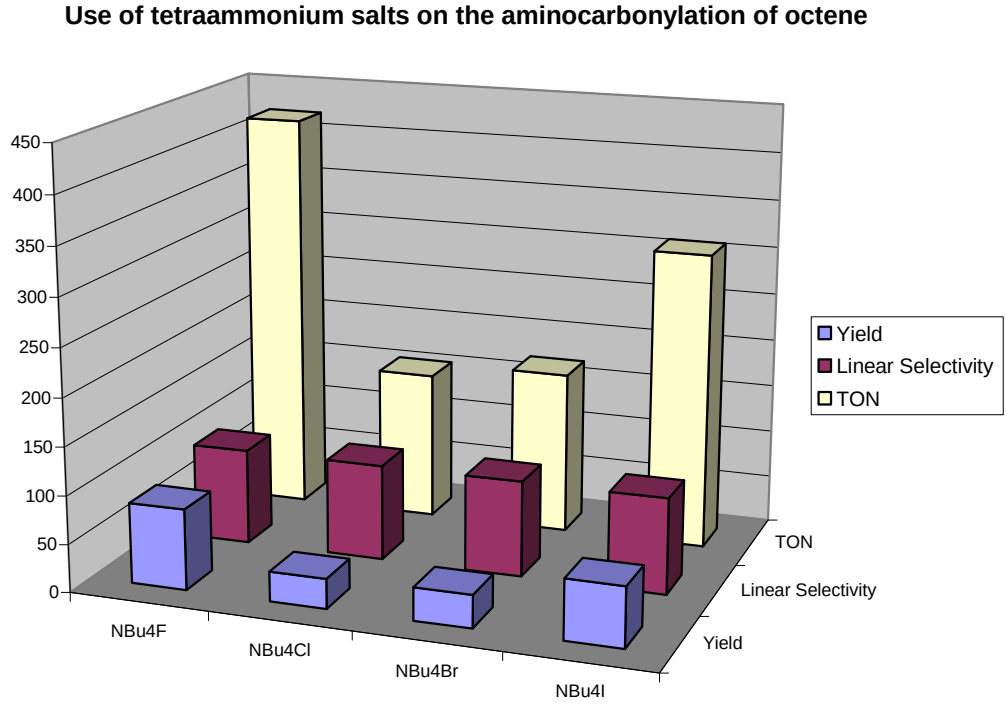
2.2.2.1.7.- Use of Tetraammonium Salts on the Aminocarbonylation of Octene.

Table 2.23. Use of tetraammonium salts on the aminocarbonylation of octene.



Entry	Ammonium salt	Yield	Linear Selectivity	TON
1	NBu_4F	84	100	420
2	NBu_4Cl	31	100	155
3	NBu_4Br	34	100	170
4	NBu_4I	62	100	310

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), 2-naphthol (1.8 g, 12,74 mmol), NBu_4X(0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



It is well known sodium ions are hard cations. Very often, hard compounds and soft compounds give different results and effects. This discrepancy between hard and soft substrates has been explained by considering the dissociation equilibrium which is higher

in hard salts, and also a benefit in the combination of soft compounds with soft compounds and hard compounds with hard compounds.

It is interesting to know if the use of halide salts of soft cations may result in a significant difference in aminocarbonylation. Tetrabutylammonium halides are quite common compounds and were chosen for this study, with the results summarised in Table 2.23.

The same trends reported in Section 2.2.2.1.6 were obtained when the sodium halide salts were replaced by tetrabutylammonium salts. NBu_4I and NBu_4F (Table 2.23, entries 1 and 4) give a more intensive effect than that obtained in the case of NBu_4Cl and NBu_4Br (Table 2.23, entries 2 and 3).

Therefore, it can be concluded that the positive effect of halides in aminocarbonylation under these conditions is not depended on the cation of the salts.

2.2.2.1.8.- Aminocarbonylation of Octene in Other Solvents.

Solvents are often ignored as important influences in processes. Usually different solvents present different effects on the reaction, due to different polarities, affinities and coordinating properties. Therefore, different solvents were tested under aminocarbonylation conditions and the results are shown in Table 2.24.

The replacement of the usual aminocarbonylation solvent (toluene) for a more polar solvent, such as dimethylsulfoxide, gave a complex mixture of products (Table 2.24, entry 1). No conversion to amide was observed in this reaction. The catalytic complex was unstable under these conditions by formation of Palladium black.

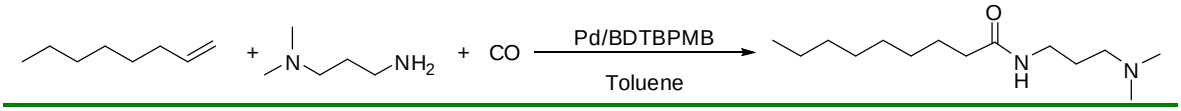
o-Dichlorobenzene is expected to be similar to toluene because both are aromatic. However, the two chloro atoms in *o*-dichlorobenzene give this molecule a higher polarity than toluene. This polarity may play a significant role in the reaction.

When the aminocarbonylation reaction was carried out in *o*-dichlorobenzene, it resulted in high conversion (Table 2.24, entry 2), but slightly lower than the obtained results in toluene (Table 2.24, entry 1).

Highly coordinating solvents such as acetonitrile gave a decrease in conversion, possibly due to a strong coordination between the acetonitrile and the palladium complex, which may therefore block the route (Table 2.24, entry 3).

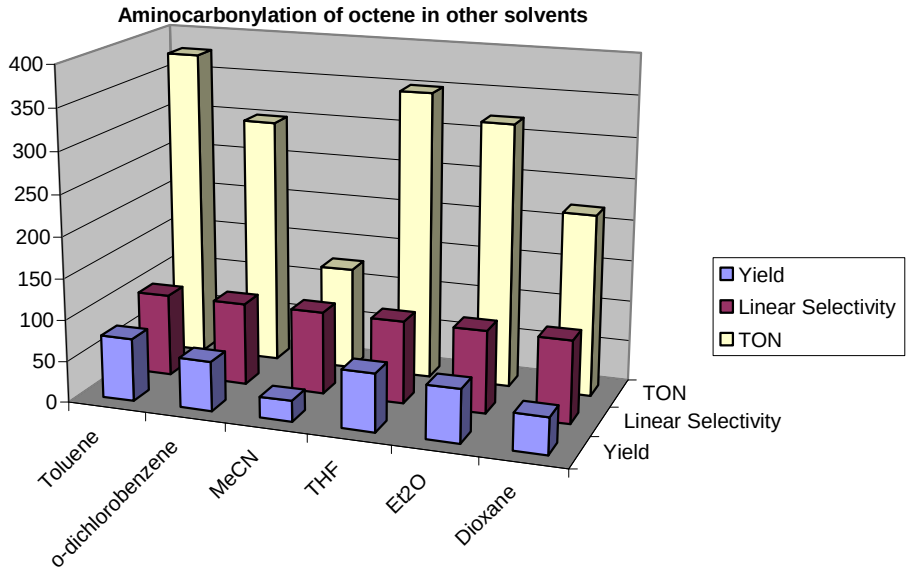
Ethereal solvents such as tetrahydrofuran, and diethyl ether gave high conversion, although slightly lower than toluene (Table 2.24, entries 4 and 5). When dioxane was used, only moderate conversion was obtained (Table 2.24, entry 6).

Table 2.24. Aminocarbonylation of octene in other solvents.



Entry	Solvent	Yield	Linear Selectivity	TON
1	Toluene	76	100	377
2	DMSO	-	-	-
3	o-dichlorobenzene	60	100	300
4	MeCN	25	100	125
5	THF	70	100	350
6	Et_2O	64	100	320
7	Dioxane	44	100	220

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.8 g, 12,74 mmol), NaI (9.5 mg, 0.0637 mmol), solvent (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



2.2.2.1.9.- Aminocarbonylation of Octene in Methanol.

To examine the limitations of this process to prepare amides, a series of reactions in methanol were carried out, as summarised in Table 2.25. Methanol is highly reactive in carbonylation reactions giving the methyl ester. Therefore, with both nucleophiles (methanol and 3-dimethylamino-1-propylamine) one might expect to obtain mixtures of esters and amides from methoxycarbonylation or aminocarbonyatlion respectively (Fig 2.34).

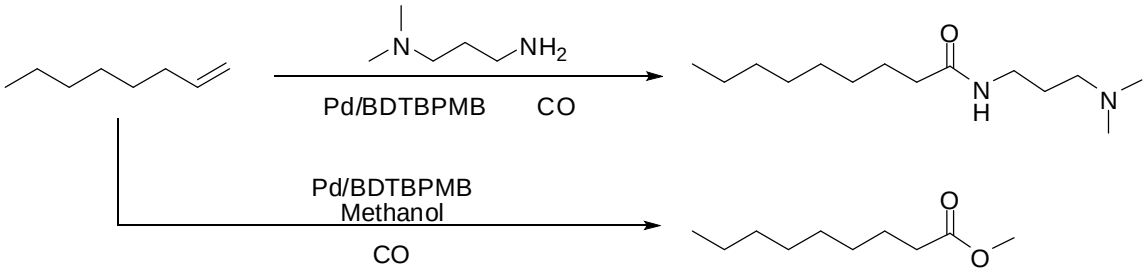


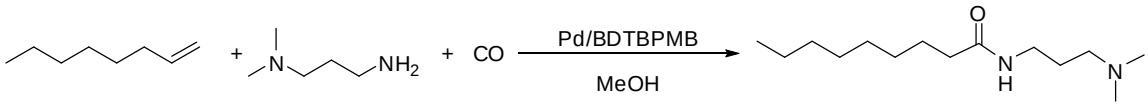
Fig 2.34. *Aminocarbonylation of octene in methanol***.**

Likewise, it should be noted that palladium complexes of BDTPMB have been proven extremely active in methoxycarbonylation.[46,47,57] High conversion and selectivities under mild conditions and a low concentration of palladium are observed in this well studied process. Hence, to obtain amides, aminocarbonylation under the described conditions may be as powerful as methoxycarbonylation, and the measurement of this will depend of the amount of ester and amide obtained.

When the reaction was carried out under typical aminocarbonylation conditions (Table 2.19, entry 7), replacing toluene for methanol, surprisingly, only amide was obtained. The yield was slightly lower than the normal aminocarbonylation (Table 2.25, entry 1). No notable difference was obtained when NaF was used instead of NaI (Table 2.25, entry 2).

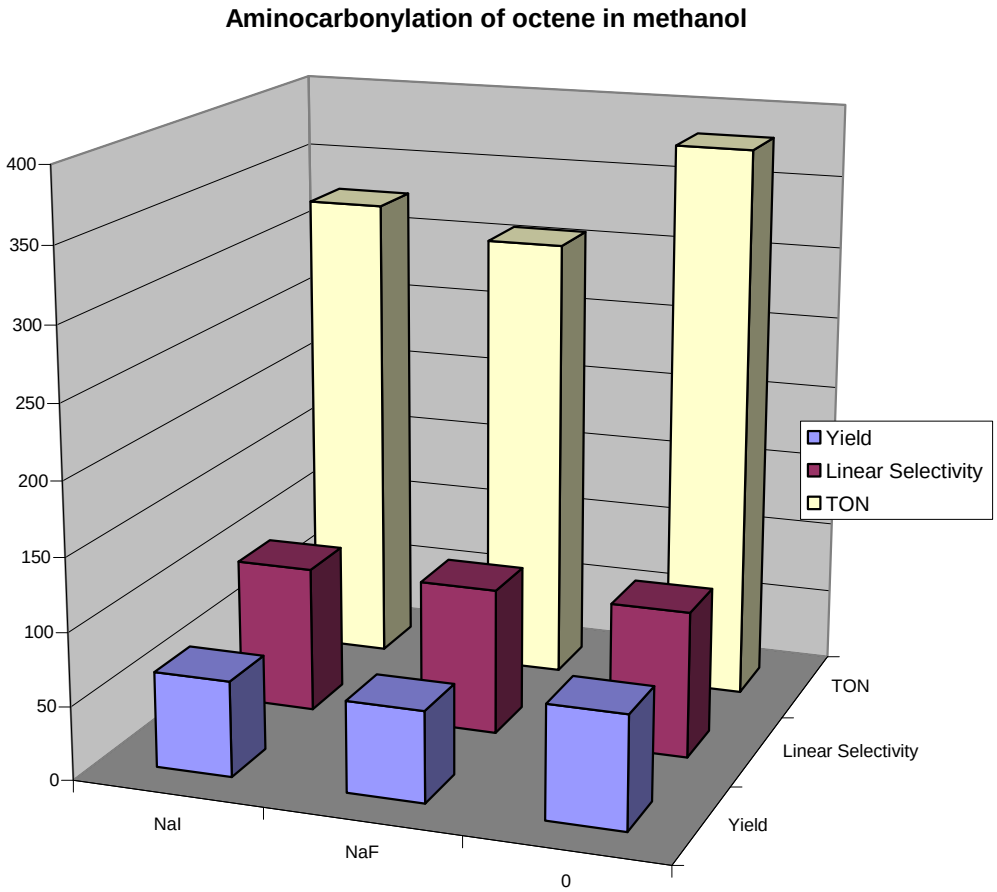
As Section 2.2.2.1.1 shows (Table 2.17, entry 2) the absence of NaI in the medium did not give any conversion. Surprisingly, during this study it was found that using the methanol aminocarbonylation protocol did not require NaI (Table 2.25, entry 3), and the reaction yielded similar results to those of aminocarbonylation under normal conditions (Table 2.19, entry 7).

Table 2.25. Aminocarbonylation of octene in methanol.



Entry	Halide salt	Yield	Linear Selectivity	TON
1	NaI	65	100	326
2	NaF	62	100	307
3	-	77	100	381

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1,6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.8 g, 12,74 mmol), MX (0.0637 mmol), methanol (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



2.2.2.1.10.- Use of $[BDTBPMBH_2][BF_4]_2$ in the Aminocarbonylation of Octene.

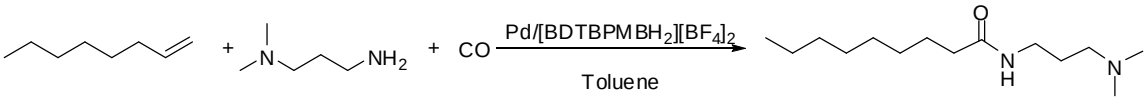
As previously mentioned in Section 2.2.1.11, $[BDTBPMH_2][BF_4]_2$ (Fig 2.26) has proven to be a highly useful and versatile air-stable BDTBPMB analogue. The manipulation of this ligand -which is stable to oxygen for long periods (>3 months)- is considerably easier and faster than BDTBPMB. For example, the use of expensive equipments such as a glove box is completely unnecessary in this case.

$[BDTBPMH_2][BF_4]_2/[Pd(OAc)_2]$ has been tested under aminocarbonylation conditions where $BDTBPM/[Pd(OAc)_2]$ has proven to be quite active. Table 2.26 shows the results obtained.

The use of NaI gave high yield, selectivity and TON (Table 2.26, entry 1). Slightly higher conversion was obtained when NaF was used instead of NaI (Table 2.26, entry 2). The absence of a proton source (methanesulphonic acid) did not result in a significant difference (Table 2.26, entry 3). This result may be considered to be not consistent with the results obtained in the preliminary studies (Section 2.2.2.1.1). During that study the use of a strong acid such as methanesulphonic acid was proven to be required in aminocarbonylation (Table 2.17, entry 3), presumably for the generation of the active hydride-palladium species **3** (Fig 2.3).

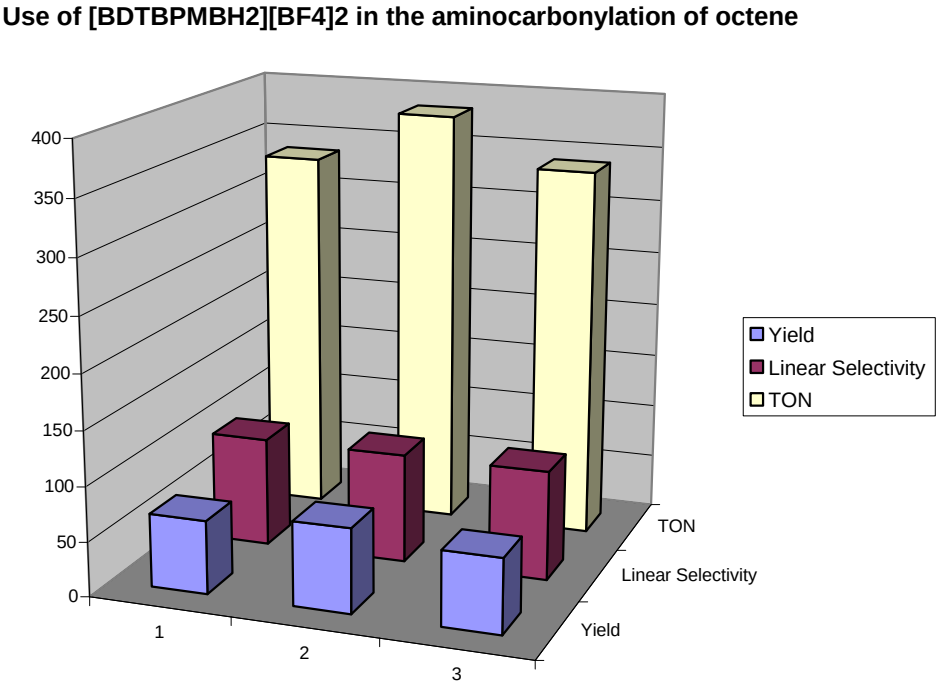
To understand this apparent discrepancy it should be noticed that $[BDTBPMH_2][BF_4]_2$ owns one proton for each phosphorus atom (Fig 2.26). Hence, $[BDTBPMH_2][BF_4]_2$ may play two roles in the reaction. Firstly, it plays the ligand role to modify the electronic and steric properties of the catalyst, and secondly as a proton source for the generation of the palladium hydride species **3**. Hence, when $[BDTBPMH_2][BF_4]_2$ was used, no extra methanesulphonic acid was needed.

Table 2.26. Use of $[BDTBPMBH_2][BF_4]_2$ in the aminocarbonylation of octene.



Entry	Solvent	Yield	Linear Selectivity	TON
1	NaI	67	100	335
2	NaF	77	100	383
3 [a)]	NaI	68	100	340

Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), $[BDTBPMBH_2][BF_4]_2$ (37 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), 2-naphthol (1.8 g, 12.74 mmol), NaX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h. a) No MSA was added

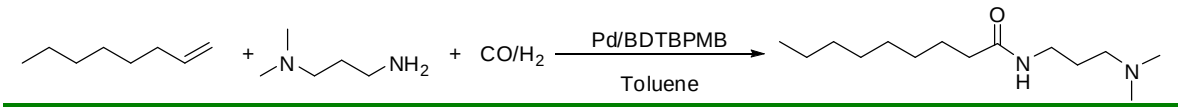


2.2.2.1.11.- Aminocarbonylation of octene under a syngas atmosphere.

The manufacture of carbon monoxide is usually via syngas, which is a mixture of carbon monoxide and hydrogen.[58] Due to the close boiling points of these gases, the separation of pure carbon monoxide is a tedious and expensive process, which increases the cost of the carbon monoxide. Therefore, from an economical viewpoint, the replacement of carbon monoxide for syngas is highly desirable.

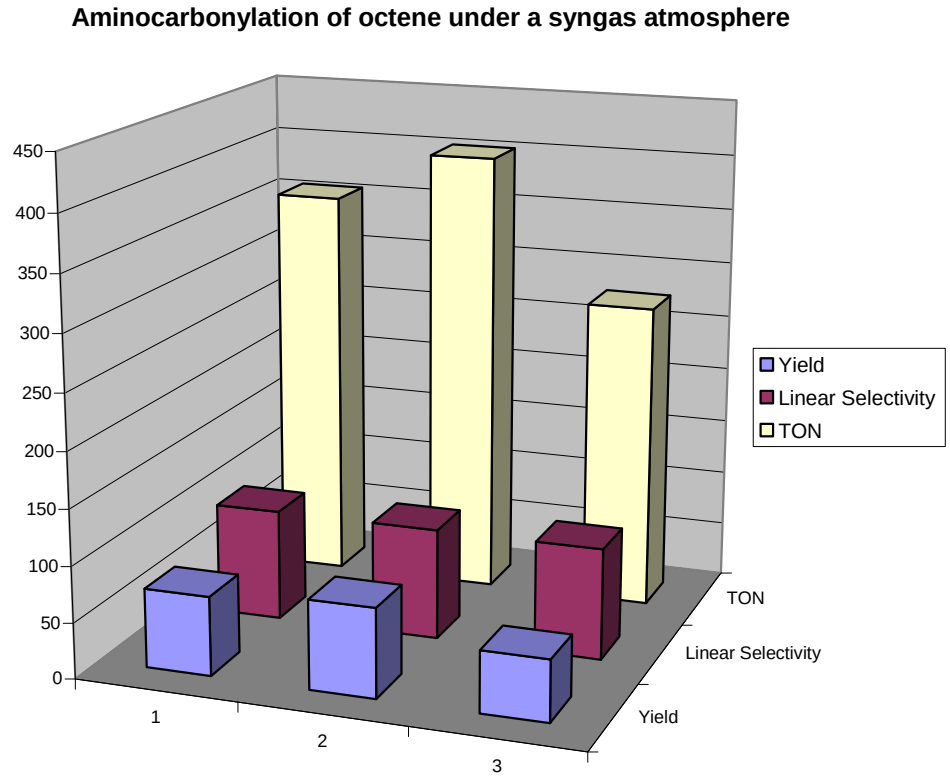
A positive role of the use of hydrogen in aminocarbonylation has been described by Alper and El-Ali in aminocarbonylation.[36-38] El-Ali suggested a hypothetical stabilization of the hydride palladium species **3** by hydrogen (Fig 2.3).[38] This stabilization may avoid **3** being destroyed by the amine (Fig 2.32).

Table 2.27. Aminocarbonylation of octene under a syngas atmosphere.



Entry	Pressure syngas (1:1)	Salt	Yield	Linear Selectivity	TON
1	40	NaI	71	100	356
2	40	NaF	80	100	402
3	20	NaI	55	100	276

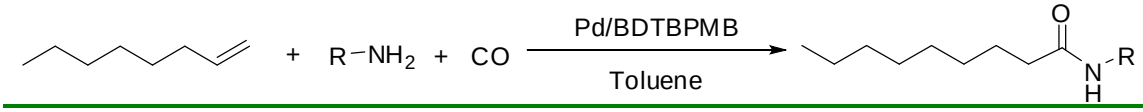
Conditions: Octene (2 mL, 12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12,74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), 2-naphthol (1.8 g, 12.74 mmol), NaI (9.5 mg, 0.0637 mmol), toluene (10 mL), 140ºC, 1 h



The use of 40 bar of syngas (1:1) yielded high conversion (Table 2.27, entry 1). Only a slight variation in conversion between this result and the result obtained under carbon monoxide atmosphere (Table 2.19, entry 7) was obtained. The use of NaF instead of NaI significantly increased the conversion (Table 2.27, entry 2), while a decrease in pressure resulted in a drop in yield (Table 2.27, entry 3).

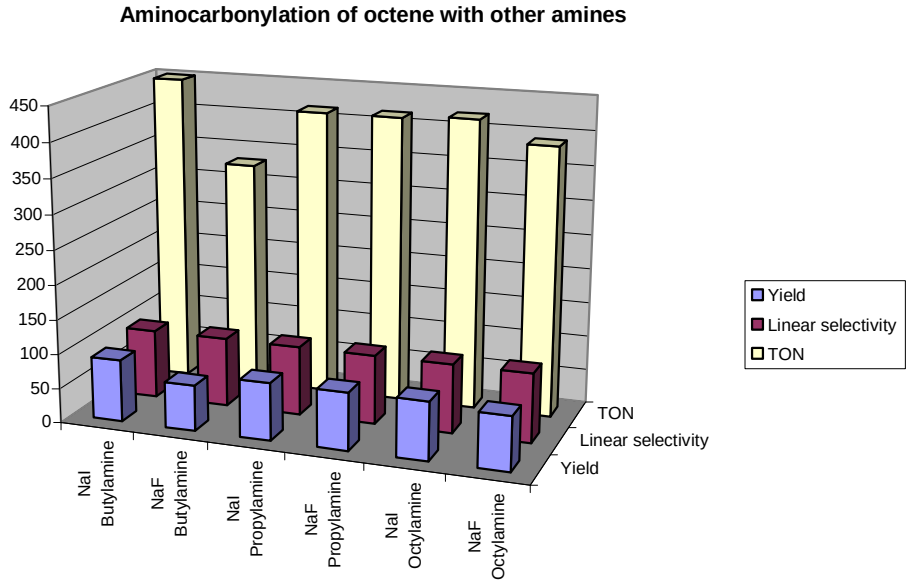
2.2.2.1.12.- Aminocarbonylation of Octene with Other Amines.

Table 2.28. Aminocarbonylation of octene with other amines.



Entry	Amine	Halide salt	Yield	Linear Selectivity	TON
1	Butylamine	NaI	90	100	450
2	Butylamine	NaF	66	100	330
3	Propylamine	NaI	83	100	415
4	Propylamine	NaF	83	100	415
5	Octylamine	NaI	84	100	420
6	Octylamine	NaF	78	100	390

Conditions: Octene (2 mL, 12.74 mmol), amine (12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.8 g, 12.74 mmol), NaI (9.5 mg, 0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



To prove the flexibility of the process, other alkylamines were tested under aminocarbonylation conditions. The chosen alkylamines were butylamine, propylamine and octylamine and the results are summarised in Table 2.28.

The aminocarbonylation of octene with butylamine yielded excellent results using NaI (Table 2.28, entry 1). The use of NaF significantly decreases the yield of the process (Table 2.28, entry 2). In the case of propylamine, both salts (NaI and NaF) gave similar conversions (Table 2.28, entry 3 and 4). The use of a highly linear amine such as octylamine did not give significant differences (Table 2.28, entry 5 and 6). High flexibility has been found and proven during this study on the aminocarbonylation of octene.

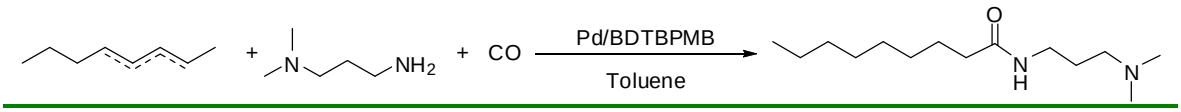
2.2.2.1.13.- Aminocarbonylation of Isomers of Octene.

It is well known that a fast isomeration takes place in the system catalysed by the palladium complex of BDTPBMB.[57] Due to this isomeration route, all isomers of octene are presented in the medium during the reaction, although this does not significantly affect the selectivity of the reaction. This was proven in Sections 2.2.1.7 and 2.2.1.8 where different isomers of octene were used obtaining high linear selectivity for hydroxycarbonylation reaction.

It is, therefore, interesting to know if this result can be extrapolated to aminocarbonylation. Hence, a study using the other three isomers of octene has been carried out and the results are shown in Table 2.29.

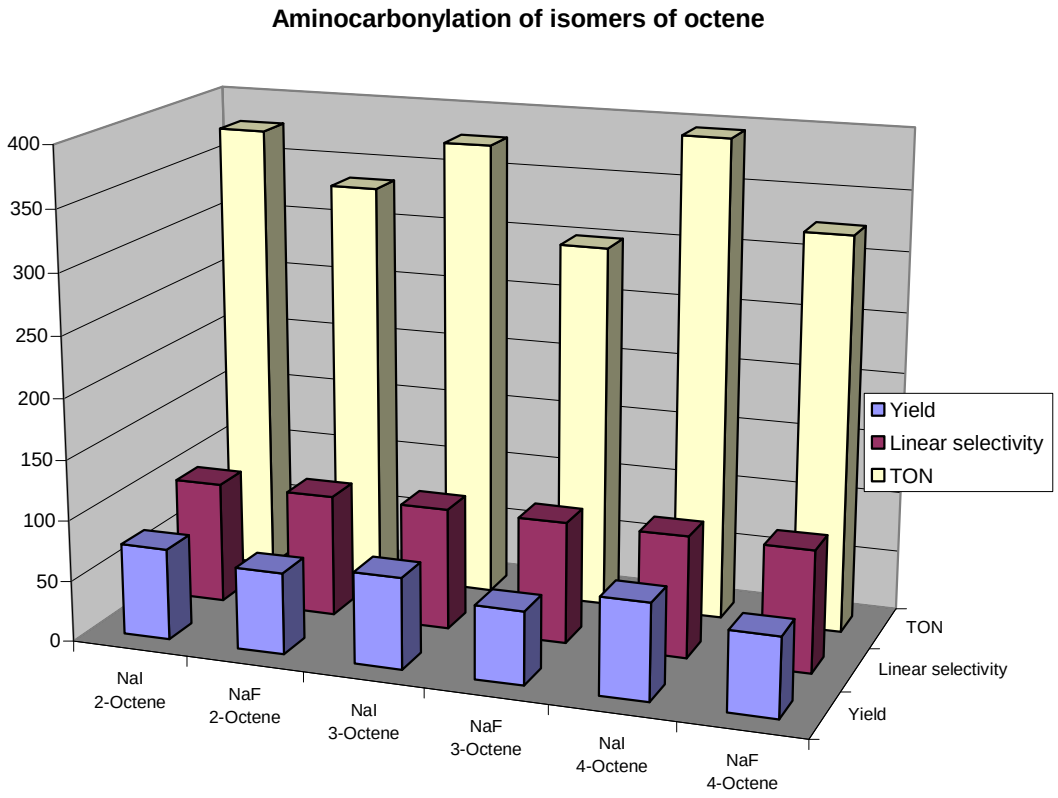
Three other isomers of octene (2-octene, 3-octene and 4-octene) yielded similar conversions when NaI was used (Table 2.29, entries 1, 3 and 5), and were similar to the reported results for 1-octene (Table 2.19, entry 7) with high linear selectivity. The yield decreased slightly when NaF was used (Table 2.29, entries 2, 4 and 6). This confirms that isomeration is much faster than the reaction with the nucleophile in aminocarbonylation process catalysed by Pd/BDTBPBM.

Table 2.29. Aminocarbonylation of isomers of octene.



Entry	Amine	Halide salt	Yield	Linear selectiviy	TON
1	2-Octene	NaI	75	100	377
2	2-Octene	NaF	67	100	335
3	3-Octene	NaI	75	100	377
4	3-Octene	NaF	60	100	300
5	4-Octene	NaI	79	100	395
6	4-Octene	NaF	65	100	325

Conditions: alkene (12.74 mmol), 3-dimethylamino-1-propylamine (1.6 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), 2-naphthol (1.8 g, 12.74 mmol), NaI (9.5 mg, 0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



2.2.2.2.- Aminocarbonylation of Alkenes Using Arylamines.

2.2.2.2.1.- Preliminary Results.

As mentioned in Section 2.2.2., alkylamines and arylamines (anilines) very often present different reactivities due to their different characteristics such as nucleophilicity and basicity.

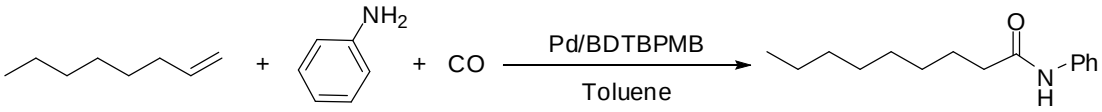
Hence, the results obtained in the previous section cannot necessarily be extrapolated to arylamines. To confirm if the generation of *N*-arylamide can be achieve by aminocarbonylation, a study using anilines has been carried out. The initial results are summarised in Table 2.30.

While no conversion was obtained when phenol, *N*-methylimidazol, cyanophenol or methyl 3-hydroxy-2-naphthoate were used as promoters (Table 2.30, entries 1 to 4), 2-naphthol gave moderate conversions (Table 2.30, entry 5). Although slightly different in terms of conversion when 2-naphthol was used, these results agree with the results obtained using alkylamines (Table 2.16). However, a discrepancy was found when 1-naphthol was used. Under these conditions, the reaction yielded low conversion (Table 2.30, entry 6), while no conversion was obtained in the case of alkylamines (Table 2.16, entry 11).

Although [$Pd(OAc)_2$] was the optimum palladium precatalyst, some activity was found when another palladium (II) precursor, [$Pd(MeCN)_2Cl_2$], was used (Table 2.30, entries 12 and 13). In this case a palladium (0) precatalyst, [Pd_2dba_3], was also found to be active (Table 2.30, entry 14).

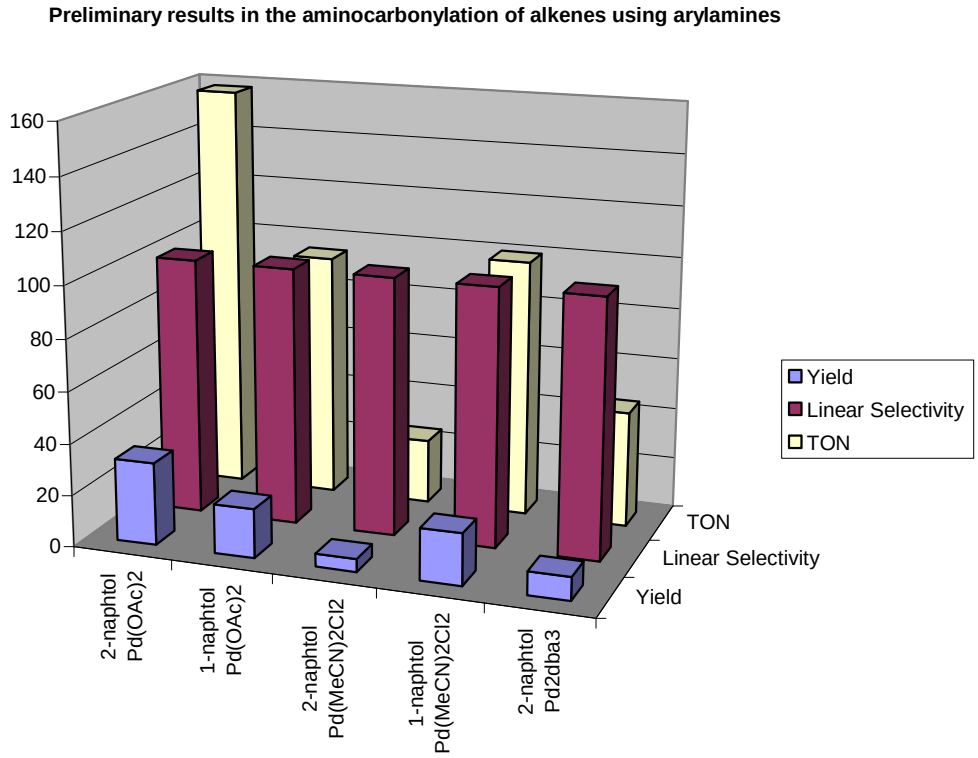
The absence of NaI or Naphthol inhibited the formation of amide (Table 2.31, entries 1 and 2), confirming what was found in Section 2.2.2.1.1, that the combination of NaI and naphthol is essential in this process.

Table 2.30. Preliminary results in the aminocarbonylation of alkenes using arylamines



Entry	Pd compound	Additive	Yield	Linear Selectivity	TON
1	$[Pd(OAc)_2]$	PhOH	0	-	0
2	$[Pd(OAc)_2]$	N-methylimidazol	0	-	0
3	$[Pd(OAc)_2]$	*p*-cyanophenol	0	-	0
4	$[Pd(OAc)_2]$	Methyl 3-hydroxy-2-naphthoate	0	-	0
5	$[Pd(OAc)_2]$	2-naphthol	32	100	158
6	$[Pd(OAc)_2]$	1-naphthol	19	100	95
7	$[Pd(MeCN)_2Cl_2]$	2-naphthol	5	100	25
8	$[Pd(MeCN)_2Cl_2]$	1-naphthol	20	100	100
9	$[Pd_2dba_3]$	2-naphthol	9	100	45

Conditions: Octene (2 mL, 12.74 mmol), aniline (1.2 mL, 12.74 mmol), Pd (0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), additive (6.37 mmol), NaI (0.0637 mmol), P_{CO}=20 bar, toluene (10 mL), 140ºC, 1 h.



As mentioned in Sections 2.2.1.6 and 2.2.2.1.1, and in agreement with the proposed mechanism (see Section 2.1.2), usually the addition of a strong acid is required for the initial generation of the hydride palladium species **3**. However, the absence of methanesulfonic acid gave some conversion in aminocarbonylation using aniline (Table 2.31, entry 3).

Table 2.31. Blank assays in the aminocarbonylation of octene

Entry	Amine	Naphol	NaI	MSA	Yield	Linear Selectivity	TON
1	aniline (1 eq)	-	0.5%	1,2 %	0	-	0
2	aniline (1 eq)	1 eq	-	1,2 %	0	-	0
3	aniline (1 eq)	1 eq	0,5 %	-	8	100	40

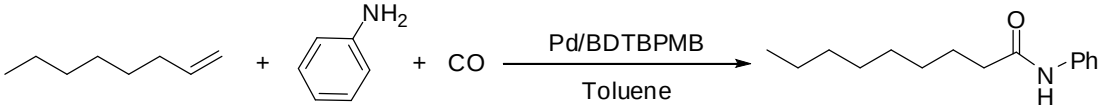
Conditions: Octene (2 mL, 12.74 mmol), aniline (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (as described), 2-naphthol (as described), NaI (as described), P_{CO}=20 bar, toluene (10 mL), 140ºC, 1 h.

2.2.2.2.2.- Study on the Variation of Naphthol Concentration in Aminocarbonylation.

A study on the effects of the variation of naphthol concentration was carried out and the results are summarised in Table 2.32.

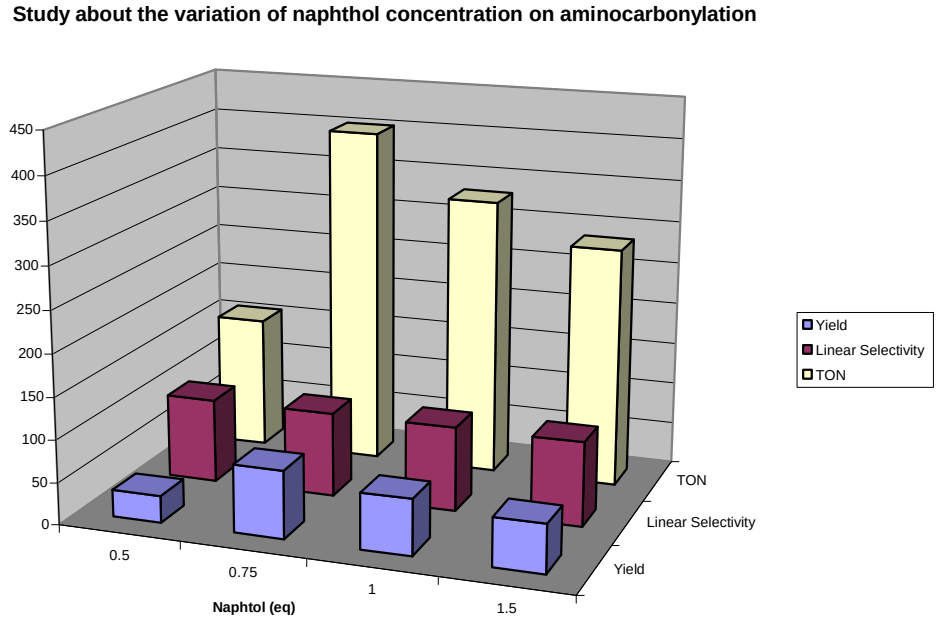
Moderate conversion was obtained at low concentrations of naphthol (Table 2.32, entry 1). When the concentration was increased, the reaction gave on excellent yield (Table 2.32, entry 2). Despite this interesting positive effect from this point a negative effect was found in increasing the concentration of naphthol still further. When 1 equivalent of naphthol per equivalent of octene was used, a significant drop in yield was obtained (Table 2.32, entry 3). This effect was more notable when 1.5 equivalents were used (Table 2.32, entry 4).

Table 2.32. Study about the variation of naphthol concentration on aminocarbonylation.



Entry	Naphol equivalent	Yield	Linear Selectivity	TON
1	0.5	32	100	158
2	0.75	80	100	402
3	1	66	100	330
4	1.5	57	100	285

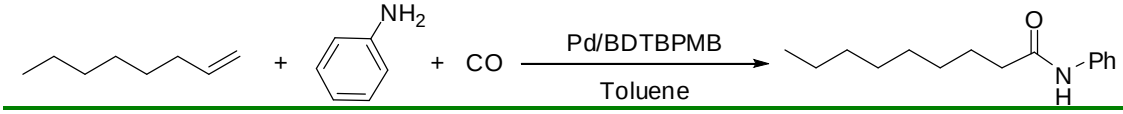
Conditions: Octene (2 mL, 12.74 mmol), aniline (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), 2-naphthol (as described), NaI (9.5 mg, 0.0637 mmol), P_{CO}=20 bar, toluene (10 mL), 140ºC, 1 h.



2.2.2.2.3.- Study on the Effect on Variation of Aniline Concentration on Aminocarbonylation.

A study on the variation of aniline concentration was carried out. Aniline concentration was varied from 1 equivalent (per equivalent of octene) to 2 equivalents, keeping the concentration of naphthol constant. This study was carried out at three concentrations of naphthol (0.75 equivalents per equivalent of octene to 1.5 equivalents) to find out the effect of both substrates on the reaction. The results are summarised in Table 2.33.

Table 2.33. Study on the variation of aniline concentration on aminocarbonylation.



Entry	Amine equivalent	Naphol equivalent	Yield	Linear Selectivity	TON
1	1	0.75	80	100	402
2	1.5	0.75	85	100	428
3	2	0.75	82	100	412
4	1	1	66	100	330
5	1.5	1	72	100	360
6	2	1	72	100	360
7	1	1.5	57	100	285
8	1.5	1.5	88	100	441
9	2	1.5	74	100	370

Conditions: Octene (2 mL, 12.74 mmol), aniline (as described), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (as described), NaI (9.5 mg, 0.0637 mmol), P_{CO}=20 bar, toluene (10 mL), 140ºC, 1 h.

These results have been fitted to a parametric equation (Eq 1). Due to the high flexibility present in linear equations, this kind of equation has been chosen for this study. Two variables can be considered -the concentration of naphthol and the concentration of aniline-. Therefore, seven parameters had to been obtained.

$$TON = a_1 + a_2 \cdot [A\min e]^{b1} + a_3 \cdot [Naphtol]^{b2} + a_4 \cdot ([A\min e] \cdot [Naphtol])^{b3}$$

Eq 1. *Chosen parametric equation for the study on the effects of aniline and naphthol*

Table 2.34. Calculation of minimization of the square residue

Entry	Amine equivalent	Naphthol equivalent	TON	Calculated TON	Residue^2	Error (%)
1	1	0.75	402	376.87	631.38	6.25
2	1.5	0.75	428	434.01	36.11	1.40
3	2	0.75	412	431.33	373.46	4.69
4	1	1	330	322.44	57.21	2.29
5	1.5	1	360	379.59	383.60	5.44
6	2	1	360	376.91	286.01	4.70
7	1	1.5	285	318.61	1129.37	11.79
8	1.5	1.5	441	375.78	4254.29	14.79
9	2	1.5	370	373.11	9.70	0.84

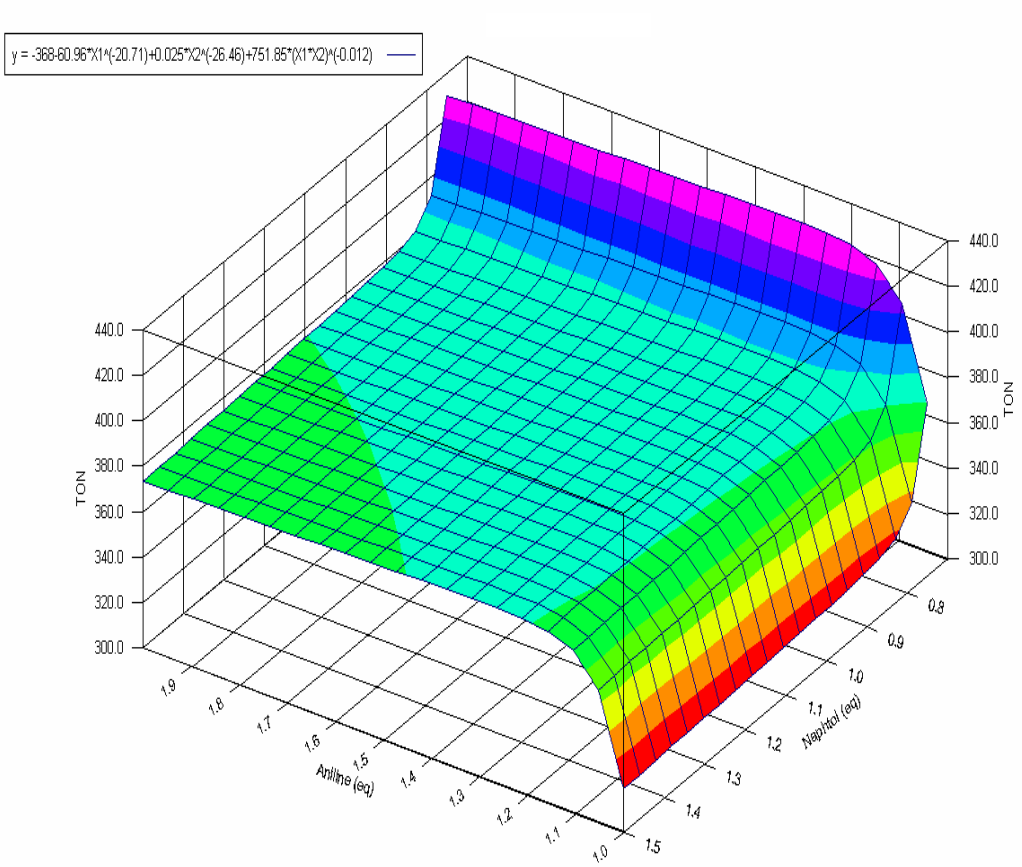
A minimization of the square residue using the Gauss-Newton algorithm was carried out. It considering residue as the subtraction of TON to TON calculated in the equation 1. The parameters obtained are shown in Table 2.35.

Table 2.35. Obtained parameters

Parameters			
a_1	-368.47		
a_2	-60.96	b_1	-20.71
a_3	0.0255	b_2	-26.46
a_4	751.85	b_3	-0.012

The calculated error for the difference between TON and calculated TON covers a range between 0.84 % and 14.8 %, giving an average of 4.7 %, which is high, but acceptable in these kinds of calculations.

Graph 1. Study on the variation of aniline concentration in aminocarbonylation



In this graph, a negative role of the concentration of naphthol is observed. While a low concentration of naphthol gave high conversion, an increase in this concentration significantly decreased the yield, although this trend did not continue beyond 0.75 equivalents.

Another interesting point about this graph is that a slight excess of aniline dramatically increased the yield. However, a high excess of aniline did not significantly affect the yield.

This graph shows an interesting square area between naphthol concentrations of 0.8 equivalents to 1.5 equivalents and concentration of aniline between 1.2 equivalents and 2 equivalents. Unexpectedly, the yield of the reaction does not depend significantly on the concentration of aniline and naphthol in this region.

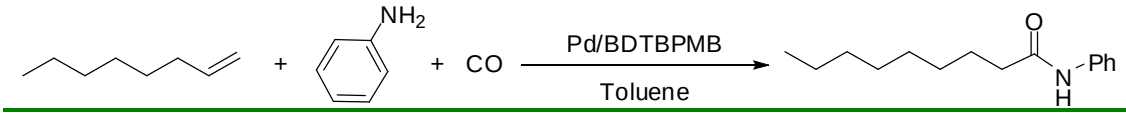
2.2.2.2.4.- Effect of Pressure in Aminocarbonylation of Octene.

A study on the effect of pressure on the aminocarbonylation of 1-octene has been carried out covering a range of pressures between 10 and 50 bar. The results are shown in Table 2.36.

High conversion was obtained when low pressures were used (Table 2.36, entry 1). A slight drop in yield was found when the pressure was increased (Table 2.36, entries 2 and 3). This effect is more notable at 50 bar, where only moderate yields were obtained (Table 2.36, entry 4). This trend is slightly different to the one obtained in the study carried out on aminocarbonylation using alkylamines (Section 2.2.2.1.5). In that case two opposite effects were observed, one positive when the pressure was increased form 10 to 20 bar, and one negative at higher pressures.

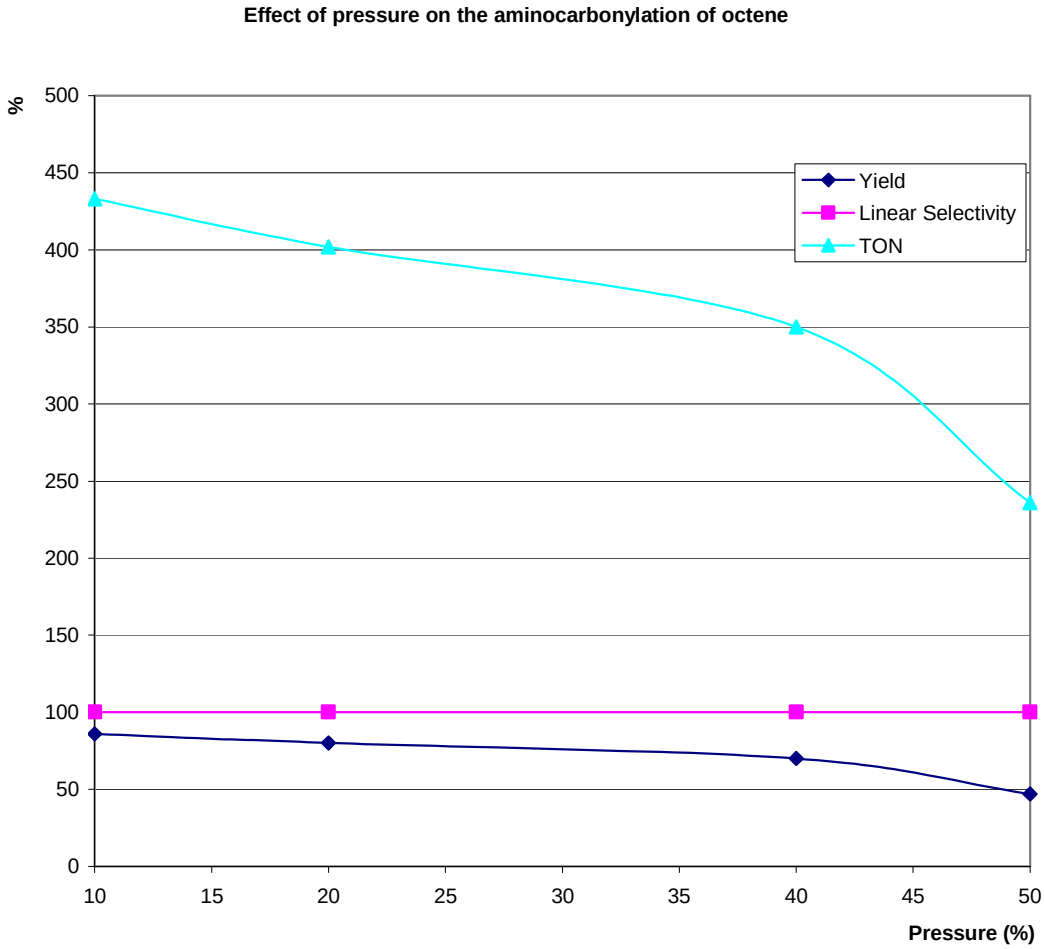
How the pressure affects the yield in the aminocarbonylation using aniline was found to be more similar to this second trend, where an increase in pressure gives a decrease in yield. This result is more similar to other carbonylation reactions such as hydroformylation,[56] than to methoxycarbonylation or hydroxycarbonylation.[2,22]

Table 2.36. Effect of pressure on the aminocarbonylation of octene.



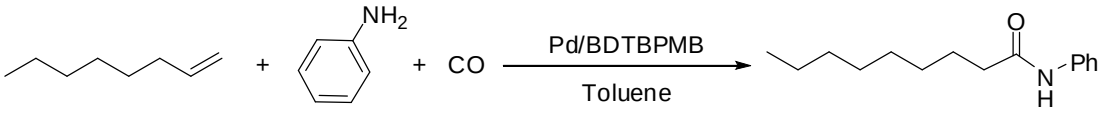
Entry	Pressure	Yield	Linear Selectivity	TON
1	10	86	100	433
2	20	80	100	402
3	40	70	100	350
4	50	47	100	236

Conditions: Octene (2 mL, 12.74 mmol), aniline (1.6 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaI (9.5 mg, 0.0637 mmol), toluene (10 mL), 140ºC, 1 h.



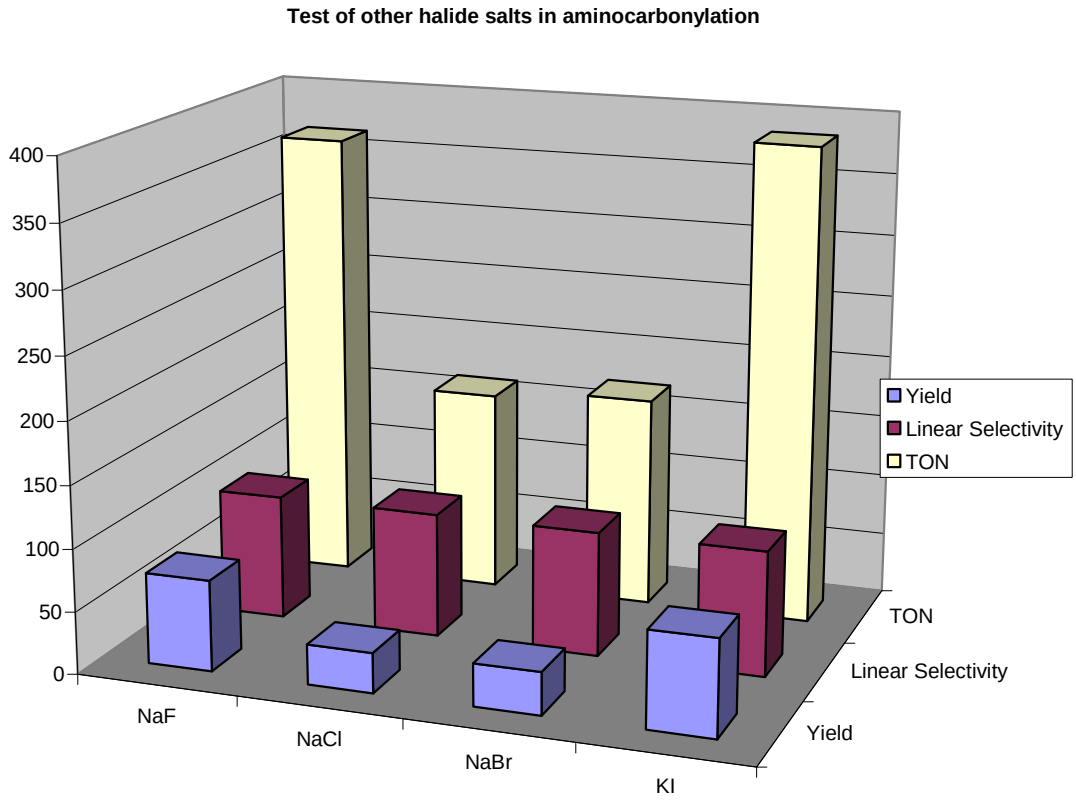
2.2.2.2.5.- Test of Other Halide Salts in Aminocarbonylation Using Aniline.

Table 2.37. Test of other halide salts in aminocarbonylation.



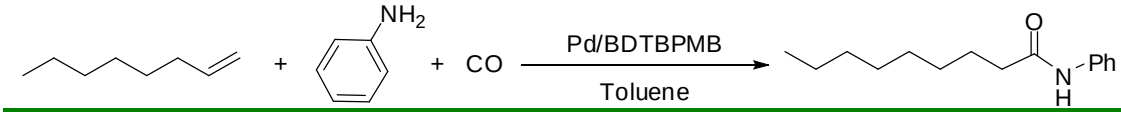
Entry	Halide salt	Yield	Linear Selectivity	TON
1	NaF	73	100	365
2	NaCl	32	100	162
3	NaBr	34	100	170
4	KI	77	100	385

Conditions: Octene (2 mL, 12.74 mmol), aniline (1.6 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), MX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



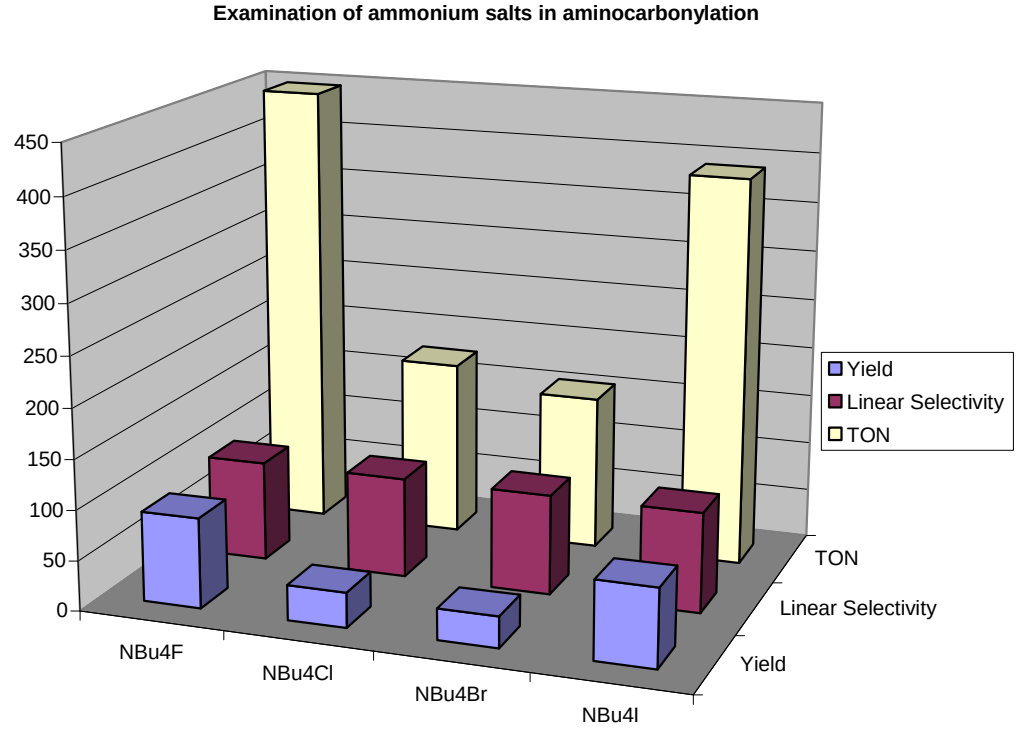
It is well known that halide salts may affect the activity of the catalyst.[54] Different hypothesis have been proposed to explain this effect.[54a] Usually coordination has been suggested to explain the role of the halide. Considering that each halide possesses different coordinating properties, it is plausible to think that each halide may show different effects in the reaction.

Table 2.38. Examination of ammonium salts in aminocarbonylation.



Entry	Ammonium salt	Yield	Linear Selectivity	TON
1	NBu_4F	90	100	447
2	NBu_4Cl	35	100	176
3	NBu_4Br	31	100	155
4	NBu_4I	78	100	390

Conditions: Octene (2 mL, 12.74 mmol), aniline (1.6 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NBu_4X(0,0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



The combination of naphthol with sodium halide has been proven to be essential in aminocarbonylation. Therefore, it is interesting to know if other halides may have the same effect in combination with naphthol. Other ionic salts have been tested under normal conditions of aminocarbonylation. The results are summarised in Table 2.37.

The use of NaCl or NaBr gave moderate conversions (Table 2.37, entries 2 and 3), but lower than the conversion obtained when using NaI (Table 2.37, entry 4). Unexpectedly, NaF gave similar results to NaI in aminocarbonylation (Table 2.32, entry 2). This result, although surprising, is in agreement with the result obtained in the aminocarbonylation of octene using alkylamine when NaI was replaced by NaF (Table 2.22, entry 1).

The substitution of sodium for potassium in the halide salts did not give significant differences (Table 2.37, entry 4). Hence, it can be concluded that the cationic ion does not play a notable role in the reaction. Rather similar trends were observed with NBu_4X (Table 2.38).

2.2.2.2.6.- Aminocarbonylation in Other Solvents.

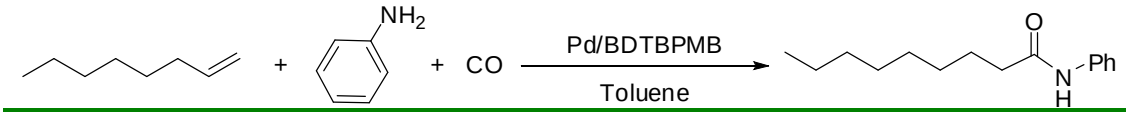
For a better understanding of the reaction in terms of the solvent role in the process, different solvents have been tested under normal aminocarbonylation condition. Different solvents with different properties were been chosen to carry out this study, and the results obtained were summarised in Table 2.39.

Two aromatic solvents (mesytilene and *o*-dichlorobencene) were tested initially. It was expected that similat results would be obtained using mesytilene instead of using toluene. However, when the reaction was carried out in mesytilene, a significant decrease in yield was found (Table 2.39, entry 1) with respect to toluene. Aminocarbonylation in the more polar *o*-dichlorobenzene yielded high conversion (Table 2.39, entry 2), similar to that obtained in the case of toluene.

MeCN, a highly coordinating solvent, significantly blocked the process, giving low conversion (Table 2.39, entry 3), possibly because it is highly coordinating. Ethereal solvents have been tested. Tetrahydrofuran yielded high conversion (Table 2.39, entry 4).

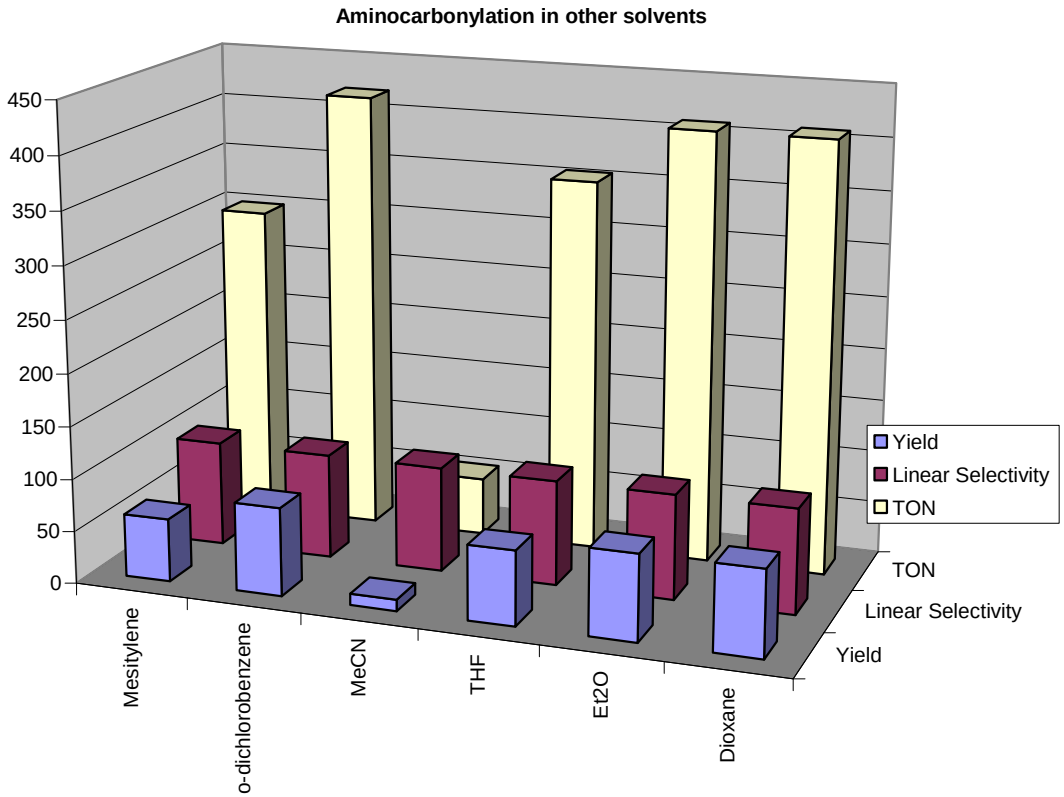
The use of diethyl ether or dioxane also gave excellent conversions (Table 2.39, entries 5 and 6).

Table 2.39. Aminocarbonylation in other solvents



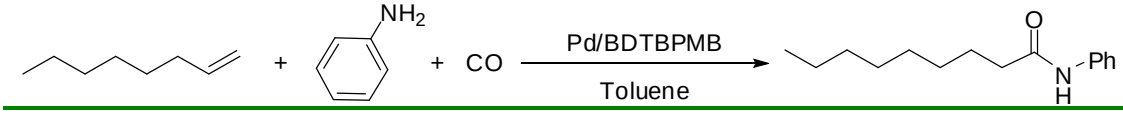
Entry	Solvent	Yield	Linear Selectivity	TON
1	Mesitylene	60	100	300
2	o-dichlorobenzene	84	100	420
3	MeCN	11	100	55
4	THF	71	100	355
5	Et_2O	82	100	410
6	Dioxane	82	100	410

Conditions: Octene (2 mL, 12.74 mmol), aniline (1.6 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaI (9.5 mg, 0.0637 mmol), solvent (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



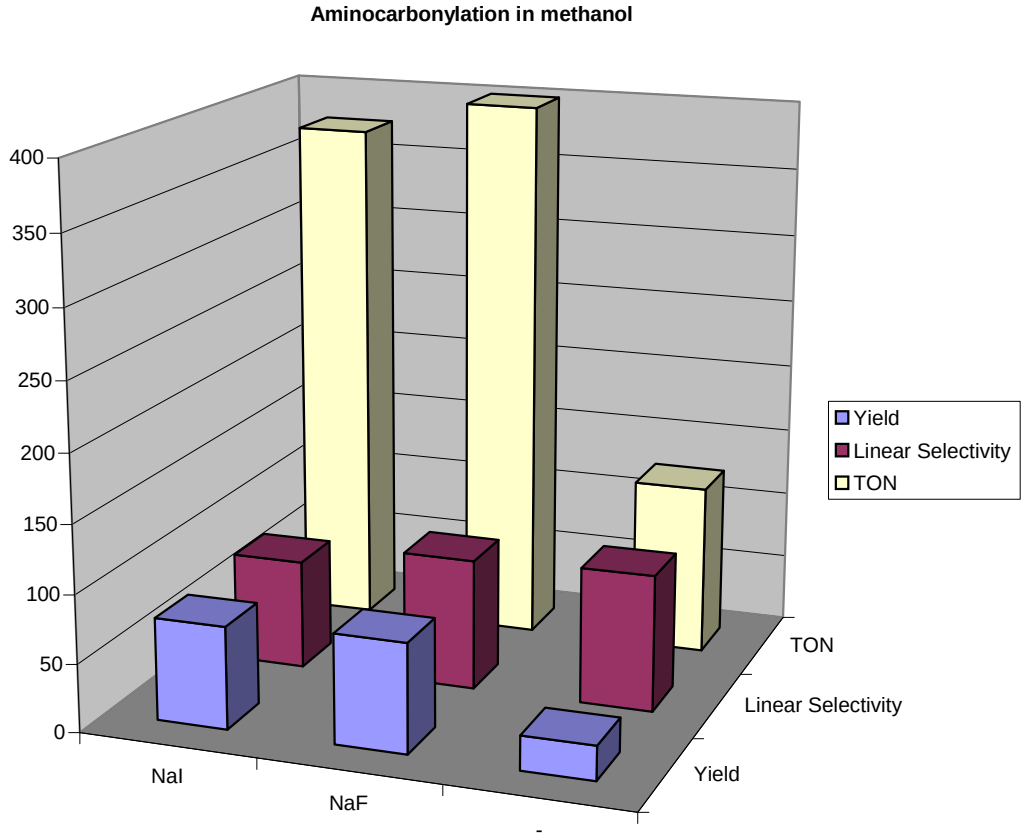
2.2.2.2.7.- Aminocarbonylation in Methanol.

Table 2.40. Aminocarbonylation in methanol



Entry	Halide salt	Yield	Linear Selectivity	TON
1	NaI	75	80	375
2	NaF	80	96	400
3	-	25	100	125

Conditions: Octene (2 mL, 12.74 mmol), aniline (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), MX (0.0637 mmol), methanol (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



As Section 2.2.2.1.9 shows, two possible products, -the amide and the ester-, may be formed under normal aminocarbonylation conditions in methanol. Hence, the aminocarbonylation results obtained may give appreciable information about the activity of this system in aminocarbonylation. Considering results such as the amide yield, and the amide/ester selectivity, it may be concluded which route is more favourable.

When the reaction was carried out in methanol with NaI as the additive, no methyl ester was found and a high amide yield was obtained (Table 2.40, entry 1). This is proof of the high activity of this system in aminocarbonylation and is evidently higher than methoxycarbonylation under these conditions. This amide/ester selectivity was validated when the reaction was carried out in presence of NaF instead of NaI, where only the amide was obtained, and in excellent yield (Table 2.40, entry 2).

The combination of naphthol with halide salt has been proven essential in this kind of reaction. Surprisingly, when the reaction was carried out in the absence of halide salts, some conversion was obtained (Table 2.40, entry 3). This result presents some similarites to the results obtained in the aminocarbonylation of octene with 3-dimethylamino-1-propylamine (Table 2.25, entry 3).

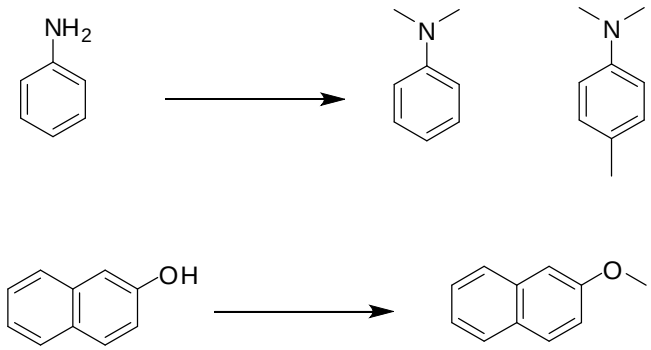


Fig 2.35. *Methylation of aniline and naphthol under aminocarbonylation conditions*

Three secondary products (*N*,*N*-dimethylaniline, *N*,*N*,*4*-trimethylaniline and methoxynaphthalene) were detected in the crude reaction product (Fig 2.35). These products may be formed in the medium by the methylation of aniline and naphthol where the methyl group may come from methanol. As Table 2.41 shows, NaI plays a bigger role in this methylation than NaF.

Table 2.41. Methylation of aniline and naphthalene under aminocarbonylation conditions

Experiment	Halide salt	*N,N*-dimethylaniline	*N,N,4*-trimethylaniline	Methoxynaphthalene
1	NaI	8	13	44
2	NaF	8	4	20

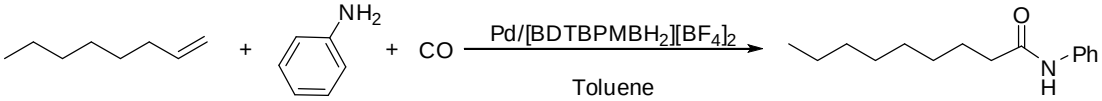
Yield based on the reactant.

2.2.2.2.8.- Use of $[BDTBPMBH_2][BF_4]_2$ in the aminocarbonylation of octene.

$[BDTBPMBH_2][BF_4]_2$ has been tested in the aminocarbonylation of octene using aniline. When the reaction was carried out using NaI, high conversion was obtained (Table 2.42, entry 1). The replacement of NaI for NaF gave excellent conversions and selectivities (Table 2.42, entry 2).

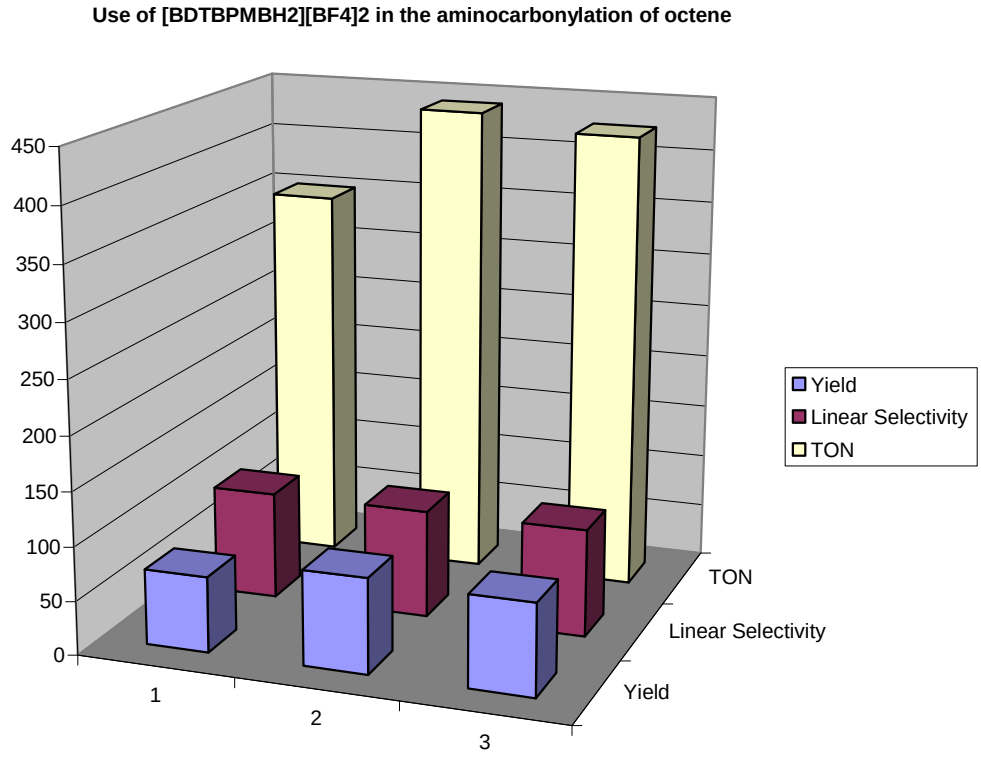
Methanesulfonic acid has been proven to be essential in the aminocarbonylation of octene (see Section 2.2.2.2.1), presumably as a proton source for the formation of the essential hydride palladium species **3** (Fig 2.3). However, using $[BDTBPMBH_2][BF_4]_2$ as the ligand in the absence of methanesulfonic acid did not give significantly different conversions (Table 2.42, entry 3). This can be explained by considering $[BDTBPMBH_2][BF_4]_2$ as a proton source as well as a ligand.[59] Therefore, no additional acid is required under these conditions.

Table 2.42. Use of $[BDTBPMBH_2][BF_4]_2$ in the aminocarbonylation of octene**.**



Entry	Solvent	Yield	Linear Selectivity	TON
1	NaI	70	100	350
2	NaF	88	100	440
3 [a)]	NaF	85	100	426

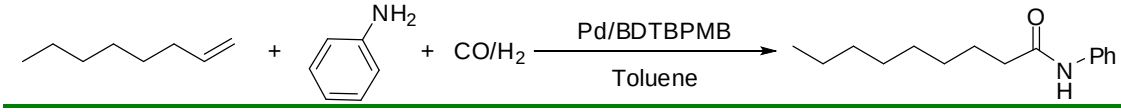
Conditions: Octene (2 mL, 12.74 mmol), aniline (1.6 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), $[BDTBPMBH_2][BF_4]_2$ (37 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h. a) No MSA



2.2.2.2.9.- Aminocarbonylation of Octene under a Syngas Atmosphere.

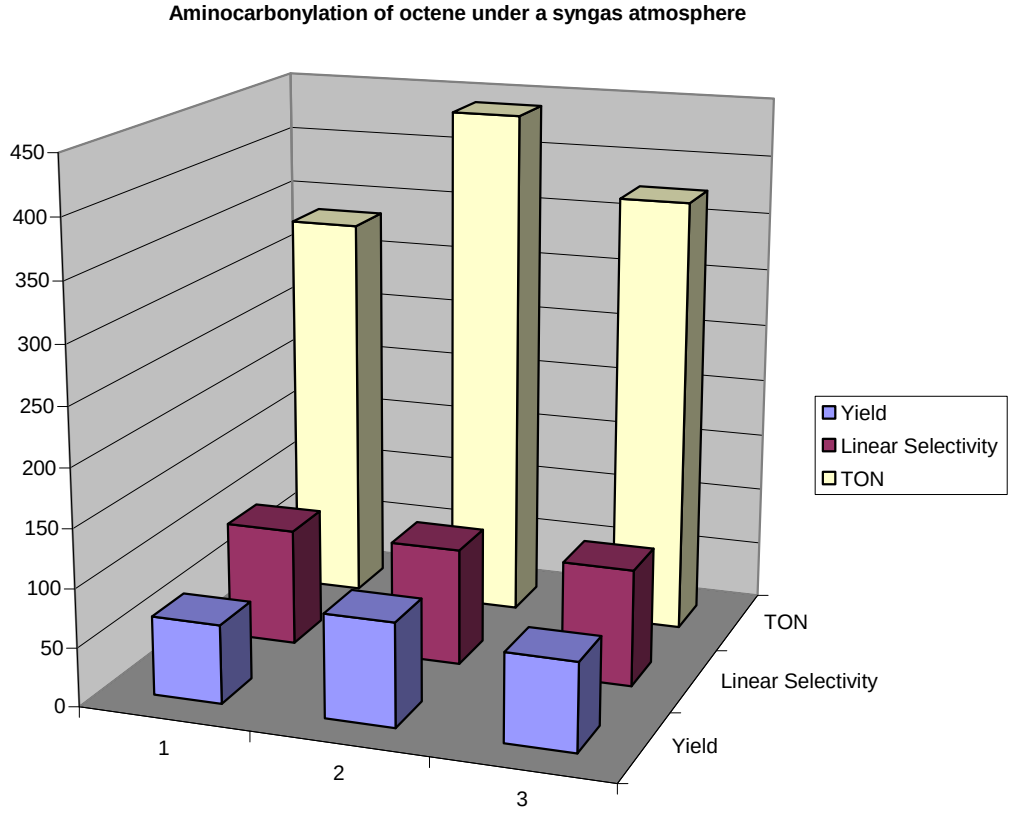
As previously mentioned in Section 2.2.2.1.11., the use of syngas instead of carbon monoxide presents an interesting economic advantage[58] and can affect catalyst stability.[36,37,38]

Table 2.43. Aminocarbonylation of octene under a syngas atmosphere.



Entry	Pressure syngas	Salt	Yield	Linear Selectivity	TON
1	40	NaI	67	100	335
2	40	NaF	88	100	440
3	20	NaF	75	100	375

Conditions: Octene (2 mL, 12.74 mmol), aniline (1.6 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaX (0.0637 mmol), toluene (10 mL), 140ºC, 1 h.



A series of experiments using syngas instead of carbon monoxide was carried out and the results are summarised in Table 2.43. High yields were obtained when 40 bar of syngas (1:1) was used (Table 2.43, entry 1). When NaI was replaced for NaF excellent conversion was obtained (Table 2.43, entry 2). A decrease in syngas pressure to 20 bar significantly lowered the yield of the reaction (Table 2.43, entry 3). This result shows a

different trend to the result obtained when only carbon monoxide was used. At low pressure this reaction yielded better results (Table 2.36, entry 1). These results are similar to those obtained when using 3-dimethylamino-1-propylamine

2.2.2.2.10.- Aminocarbonylation of Octene Using Other Anilines.

To examine the limitations of the reaction, and its flexibility, a series of the experiments was carried out. This study was based on the use of substituted anilines, which can significantly modify the nucleophilicity and basicity of the aniline.

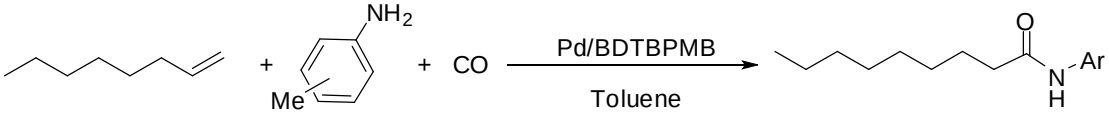
2.2.2.2.10.1.- Aminocarbonylation of Octene Using Methylanilines.

The first study of this series was carried out using methylanilines. These substrates have similar differences in electronic properties to aniline, due to the fact that the methyl group is only slightly electron donating. However, the steric properties must be taken into consideration when the methyl group is in the *ortho* position. In this position, the methyl group may significantly affect the reaction, due to the lower accessibility of the amino group in the aniline. This may result is a significant decrease of activity. This principle was confirmed when the reaction was carried out using *o*-methylaniline where only moderate conversions were recorded (Table 2.44, entries 1 and 2).

However, when the methyl group was placed in the *meta* position, where the steric effects are insignificant, excellent conversions were obtained (Table 2.44, entries 3 and 4), similar to those obtained in the aminocarbonylation using aniline (Table 2.32, entry 2). 4-Methylaniline gave high conversion (Table 2.44, entries 5 and 6). When anilines with two methyl groups (3,4-dimethylaniline) were tested under aminocarbonylation conditions, a high conversion was obtained (Table 2.44, entry 7).

Therefore, it can be concluded that when the aromatic ring of aniline contains one or more methyl groups, the result is not affected, except in the case of *o*-methylaniline where the steric factor was found to be quite significant.

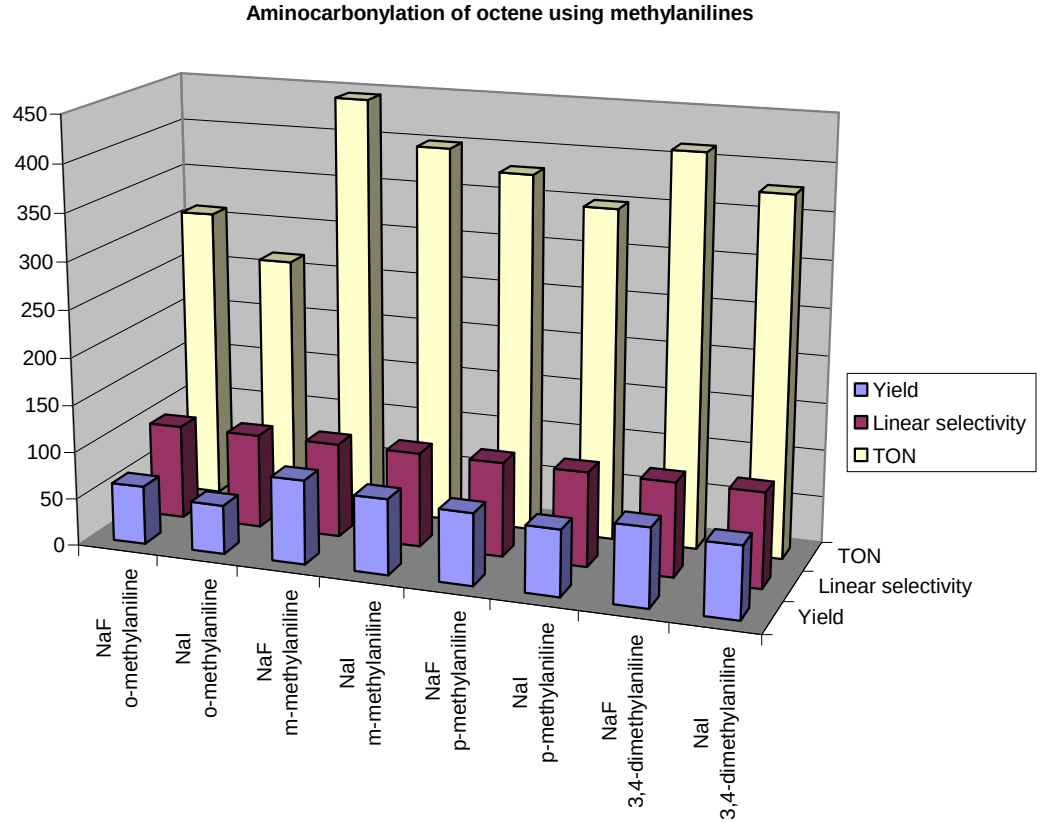
Table 2.44. Aminocarbonylation of octene using methylanilines.



Ar= methylphenyl

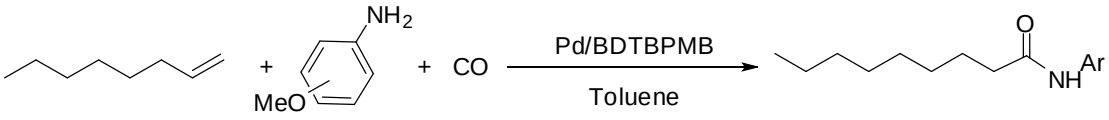
Entry	Amine	Halide salt	Yield	Linear Selectivity	TON
1	*o*-methylaniline	NaF	62	100	311
2	*o*-methylaniline	NaI	52	100	266
3	*m*-methylaniline	NaF	89	100	445
4	*m*-methylaniline	NaI	80	100	400
5	*p*-methylaniline	NaF	76	100	379
6	*p*-methylaniline	NaI	70	100	350
7	3,4-dimethylaniline	NaF	83	100	414
8	3,4-dimethylaniline	NaI	76	100	378

Conditions: Octene (2 mL, 12.74 mmol), amine (12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



2.2.2.2.10.2- Aminocarbonylation of Octene Using Methoxyanilines.

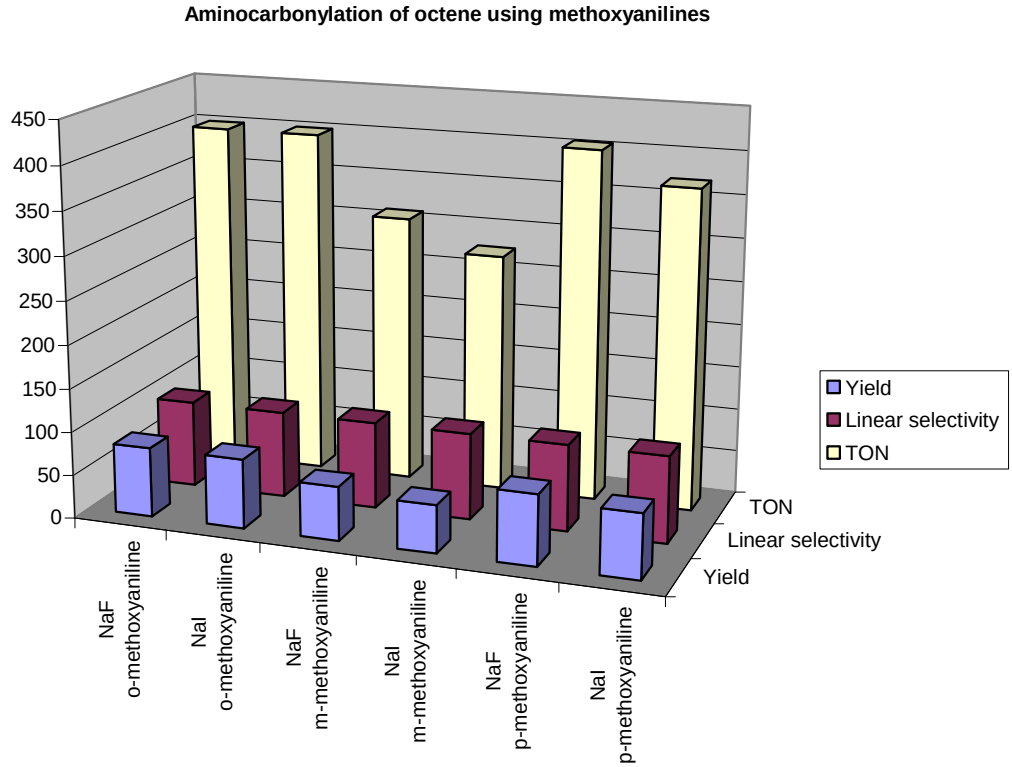
Table 2.45. Aminocarbonylation of octene using methoxyanilines.



Ar= Methoxyphenyl

Entry	Amine	Halide salt	Yield	Linear Selectivity	TON
1	*o*-methoxyaniline	NaF	80	100	400
2	*o*-methoxyaniline	NaI	80	100	400
3	*m*-methoxyaniline	NaF	62	100	310
4	*m*-methoxyaniline	NaI	55	100	275
5	*p*-methoxyaniline	NaF	81	100	405
6	*p*-methoxyaniline	NaI	74	100	370

Conditions: Octene (2 mL, 12.74 mmol), amine (12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



To increase the electron donating properties of the aromatic ring of aniline, methoxyanilines were used. By increasing the electron donating properties, it is expected that the nucleophilicity of the aniline will be increased, so this study is an important tool to know the effects of highly nucleophilic anilines on the reaction.

When *o*-methoxyaniline was used, high conversions were obtained (Table 2.45, entries 1 and 2). The apparent discrepancy between these results and the results obtained using *o*-methylaniline, where an appreciable drop in the conversion was reported should be noted (Table 2.45, entries 1 and 2). This is assumed to be due to an increase in the steric effect. However, if both substrates are compared, *o*-methoxyaniline has a significant steric effect. It is smaller than *o*-methylaniline, and the methoxy group is appreciably more electron donating. Hence, the smaller steric effect of *o*-methoxyaniline, and its high electron donating properties increase the yield, while the evident steric hindrance of *o*-methylaniline lowered the yield.

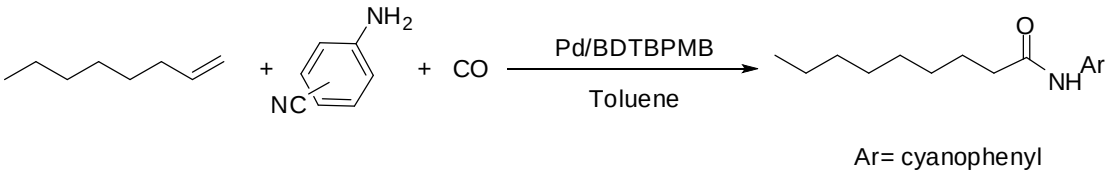
When *m*-methoxyaniline was used, only a moderate yield was obtained (Table 2.45, entries 3 and 4). *p*-Methoxyaniline gave excellent conversions (Table 2.45, entries 5 and 6).

2.2.2.2.10.3.- Aminocarbonylation of Octene Using Cyanoanilines.

To complete the study of electronic effects on aminocarbonylation it was considered interesting to test highly electron deficient anilines such as cyanoanilines. The cyano group is highly electron withdrawing, and it is expected that this group will decrease the yield of the reaction due to a decrease in the substrate nucleophilicity. There could also be a problem associated with coordination of the cyano group. It was shown earlier that MeCN inhibits carbonylation reaction (see Sections 2.1.4, 2.2.2.1.8 and 2.2.2.2.6.)

The experimental reaction confirmed this hypothesis. Only *ortho*-cyanoaniline was found to be active in aminocarbonylation although the reaction yielded low conversion (Table 2.46, entries 1 and 2). *meta*-Cyanoaniline and *para*-cyanoaniline did not give any conversion (Table 2.46, entries 3 to 6).

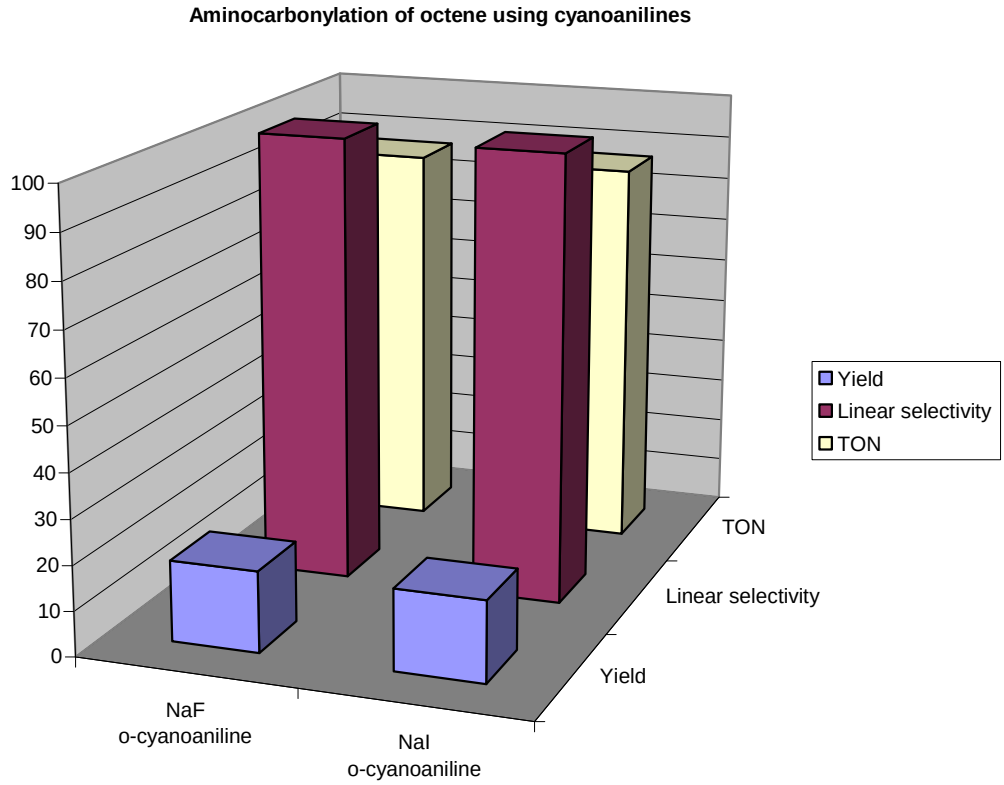
Table 2.46. Aminocarbonylation of octene using cyanoanilines.



Ar= cyanophenyl

Entry	Amine	Halide salt	Yield	Linear Selectivity	TON
1	*o*-cyanoaniline	NaF	18	100	87
2	*o*-cyanoaniline	NaI	18	100	87
3	*m*-cyanoaniline	NaF	0	-	0
4	*m*-cyanoaniline	NaI	0	-	0
5	*p*-cyanoaniline	NaF	0	-	0
6	*p*-cyanoaniline	NaI	0	-	0

Conditions: Octene (2 mL, 12.74 mmol), amine (12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



These results, although partially explicable due to the characteristics of the cyano group, are inexplicable in the case of *ortho*-cyanoaniline, as low conversion was expected.

This would be lower than that expected for the *meta* isomer, due to steric and electronic effects. However, as mentionated above, only *ortho*-cyanoaniline was slightly active in aminocarbonylation.

2.2.2.2.10.4.- Aminocarbonylation of Octene Using Fluoroanilines.

Fluoro compounds are widely used in different areas, such as in new materials[60] and in drugs.[61] Nowadays, new properties of these compounds have been discovered, raising the importance of these compounds, and creating new requirements. Therefore, the requirement of new protocols and pools of these compounds is clear.

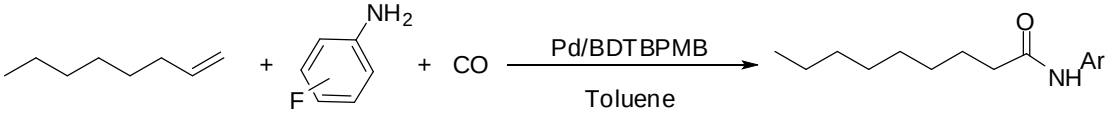
Hence, a study to prepare *N*-fluorophenylnonamide was undertaken for a better understanding of how highly electronegative compounds can affect the reaction.

When *o*-fluoroaniline was used as the nitrogen compound, excellent yields were obtained in aminocarbonylation (Table 2.47, entries 1 and 2).

Meta isomers present an appreciable variation in electronic properties of the aromatic ring. However, when *m*-metafluoroaniline was used with NaF, a decrease in conversion was observed (Table 2.47, entry 4), while high conversion was obtained in the case of NaI (Table 2.47, entry 3).

The use of *p*-fluoroaniline did not produce any substantial difference in the reaction, as high conversions were obtained (Table 2.47, entries 5 and 6). When two fluoro atom were present (2,5-fluroaniline), no significant difference was found (Table 2.47, entry 7) compared to the use of only one atom (Table 2.47, entries 1 and 2). Only a slight decrease in yield was found when NaF was used (Table 2.47, entry 8).

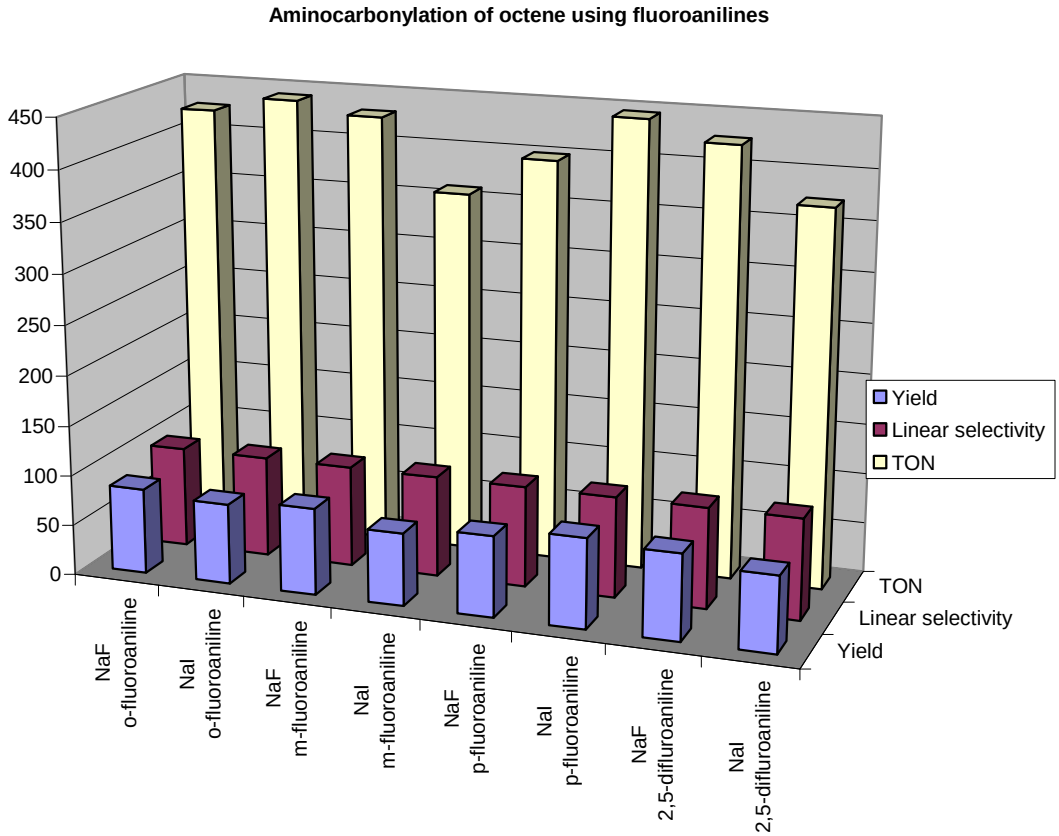
Table 2.47. Aminocarbonylation of octene using other Fluoroanilines.



Ar= Fluorophenyl

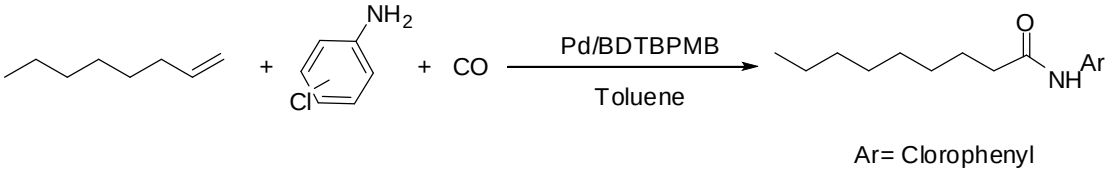
Entry	Amine	Halide salt	Yield	Linear Selectivity	TON
1	*o*-fluoroaniline	NaF	85	100	426
2	*o*-fluoroaniline	NaI	80	100	441
3	*m*-fluoroaniline	NaF	86	100	430
4	*m*-fluoroaniline	NaI	72	100	360
5	*p*-fluoroaniline	NaF	80	100	399
6	*p*-fluoroaniline	NaI	89	100	445
7	2,5-difluroaniline	NaF	85	100	426
8	2,5-difluroaniline	NaI	75	100	373

Conditions: Octene (2 mL, 12.74 mmol), amine (12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



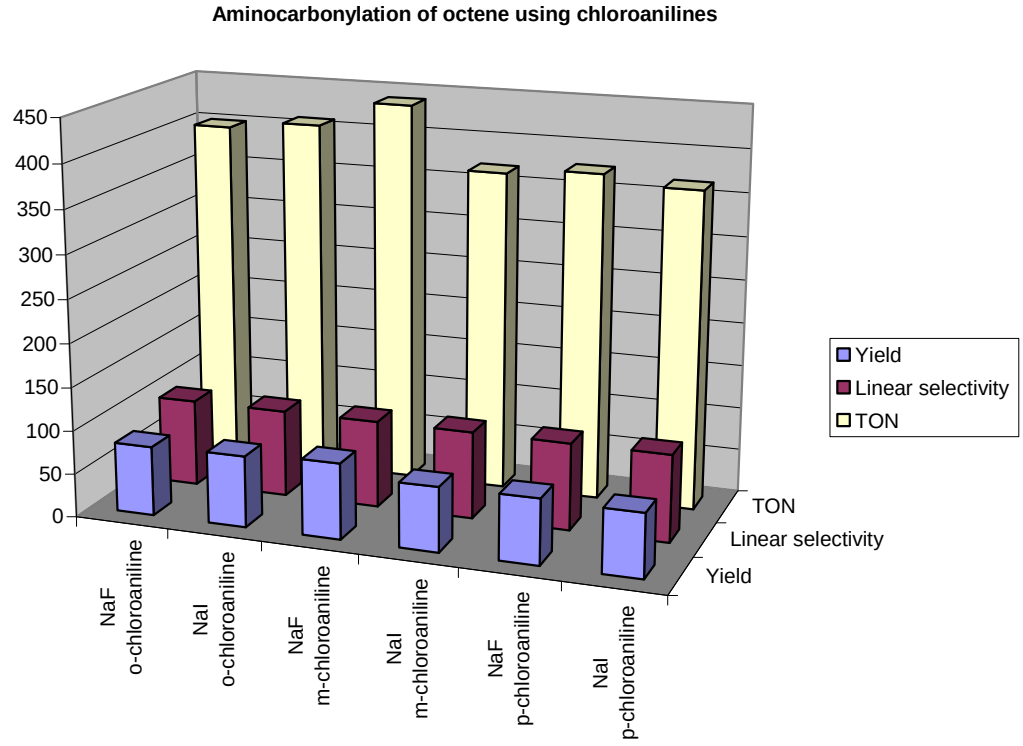
2.2.2.2.10.5.- Aminocarbonylation of Octene Using Chloroanilines.

Table 2.48. Aminocarbonylation of octene using other chloroanilines.



Entry	Amine	Halide salt	Yield	Linear Selectivity	TON
1	*o*-chloroaniline	NaF	80	100	400
2	*o*-chloroaniline	NaI	82	100	409
3	*m*-chloroaniline	NaF	87	100	439
4	*m*-chloroaniline	NaI	74	100	369
5	*p*-chloroaniline	NaF	75	100	376
6	*p*-chloroaniline	NaI	73	100	366

Conditions: Octene (2 mL, 12.74 mmol), amine (12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



To conclude this study of aminocarbonylation with different anilines, it was considered interesting to generate of *N*-chlorophenylamides. The possibility of the

generation of a wide group of compounds from chloro substrates via, the cross coupling reaction, and Heck reaction, converts this kind of compound into one of the most versatile interesting substrates.[62]

In the study to generate *N*-chlorophenylamide, the three isomers of chloroaniline were tested under aminocarbonylation conditions and the results are shown in Table 2.48.

While *o*-chloroaniline gave high yields in aminocarbonylation (Table 2.48, entries 1 and 2) and no significant difference between the use of NaI or NaF was observed, *m*-chloroaniline led to high conversions when NaI was used (Table 2.48, entry 3). However an evident decrease in yield was found when NaF was used (Table 2.48, entry 4). Moderate yields were obtained in the case of *p*-chloroaniline (Table 2.48, entries 5 and 6).

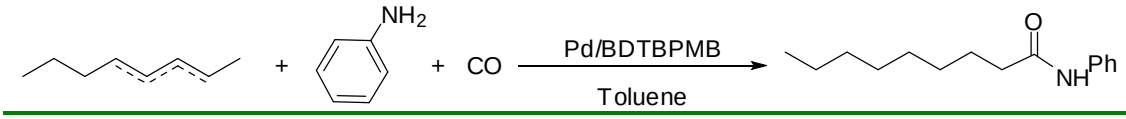
2.2.2.2.11.- Aminocarbonylation of Octene Isomers.

In Section 2.2.1.7 it was proven that the isomeration route is appreciably faster than the reaction between the nucleophile and the acylpalladium intermediate **6**. This reaction between the nucleophile and the acylpalladium species is evidently faster in terminal position than in internal ones. This was applied in the generation of linear acid and *N*-alkylamide starting from an internal isomer of octene (see Sections 2.2.1.8 and 2.2.2.1.13). These two studies proved that the selectivity of the process is not limited by the initial position of the double bond in the alkene.

To complete these Sections, 2-octene, 3-octene and 4-octene were tested under aminocarbonylation conditions using aniline as the nucleophile. The results were summarised in Table 2.48. It can be seen that when NaF was used, the three internal octene isomers (2-octene, 3-octene and 4-octene) gave high conversion (Table 2.49, entries 1, 3 and 5), similar to the yield obtained in the case of 1-octene (Table 2.37, entry 1). This confirms the sensitivity in this system to the initial octene isomer.

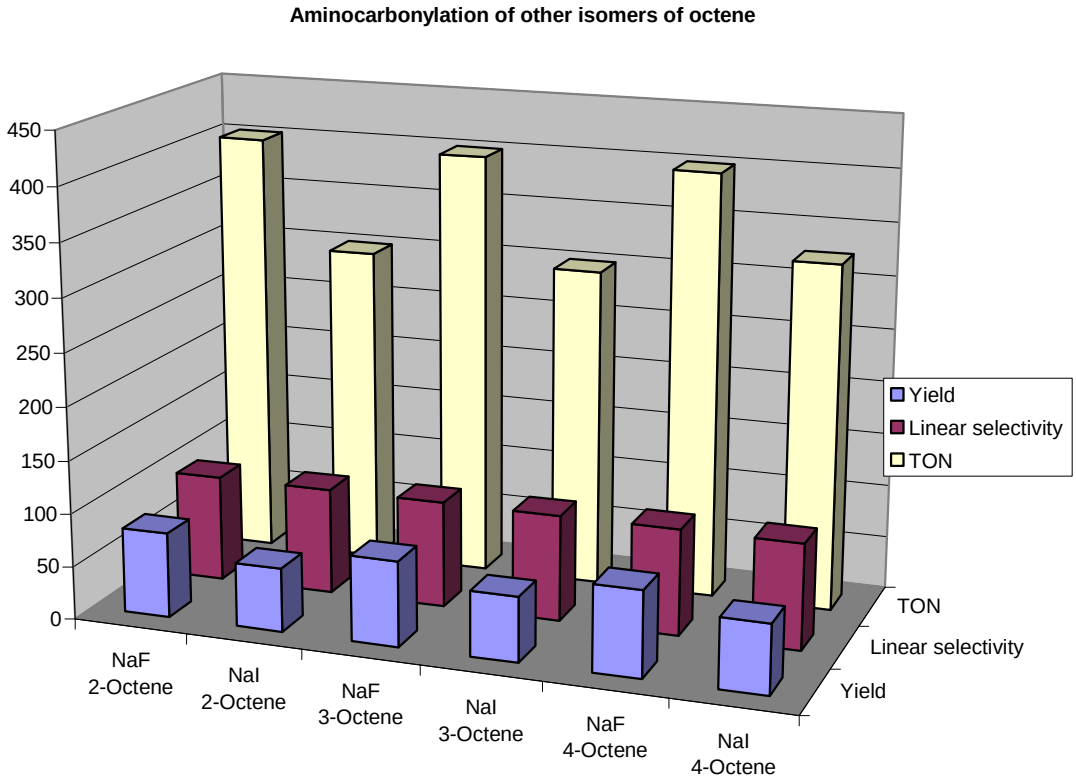
However, unexpectedly, when NaI was used, a significant decrease in the yield was obtained when the internal octene isomer was tested (Table 2.49, entries 2, 4 and 6) versus the internal octene (Table 2.32, entry 2).

Table 2.49. Aminocarbonylation of octene isomers.



Entry	Alkene	Halide salt	Yield	Linear Selectivity	TON
1	2-Octene	NaF	80	100	402
2	2-Octene	NaI	60	100	300
3	3-Octene	NaF	80	100	400
4	3-Octene	NaI	61	100	300
5	4-Octene	NaF	81	100	400
6	4-Octene	NaI	65	100	325

Conditions: Alkene (12.74 mmol), aniline (1.6 mL, 12.74 mmol), [$Pd(OAc)_2$] (5.6 mg, 0.025 mmol), BDTBPMB(25.1 mg, 0.0637 mmol), MSA (10 µL, 0.15 mmol), 2-naphthol (1.4 g, 9.55 mmol), NaX (0.0637 mmol), toluene (10 mL), 140ºC, P_{CO}=20 bar, 1 h.



2.2.2.3.- HPNMR Study of Aminocarbonylation

For a better understanding of the active system in aminocarbonylation, a $^{31}P\{^{1}H\}$-HPNMR has been carried out under 20 bar of carbon monoxide at 140ºC (Fig 2.36).[65] Two doublet peaks were found, with chemical shifts of 88.5 ppm and 38.0 ppm respectively. These chemical shifts are significantly higher than the normal hydride palladium complex of BDTBPMB (Table 2.48).[57h]

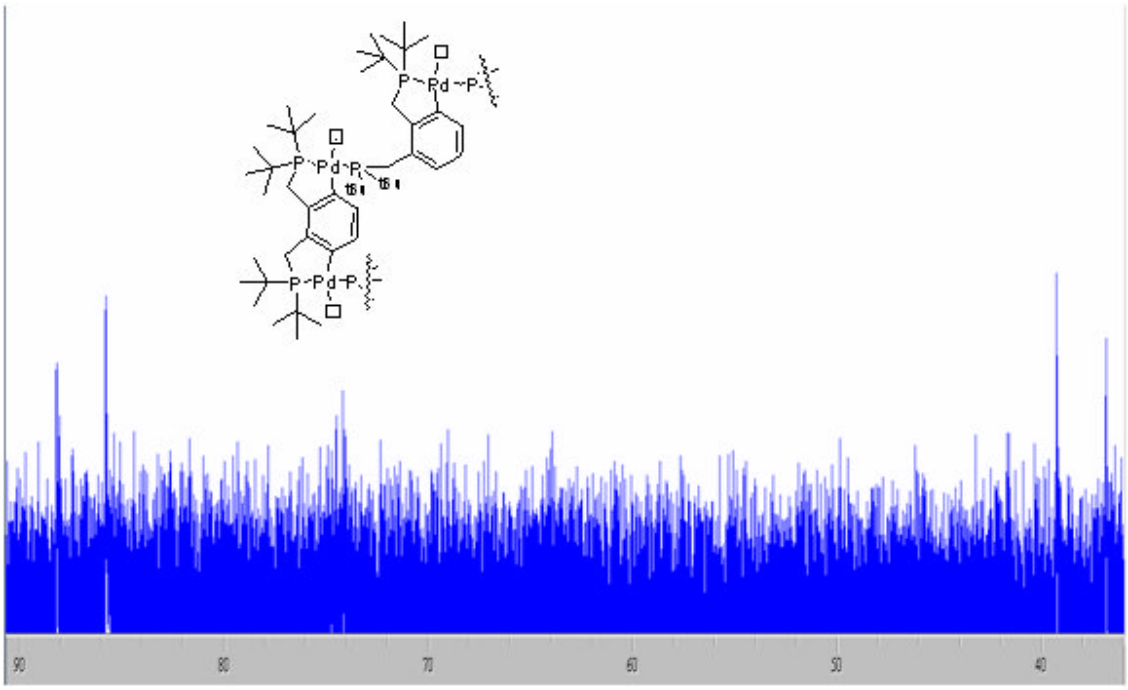


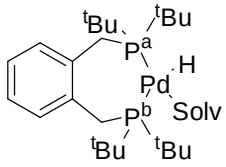
Fig 2.36. *HP-^{31}P NMR of aminocarbonylation of alkenes under 20 bar of CO.*

Likewise, the coupling constant (294 Hz) is appreciable higher and is more in accordance with a *trans* coupling between phosphorus atoms, than with the expected *cis* coupling between phosphorus atoms. *Trans* coupling can only be observed between inequivalent phosphorus atoms. The high chemical shift of one phosphorus atom may suggest it is contained in a five member ring.[63]

C-H activation of the BDTBPMB aromatic ring has been reported when $Pd(OAc)_2$ has been used as the precatalyst, generating a palladacycle. This palladacycle presents a

single peak at 111.7 ppm in the $^{31}P\{^{1}H\}$NMR spectrum, which is significantly higher than that of [Pd(BDTBPMB)H(solv)] (Table 2.50).[57h]

Table 2.50. $^{31}P\{^{1}H\}$ NMR data for [Pd(BDTBPMB)H(solv)] in different solvents at 293 K (*Adapted from reference 57h)*



Solvent	**δP_A**	**δP_B**	**^{2}J(PA–PB)/Hz**
THF	21.3	69.7	18.3
CH_3CN	23.9	68.8	19.8
EtCN	23.0	69.4	19.6

We tentatively propose, therefore, the structure shown in Fig 2.37. This structure is consistent with the NMR data. The palladacycle contains two phosphines in *trans* positions and an aryl-Pd bond which blocks the route to generate the *cis*-complex. This high chemical shift of the phosphorus atom in the metallated ring is expected for a five membered ring.[63]

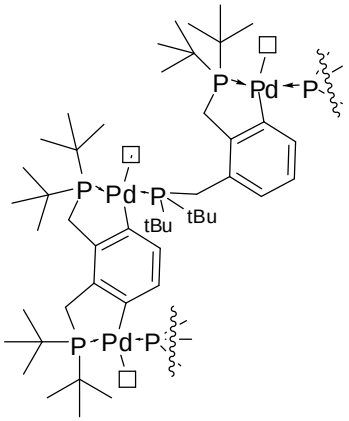
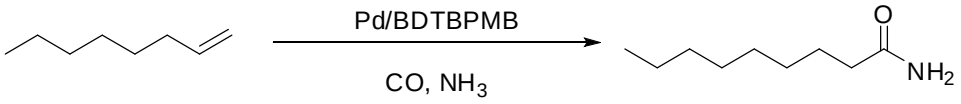


Fig 2.37. *Proposed palladacycle as the species identified by NMR spectrum under aminocarbonylation conditions*

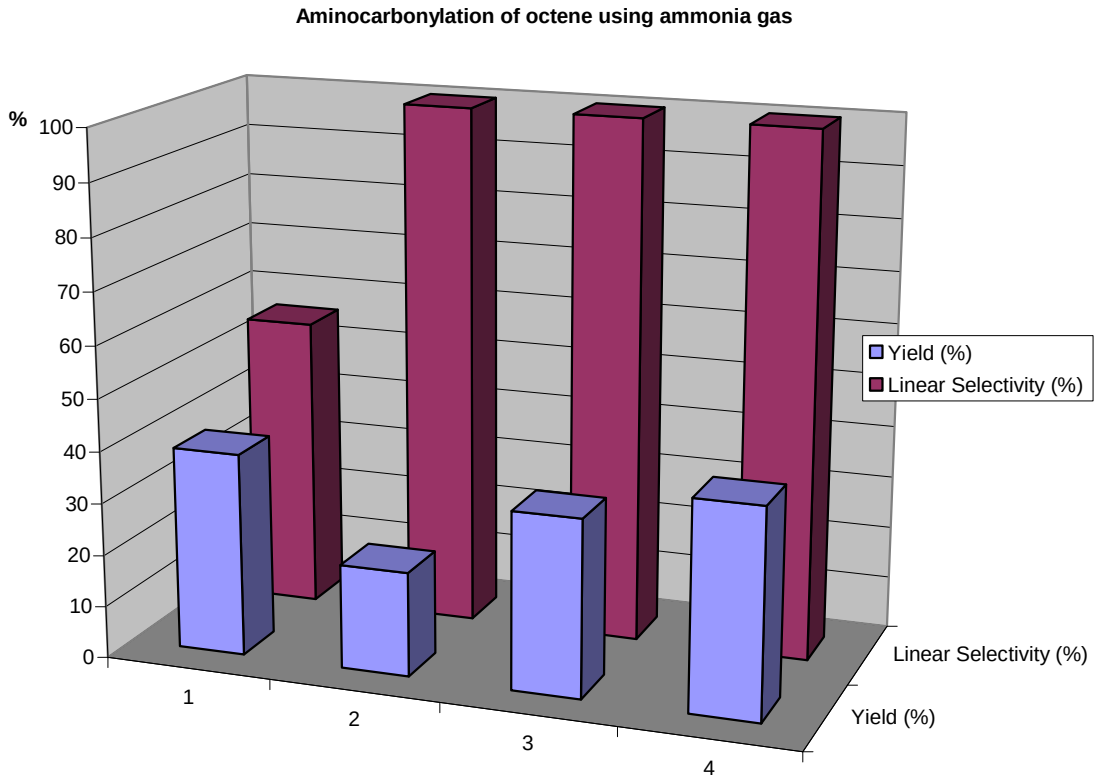
2.2.2.4.- Aminocarbonylation Using Ammonia Gas.

Table 2.51. Aminocarbonylation of octene using ammonia gas.



Entry	Solvent	NH_3 amount	Yield (%)	Linear Selectivity (%)
1	Pentanoic acid	4 bar	39	56
2	Pentanoic acid/water (10:1)	4 bar	20	100
3[a]	Pentanoic acid/water (10:1)	4 bar	34	100
4[a]	Pentanoic acid/water (10:1)	10 mL	40	100

Conditions: Octene (1 mL, 6.3 mmol), $[Pd(OAc)_2]$ (14 mg, 0.063 mmol), BDTBPMB (125.5 mg, 0.31 mmol), pentanoic acid (10 mL), P_{CO} = 60 bar, 135ºC, 17 h
a) 247 mg (0.63 mmol) $nHex_4N^+Cl^-$ was added.



Primary amides are the most important amides. Aminocarbonylation of alkenes may be a very elegant and interesting route to generate these highly valuable products from cheap and available feedstocks (alkenes, carbon monoxide and ammonia). However, only a few processes have been reported to be catalysed by heterogeneous system.[33] Recently, the Drent group has patented the generation of pentenamide from 1,3-butadiene in a system based on a palladium complex of BDTBPMB.[34a] In this system, an organic acid is used as solvent and it was proven to be essential in the activity of the catalyst.

To finish this study of the aminocarbonylation of alkenes, it was considered interesting to expand the results obtained by Drent in the aminocarbonylation of 1,3-butadiene to linear alkenes. Surprisingly under the conditions described by Drent, only moderate conversion was obtained and selectivity was low (Table 2.51, entry 1).

The addition of water significantly increases the selectivity of the reaction. However, an evident drop of yield was obtained (Table 2.51, entry 2). To explore if the origin of this drop in yield was due to solubility problems, a phase transfer agent, $nHex_4N^+Cl^-$, was used. A better conversion was obtained in the presence of this compound, keeping selectivity at excellent levels (Table 2.51, entry 3).

A significant amount of pentanamide had been formed, most likely from the reaction of pentanoic acid and ammonia gas. Hence, this may be an explanation of why the yield is only moderate. This secondary reaction to generate pentanamide removes the ammonia from the medium and therefore stopps the aminocarbonylation reaction.

In an attempt to improve the yield, liquid ammonia was used. Only a slight increase in yield was obtained when 10 mL of liquid ammonia were used (Table 2.51, entry 4).[65] However, all the pentanoic acid used was converted to pentanamide, confirming the theory that this secondary route removes ammonia, therefore, affecting the aminocarbonylation route.

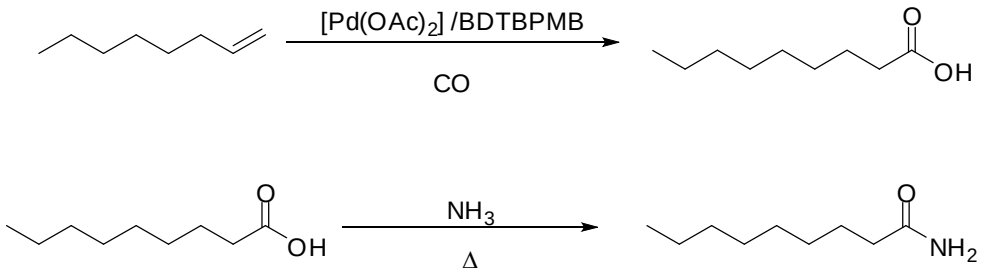


Fig 2.38. *Explanation of the role of water in aminocarbonylation with ammonia gas.*

To explain the role of water in the increase in selectivity of this reaction, an experiment without ammonia gas was performed (Fig 2.38). In this experiment, nonanoic acid was obtained. This suggests that the mechanism of formation of the amide in the presence of water involves two steps. The first step follows the mechanism of hydroxycarbonylation and the acid formed then reacts with ammonia to give the amide.

In an attempt to increase the conversion, 2-naphthol was used as a promoter. No conversion was found under these conditions.

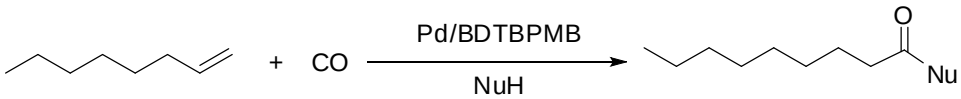
2.2.3.- Methoxycarbonylation and Hydroxycarbonylation of Octene Using Arylalcohols as Promoters.

As Section 2.2.2 shows, aminocarbonylation of octene catalysed by palladium in the presence of an arylalcohol as a promoter has been proven to be an effective in the generation of amides.[64] It is, therefore, interesting to know if this kind of promoter can play the positive role described in aminocarbonylation in other carbonylations, such as methoxycarbonylation or hydroxycarbonylation.

The system Pd/BDTBPMB system has been proven to be highly active in methoxycarbonylation, giving high conversion and selectivity under mild conditions.[47,57] However, a high loading of palladium is required to obtain quantitative conversion of linear alkenes.[47] To try to improve these results a series of experiments with the addition of different arylalcohols has been carried out, with results shown in Table 2.52.

As a reference, an experiment was carried out without any promoter. This gave low conversion (Table 2.52, entry 1). Surprisingly, the addition of phenol to the system completely blocked the route when the reaction was run at 120ºC (Table 2.52, entry 2). The addition of 1-naphthol gave lower conversion than that obtained without a promoter (Table 2.52, entry 3). However, 2-naphthol showed a positive effect (Table 2.52, entry 4), giving almost double the conversion compared with that obtained in the reference experiment (Table 2.52, entry 1).

Table 2.52. Methoxycarbonylation and hydroxycarbonylation of octene using arylalcohols as promoters**.**

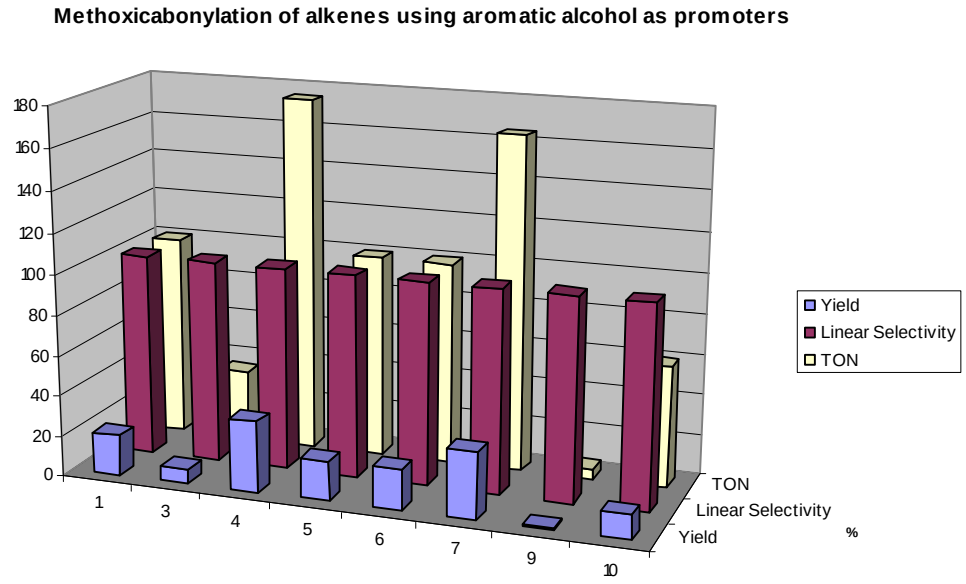


Entry	Conditions	T	Additive	Yield	Linear Selectivity	TON
1	A	120	-	20	>99	100
2	A	120	PhOH	-	-	-
3	A	120	1-naphthol	7	>99	35
4	A	120	2-naphthol	35	>99	175
5	A	140	PhOH	20	>99	100
6	A	140	1-naphthol	20	>99	100
7	A	140	2-naphthol	33	>99	165
8[a)]	A	140	PhOH	-	-	-
9 [a)]	A	140	1-naphthol	1	>99	6
10 [a)]	A	140	2-naphthol	12	>99	64
11	B	140	PhOH	-	-	-
12	B	140	1-Naphthol	-	-	-
13	B	140	2-Naphthol	-	-	-
14[a)]	B	140	2-Naphthol	-	-	-

Conditions A: Octene (2 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), additive (12.74 mmol), P_{CO}=20 bar, methanol (10 mL), 1 h

Conditions B: Octene (2 mL, 12.74 mmol), $[Pd(OAc)_2]$ (5.6 mg, 0.025 mmol), BDTBPMB (25.1 mg, 0.0637 mmol), MSA (10 μL, 0.15 mmol), additive (12.74 mmol), P_{CO}=20 bar, dioxane (10 mL), water (2 mL).

a) NaI (9.5 mg, 0.0637 mmol) was added.



When the temperature was increased, the reaction in the presence of phenol gave low conversion (Table 2.52, entry 5). This result was unexpected considering that when the reaction was carried under the same conditions at 120ºC no conversion was obtained (Table 2.52, entry 2). Hence, a decrease of 20ºC under these conditions blocks the route.

This positive effect of the use of arylalcohol at high temperatures was also observed when 1-naphthol was used as a promoter. In that case, the conversion at 140ºC (Table 2.52, entry 6) was more than double that obtained at 120ºC. In the use of 2-naphthol no appreciable difference was obtained. At 120ºC (Table 2.52, entry 4) and 140ºC (Table 2.52, entry 7), moderate conversions were found.

A negative effect has been found in the addition of NaI in methoxycarbonylation. In the case of methoxycarbonylation in the presence of phenol, the route did not give significant yields (Table 2.52, entry 8). When 1-naphthol or 2-naphthol were used as promoters, the addition of NaI caused a drop in conversion (Table 2.52, entries 9 and 10).

The use of a promoter in hydroxycarbonylation reactions has also been studied. However, no conversion was found when the reaction was carried out in the presence of phenol, 1-naphthol or 2-naphthol (Table 2.52, entries 11 to 13). The addition of NaI does not give a significant difference (Table 2.52, entry 14).

2.2.4.- Transamidation and Ester/amide Exchange.

As Section 2.2.2 shows, the Pd/BDTBPMB system has been proven to be very active in the aminocarbonylation of alkenes. Although during this study high conversions in the generation of *N*-substituted amides have been obtained, the formation of primary amides required a high load of catalyst to give moderate conversion (See Section 2.2.2.4).

An alternative for the generation of this primary amide is the transamidation of *N*-subtituted amides or ester/amide exchange of an ester, both of which are available via carbonylation (Fig 2.39). Therefore, starting from an ester or *N*-subtituted amide in the presence of ammonia, primary amides may be formed.

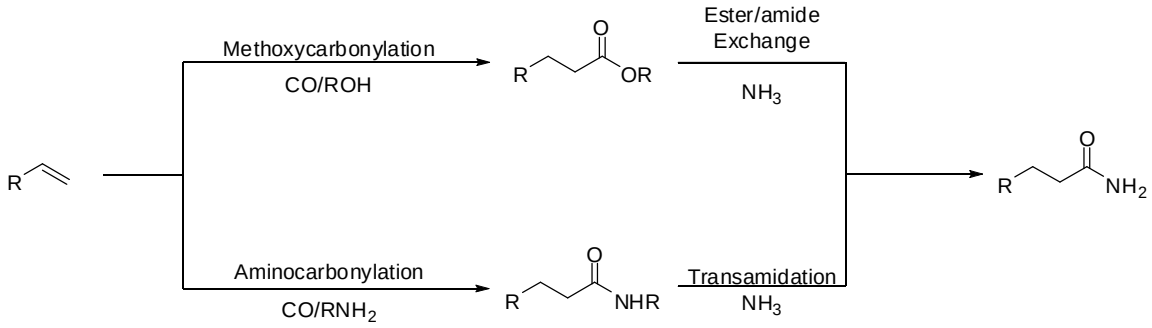


Fig 2.39. *Generation of primary amides in two steps*

Transamidation and exchange ester/amide have been reported for a wide range of active catalytic systems in this kind of reaction.[66] Lewis acids, normally titanium complexes are the most active of these systems. Three Lewis acids ([$Ti(NMe_2)_4$], [$Ti(O^iPr)_4$] and [$Sc(OTf)_3$]), were been chosen for this study.

2.2.4.1.- Transmidation Reactions Catalysed by Tetrakis(diamino)titanium (IV).

This highly hydroscopic titanium complex, [$Ti(NMe_2)_4$], has been proven to be highly active in transmiadation.[66c] Therefore, it was considered interesting to start this study using this complex.

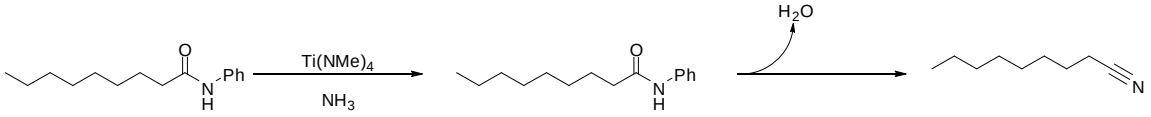
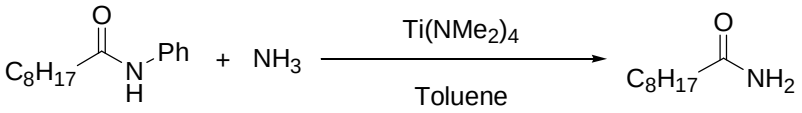


Fig 2.40. *Transamidation of N-phenylnonamide*

When the reaction was carried out at 120ºC using 5 mL of liquid ammonia,[66] high conversion was obtained (Table 2.53, entry 1). However, a secondary product, nonanenitrile, was also detected. This product is presumably formed by the dehydratation of the main product, nonamide (Fig 2.40).

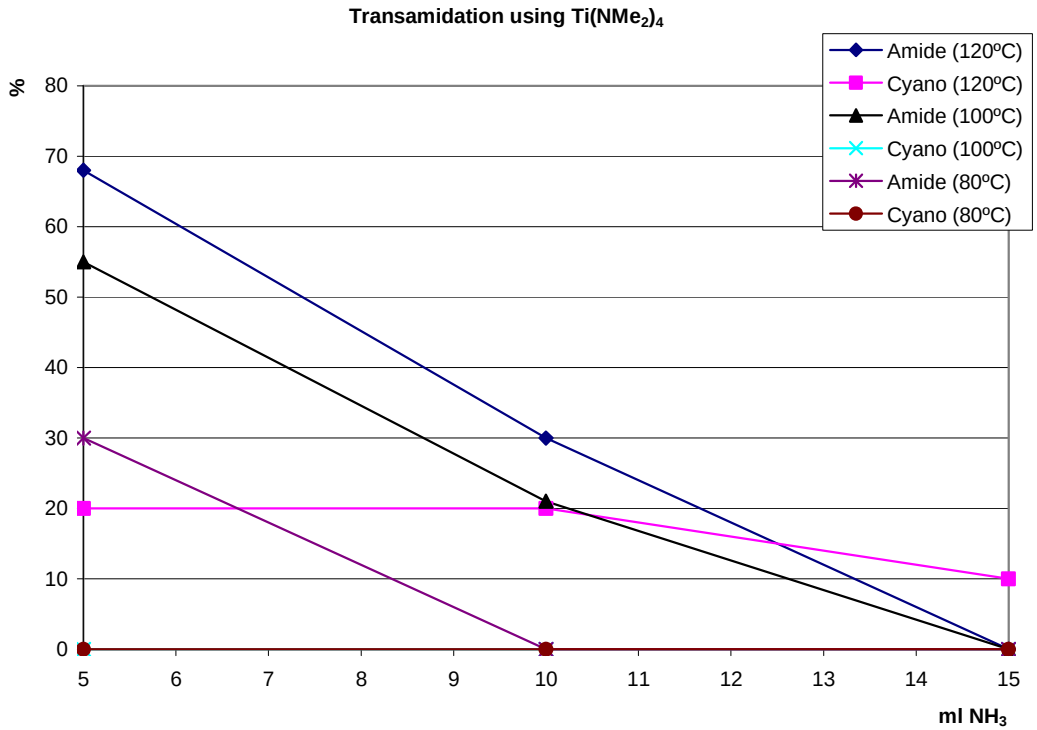
Surprisingly an increase of ammonia in the medium had a significantly negative role in the reaction giving only a moderate yield (Table 2.53, entry 2). Only nonanenitrile was obtained when a large excess of ammonia was used (Table 2.53, entry 3).

Table 2.53. Transmidation reactions catalysed by tetrakis(diamino)titanium (IV).



Entry	T (ºC)	NH_3	Yield (%)	Amide (%)	Cyano (%)
7	120	5 mL	88	68	20
8	120	10 mL	50	30	20
9	120	15 mL	10	0	10
10	100	5 mL	55	55	0
11	100	10 mL	21	21	0
12	100	15 mL	0	0	0
13	80	5 mL	30	30	0
14	80	10 mL	0	0	0
15	80	15 mL	0	0	0

Conditions: N-phenylnonamide (1g, 4.2 mmol), [$Ti(NMe_2)_4$] (20 µL, 0.08 mmol), toluene (10 mL), NH_3 (as described), 14 h.



Dehydratation depends drastically on the temperature, and attempting to decrease the amount of nonanenitrile formed, the reaction was carried out at moderate temperatures (100ºC). When 5 mL of ammonia was used at this temperature, no formation of nonanenitrile was observed, however a significant decrease in yield of amide was obtained (Table 2.53, entry 4). An increase of ammonia in the medium yielded lower conversion (Table 2.53, entry 5), keeping the trend observed at 120ºC. No conversion was obtained when a large excess of ammonia was used (Table 2.53, entry 6)

When the reaction was carried out at 80ºC, only low concentration of ammonia gave some conversion (Table 2.53, entry 7). The reaction was completely inhibited at high ammonia concentration (Table 2.53, entries 8 and 9).

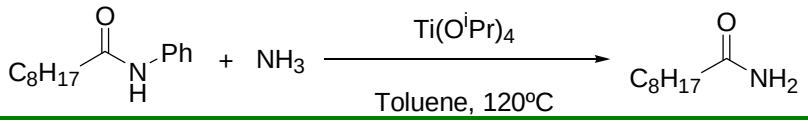
2.2.4.2.- Transmidation Reaction Catalysed by Titanium Isopropoxide.

Another titaninum species, titanium isopropoxide, has been tested in transamidation. This complex is more stable and cheaper than tetrakis(diamino)titanium (IV). Therefore, from the viewpoint of manipulation and industrial application, this catalyst is more attractive than tetrakis(diamino)titanium (IV).

No conversion was obtained at low ammonia concentrations (Table 2.54, entry 1). An increase in ammonia in the medium increased conversion (Table 2.54, entry 2). This effect is more evident when a high excess of liquid ammonia was used, where moderate conversion was obtained (Table 2.54, entry 3). No formation of nonanenitrile was observed during this study.

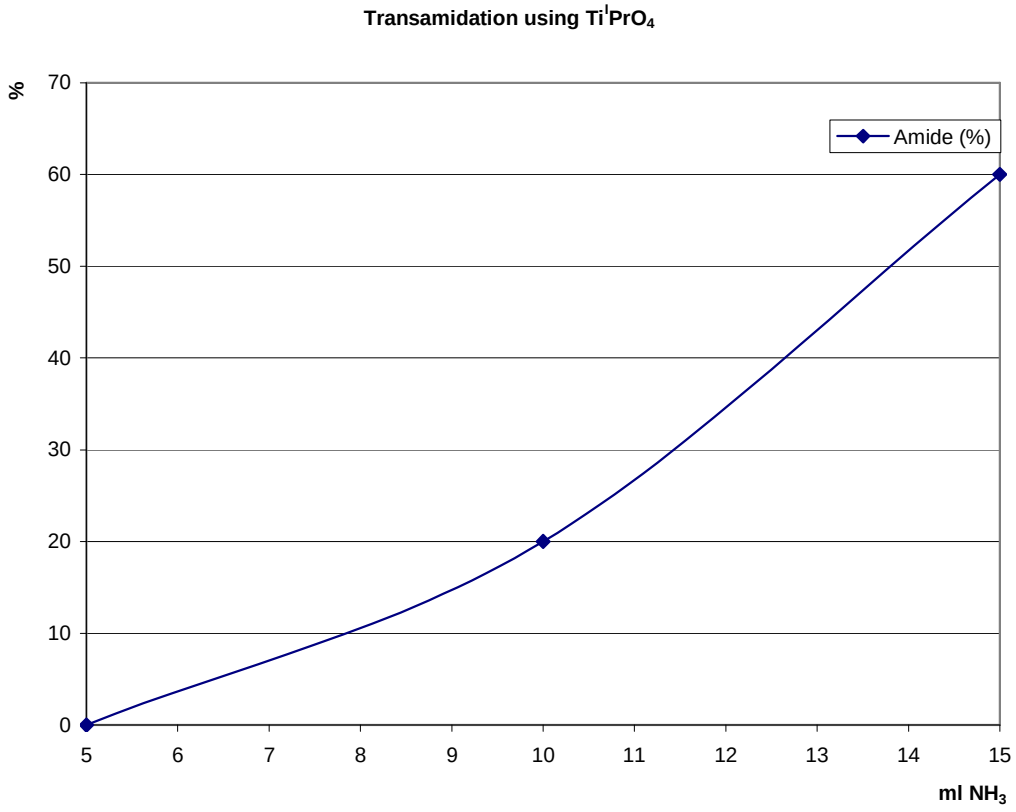
Unexpectedly, this titanium complex showed different behaviour from that of $[Ti(NMe_2)_4]$. While an increase in concentration plays a negative role in transamidation catalysed by $Ti(NMe_2)_4$, in the presence of $[Ti(^iOPr)_4]$, transamidation required a high excess of ammonia for good conversion.

Table 2.54. Transmidation reaction catalysed by titanium isopropoxide.



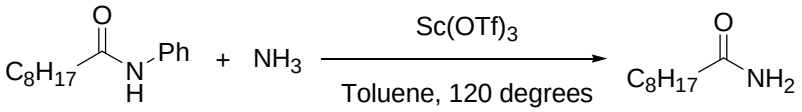
Entry	NH_3	Yield (%)	Amide (%)	Cyano (%)
1	5 mL	0	0	0
2	10 mL	20	20	0
3	15 mL	60	60	0

Conditions: N-phenylnonamide (1g, 4.2 mmol), [$Ti(O^iPr)_4$] (25 μL, 0.08 mmol), toluene (10 mL), NH_3 (as described), 120ºC, 14 h.



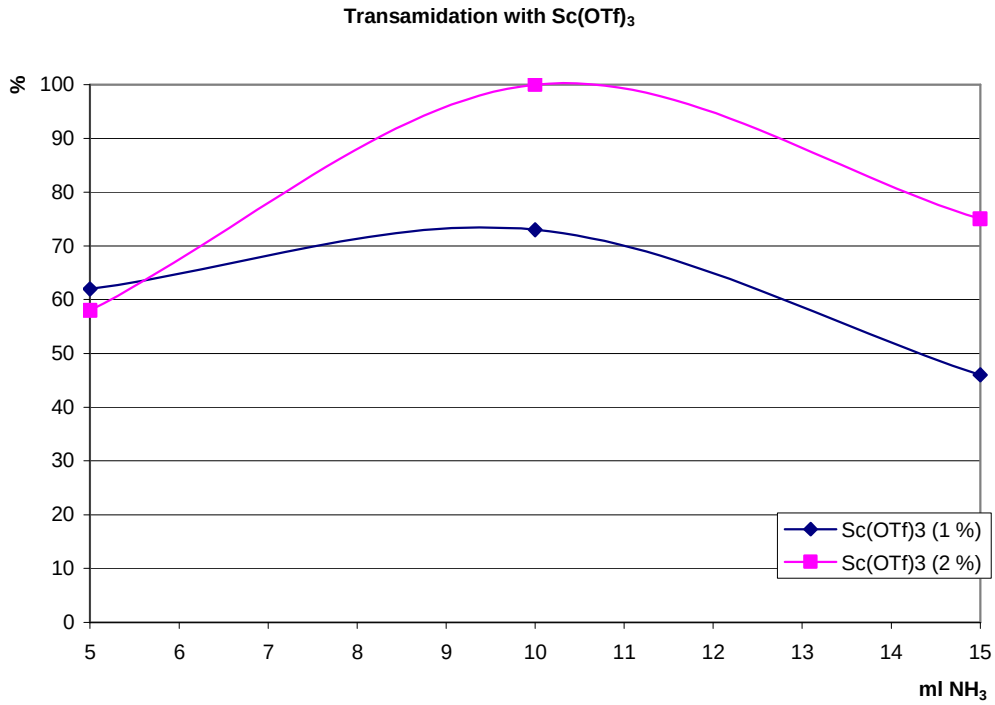
2.2.4.3.- Transmidation Reaction Catalysed by Scandium (III) Triflate.

Table 2.55. Transmidation reaction catalysed by Scandium (III) triflate.



Entry	NH_3	Lewis acid	Yield (%)
1	5 mL	$[Sc(OTf)_3]$ (1 %)	62
2	10 mL	$[Sc(OTf)_3]$ (1 %)	73
3	15 mL	$[Sc(OTf)_3]$ (1 %)	46
4	5 mL	$[Sc(OTf)_3]$ (2 %)	58
5	10 mL	$[Sc(OTf)_3]$ (2 %)	100
6	15 mL	$[Sc(OTf)_3]$ (2 %)	75

Conditions: N-phenylnonamide (1g, 4.2 mmol), $[Sc(OTf)_3]$ (as described), toluene (10 mL), NH_3 (as described), 120ºC, 14 h.



Although titanium complexes are widely used for this kind of reaction, other Lewis acids have been proven to be active. Recently, Stahl and co-workers have discovered that scandium triflate is particularly active in transamidations.[66c] Therefore, it was considered

interesting to examine this Lewis acid as a catalyst in the transamidation of *N*-phenylnonamide to nonamide in the presence of liquid ammonia.

The use of 1 mol % of scandium triflate in the presence of 5 mL of liquid ammonia gave high conversion (Table 2.55, entry 1). A Slight increase in yield was obtained when 10 mL of liquid ammonia were used (Table 2.55, entry 2). However, with a high excess of liquid ammonia, a significant decrease in yield was observed (Table 2.55, entry 3). In this study no nonanenitrile was detected.

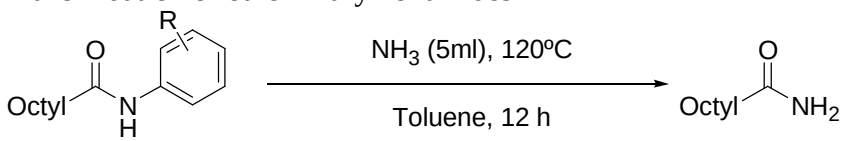
The same trend was observed when 2 mol % of scandium triflate was used. At low concentrations of liquid ammonia, the reaction yielded moderate conversion (Table 2.55, entry 4). An evident increase in conversion was obtained when 10 mL of liquid ammonia were added (Table 2.55, entry 5). High concentrations of liquid ammonia (15 mL) yielded moderate conversion (Table 2.55, entry 6).

2.2.4.4.- Transmidation of Other *N*-Arylnonamides.

For a better understanding of the limitations of transmidation reaction, a series of experiments were carried out using *N*-arylnonamide, which contains different electron donating and electron withdrawing substituents.

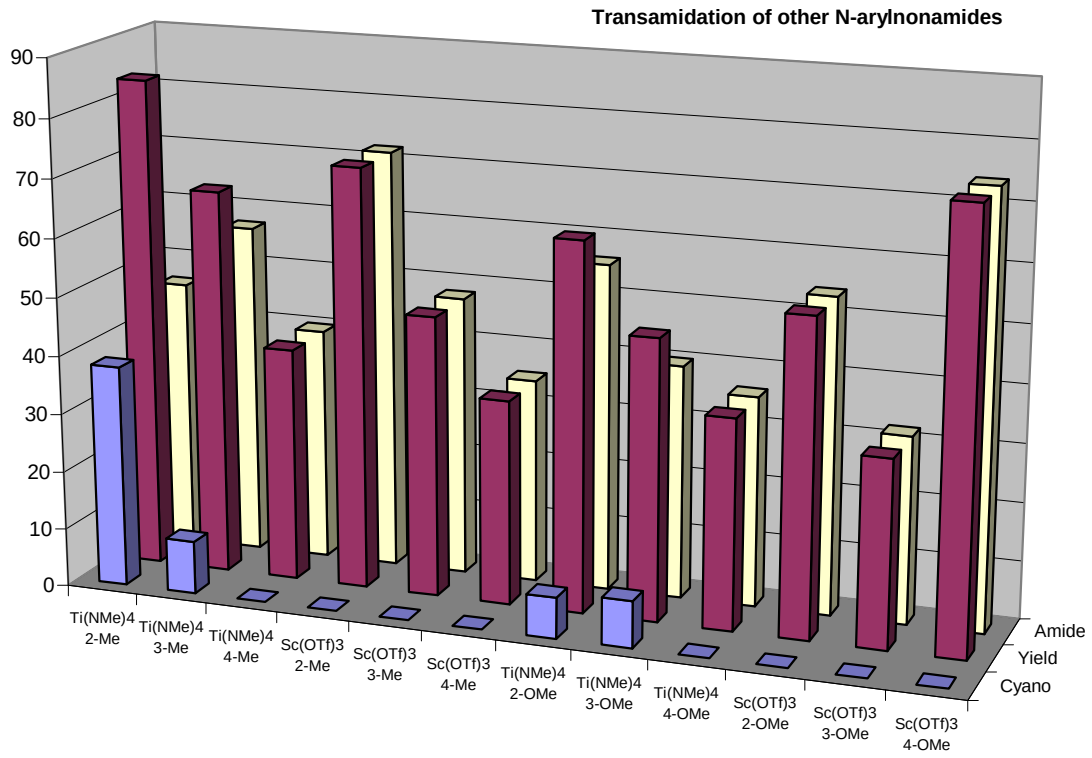
N-(methylphenyl)nonamide was tested initially. $[Ti(NMe_2)_4]$ and $[Sc(OTf)_3]$ gave high conversion when *N*-(2-methylphenyl)nonamide was used as the subtrate (Entry 2.56, entries 1 and 4). However, a significant amount of nonanenitrile was formed when $[Ti(NMe_2)_4]$ was used (Table 2.56, entry 1). No nonanenitrile was detected under $[Sc(OTf)_3]$ catalysis (Table 2.56, entry 4). *N*-(3-Methylphenyl)nonamide gave moderate conversion under the catalysis of $[Ti(NMe_2)_4]$ and $[Sc(OTf)_3]$ (Table 2.56, entries 2 and 5). Some nonanenitrile was found in the reaction catalysed by $[Ti(NMe_2)_4]$. An appreciable decrease in yield was found when *N*-(4-methylphenyl)nonamide was tested, obtaining only low conversions (Table 2.56, entries 3 and 6).

Table 2.56. Transmidation of other *N*-arylnonamides



Entry	R	Catalyst	Yield	Amide	Cyano
1	2-Me	$[Ti(NMe_2)_4]$	84	46	38
2	3-Me	$[Ti(NMe_2)_4]$	66	57	9
3	4-Me	$[Ti(NMe_2)_4]$	40	40	0
4	2-Me	$[Sc(OTf)_3]$	72	72	0
5	3-Me	$[Sc(OTf)_3]$	48	48	0
6	4-Me	$[Sc(OTf)_3]$	35	35	0
7	2-OMe	$[Ti(NMe_2)_4]$	63	56	7
8	3-OMe	$[Ti(NMe_2)_4]$	48	40	8
9	4-OMe	$[Ti(NMe_2)_4]$	36	36	0
10	2-OMe	$[Sc(OTf)_3]$	54	54	0
11	3-OMe	$[Sc(OTf)_3]$	32	32	0
12	4-OMe	$[Sc(OTf)_3]$	74	74	0
13	2-CF_3	$[Ti(NMe_2)_4]$	14	14	0
14	3-CF_3	$[Ti(NMe_2)_4]$	55	48	7
15	4-CF_3	$[Ti(NMe_2)_4]$	51	51	0

Conditions: Amide (4.2 mmol), Lewis acid (0.08 mmol), toluene (10 mL), NH_3 (5 mL), 120ºC, 14 h.



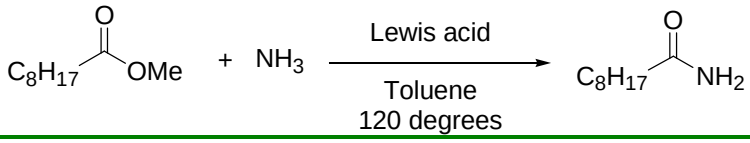
N-(methoxyphenyl)nonamide contains a highly electron rich aromatic ring, which may give some variation in the results obtained, in the case *N*-(methylphenyl)nonamide. It was therefore considered interesting to test this kind of substrate in transamidation. Transamidation of *N*-(2-methoxyphenyl)nonamide yielded moderate conversion (Table 2.56, entries 7 and 10). Both catalysts gave similar activity, however, some nonanonitrile was formed when $[Ti(NMe_2)_4]$ was used. $[Ti(NMe_2)_4]$ and $[Sc(OTf)_3]$ gave different results when *N*-(3-methoxyphenyl)nonamide was used (Table 2.56, entries 8 and 11). While $[Ti(NMe_2)_4]$ gave moderate conversion (some nonanenitrile was obtained), $[Sc(OTf)_3]$ reported only low yields (Table 2.56, entry 11). In the case of *N*-(4-methoxyphenyl)nonamide, low conversion was obtained when $[Ti(NMe_2)_4]$ was used, while $[Sc(OTf)_3]$ yielded high conversion (Table 2.56, entries 9 and 12).

N-(trifluoromethylphenyl)nonamide was also tested. These amides have a highly electron deficient aromatic ring due to the trifluoromethyl substituent. When *N*-(2-trifluoromethylphenyl)nonamide was examined under the catalysis of $[Ti(NMe_2)_4]$, a low yield was obtained (Table 2.56, entry 13). *N*-(3-trifluoromethylphenyl)nonamide yielded higher conversion, however, nonanenitrile was detected (Table 2.56, entry 14). *N*-(4-trifluoromethylphenyl)nonamide gave similar yields to *N*-(3-trifluoromethylphenyl)nonamide, but no formation of nonanenitrile was observed (Table 2.56, entry 15).

2.2.4.5.- Ester/amide Exchange

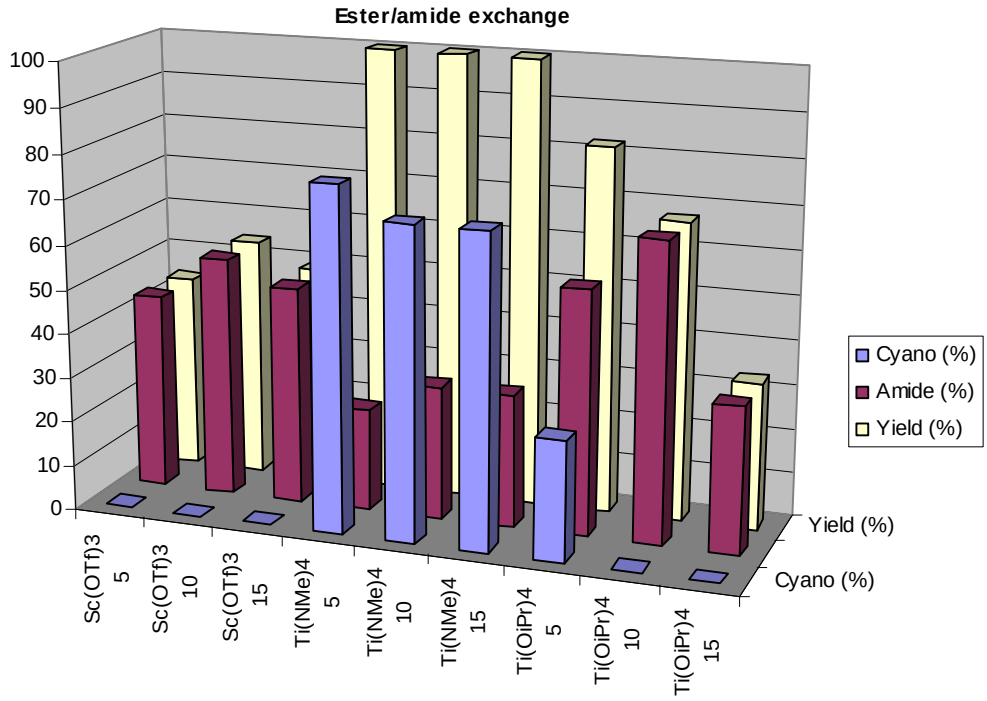
The Pd/BDTBPMB system has been proven to be extremely active in methoxycarbonylation.[57] The formation of the methylester under the catalysis of this system is highly favourable, requiring mild conditions (1 bar of CO and room temperature), and giving high conversion and linear/branched selectivities. Therefore it was considered especially attractive to conclude this transamidation study with a series of experiments to generate primary amides form methylesteres. This reaction has been reported under Lewis acid catalysis.[66e] The three Lewis acids ($[Sc(OTf)_3]$, $[Ti(NMe_2)_4]$ and $[Ti(O^iPr)_4]$), active in transamidation were tested in this reaction and the results are summarised in Table 2.57.

Table 2.57. Ester-amide exchange.



Entry	NH_3	Lewis acid	Yield (%)	Amide (%)	Cyano (%)
1	5 mL	$[Sc(OTf)_3]$	44	44	0
2	10 mL	$[Sc(OTf)_3]$	54	54	0
3	15 mL	$[Sc(OTf)_3]$	49	49	0
4	5 mL	$[Ti(NMe_2)_4]$	100	23	77
5	10 mL	$[Ti(NMe_2)_4]$	100	30	70
6	15 mL	$[Ti(NMe_2)_4]$	100	30	70
7	5 mL	$[Ti(O^iPr)_4]$	82	55	27
8	10 mL	$[Ti(O^iPr)_4]$	67	67	0
9	15 mL	$[Ti(O^iPr)_4]$	33	33	0

Conditions: Methyl nonanoate (0.84 mL, 4.2 mmol), lewis acid (0.08 mmol), toluene (10 mL), NH_3 (as described), 120ºC, 14 h.



$[Sc(OTf)_3]$ gave moderate yields when a low concentration of liquid ammonia was used (Table 2.57, entry 1). A slight increase in yield was observed when higher concentrations of ammonia were used (Table 2.57, entries 2 and 3).

Excellent conversions were obtained in the reactions catalysed by [$Ti(NMe_2)_4$]. However, the main product was nonanenitrile (Table 2.57, entry 4). No significant difference was observed when higher concentrations of ammonia were used (Table 2.57, entries 5 and 6).

[$Ti(O^iPr)_4$] gave high conversion in a low concentration of ammonia (Table 2.57, entry 7). However, a significant amount of nonanenitrile was obtained. An increase in ammonia in the medium decreased the yield (Table 2.57, entry 8), but the formation of nonanenitrile was apparently inhibited under these conditions. Low conversion was obtained when a large excess of ammonia was used (Table 2.57, entry 9).

2.3.- Conclusions.

The aim of the studies in this chapter was the generation of acids and amides under mild conditions in reactions catalysed by homogenoues systems.

The first study consisted of the generation of acids via the carbonylation of alkenes. Pd/BDTBPMB was found to be highly active in these kinds of reaction, leading to high conversions and selectivities. Different substrates were tested for a better understanding of the reaction, giving high conversions and selectivities. In this study, an essential role of the solvent was reported. Dioxane was proven to be the optimum solvent, due mainly to its miscibility, which allowed a high concentration of water in the medium.

In aminocarbonylation, a combination of halide salts/arylalcohol were found to be an interesting promoter system in this kind of reaction, raising the conversion obtained for the Pd/BDTBPMB system, and giving high selectivities and yields (TON between 300 and 400 mol product/mol catalyst). An intensive study on different halide salts and conditions has been carried out for a better understanding of the reaction. However, these excellent results have not been able to extend to primary amides where only moderate conversions were obtained.

To resolve this, a synthesis of primary amides in two steps was taken into consideration. This synthesis consisted of methoxycarbonylation or aminocarbonylation followed by transamidation or exchange ester/amide with ammonia. In this reaction, three different Lewis acids have been examined, giving different selectivities. The conversions

were moderate, although a secondary product, nonanenitrile, was formed by dehydratation during the reaction.

To complete the study, an air stable phosphonium salt, $[BDTBPMBH_2][BF_4]_2$ was prepared. It was proven to be as active as BDTBPMB in both hydroxycarbonylation and aminocarbonylation, converting it to be an air stable alternative to the use of BDTBPMB.

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Chapter 3: Hydrogenation of amides

3.- Hydrogenation of Amides

3.1.- Introduction.

The reduction and oxidation of carbonyl groups are some of the most used reactions in chemistry.[1] Organic acids and their derivatives such as esters, anhydrides and amides, are the most difficult carbonyl compounds to reduce.[2] However, since Finholt and co-workers proved the activity of lithium aluminum hydride in reduction of these groups,[3] this reaction has been widely used in chemistry, especially in the fine chemical and pharmaceutical industries. This common reaction in laboratories is not acceptable for use in industrial processes, such as in bulk chemistry, due to the large amount of waste formed, and the high cost of the hydride compounds.

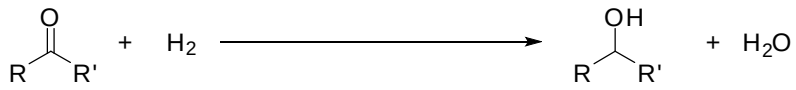


Fig 3.1. *Hydrogenation of carbonyl groups.*

Industrial processes for the reduction of carbonyl groups often involve catalytic hydrogenation.[4] Hydrogenation processes consist of the reduction of the carbonyl group using hydrogen (Fig 3.1). *A priori*, this process presents several economic and environmental benefits, compared to the reduction with lithium aluminum hydride, due to the low cost of hydrogen gas, and the fact that only water is produced as waste.

3.1.1.- Heterogenous Catalytic Systems.

The systems developed initially were based on heterogeneous catalysts. Harsh conditions must be used in these processes to generate the desired product due to the low reactivity of carboxylic acids and their derivates during reduction.[5] For example, common catalysts based on copper require temperatures up to 250ºC and pressures up to 300 bar to reduce ethyl acetate to ethanol.[6] Only low conversion was obtained (~30%) when the

reaction was carried out at temperature below 200 ºC.[6a] The use of promoters such as cobalt, manganese or magnesium salts increased the selectivity to ethanol (Fig 3.2).

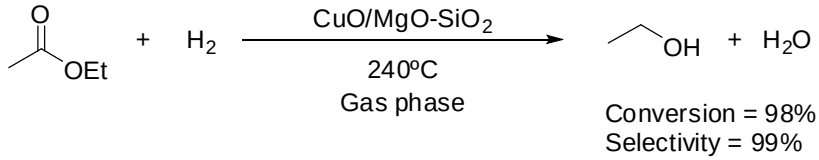


Fig 3.2. *Hydrogenation of ethyl acetate catalysed by copper.*

Alternatively, a combination of rhenium and rhodium salts has been proven to be active in reducing carboxylic acids (Fig 3.3).[7] Under these conditions, a decrease in the required temperature and pressure was observed, with respect to copper catalysis giving a high conversion to the alcohol (97 %). This system (which preferentially reduces acids over ester) suffers from carbon monoxide poisoning, therefore requiring frequent catalyst changes.[7c] A process to regenerate the catalyst was developed, which involves thermal treatment under a hydrogen atmosphere.

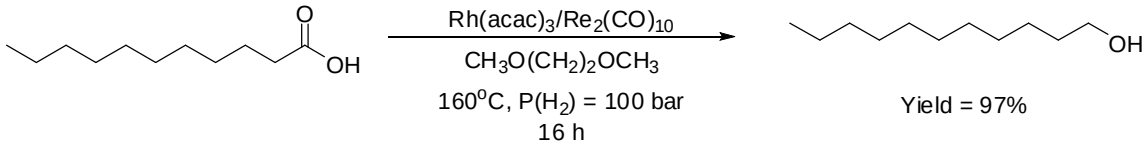


Fig 3.3. *Hydrogenation of decanoic acid catalysed by Rh/Re system.*

It should be noted that the conditions of these reductions are harsh, and usually under these conditions, the selectivity of the processes is low. However, the Maki group has developed a catalyst based on a mixture of chromium and zirconium salts, which is able to generate aldehydes from acids (Fig 3.4).[8] It should also be noted that in the reduction of acids to alcohols using a two step process (firstly reduction to the aldehyde followed by reduction to the alcohol), the second step is normally significantly faster than the first. Thus, the selective reduction of acids is a difficult process which has significant importance in chemistry. Under conditions developed by the Maki group, benzaldehyde could be formed in high yield (98%) and selectivity (96%) by the reduction of benzoic acid. The

pressure must be kept constant at 1 bar, but with high temperature (350ºC). Similar results were obtained using CeO_2 as catalyst.[9]

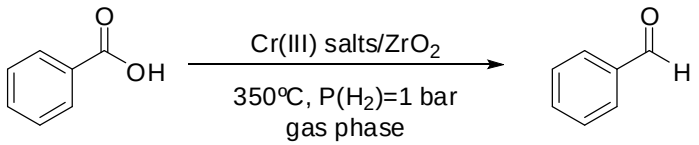


Fig 3.4. *Selective reduction of benzoic acid catalysed by the Cr/Zr system.*

With a production of 100,000 t/a, amines are an important group of compounds in bulk chemistry, but they are also useful intermediates in organic synthesis.[10] Thus, the route to amines by reduction of amides is an attractive process. Copper chromite has been proven to be active in the reduction of *N*,*N*-disubstituted amides at high temperature and pressure.[11] Although the yield and selectivity were high (95.4% and 99% respectively), the alcohol was also formed in the reaction. The use of zeolites to support the catalyst both increased the reaction rate, and increased the formation of other by-products, (such as tertiary amines), therefore, lowering the selectivity (Fig 3.5).[12]

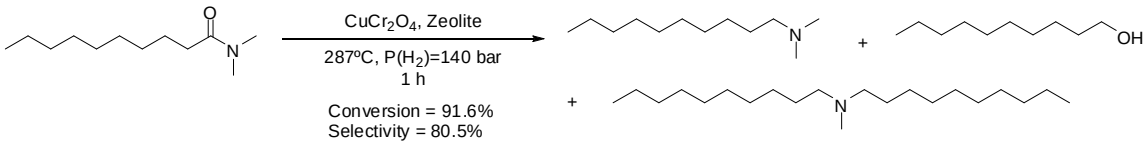
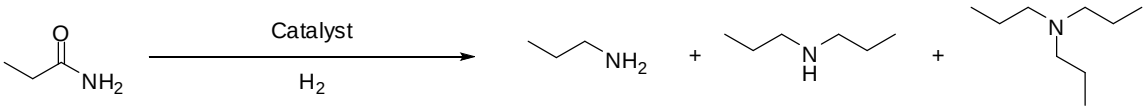


Fig 3.5. *Hydrogenation of N,N-disubstituted amides.*

A Pd/Re catalyst was developed and applied to the reduction of propanamide.[13] The reduction process based on this catalyst still required high temperatures and pressures. However, it was proven to be more active than the copper chromite system (Table 3.1, entries 1 and 2). A mixture of products was described where the main product was the secondary amine and not the expected primary amine. Milder reaction conditions did not result in significantly different conversion but the selectivity to the primary amine was increased (Table 3.1, entry 3).

Table 3.1. Reduction of propanamide catalysed by the Pd/Re system (Adapted from reference 13).



Entry	Catalyst	T (ºC)	P (bar)	Propylamine	Dipropylamine	Tripropylamine
1	Pd/Re	250	275	2.7	44.4	17.9
2	$CuCr_2O_4$	250	275	3.0	29.0	19.0
3	Pd/Re	200	137	20.5	46.2	7.7

3.1.2.- Homogeneous Catalytic Systems.

As previously mentioned in Section 1.2.1., homogeneous catalysis tends to require milder conditions than heterogeneous catalysis. Thus, the harsh conditions required in hydrogenation of acids and their derivates under heterogeneous conditions is due to the fact that heterogeneous catalysts are not highly active for the process.[14] This opened the doors to the study of carboxylic acid and ester hydrogenation under homogeneous conditions. Also, ligands facilitate the activation of H_2 and the stabilisation of metal hydrides.[4,15] the majority of systems developed for this reaction are based on ruthenium due to its strong affinity towards heteroatomic compounds such as the oxygen of the carbonyl group.[16] Ruthenium (III) and ruthenium (II) precatalysts have been described as active in this reaction with little difference between the two precatalysts. This suggests an initial reduction of ruthenium (III), which is a weak oxidant,[15] to ruthenium (II) which is proposed to be the active species.

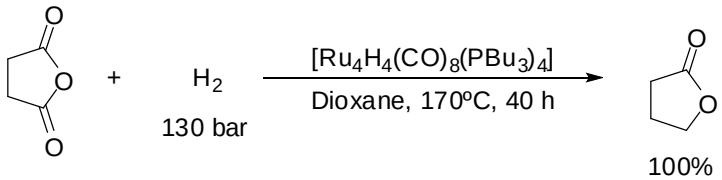


Fig 3.6. *Hydrogenation of succinic anhydride catalysed by homogeneous ruthenium.*

The most studied substrates for this reaction are the cyclic anhydrides, especially succinic anhydride. γ-Butyrolactone can be formed by the reduction of this cheap feedstock. Systems based on a phosphine complex of ruthenium have been proven to be active in this reaction (Fig 3.6).[17,18] These systems required significantly milder conditions than the heterogeneous ones. However, the change in conditions may be due to the fact that succinic anhydride is considered to be an active substrate due to the presence of an electron withdrawing carbonyl group), which facilitates the hydrogenation of acid derivates.[19] It should be noted that the reaction does not involve a second reduction step generating the corresponding ether or diol from γ-butyrolactone because it does not have any additional activating electron withdrawing groups. However, this reaction is not forbidden, and low conversions have been obtained in the reduction of γ-butyrolactone to butanediol, although a high temperature is required (Fig 3.7).[20]

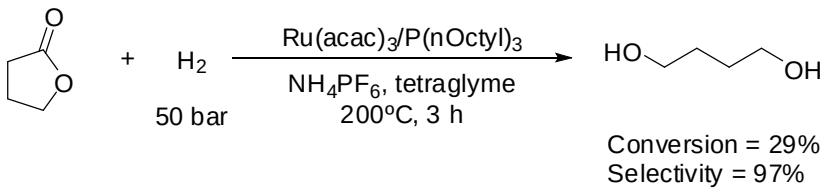


Fig 3.7. *Hydrogenation of γ-butyrolactone catalysed by homogeneous ruthenium.*

The use of additives such as triethylamine, *ortho*-phosphoric acid or NH_4PF_6 plays a beneficial role in this reaction.[17,20] The additives which were found to be most active were the Lewis acids such as ZrO_2 or $SnCl_2$.[17d,f] In this case, it is assumed that the Lewis acid is aiding the generation of the active ruthenium hydride species.[16f]

The hydrogenation of cyclic anhydrides has been shown to be regioselective.[21] Ikariya and co-workers described that only the less hindrered carbonyl group of 3,3-dimethyldihydro-2*H*-pyran-2,6(3*H*)-dione was reduced under the hydrogenation conditions catalysed by [$RuCl_2$(TPP)] (Fig 3.8).

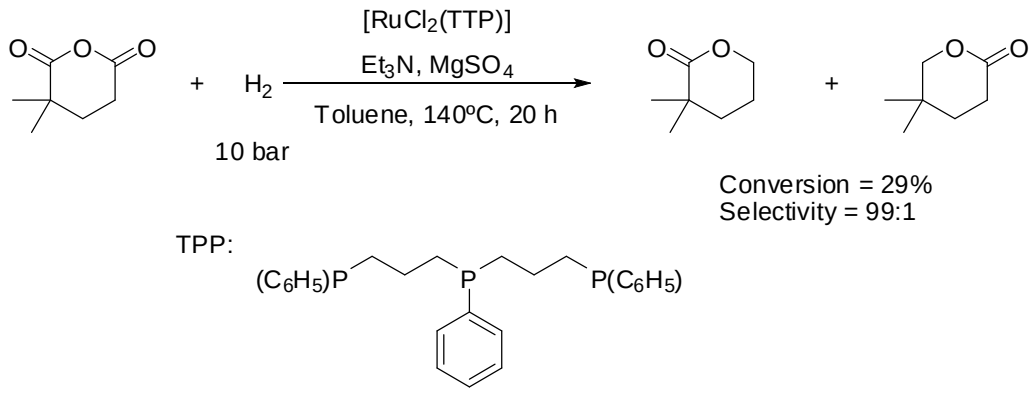


Fig 3.8. *Hydrogenation of 3,3-dimethyldihydro-2H-pyran-2,6(3H)-dione catalysed by [$RuCl_2$(TPP)].*

Asymmetric hydrogenation of the prochiral 4-subtituted glutaric anhydride has been described using chiral phoshpines such as BINAP or DIOP which give respectively 60% and 28% ee.[22] Although the initial enantiomeric excess was low, this is still an attractive route to generate chiral lactones, which are important intermediates in organic synthesis.

A flow diagram has been proposed for the industrial application of the hydrogenation of succinic anhydride to γ-butyrolactone.[18] As Fig 3.9 shows, the process consists of a single reactor, and a separation unit which consists of a flash separator and four columns. Hydrogen, succinic anhydride and the catalyst are recycled back into the reactor The initial flash column allows the separation and recycle of the hydrogen from the solution. The heavy liquid phase flows from the bottom of the flash column to the other column where water and lactone are separated from solvent and catalyst. The volatile fraction containing water and lactone is pumped into a third column and the heavy fraction is recycled. In the third column, water is separated from the lactone. The fraction which contains the lactone is purified in the fourth column. The heavy fraction of this column is then combined with the fraction entering column 1.

The heavy fraction of column 1 consists mainly of the catalyst and solvent can be pumped into another column (Column 4) in order to recycle the catalyst. If this fraction contains high concentrations of lactone, the volatile fraction of this column can be mixed with the fraction coming to the first column to improve the separation yield.

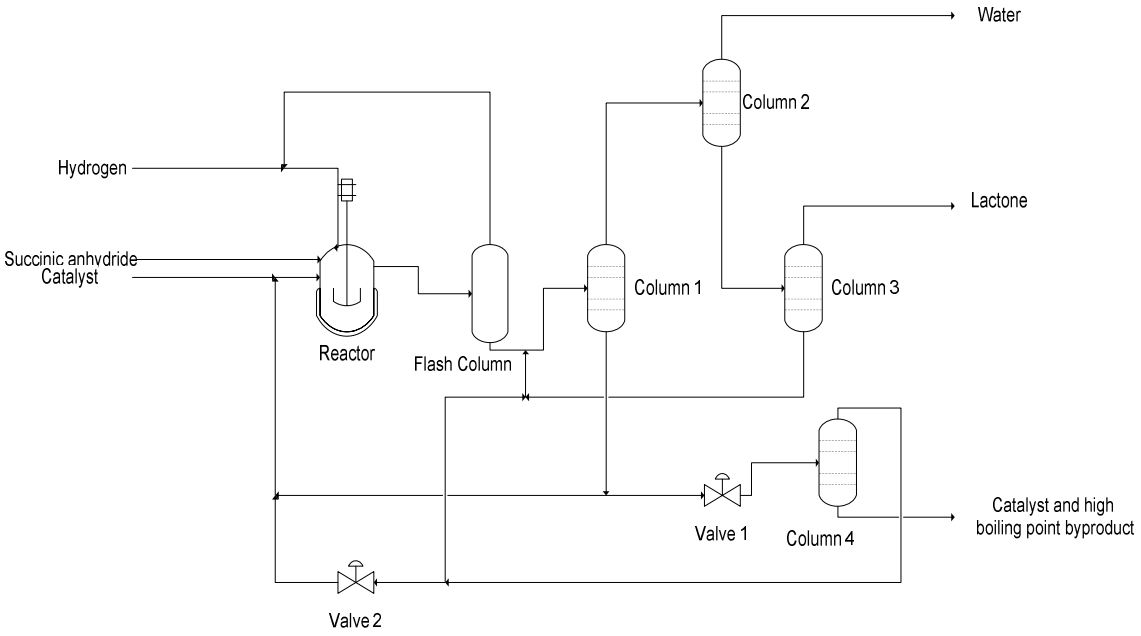


Fig 3.9. *Flow diagram of the process to reduce succinic anhydride to γ-butyrolactone.*[18]

Recently a selective hydrogenation of imides has been developed,[22] improving the described systems of $RuCl_3 \cdot 3H_2O$, $[RuCl_2(DMSO)_4]$ or $[Ru(dmp)(H_2O)_2](PF_6)$, which gave only low conversion in this reaction (<28%).[23] These systems based on π-aromatic ruthenium precatalysts such as $[RuCl_2(p\text{-cymene})]_2$ or $[Ru_4H_6(p\text{-cymene})_4]Cl_2$ gave high conversion in this reaction using an aqueous medium (Fig 3.10).

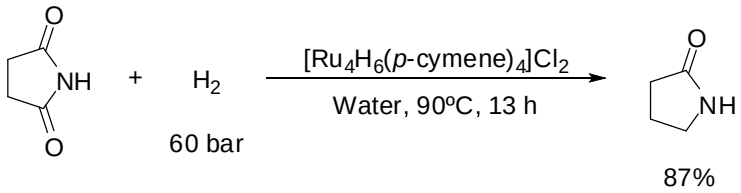


Fig 3.10. *Selective hydrogenation of imides.*[22]

The first system developed for the reduction of acids and esters was based on a mixture of $RuCl_3/FeCl_3$ using syngas for the hydrogenation (Fig 3.11).[24] The conditions of this process were very harsh (~220 ºC and 200 bar of syngas) and more similar to a heterogeneous system than to a homogeneous process. The main product, in the case of the hydrogenation of acetic acid, was ethyl acetate (46% yield), with ethanol and diethyl ether

being obtaining as by-products (39% yield). The addition of $SnCl_2$ significantly increased the selectivity to ethyl acetate (99%), giving a highly attractive process for the preparation of this common solvent.

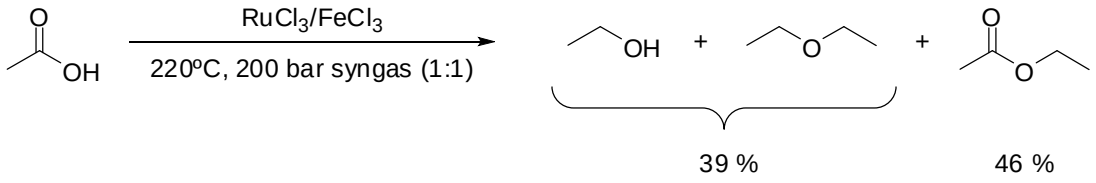


Fig 3.11. *Hydrogenation of acetic acid.*

The first system based on a phosphine complex of ruthenium was described by Elsevier and co-workers (Fig 3.12).[19] In this system, dimethyl oxalate was chosen as the substrate for hydrogenation. This substrate is a cheap feedstock and the expected product after hydrogenation is ethylene glycol which is an essential component of polyester resins. Also, this substrate has a second electron withdrawing group, which may aid the hydrogenation. It was found that the addition of Zn was beneficial to the reaction. The possible reduction of Ru(III) to Ru(II) promoted by zinc, and the role of the Lewis acid of Zn(II) account for this observation.[25]

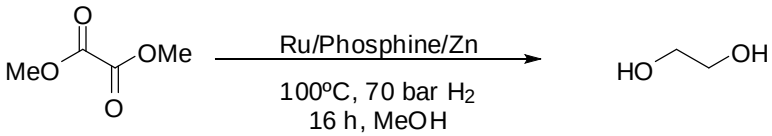
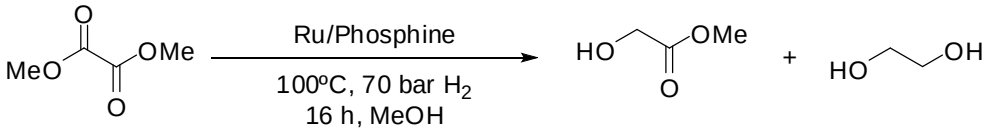


Fig 3.12. *Hydrogenation of dimethyl oxalate as described by Elsevier.*[19]

It was found that ruthenium complexes of triphosphines are the most active in this catalysis. Diphosphines and monophosphines gave low conversions, and only methyl-hydroxyacetate was recovered and therefore, no second hydrogenation was obtained. Only ethylene glycol was formed when the Ru/Triphos system was tested (Table 3.2, entry 1).[26] Tetraphosphines such as tetraphos, or other triphosphines such as bis(2-diphenylphosphinoethyl)phenylphosphine gave moderate conversion to methyl-hydroxyacetate (Table 3.2, entries 2 and 3). No ethylene glycol was formed. Arsines and amines were tested as ligand, but gave low conversion.

Table 3.2. Hydrogenation of dimethyl oxalate (adapted from reference 25).



Entry	Phosphine	Conversion (%)	Methyl-hydroxyacetate (%)	Ethylene glycol (%)
1	$PhP(C_2H_4PPh_2)_2$	76	67	0
2	$CH_3C(CH_2PPh_2)_3$	100	1	95
3	$(CH_2PPhC_2H_4PPh_2)_2$	91	85	0

This discrepancy between Triphos and other triphosphines such as bis(2-diphenylphosphinoethyl)phenylphosphine was explained by Elsevier, by considering the *fac* isomer is more reactive than the corresponding *mer* isomer (the cap effect).[25] Therefore, while Triphos complexes give only one reactant configuration, other triphosphines may coordinate in either the *fac* or the *mer* configuration, therefore decreasing the activity of the catalyst.

Solvents such as methanol (and other alcohols), gave the best results in these reactions. Normally the role of this kind of solvent in hydrogenation is in the generation of the initial hydride complex, which is the active species in the reaction.[27] Considering that the alcohol is essential in the medium (usually as solvent) an elegant process based on the use of electron deficient alcohols (such as 2,2,2-trifluoroethanol) to improve the reactivity of different unactivated substrates such as benzyl benzoate has been developed (Fig 3.13).[28] 2,2,2-Trifluoroethanol can give the corresponding 2,2,2-trifluroethyl ester by transesterification with the reactants. The newly-formed ester is significantly more reactive than the initial one due to the electron withdrawing properties of the 2,2,2-trifluoroethyl group, therefore resulting in higher conversions.

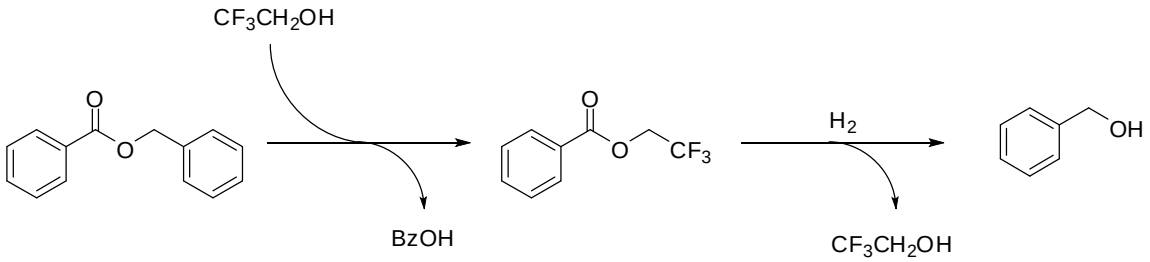


Fig 3.13. *Hydrogenation of benzyl benzoate in 2,2,2-trifluoroethanol (Adapted from reference 28).*

Recently, this system has been proven to be active in the hydrogenation of maleic acid (Fig 3.14).[29] Tetrahydrofuran was formed as the main product (51.1%) with a significant amount of 1,4-butanodiol (16.5%) and γ-butyrolactone (15.1%) also being formed. Traces of propanol and propanoic acid were formed as well. The addition of sodium *para*-toluenesulfonate significantly lowered the conversion (Fig 3.14), giving γ-butyrolactone as main product. It should be noted that the formation of the γ-lactone can be considered the first step in the generation of tetrahydrofuran from maleic acid.[30] The Ru/Triphos catalyst has been proven to be stable in the medium although the reaction required high temperatures (~200 ºC). The catalyst was recycled eight times without a significant loss of activity.[31]

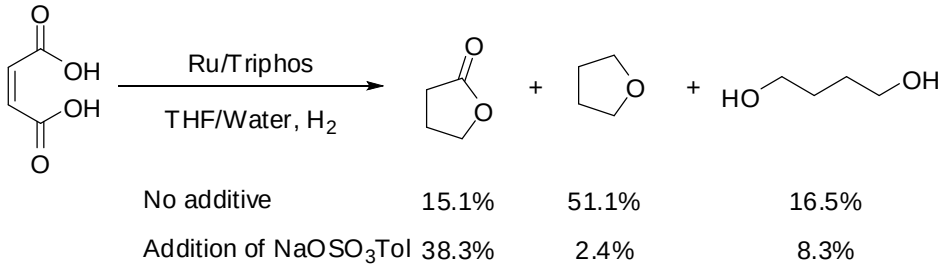
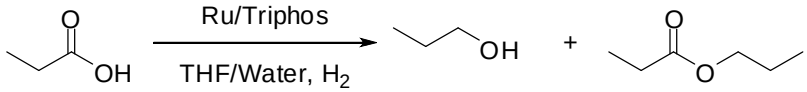


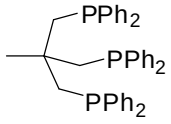
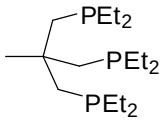
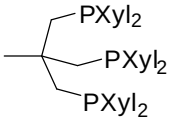
Fig 3.14. *Hydrogenation of maleic acid catalysed by the Ru/Triphos system*.

Linear acids give a mixture of alcohols and esters under hydrogenation conditions catalysed by the Ru/Triphos system (Table 3.3, entry 1). Considering that Elsevier suggested an initial nucleophilic attack of the ruthenium complex onto the carbonyl group as an essential part of the catalytic cycle,[25] an increase in the nucleophilicity of the complex

may therefore increase its activity. However, highly electron donating analogues of Triphos, such as 1,1,1-tris(diethylphosphinomethyl)ethane or 1,1,1-tris(dixylylphosphinomethyl)ethane, gave lower conversions (Table 3.3, entries 2 and 3). This evident discrepancy may be explained by the stability of the ruthenium complex. Therefore, although ruthenium complexes of 1,1,1-tris(diethylphosphinomethyl)ethane and 1,1,1-tris(dixylylphosphinomethyl)ethane are significantly more nucleophilic than those formed from ruthenium and Triphos, these alternative complexes may be less labile, and therefore they may be less active in the reaction.[25]

Table 3.3. Hydrogenation of propanic acid catalysed by the Ru/Triphosphine system (adapted from 31).



Entry	Phosphine	TON	Propanol (%)	Propylpropionate (%)
1		807	47	52
2		250	8	92
3		66	4	92

The role of the water is crucial in the Ru/Triphos hydrogenation. Dry conditions were suggested by Elsevier in order to decrease the generation of carbonyl-Ru species which are not active.[25] The formation of these species has been proposed to occur via the decarbonylation of the aldehyde, which is formed by the first hydrogenation. However, in similar reactions, Crabtree and co-workers, defended the opposite role by proposing a stabilisation of the hydride complex by the addition of water, and also the regeneration *in situ* of the active species from the carbonyl-Ru species.[29] These species, according to Crabtree's studies, are formed in the medium by the reaction of the product (the alcohol)

with the ruthenium complex.[32] It is, then, regenerated by the water-gas shift reaction of the carbonyl-species, generating carbon dioxide and the active dihydride ruthenium species (Fig 3.15).

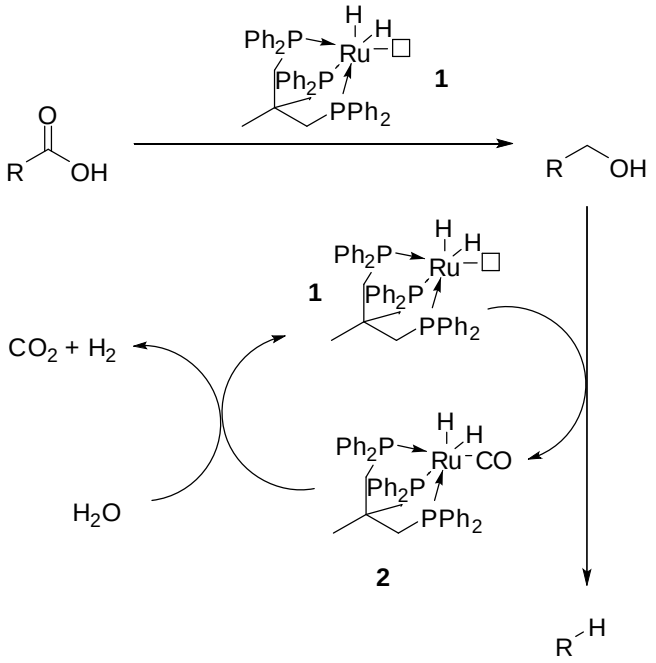


Fig 3.15. *Role of water in the regeneration of the ruthenium catalyst*

Other positive effects due to the addition of water have been observed in other hydrogenations, such as the hydrogenation of carbon dioxide, or the hydrogenation of the double bond in maleic acid. In the hydrogenation of carbon dioxide, this beneficial role of water has been explained by the coordination of water to the dihydride ruthenium complex. Hydrogen bonding then assits addition of the hydride to the carbon dioxide (Fig 3.16).[33]

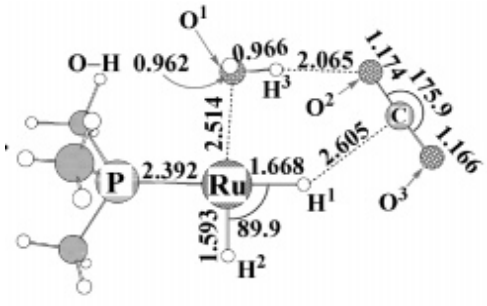
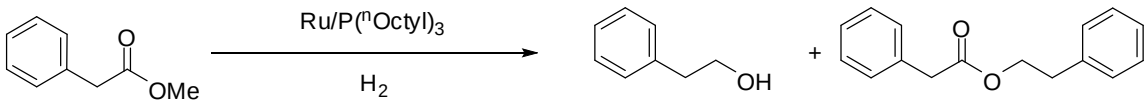


Fig 3.16. *Acitive hydro-ruthenium complex in hydrogenation of carbon dioxide*.[35]

In the hydrogenation of the double bond of maleic acid, deuterium studies carried out in the presence of water have proven that water is indeed the final hydride donor, acting as an intermediate between molecular hydrogen and the ruthenium complex.[15] Supporting the suggestions concerning the role of water in the Ru/Triphos hydrogenation system.

A similar system to the system which was proven to be active in the hydrogenation of an maleic anhydride to γ-butyrolactone has been tested with methyl-phenylacetate, which is an inactivate substrate (Fig 3.17).[34,35] Low conversions and selectivities to the alcohol were obtained. Increasing the concentration of substrate significantly increased the activity of the catalyst, and therefore increased the generation of phenethyl-phenylacetate. The generation of this ester as a product in the reaction may suggest that hydrogenation of the ester is slower than the hydrogenation of the intermediate aldehyde.[35]



Low [Substrate] (TON):	10.4	13.5
High [Substrate] (TON):	59.8	119.8

Fig 3.17. *Hydrogenation of methyl-phenylacetate catalysed by Ru/P(^{n}Octyl)$_3$*

A tridentate sulphur ligand, related to Triphos has been described recently (Fig 3.18).[36] The ruthenium complex of this ligand gave only moderate conversion in the hydrogenation of dimethyloxalate, due to the low stability of the complex. It should be noted that a high amount of ruthenium black was formed during the reaction. Only methyl-hydroxyacetate was obtained in this system. Low induction periods have been described in this system which can be lowered further by the addition of Zn. This addition also improved the reaction rate.

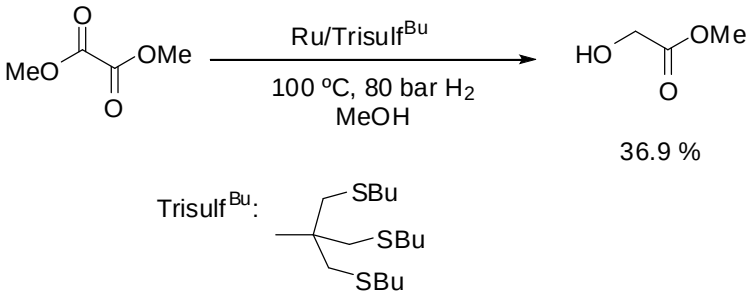
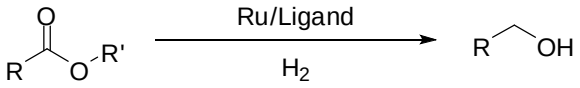
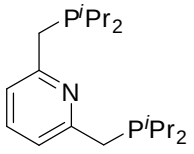


Fig 3.18. *Hydrogenation of dimethyloxalate catalysed by Ru/Trisulf^{Bu}.*

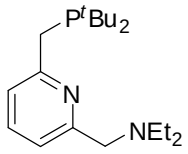
Far from the cap effect presented in Triphos, PNP and PNN ligands, which coordinate meridionally, have been proven to be active in the hydrogenation of esters (Table 3.4).[37] Low conversion was observed when the ruthenium complex of the PNP ligand was tested (Table 3.4, entry 1). Higher conversions were obtained using the PNN ligand (Table 3.4, entry 2), including when linear acids were tested (Table 3.4, entry 3), which suggests a possibly important role of pincer ligand hemilability in the activity of the catalyst.[37,38]

Table 3.4. Hydrogenation of esters catalysed by ruthenium complexes of pincer ligands (adapted from reference 37).





PNP ligand



PNN ligand

Entry	Ligand	Substrate	Time (h)	Conversion (%)
1	PNP	Ethyl benzoate	16	7.5
2	PNN	Ethyl benzoate	4	99.2
3	PNN	Hexyl hexanoate	5	82.2

The selective hydrogenation of acids to aldehydes under homogeneous conditions has been described (3.19).[39] As mentioned in Section 3.1.1., the selective hydrogenation of acids to aldehydes is an attractive process due to the high reactivity of aldehydes, compared to acids. The Yamamoto group has overcome these problems describing a system based on a palladium complex. This system gave high conversion and selectivity to the aldehyde. The addition of an anhydride was proven to be essential for high selectivity. It should be noted that this system is specific to acids, and did not give any conversion in the hydrogenation of other functional groups such as the C=C double bond which is usually relatively easy to reduce. These factors result in the system being highly useful in organic synthesis.

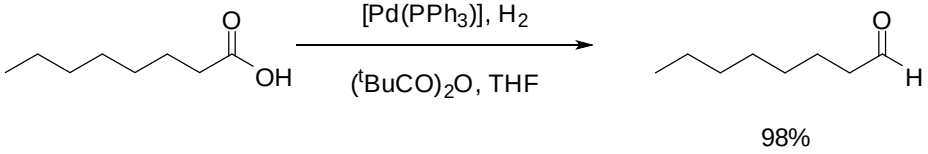


Fig 3.19. *Selective hydrogenation of acids catalysed by palladium.*

The catalytic hydrogenation of amides by homogeneous systems has not had as much attention as that of acids and esters. This may be due to the resistance of these substrates in reduction reactions. In the only study presented in the literature, Crabtree and co-workers described a complex product mixture of propanol, propylpropanoate, *N*,*N*-dipropylamine and *N*-propylpropanamide in the hydrogenation of propanamide when catalysed by Ru/Triphos system.[29] No primary amine was obtained in the reaction.

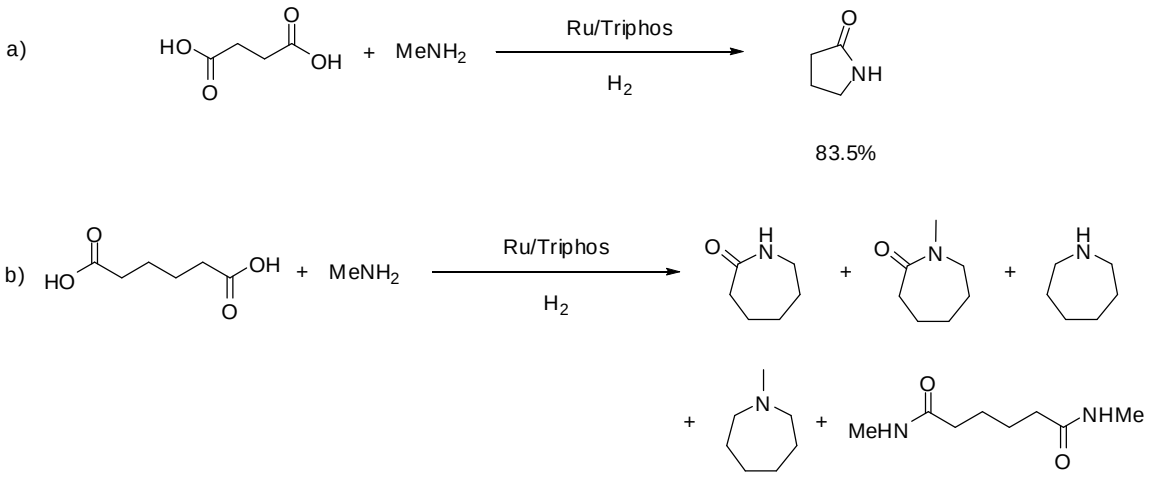


Fig 3.20. *Hydrogenation of di-acid in presence of an amine.*

However, an elegant method to prepare lactams by hydrogenation has been described.[40] This system consists of the hydrogenation of an organic di-acid in the presence of an amine. This then, gives lactams via a tandem reaction of the cyclic imide and hydrogenation (Fig 3.20). Therefore, NMP can be formed by the hydrogenation of succinic acid in the presence of methylamine with high conversion (Fig 3.20a). However, the hypothetical generation of the caprolactam by the hydrogenation of adipic acid in the presence of an amine gave a mixture of caprolactams, along with adipamides and hexahydroazepines (Fig 3.20b).

3.2.- Results and Discussion.

3.2.1.- Hydrogenation of *N*-Phenylnonamide.

As mentioned in Section 3.1.2. only one study has been carried out in the hydrogenation of amides.[29] This study demonstrated the difficulties presented in this route to produce amines, which results in low selectivities and conversions. Because these difficulties and because amines are important chemicals it was attractive to study this process further. The chosen system was the Ru/Triphos system due to its success in homogenous hydrogenations (Section 3.1.2). The first series of experiments was carried

out in order to prove if both a ruthenium complex and Triphos were necessary in order successfully to hydrogenate the amide (Fig 3.21).

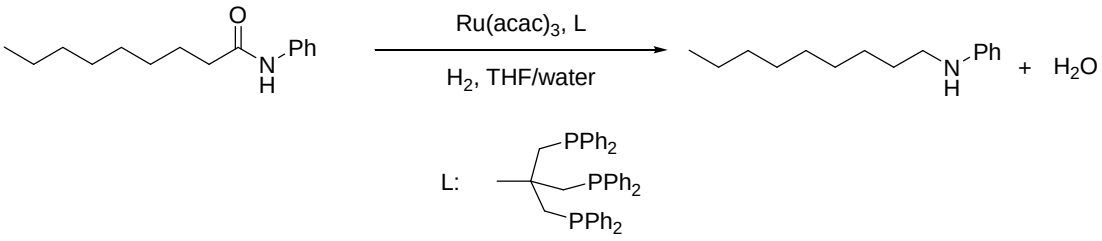


Fig 3.21. *Hydrogenation of N-phenylnonamide catalysed by the Ru/Triphos system.*

In the absence of the catalyst, no conversion was obtained (Table 3.5, entry 1). The addition of [$Ru(acac)_3$] gave moderate conversion (Table 3.5. entry 2). A by-product (nonanol) was formed during the reaction. The formation of this by-product is probably due to the water present in the medium. This, therefore, suggests a sequential hydrogenation mechanism, in which *N*-phenylnonamide is hydrogenated to *N*-nonylideneaniline, which is then, reduced to the final product (*N*-phenylnonamide). It is therefore plausible to think that the formation of nonanoic acid and nonanal by hydrolysis of amide and imine respectively. The acid and aldehyde may then, be reduced to alcohol by successive hydrogenation steps (Fig 3.22).

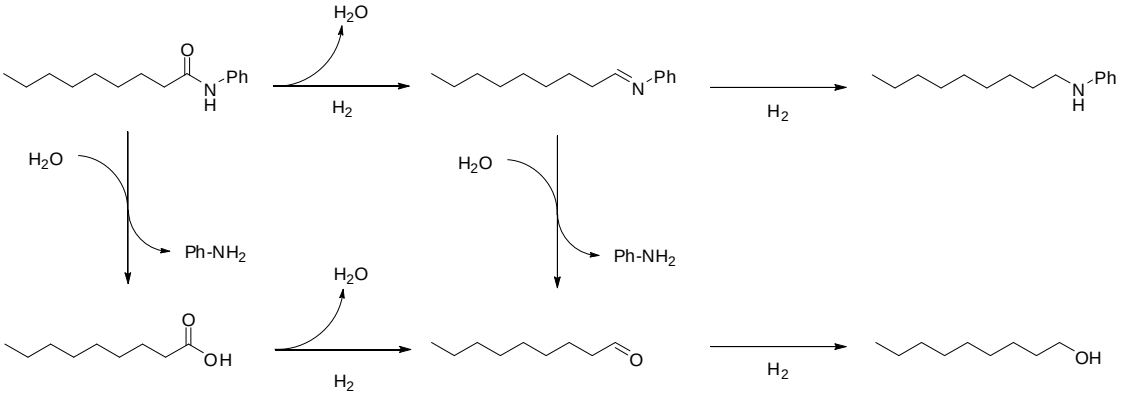
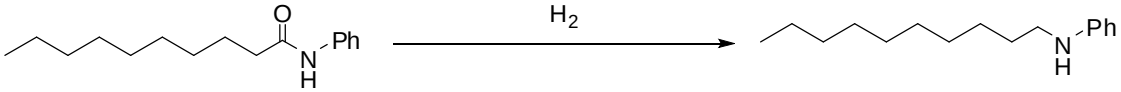


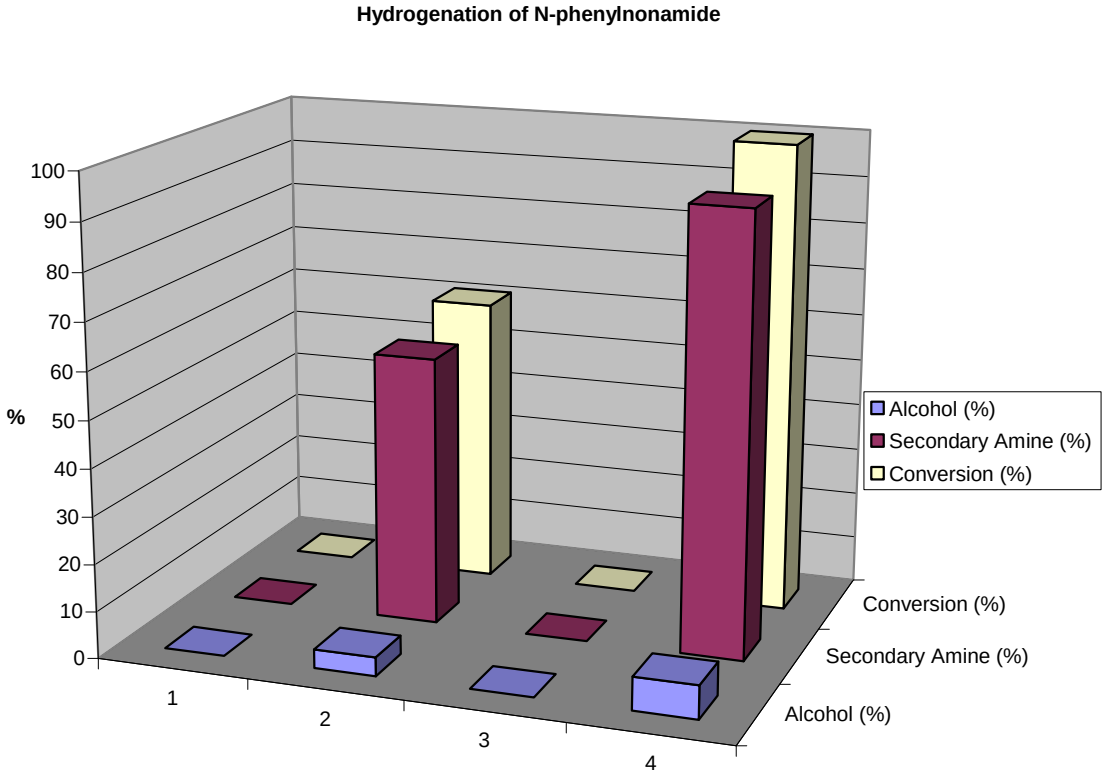
Fig 3.22. *The origin of alcohol in the hydrogenation of N-phenylnonamide.*

Table 3.5. Hydrogenation of *N*-phenylnonamide.



Entry	$Ru(acac)_3$ (%)	Triphos (%)	Conversion (%)	Secondary Amine (%)	Alcohol (%)
1	-	-	0	0	0
2	1 %	-	61	57	4
3	-	2 %	0	0	0
4	1 %	2 %	100	93	7

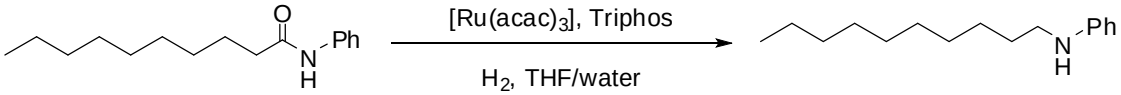
Conditions: *N*-phenylnonamide (1 g, 4.2 mmol), [$Ru(acac)_3$] (as described), triphos (as described), THF (10 mL), water (0.1 mL), P(H_2) = 40 bar, 164 ºC, 14 h.



The presence of only the ligand did not yield any conversion (Table 3.5, entry 3). The combination of $Ru(acac)_3$ and Triphos gave full conversion with 93 % selectivity to the desired secondary amine (Table 3.5, entry 4), proving the requirement of a ruthenium complex to obtain high conversion in the reaction.

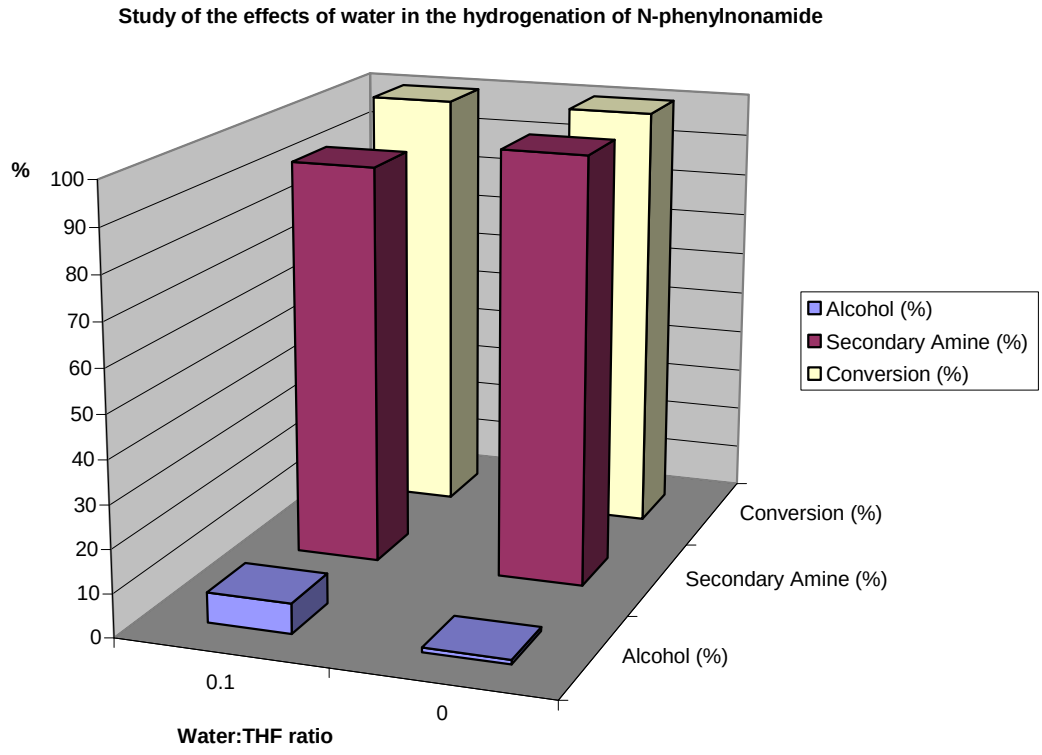
3.2.1.1.- Study of the Effects of Water in the Hydrogenation of *N*-Phenylnonamide.

Table 3.6. Study of the effects of water in the hydrogenation of *N*-phenylnonamide.



Entry	Water:THF ratio	Conversion (%)	Secondary Amine (%)	Alcohol (%)
1	0.1	100	93	7
2	0	100	99	1

Conditions: *N*-phenylnonamide (1 g, 4.2 mmol), $[Ru(acac)_3]$ (17 mg, 0.04 mmol), triphos (53 mg, 0.08 mmol), THF (10 mL), water (as described), $P(H_2)$ = 40 bar, 164 ºC, 14 h.



The presence of water has been suggested as the reason why nonanol is formed in the reaction (Fig 3.22). However, the beneficial role of water is far from being known. As indicated in Section 3.1.2, Elsevier and co-workers proposed the benefits of an anhydrous medium,[25] while the Crabtree group has found a positive effect of the addition of water to

the medium. Therefore, to prove the hypothesis proposed by Crabtree, an experiment in the absence of water was carried out. Under these conditions, full conversion was obtained (Table 3.6, entry 2). As expected, the amount of nonanol generated under these conditions was significantly lower than when the reaction was carried out in the presence of water (Table 3.6, entry 1). This is due to the requirement of water to hydrolyse the amides or imides (the first step toward nonanol formation) (Fig 3.22).

a) b)

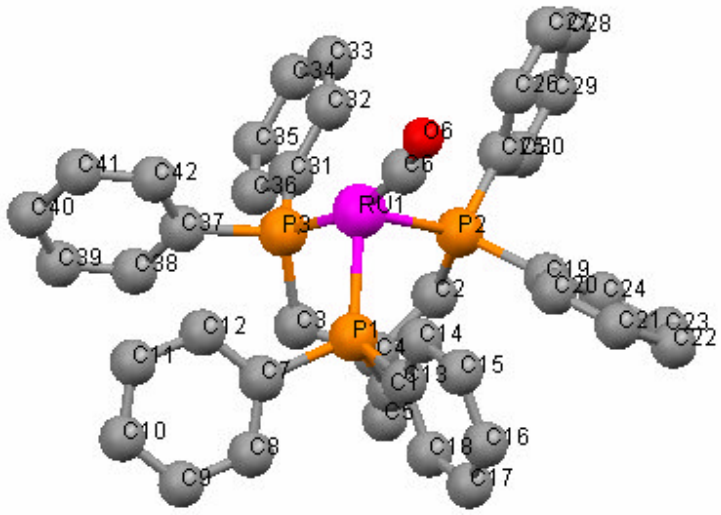
Fig 3.23. *Catalytic solution after the hydrogenation reaction.*

When the reaction was stopped, the orange solution normally formed in the presence of water (Fig 3.23a) was not obtained. Instead a dark solution was observed (Fig 3.23b). This result may confirm the Crabtree hypothesis. In order to confirm the hypothesis a experiment was carried out in which [$Ru(acac)_3$] and Triphos were heated up in dry THF at 164 ºC under 40 bar of hydrogen for two hours. The solvent was then removed *in vacuo* and methanol was added while heating the solution over 5 min. When the solution was cooled, the addition of hexane resulted in crystallisation. [$RuH_2(CO)$(Triphos)] (Table 3.7), showing that methanol decarbonylation occurs very readily.[31]

However, it should be noted that when the reaction was stopped (before the addition of methanol) the solution was black.

The structure of $[RuH_2(CO)(Triphos)]$, isolated as described above, was confirmed by X-ray crystallography (Table 3.7). As expected, the Triphos ligand is face capping with the Co and two hydrides occupying the remaining coordination sites of the octahedron.

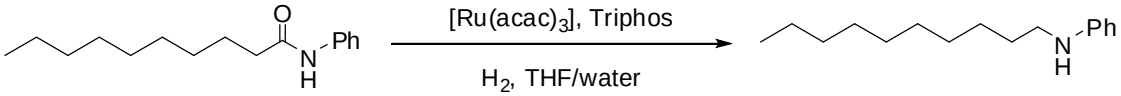
Table 3.7. Selection of bond lengths and angles in $[RuH_2CO(Triphos)]$ *(Hydrogen atoms omitted for clarity).*



Bond lengths (Aº)		**Angles (º)**	
Ru(1)-H(1)	1.581(5)	C(6)-Ru(1)-P(3)	163.7 (4)
Ru(1)-H(2)	1.583 (5)	C(6)-Ru(1)-P(1)	105.2 (4)
Ru(1)-P(1)	2.326 (2)	P(3)-Ru(1)-P(1)	87.43 (9)
Ru(1)-P(2)	2.329 (3)	C(6)-Ru(1)-P(2)	102.5 (4)
Ru(1)-P(3)	2.325 (3)	C(6)-Ru(1)-H(1)	69 (4)
Ru(1)-C(6)	1.83 (1)	P(3)-Ru(1)-H(1)	100 (3)
C(6)-O(6)	1.16 (1)	P(1)-Ru(1)-H(1)	94 (3)

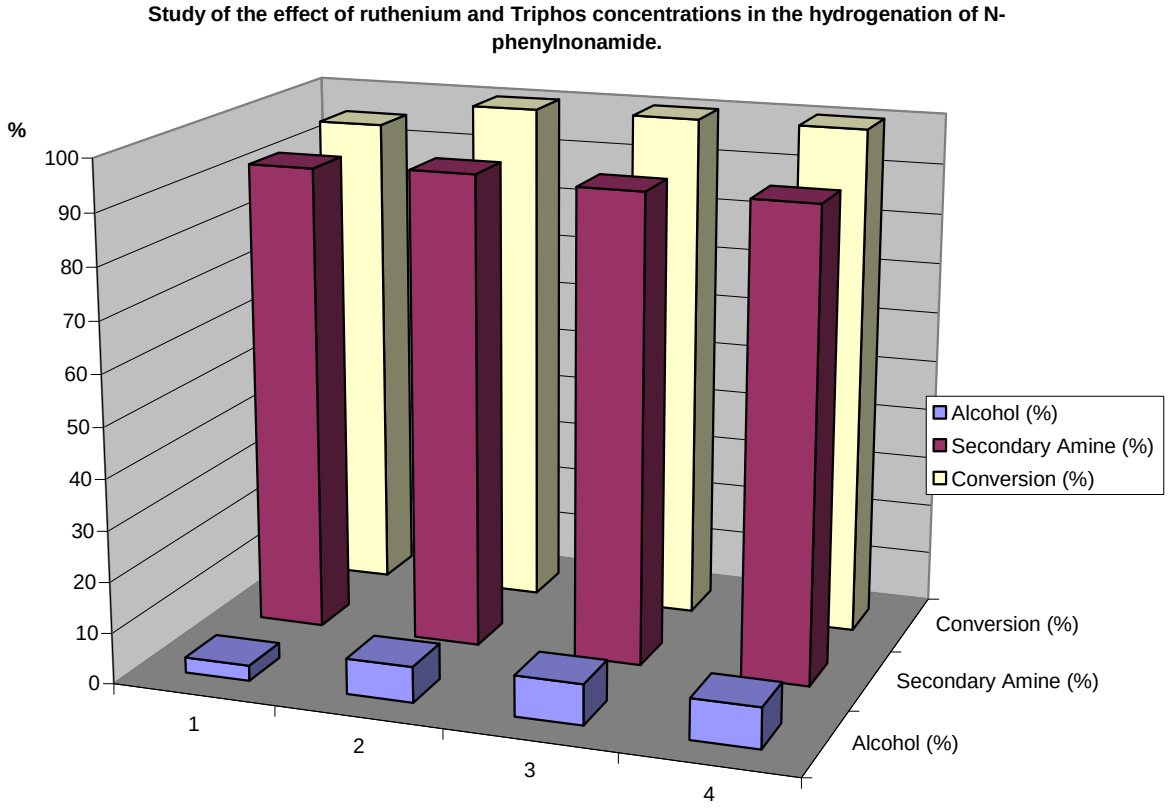
3.2.1.2.- Study of the Effect of Ruthenium and Triphos Concentrations in the Hydrogenation of *N*-Phenylnonamide.

Table 3.8. Study of the effect of ruthenium and Triphos concentrations in the hydrogenation of *N*-phenylnonamide.



Entry	[Ru]	L:Ru ratio	Conversion (%)	Secondary Amine (%)	Alcohol (%)
1	1%	1.2	95	92	3
2	1%	2	100	93	7
3	1%	4	100	92	8
4	0.5%	2	100	92	8

Conditions: *N*-phenylnonamide (1 g, 4.2 mmol), [$Ru(acac)_3$] (as described), triphos (as described), THF (10 mL), water (0.1 mL), P(H_2) = 40 bar, 164ºC, 14 h.



Assuming that the active species in the reaction is a triphos complex of ruthenium, the concentration of the ligand in the medium may be an important variable. This is due to the fact that the formation of the complex is considered to be an equilibrium, and therefore, is highly dependent upon the concentration of ruthenium and Triphos (*Le'Chatelier* principle). However, although *a priori* the concentration of ligand should be as high as possible, the high cost of these compounds significantly limits their use in high concentrations.

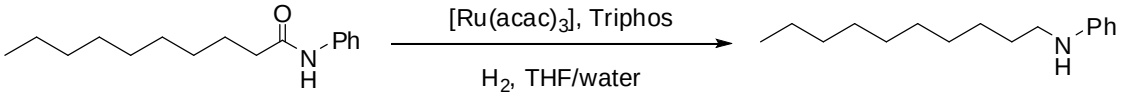
The Ru/Triphos ratio must be studied thoroughly to obtain the optimum concentration of triphos, taking into account both the positive and negative factors. When this study was carried out, it was found that at low Ru/Triphos ratios, the conversion was excellent (Table 3.8, entry 1). Full conversion was obtained when the reaction was carried out with a Ru/Triphos ratio of 2 (Table 3.8, entry 2). No substantial difference was found when a large excess of ligand was used (Table 3.8, entry 3). The similarities of the results obtained confirms the high stability of the Triphos-ruthenium complex,

The conversion of a catalytic system is usually directly related to the concentration of the catalyst in the medium. However, the increase in concentration of a catalyst in the medium results in a significant increase in production cost (see Section 1.2). Therefore, the concentration of the catalyst must be as high as possible, but with costs considered. To know if it is possible to decrease the concentration of ruthenium in the medium, an experiment with low ruthenium concentration has been carried out. 100 % conversion was obtained after 14 h when 0.5 % of ruthenium was used in the reaction (Table 3.8, entry 4).

3.2.1.3.- Study of the Effects of Pressure in the Hydrogenation of *N*-Phenylnonamide.

Pressure is an essential variable in gas-liquid reactions (see Section 2.2.1.2.). This is due to the fact that variables such as wall thickness and kinetics of the reaction must be taken into consideration when a process is being designed. Full conversion in 14 h, with > 90 % selectivity to the desired secondary amine, was observed over a wide range of pressures (10-40 bar, Table 3.9). Only when the reaction was carried out under a low pressure of hydrogen was the amine/alcohol selectivity slightly lowered (Table 3.9, entry 4).

Table 3.9. Study of the effect of pressure in the hydrogenation of *N*-phenylnonamide.



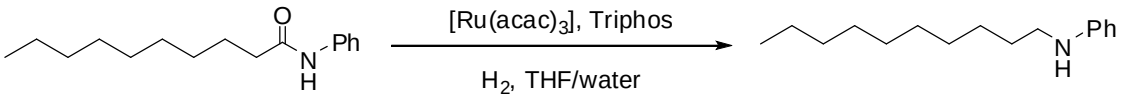
Entry	Pressure (bar)	Conversion (%)	Secondary Amine (%)	Alcohol (%)
1	40	100	93	7
2	20	100	92	8
3	15	100	93	7
4	10	100	90	10

Conditions: *N*-phenylnonamide (1 g, 4.2 mmol), [Ru(acac)$_3$] (17 mg, 0.04 mmol), triphos (53 mg, 0.08 mmol), THF (10 mL), water (0.1 mL), 164ºC, 14 h.

3.2.1.4.- Study of the Effect of Temperature in the Hydrogenation of *N*-Phenylnonamide.

As previously mentioned in Section 2.2.1.1. high temperatures often increase the reaction rate, and therefore the activity of the catalyst. However, catalyst decomposition suffered at high temperatures gives an increase in production cost and can result in destabilisation of the catalyst with its irreversible loss. As mentioned in Section 3.1. it should be noted that hydrogenation of acid derivates often require high temperatures to give high conversions.

Table 3.10. Study of the effect of temperature in the hydrogenation of *N*-phenylnonamide.



Entry	Temperature (ºC)	Conversion (%)	Secondary Amine (%)	Alcohol (%)
1	164	100	93	7
2	140	100	91	9
3	120	80	48	32
4	100	40	0	40

Conditions: *N*-phenylnonamide (1 g, 4.2 mmol), [Ru(acac)$_3$] (17 mg, 0.04 mmol), triphos (53 mg, 0.08 mmol), THF (10 mL), water (0.1 mL), P(H_2) = 40 bar, 14 h

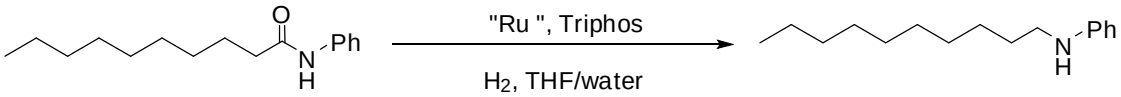
The reaction carried out at 164 ºC gave full conversion and high selectivity to the amine (Table 3.10, entry 1). The hydrogenation of amides could be carried out at 140 ^{o}C still gave 100 % conversion in 14 h and >90 % selectivity to the secondary amine (Table 3.10, entry 2) but reducing the temperature further to 120 ^{o}C resulted incomplete reactions with lower selectivity. This gave more alcohol from the acid or aldehyde, which is easier to reduce (Table 3.10, entry 3). Only alcohol (no amine) was produced at 100 ^{o}C (Table 3.10, entry 4).

3.2.1.5.- Hydrogenation of *N*-Phenylnonamide Catalysed by Ruthenium.

The most popular ruthenium precatalyst for hydrogenation is [Ru(acac)$_3$]. Elsevier and co-workers proved that the presence of chlorine in the medium may be detrimental to the activity of the catalyst.[25] This observation was explained by strong coordination of chlorine to ruthenium leading to inhibition of the reaction.[41] This fact significantly limited the use of other ruthenium precatalysts. However, it would be beneficial to know if this inhibition, observed by Elsevier, can be extrapolated to the hydrogenation of amides and, therefore, if it is possible to use other precatalysts in this reaction. A series of reactions using other precatalysts was carried out. The results are summarised in Table 3.11.

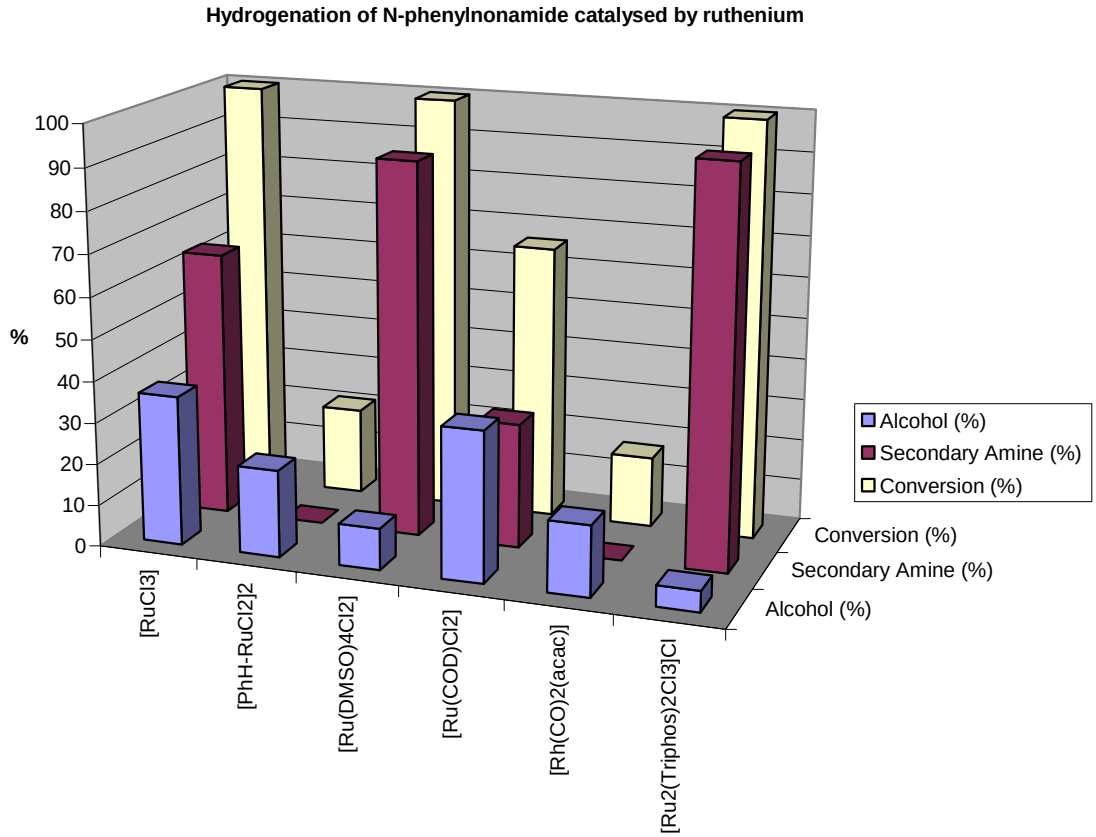
Although $RuCl_3$ gave full conversion, the selectivity of the reaction was significantly lower (Table 3.11, entry 1), giving a greater amount of nonanol than when using [Ru(acac)$_3$]. A low yield of nonanol was obtained when [PhH-$RuCl_2$]$_2$ was used, and no amine was formed (Table 3.11, entry 2). [Ru(DMSO)$_4$Cl$_2$] showed similar activity to that of [Ru(acac)$_3$], giving high conversion and selectivity to the amine (Table 3.11, entry 3). [Ru(COD)Cl$_2$] yielded moderate conversion and low selectivity (Table 3.11, entry 4). For a better understanding of the reaction and to determine if only ruthenium complexes are active as catalysts in this kind of hydrogenation, a catalyst based on rhodium ([Rh(CO)$_2$(acac)]) was tested and gave only a moderate yield of nonanol (Table 3.11, entry 5). No formation of the amine was observed in the reaction catalysed by rhodium.

Table 3.11. Hydrogenation of *N*-phenylnonamide catalysed by Ruthenium.



Entry	Compound	Conversion (%)	Secondary Amine (%)	Alcohol (%)
1	$[RuCl_3]$	100	64	36
2	$[PhH\text{-}RuCl_2]_2$	21	0	21
3	$[Ru(DMSO)_4Cl_2]$	100	90	10
4	$[Ru(COD)Cl_2]$	66	30	36
5	$[Rh(CO)_2(acac)]$	17	0	17
6[a)]	$[Ru_2(Triphos)_2Cl_3]Cl$	100	95	5

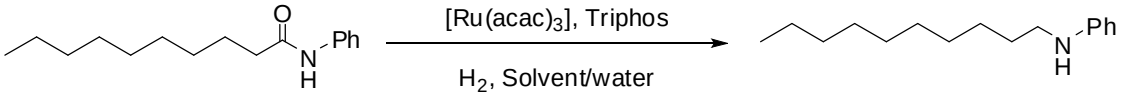
Conditions: *N*-phenylnonamide (1 g, 4.2 mmol), "Ru" (0.04 mmol), Triphos (53 mg, 0.08 mmol), THF (10 mL), water (0.1 mL), $P(H_2)$ = 40 bar, 164ºC, 14 h. a) No Triphos was added.



$[Ru_2(Triphos)_2Cl_3]Cl$ was proven to be active in the reaction, giving similar results to those obtained using of the use of $[Ru(acac)_3]$ or $[Ru(DMSO)_4Cl_2]$ (Table 3.11, entry 6). No additional ligand was required.

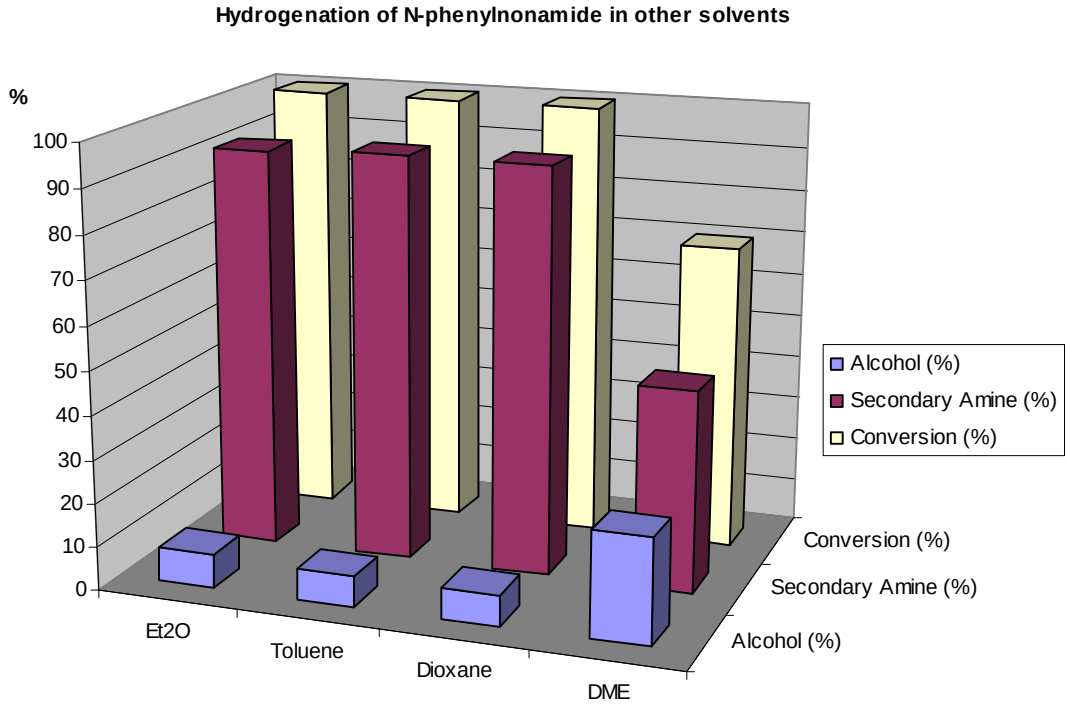
3.2.1.6.- Hydrogenation of *N*-Phenylnonamide in Other Solvents.

Table 3.12. Hydrogenation of *N*-phenylnonamide in other solvents



Entry	Solvent	Conversion (%)	Secondary Amine (%)	Alcohol (%)
1	Et_2O	100	92	8
2	Toluene	100	93	7
3	Dioxane	100	93	7
4	DME	70	46	24

Conditions: *N*-phenylnonamide (1 g, 4.2 mmol), $[Ru(acac)_3]$ (17 mg, 0.04 mmol), triphos (53 mg, 0.08 mmol), solvent (10 mL), water (0.1 mL), $P(H_2)$ = 40 bar, 164ºC, 14 h.



Different solvents may result in different catalytic activity due to the fact that their properties play a strong role in the reaction. Therefore, for a better understanding of the

reaction and the role played by the solvent, a series of hydrogenation experiments was carried out in different solvents and the results are summarised in Table 3.12.

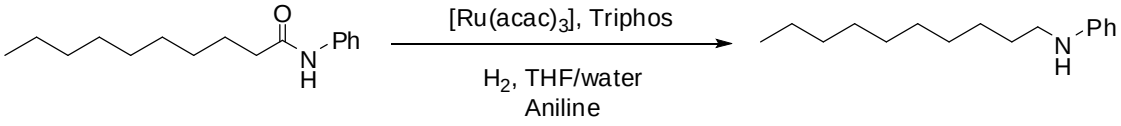
Hydrogenation reactions under standard conditions were carried out using THF as the solvent (Table 3.5, entry 4). Therefore, it is plausible to think that the results would not differ significantly when carrying out reactions in other ethereal solvents, which present similar properties. As expected, the reaction in diethyl ether gave high conversion and selectivity (Table 3.12, entry 1), as did the more water-miscible dioxane, (Table 3.12, entry 4). However, DME lowered the conversion and selectivity (Table 3.12, entry 5). When the reaction was carried out in aromatic solvents such as toluene, high conversion and selectivity were obtained (Table 3.12, entry 3).

3.2.1.7.- Study of the Effect of Aniline in the Hydrogenation of *N*-Phenylnonamide.

The proposed mechanism of the formation of nonanol (Fig 3.23) involves the hydrolysis of amides and imines (a reaction intermediate) following successive hydrogenation steps. During hydrolysis, aniline is liberated into the medium, and it is therefore possible that the concentration of aniline can affect the selectivity of the reaction. A greater amount of aniline may inhibit the hydrolysis, in turn increasing the selectivity of the process.

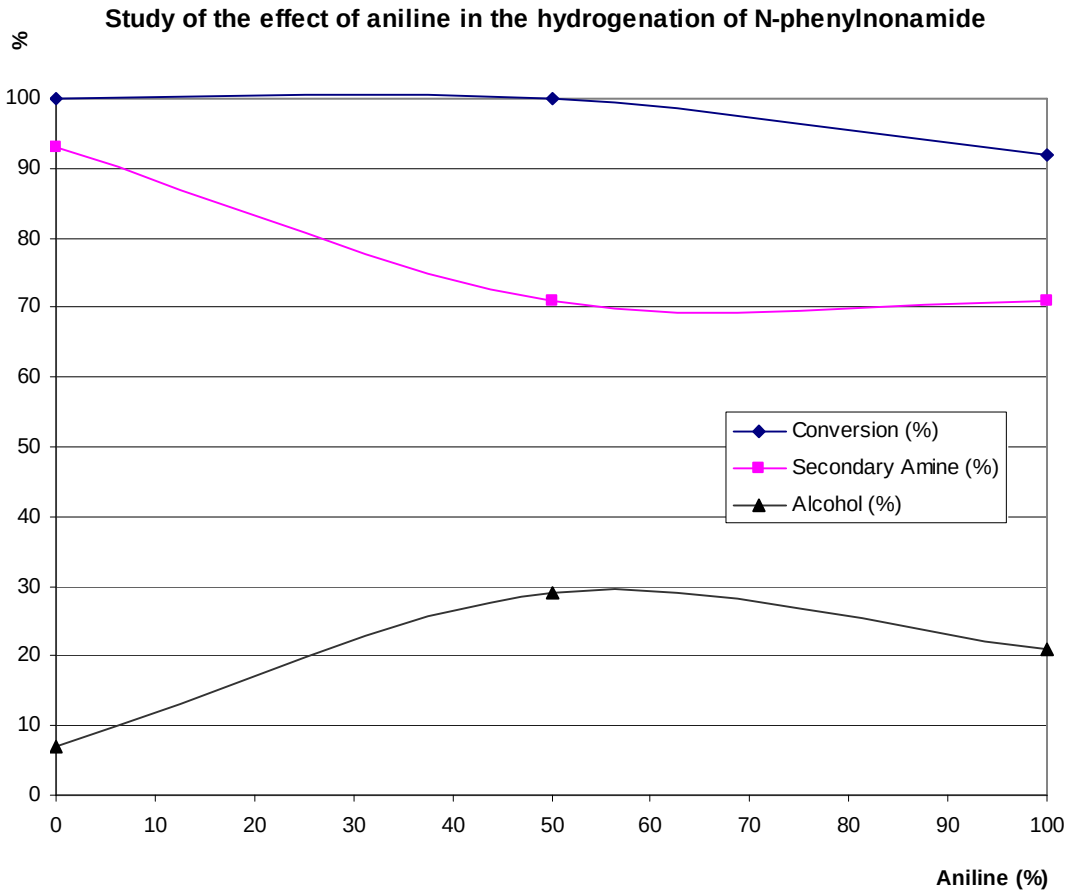
To test this hypothesis, experiments were carried out with the addition of aniline. When 50 % of aniline (compared to *N*-phenylnonamide) was added, the selectivity was lower (Table 3.13, entry 2). An increase in aniline concentration not only confirmed this loss of selectivity, a decrease in conversion was also obtained (Table 3.13, entry 3). However, it should also be noted that in both cases, the reaction solution was dark when the reaction was stopped. Therefore, this loss of catalyst activity may be due to instability of the catalyst in the presence of high aniline concentration. Bases are known to promote the decarbonylation of alcohols.[32]

Table 3.13. Study of the effect of aniline in the hydrogenation of *N*-phenylnonamide.



Entry	Aniline (%)	Conversion (%)	Secondary Amine (%)	Alcohol (%)
1	0	100	93	7
2	50	100	71	29
3	100	92	71	21

Conditions: *N*-phenylnonamide (1 g, 4.2 mmol), [Ru(acac)$_3$] (17 mg, 0.04 mmol), triphos (53 mg, 0.08 mmol), THF (10 mL), water (0.1 mL), aniline (as described), P(H_2) = 40 bar, 164ºC, 14 h.



3.2.1.8.- Hydrogenation of *N*-Phenylnonamide catalysed by the [Ru(acac)$_3$]/TDTBPMB system.

The high activity of the Ru/triphos system in hydrogenation has been explained by the high reactivity of the *fac* isomer of the ruthenium complex (*cap effect*).[25] Following this hypothesis, the use of an alternative ligand, 1,3,5-tris((di-*tert*-butylphosphino)methyl)benzene (TDTBPMB), can be proposed (Fig 3.24).

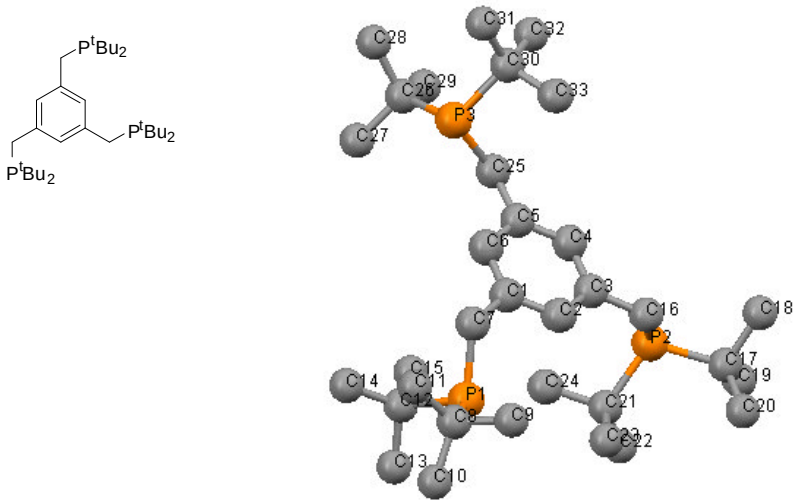


Fig 3.24. *1,3,5-tris((di-tert-butylphosphino)methyl)benzene (TDTBPMB).*

Two synthetic routes to this ligand were considered (Fig 3.25):[42] a) The reaction of di-tertbutylchlorophosphine with the potassium salt obtained by the deprotonation of mesitylene; or b) the reaction of 1,3,5-tris(bromomethyl)benzene with di-*tert*butylphosphine.

Although the first method was examined the potassium salt was highly insoluble in THF (the solvent used in the second step) giving a mixture of products in the reaction with *tert*-butylclorophosphine.

The first attempt of the second route was carried out in acetone. After three hours an abundant white solid had formed. In order to ensure that the reaction had gone to completion, it was stirred at room temperature overnight. After removal of the solvent and deprotonation of the phosphonium salts by triethylamine, the desired product was recovered

(1,3,5-tris((di-*tert*-butylphosphino)methyl)benzene). However, some 1,3-bis(di-*tert*-butylphosphino)methyl)-5-methylbenzene was also formed. The reaction was improved by using methanol as the solvent. Only 1,3,5-tris((di-*tert*-butylphosphino)methyl)benzene was formed, in this case with good yield (63 %).

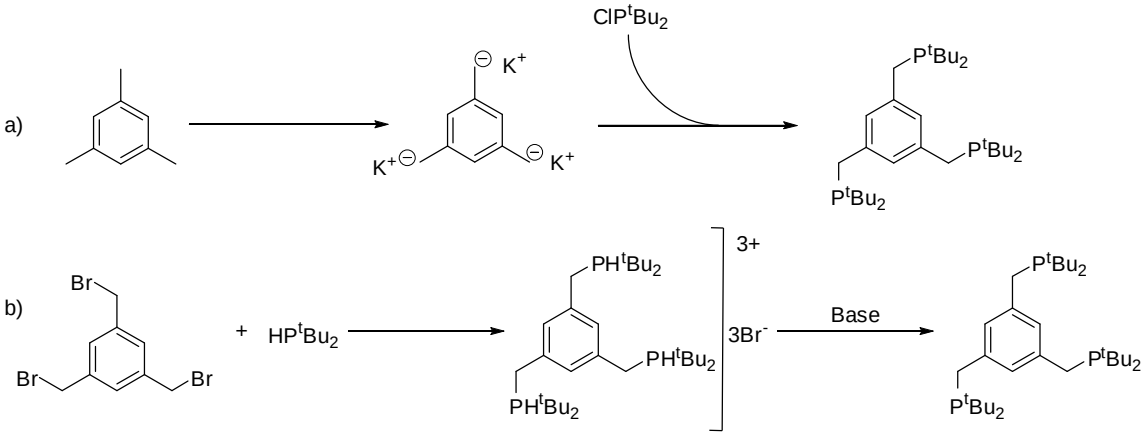


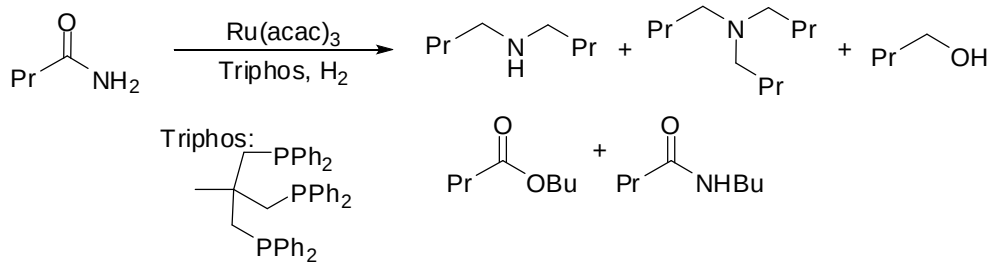
Fig 3.25. *Proposed route for the generation of TDTBPMB.*

When the hydrogenation of *N*-phenylnonamide was carried out under standard conditions (i. e. this shown in Table 3.5, entry 4) using 1,3,5-tris((di-*tert*-butylphosphino)methyl)benzene instead of Triphos, a mixture of products was formed. It is plausible that the high steric hindrance present in 1,3,5-tris((di-*tert*-butylphosphino)methyl)benzene completely inhibited the hydrogenation reaction.

3.2.2.- Hydrogenation of Butanamide.

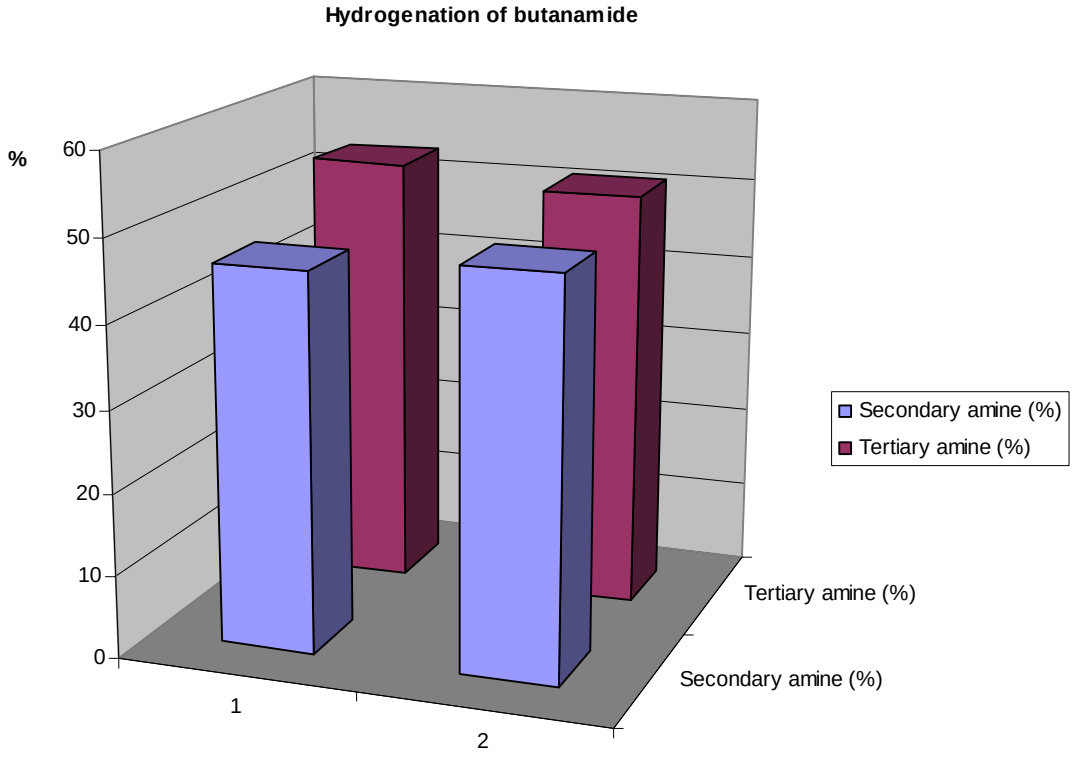
The hydrogenation of primary amides may be an attractive route to the preparation of primary amines. The good results obtained in the hydrogenation of *N*-phenylnonamide, (a secondary amide), could be perhaps be extrapolated to primary amides. However, the results obtained by Crabtree's group did not agree with this theory.[29] A mixture of products such as secondary amines, alcohols, esters and secondary amides, were obtained in the study, which involved the hydrogenation of primary amides catalysed by the Ru/Triphos system.

Table 3.14. Hydrogenation of butanamide**.**



Entry	Water:Solvent ratio (v/v)	Conv. (%)	Primary amine (%)	Secondary amine (%)	Tertiary amine (%)	Secondary ester (%)	Secondary amide (%)	Alcohol (%)
1	0.1	100	0	46	53	Traces	Traces	Traces
2	0.01	100	0	48	51	Traces	Traces	Traces

Conditions: butanamide (1 g, 11.4 mmol), [Ru(acac)$_3$] (45 mg, 0.1 mmol), triphos (142 mg, 0.2 mmol), THF (10 mL), water (as described), P(H_2) = 40 bar, 164ºC, 14 h.



The initial results of the study gave a mixture of products (Table 3.14, entry 1), with the tertiary amine (*N*,*N*,*N*-tributylamine) being the main product. A significant amount of the secondary amine (*N*,*N*-dibutylamine) was also formed. A decrease in the water concentration did not result in a significant difference.

The reason for the recovery of a complex mixture of products must be associated with the high nucleophilicity of the forming amine (**14**). According to the hypothetical mechanism proposed here (Fig 3.26), the primary amine (**14**) can react with either the substrate, primary amide (**12**) giving a secondary amide (**19**) or with the aldehyde (**15**) to generate an imine (**18**). Both compounds (**18**) and (**19**) can then lead to the secondary amine (**20**) by hydrogenation. The tertiary amine (**21**) presumably arises from the reaction of **20** with **12** followed by hydrogenation

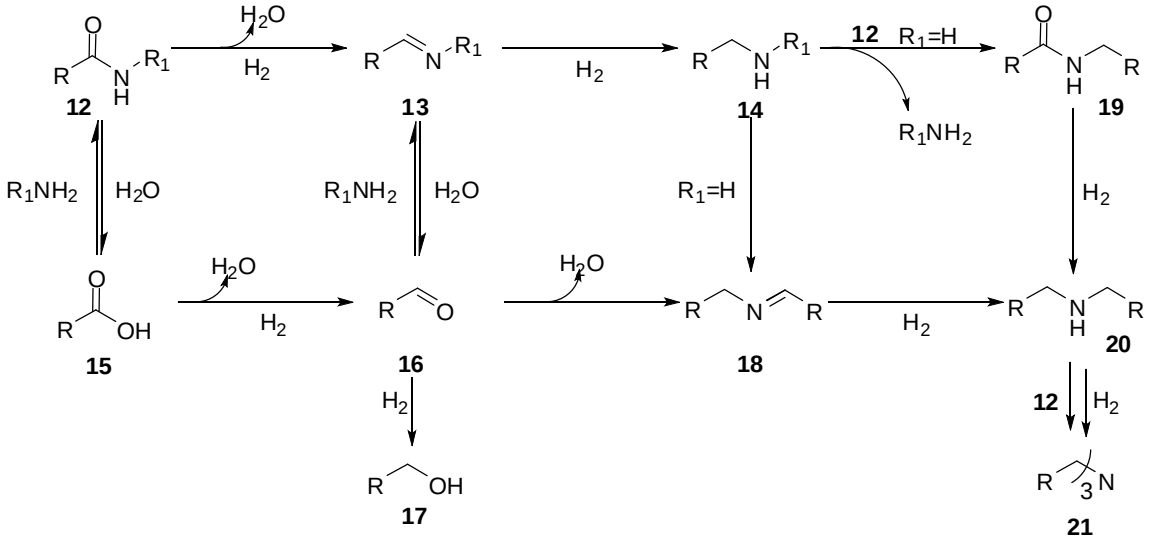
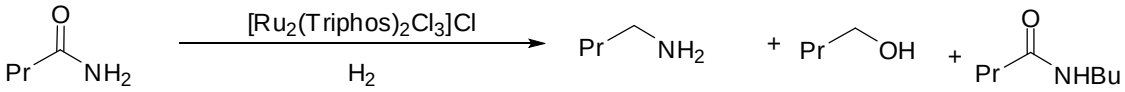


Fig 3.26. *Proposed mechanism for the hydrogenation of amides.*

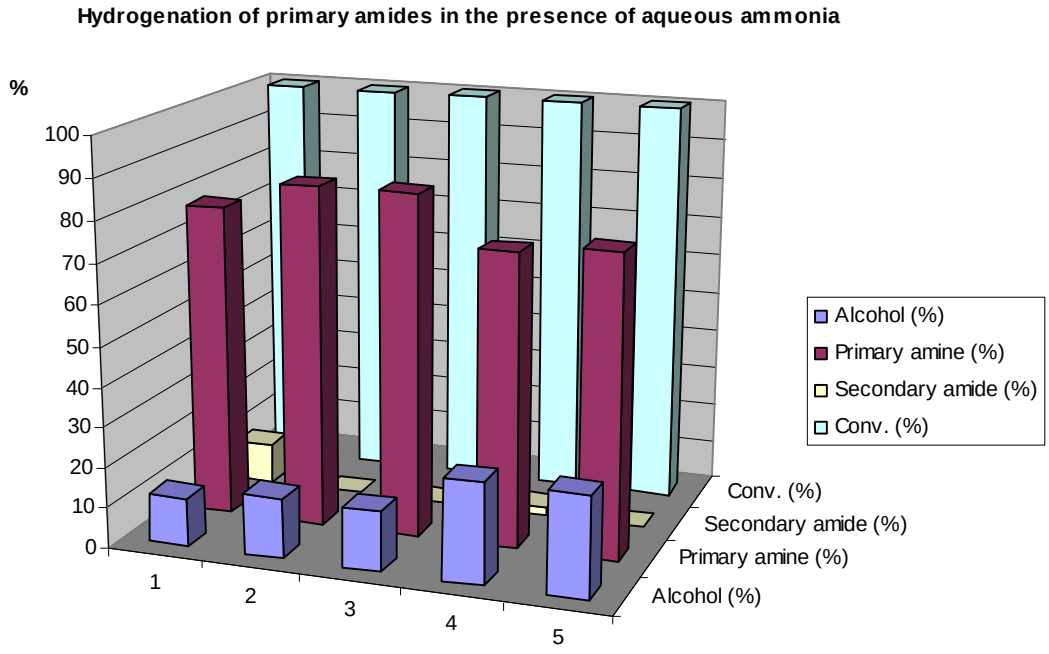
It should be noted that according to the proposed mechanism for the generation of compounds **15, 16** and **19** ammonia will be liberated from the reaction where primary amides were used. Therefore, it is reasonable to think that increasing the concentration of ammonia in the medium may play some beneficial role in the selectivity of the reaction and in the formation of only primary amines. To examine this hypothesis, experiments involving the addition of aqueous ammonia were carried out. The results are summarised in Table 3.15.

Table 3.15. Hydrogenation of primary amides in the presence of aqueous ammonia



Entry	P(NH_3) (bar)	Aqueous ammonia:THF ratio (v/v)	Conv. (%)	Primary amine (%)	Secondary amide (%)	Alcohol (%)
1	-	0.3	100	78	10	12
2	-	0.5	100	85	0	15
3	-	0.7	100	85	0	15
4	-	1	100	73	2	25
5	4	1	100	75	0	25

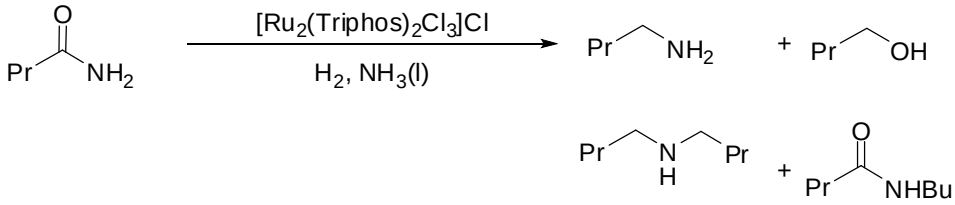
Conditions: butanamide (1 g, 11.4 mmol), $[Ru_2(Triphos)_2Cl_3]Cl$ (91 mg, 0.05 mmol), THF (10 mL), aqueous ammonia (as described), P(H_2) = 40 bar, 164ºC, 14 h.



The reaction in the presence of aqueous ammonia gave high conversion and selectivity to butylamine (Table 3.15, entry 1). An increase in ammonia increased the selectivity to butylamine to 85% (Table 3.15, entries 2 and 3). A high excess of aqueous ammonia lowered the selectivity, due to the significant increase in the water concentration,

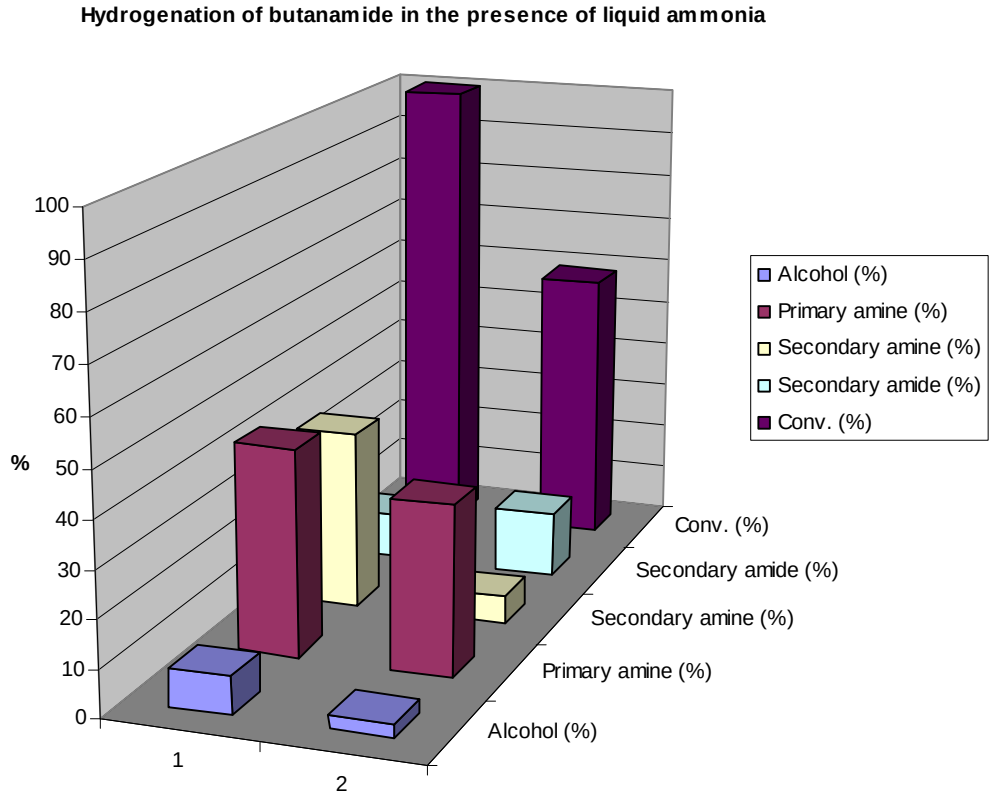
(Table 3.15, entry 4). The use of a combination of ammonia gas and aqueous ammonia did not result in significant difference (Table 3.15, entry 5) from a similar reaction using aqueous ammonia..

Table 3.16. Hydrogenation of butanamide in the presence of liquid ammonia**.**



Entry	Liquid Ammonia :THF ratio (v/v)	Conv. (%)	Primary amine (%)	Secondary amine (%)	Secondary amide (%)	Alcohol (%)
1	0.5	100	44	38	10	8
2	1	59	36	6	14	3

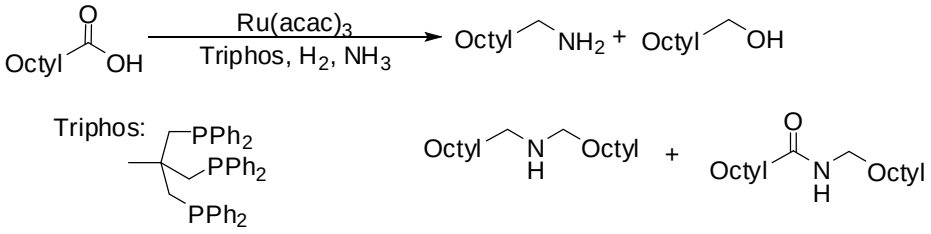
Conditions: butanamide (1 g, 11.4 mmol), $[Ru_2(Triphos)_2Cl_3]Cl$ (91 mg, 0.05 mmol), THF (10 mL), water (1 mL), liquid ammonia (as described), $P(H_2)$ = 40 bar, 164ºC, 14 h.



In an attempt to avoid the use of large amounts of water, liquid ammonia was used.[43] However, when liquid ammonia was used the selectivity was significantly lower and a large amount of secondary amine was formed (Table 3.16, entry 1). An increase in liquid ammonia concentration decreased the conversion (Table 3.16, entry 2).

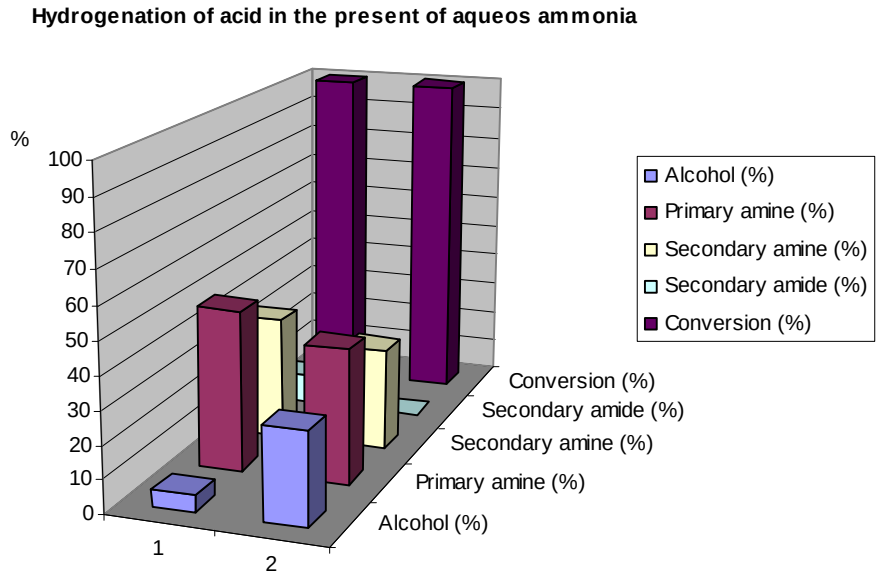
3.2.3.- Hydrogenation of Nonanoic Acid in the Presence of Ammonia.

Table 3.17. Hydrogenation of nonanoic acid in the presence of aqueous ammonia.



Entry	Aqueous ammonia : THF ratio	Conversion (%)	Primary amine (%)	Secondary amine (%)	Alcohol (%)	Secondary amide (%)
1	0.5	100	49	37	5	9
2	1	100	41	31	28	Traces

Conditions: Nonanoic acid (1 mL, 5.7 mmol), $[Ru_2(Triphos)_2Cl_3]Cl$ (45 mg, 0.03 mmol), THF (10 mL), aqueous ammonia (as described), 164ºC, $p(H_2)$ = 40 bar, 14 h.



It is well known that acids in the presence of ammonia at high temperature form amides.[1] This reaction is widely used in the production of amides on an industrial scale (Fig 3.27). Therefore, it is desirable to know if it is possible to generate amines under hydrogenation conditions in a single step from acids. This would give the amides *in situ,* which in turn can give the amines by hydrogenation. In the initial experiments moderate conversions were obtained (Table 3.17, entry 1). Other products included secondary amines (major), alcohols and secondary amides. An increase in the concentration of ammonia in the medium slightly lowered the selectivity to the primary amine (Table 3.17, entry 2).

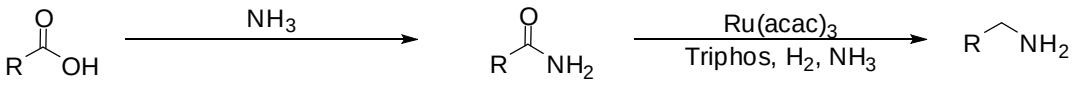
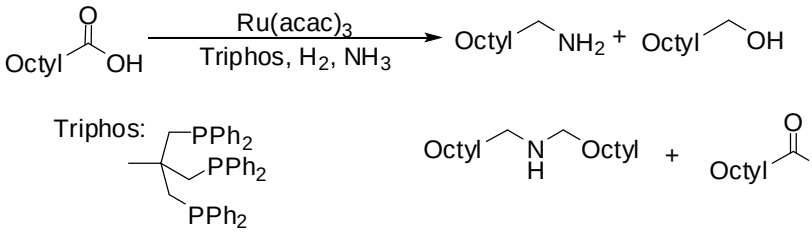


Fig 3.27. *Hydrogenation of acids in the presence of ammonia.*

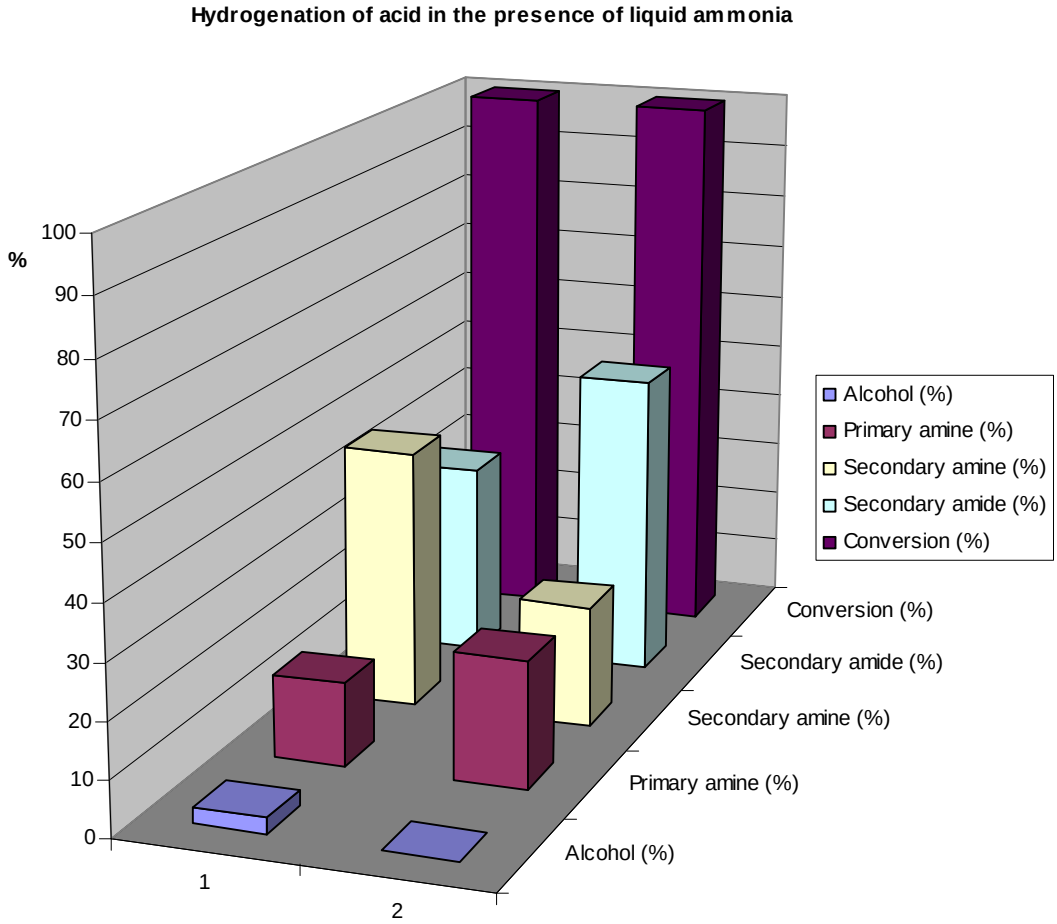
Liquid ammonia[43] has also been examined as source of ammonia for this reaction. When the reaction was carried out in the presence of liquid ammonia, the secondary amine was the main product, with only a small amount of acid being transformed into primary amine (Table 3.18, entry 1). Some alcohol and secondary amide were also formed. An increase in the concentration of ammonia slightly increased the formation of the primary amine. The main product under these conditions was the secondary amide (Table 3.18, entry 2).

Table 3.18. Hydrogenation of nonanoic acid in the presence of liquid ammonia.



Entry	Liquid NH_3:THF ratio	Conversion (%)	Primary amine (%)	Secondary amine (%)	Alcohol (%)	Secondary amide (%)
1	0.5	100	15	47	3	35
2	1	100	23	22	0	55

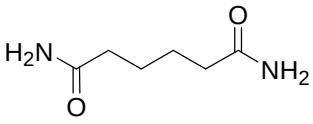
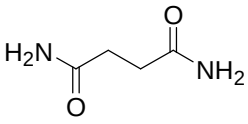
Conditions: Nonanoic acid (1 mL, 5.7 mmol), $[Ru_2(Triphos)_2Cl_3]Cl$ (45 mg, 0.03 mmol), THF (10 mL), water (1 mL), liquid ammonia (as described), 164ºC, $p(H_2)$ = 40 bar, 14 h.



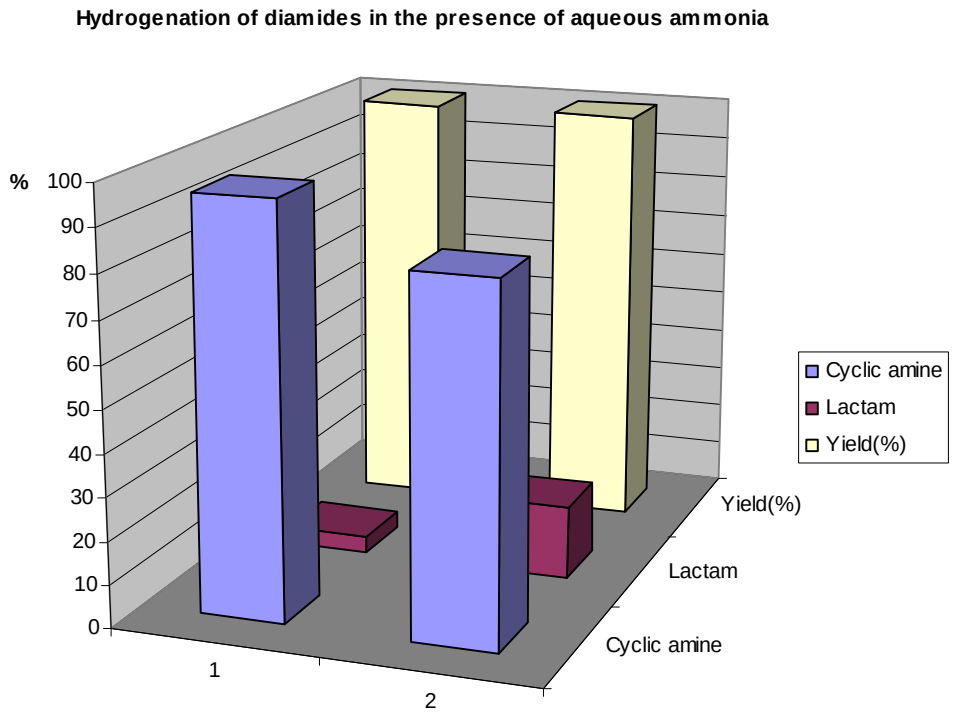
3.2.4.- Hydrogenation of Diamides in the Presence of Ammonia.

A series of experiments was carried out on the hydrogenation of diamides, in order to generate diamines, which are useful substrates in polymer chemistry.

Table 3.19. Hydrogenation of diamides in the presence of aqueous ammonia.

Entry	Structure	Yield(%)	Cyclic amine (%)	Lactam (%)
1		100	96	4
2		100	83	17

Conditions: diamide (11.4 mmol), $[Ru_2(Triphos)_2Cl_3]Cl$ (91 mg, 0.05 mmol), THF (10 mL), aqueous ammonia (10 mL), $P(H_2)$ = 40 bar, 164ºC, 14 h.



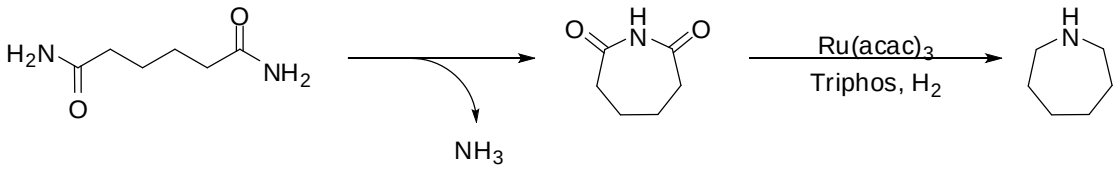
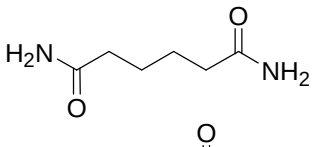
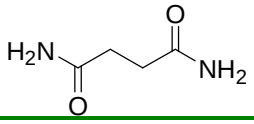


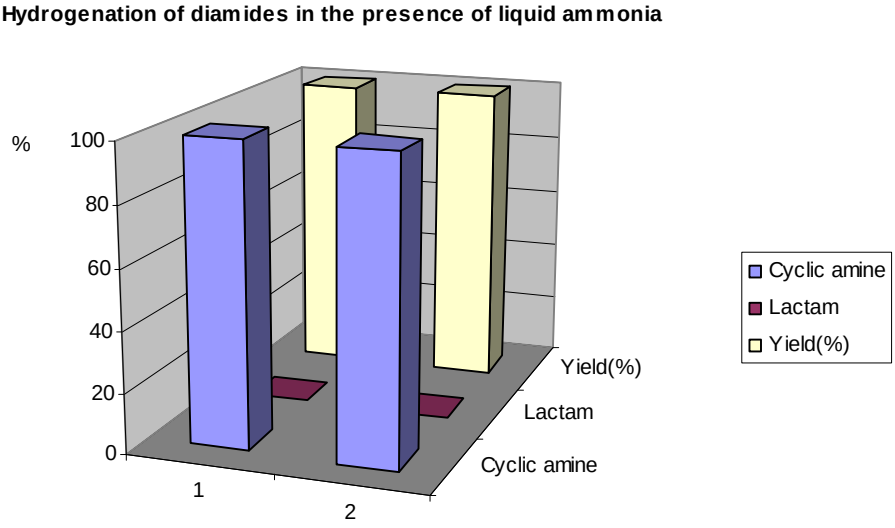
Fig 3.28. *Plausible mechanism for the formation of the hexane-1,6-diamine.*

However, when adipamide was tested under the hydrogenation conditions, no formation of 1,6-diamine was observed. Hexamethyleneimine was the main product (Table 3.19, entry 1), probably due to a highly favourable cyclisation taking place before the hydrogenation (Fig 3.28). Some caprolactam was also formed, which supports the cyclisation hypothesis.

Table 3.20. Hydrogenation of diamides in the presence of liquid ammonia.

Entry	Structure	Yield(%)	Cyclic amine (%)	Lactam (%)
1		100	100	0
2		100	100	0

Conditions: diamide (11.4 mmol), $[Ru_2(Triphos)_2Cl_3]Cl$ (91 mg, 0.05 mmol), THF (10 mL), water (1 mL), liquid ammonia (10 mL), $P(H_2)$ = 40 bar, 164ºC, 14 h



Hydrogenation of succinamide gave similar results. Full conversion and high selectivity to pyrrolidine was observed (Table 3.19, entry 2). The use of liquid ammonia[43] resulted in the full hydrogenation of diamides giving only cyclic amines (Table 3.19, entries 1 and 2).

3.2.4.- Hydrogenation of Other Substrates.

To complete the study, hydrogenation of *N,N'*-diphenyl oxalamide was tested. These substrates can be considered to be the analogue to dimethyl oxalate, which has been widely studied in hydrogenation. Therefore, it was interesting to know if the excellent results obtained in the hydrogenation of dimethyl oxalates[19,23] could be extrapolated to *N,N'*-diphenyl oxalamide. When the reaction was carried out, mainly *N,N'*-diphenyl-1,2-diaminioethane was obtained (Fig 3.29). But, an unknown secondary product was also formed in a significant amount.

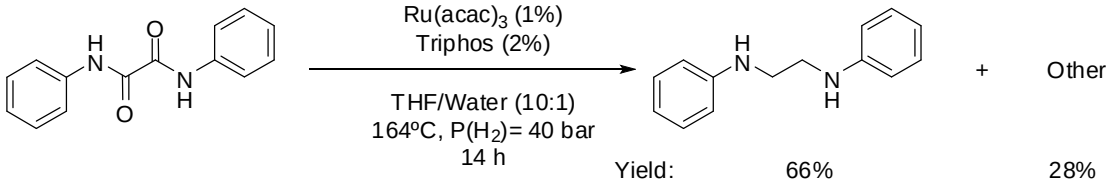


Fig 3.29. *Hydrogenation of N,N'-diphenyl oxalamide.*

Another substrate studied was 1-acetylazacyclohaptan-2-one, in order to determine which carbonyl group will be reduced first. The majot product was N-ethylazacycloheptane from hydrogenation of both carbonyl groups, but 1-Acetylazacycloheptane was recovered as the secondary product, showing that internal carbonyl groups are reduced more easily than external carbonyl groups in this case (Fig 3.30).

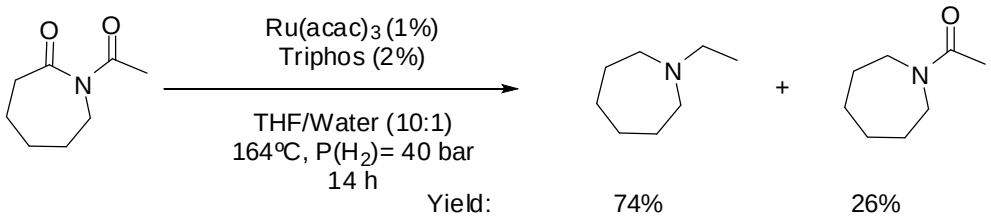


Fig 3.30. *Hydrogenation of N-acetylazacycloheptan-2-one.*

3.3.- Conclusions.

The Ru/Triphos system has been proven to be highly active in the hydrogenation of amides. Secondary amides were successfully reduced by catalytic hydrogenation under mild conditions, obtaining both high conversions and high selectivities.

The initial loss of selectivity in the hydrogenation of primary amides was studied, and a mechanism was proposed which accounts for this drop of selectivity. The study of this mechanism has shown that the presence of ammonia is beneficial and allows the generation of primary amines in high conversions and in high selectivities.

Acids have also been tested under hydrogenation conditions in the presence of ammonia. Moderate conversions to primary amines were obtained, therefore opening the door to this attractive route for primary amine synthesis.

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43. For use of liquid ammonia, see Section 6.3.2.

Chapter 4: Decarboxylation and Desulfonation

4.- Decarboxylation and Desulfonation

4.1.- Introduction.

4.1.1.- Decarboxylation.

C-C bond formation is the philosopher's stone of chemistry. The formation of new molecules is essentially the generation of C-C bonds. For this transformation, new reactions are being developed everyday, giving organic chemists new tools for the synthesis of interesting molecules. However, very often the reactions need certain functional groups to lead the reaction down a specific pathway. This, then, improves the selectivity of the route. For example, the generation of C-C bonds by C-H activation is a highly desirable route due to the low levels of waste produced. However, these reactions usually require functional groups which are able to coordinate to the catalyst, and in turn, place the catalyst in the correct position for the C-H activation. One example is the Murai reaction,[1] which involves the ethylation of aromatic rings. This ethylation is *ortho*-directed by a carbonyl group, which coordinates to the catalyst (Fig 4.1).

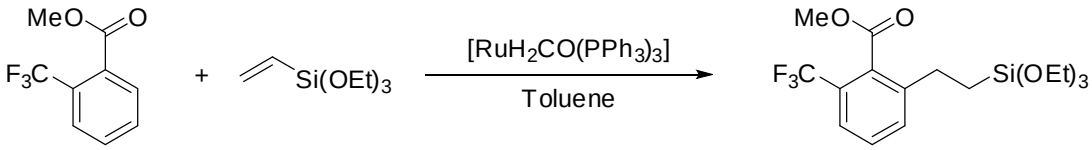


Fig 4.1. *Ethylation of benzoates catalysed by [$RuH_2(CO)(PPh_3)_3$] (Adapted from reference 1a).*

In this case, or in the case where the functional group is bonded during the reaction, (for example the formation of ethyl 4-hydroxybenzoate from 4*H*-pyran-4-one (Fig 4.2)[2]) often these groups must be removed to generate the desired molecules.

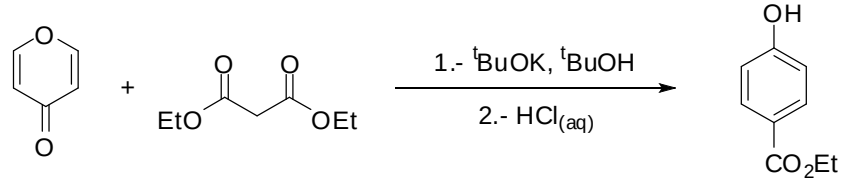


Fig 4.2. *Generation of ethyl-4-hydroxybenzoate from 4H-pyran-4-one.*[2]

However, the breaking of a C-C bond is also unusual and only few routes have been described for this removal. One route to C-C bond breaking is decarboxylation. This reaction involves the breaking of a C-C bond in a carboxylic acid on acidic medium, liberating a molecule of CO_2 (Fig 4.3).[3,4] A long reaction time and a high temperature is usually required for this reaction. No conversion was reported in the absence of acid.[5]

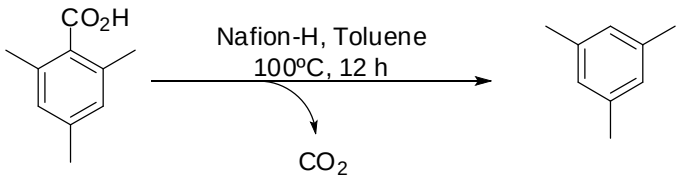


Fig 4.3. *Decarboxylation of an aromatic substrate in acidic medium.*

A carbonyl group in the β-position significantly decreases the harsh conditions usually required for the decarboxylation reaction, due to the possibility of having a 5-membered ring transition state, which in turn lowers the energy of the transition state (Fig 4.4).[6]

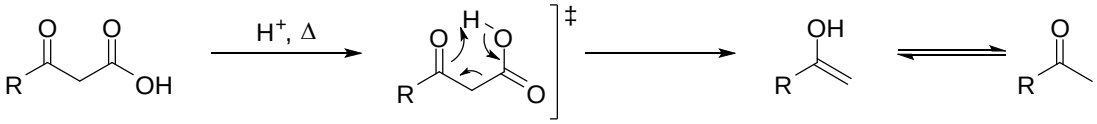


Fig 4.4. *Decarboxylation of a β-oxocarboxylic acid*

One of the first catalytic systems for the decarboxylation of organic acids was based on mercury salts.[7] Although, this system focused more on the generation of arylmercurial complexes than on the decarboxylation of carboxylic acids, the protonolysis of the Hg-C bond may generate the decarboxylated product (Fig 4.5). This reaction can be carried out in the presence of oxygen and light without any change in the outcome, therefore proving the robustness of this system. However, the high toxicity of mercury compounds, especially mercury(II) chloride, which is often used, has limited the use of route.[8]

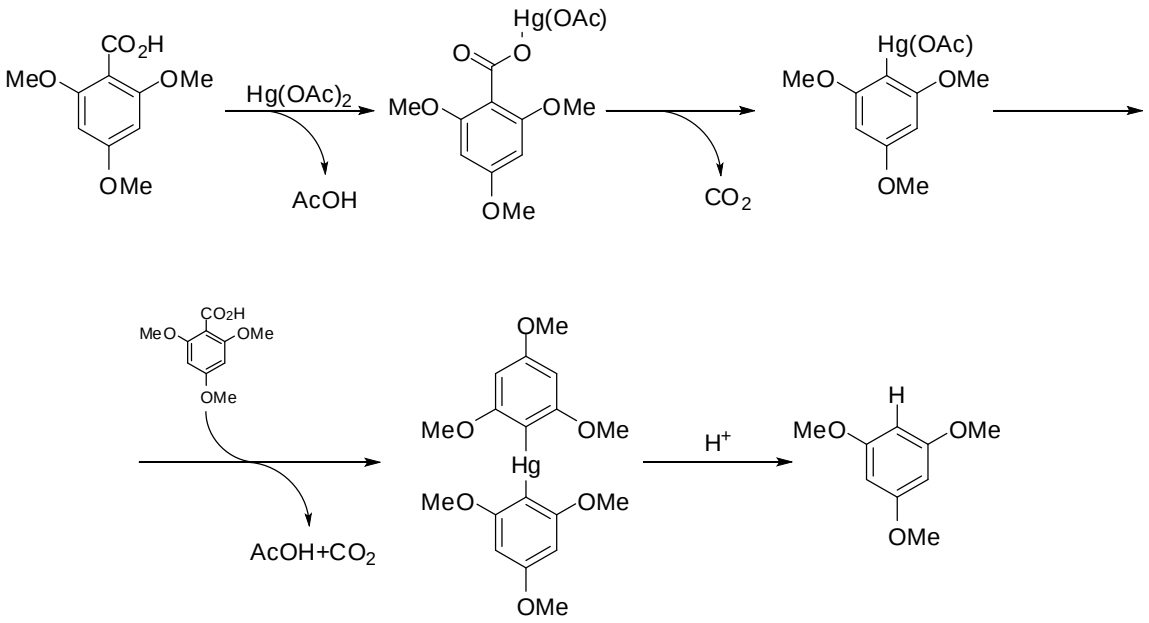


Fig 4.5. *Decarboxylation of an aromatic carboxylic acid catalysed by $Hg(OAc)_2$.*[7]

An interesting alternative to the use of mercury salts is the use of copper catalysts (Fig 4.6).[9] Copper salts in the presence of quinoline or pyridine at high temperaturse (~200ºC), give moderate conversions on the decarboxylation of aromatic acids (~70 %). However, this catalytic system is not suitable for saturated substrates such as dodecanoic acid. Studies on this showed no conversion.[9b]

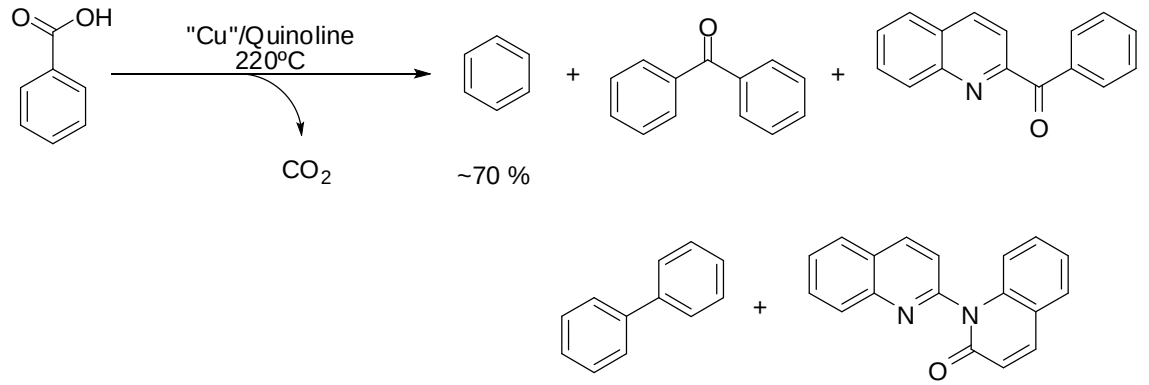


Fig 4.6. *Decarboxylation of an aromatic carboxylic acid catalysed by the Cu/quinoline system.*

Secondary reactions such as oxidation and coupling may take place during the reaction, giving by-products such as benzophenone, phenyl(quinolin-2-yl)methanone, biphenyl and 2*H*-1,2'-biquinolin-2-one (Fig 4.6). However, the reaction can still be considered to be highly selective due to the fact that yields of these secondary products were always lower than 20 %.

The rate of this system was proven to be first order with respect to copper, and was highly dependent on the electron density within the aromatic ring. A faster rate was observed when the aromatic ring was highly electron-deficient. Therefore, highly electron withdrawing groups such as a nitro group in the *para* position significantly increased the rate constant for the reaction from $k = 0.45 \times 10^4\ s^{-1}$ to $k = 14.9 \times 10^4\ s^{-1}$ (with respect to benzoic acid). The presence of a bidentate nitrogen ligand such as 2,2'-bipyridine or 1,10-phenanthroline increased the reaction rate, most probably because of coordination with copper.[9a] According to this principle, quinoline may coordinate the copper generating the active species. Quinoline also possesses important properties which are essential for the reaction –a high boiling point and significant basicity.

Copper bronze reacts significantly slower than Cu^I or Cu^{II} salts, which give similar reaction rates. According to the proposed mechanism, the active species would be a Cu^I complex of quinoline (Fig 4.7). Thus, Cu^{II} must be reduced in the medium. Cohen and co-workers suggest a reduction of Cu^{II} to Cu^I by quinoline, generating the corresponding quinoline oxide.[9a,10] This fact may explain why the reaction must be carried out under a strictly inert atmosphere. In the presence of oxygen, Cu^I may be oxidised to Cu^{II}, which is inactive in this system.

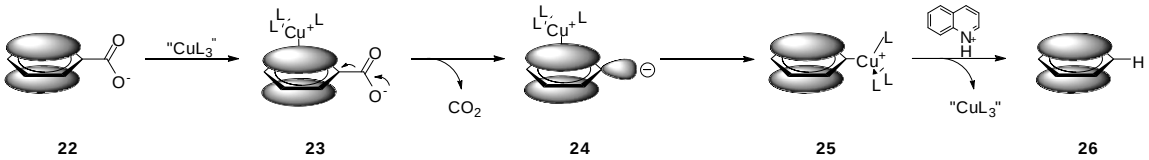


Fig 4.7. *Proposed mechanism for decarboxylation of aromatic carboxylic acid catalysed by Cu/Quinoline system (Adapted from reference 9a)*

The proposed mechanism involves a π complex of copper (**23**).[11] The coordinating copper will result in a decrease in the electron density of the aromatic ring, therefore

facilitating the decarboxylation reaction. After the decarboxylation, a σ-complex of copper (**25**) is formed. The final decarboxylated product (**26**) is obtained by protonolysis. Two possible roles of the ligand have been suggested: 1) the stabilization of the π complex of copper; and 2) increasing the electron/withdrawing properties of the cuprous ion.[9a]

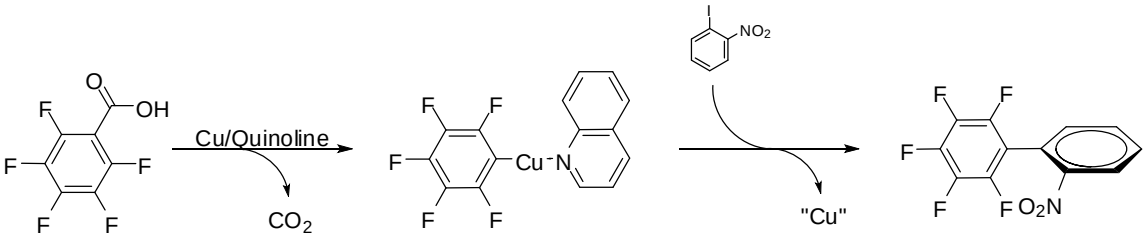
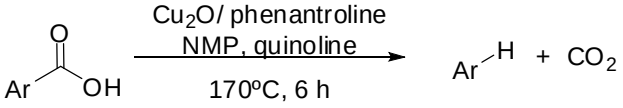


Fig 4.8. *Generation of a biphenyl by decarboxylation/cross coupling reaction.*

The preparation of $[Cu(C_6F_5)(C_9H_7N)]$ by decarboxylation may confirm this mechanism.[12] However, it should be noted that $[Cu(C_6F_5)(C_9H_7N)]$ was not isolated, but was trapped by 1-iodo-2-nitrobenzene, therefore proving its presence (Fig 4.8).

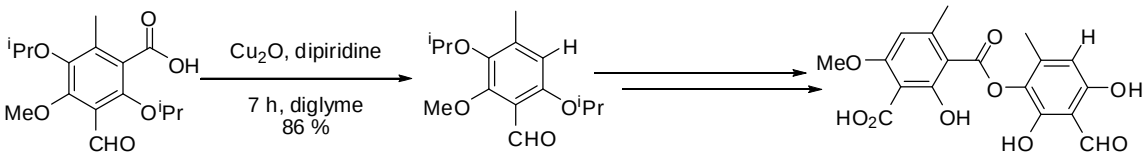
Table 4.1. Decarboxylation of benzoic acids (Adapted from reference 13).



ArCOOH	Yield (%) with the following relative amount of KBr		
	0 %	**15 %**	**100 %**
4-formylbenzoic acid	67	67	-
2-acetylbenzoic acid	79	76	-
2-cyanobenzoic acid	40	25	10
4-nitrobenzoic acid	52	25	10

Recently the negative role of bromide on the system has been described (Table 4.1).[13,14] While in some cases the addition of 15 mol % of KBr did not result in a significant effect (i.e. with the use of 4-formylbenzoic acid or 4-acetylbenzoic acid) (Table 4.1, entries 1 and 2), in other cases (i.e. with 2-cyanobenzoic acid or 4-nitrobenzoic acid a negative

effect was observed (Table 4.1, entries 3 and 4). This effect was more evident when a stoichiometric amount of KBr was added (Table 4.1, entries 3 and 4).



27 **28** **29**

Fig 4.9. *Preparation of meta-depside decarboxythamnolic acid involving a decarboxylation step.*

One application of this reaction was described by Tabacchi and co-workers in the synthesis of *meta*-depside decarboxythamnolic acid, an anti-inflammatory (**29**).[15] In this synthesis, species **28** was accessible in good yield by decarboxylation of **27,** giving an interesting synthetic route to **29** (Fig 4.9).

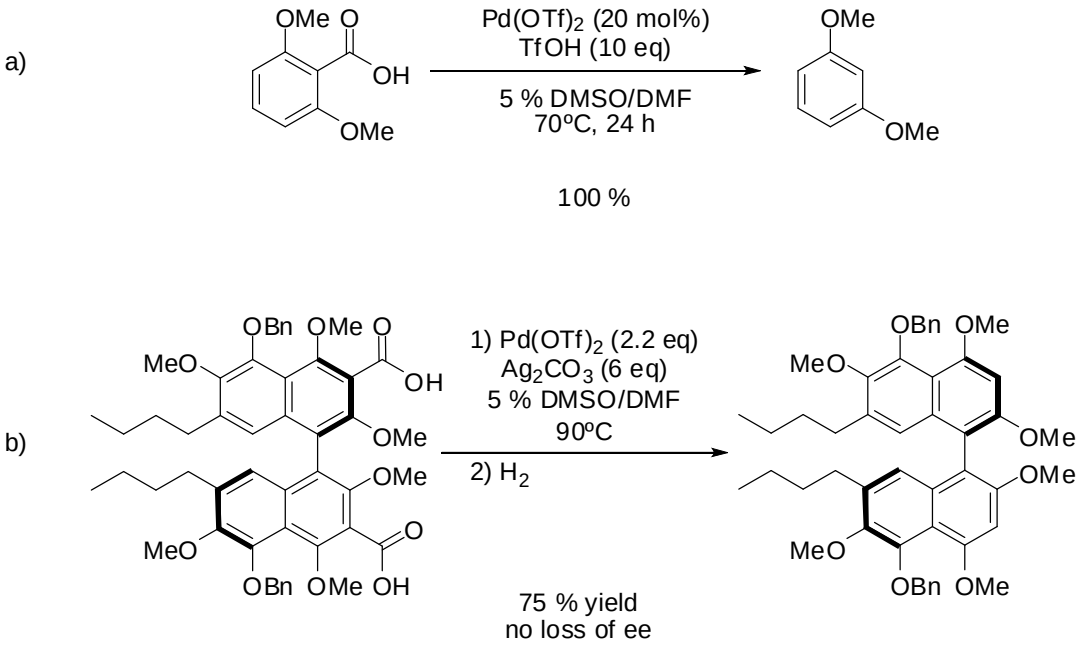


Fig 4.10. *Decarboxylation of an aromatic carboxylic acid catalysed by palladium complexes.*[16]

A palladium system, $Pd(OTf)_2$/DMSO, has recently been developed, which requires much lower temperatures in the reaction (Fig 4.10a).[16] Also this procedure results in no loss of enantioselectivity, making the system especially interesting for the generation of the biaryl compound (Fig 4.10b). This substrate is not available in the copper system due to the fact that when the reaction is carried out under Cu/quinoline catalysis all the stereochemistry is lost. However, a stoichiometric amount of the palladium complex (2.5 equivalents with respect to substrate) must be used under these conditions to maintain the enantiomeric excess. Under these conditions, removal of the Pd complex generated is required. The removal was carried out by the use of hydrogen or $NaBH_4$, giving the desired product.

A mechanism has been proposed for this decarboxylation (Fig 4.11). Initially it was postulated that the formation of a palladium carboxylate (**30**) stabilised by two molecules of dimethylsulfoxide is the first stage, explaining why 5 % of dimethylsulfoxide is required in the reaction. The decarboxylation takes place *via* a 4-membered ring intermediate generating an aryl-palladium species (**31**), which gives the decarboxylated product (**32**) by protonolysis.

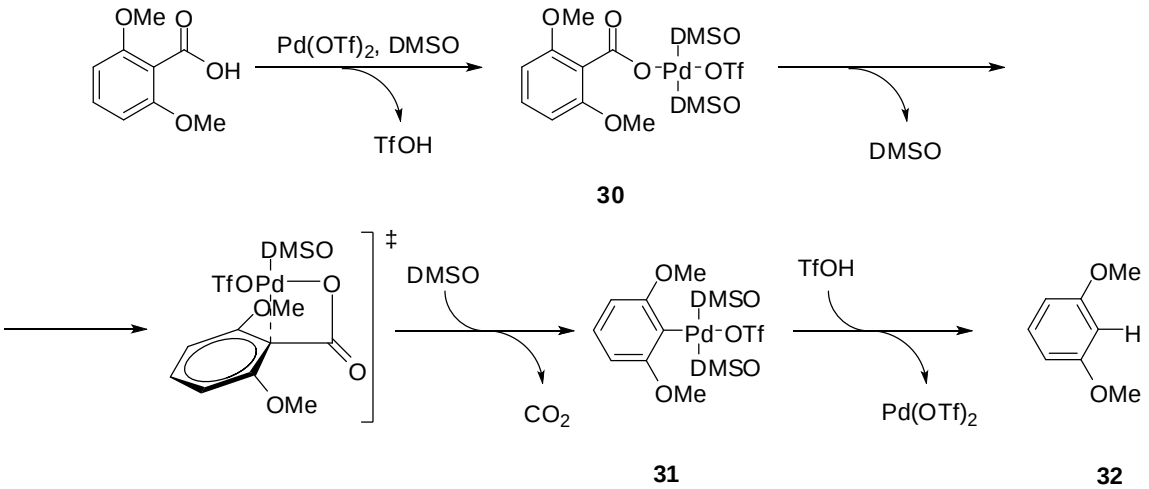


Fig 4.11. *Proposed mechanism for decarboxylation of aromatic carboxylic acid catalysed by Pd.*[16]

The kinetics of the reaction have been measured, showing that protonolysis (k = 2.73 $mM \cdot h^{-1}$, $t_{1/2}$ = 17.7 h) is significantly slower than decarboxylation (k = 0.25 h^{-1}, $t_{1/2}$ =

2.8 h). This gave the possibility of the use of the arylpalladium species **31** in other reactions such as cross coupling or Heck reactions (Fig 4.12). Recently, Myers and co-workers,[17] along with Becht and co-workers,[18,19] have developed elegant systems for tandem decarboxylation/Heck and decarboxylation/Suzuki respectively. This replaces the use of aromatic halides in the case of Heck reaction, and the expensive boronic acids in Suzuki reaction.

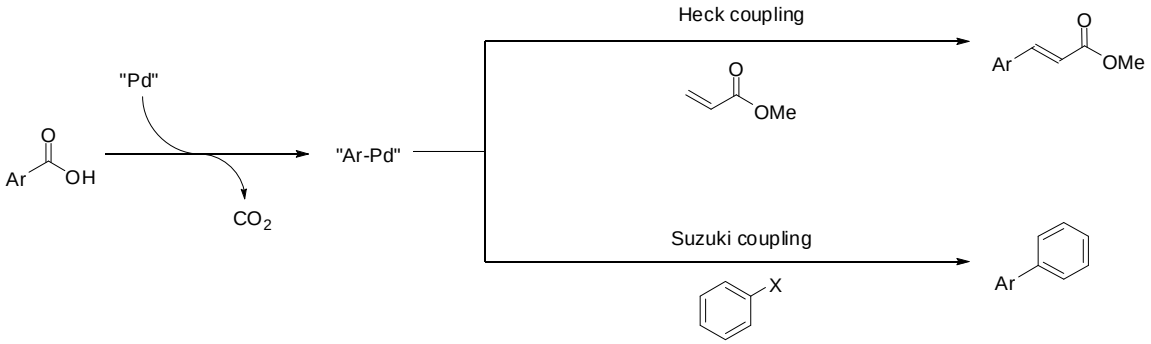


Fig 4.12. *Tandem decarboxylation/Heck and decarboxylation/Suzuki.*

An interesting alternative route was developed by Barton and co-workers. Under Barton's conditions, bromo compounds can be prepared by radical decarboxylation (Fig 4.13).[20] The preparation of iodocompounds was proven to be possible only by the replacement of $CBrCl_3$ in Barton's procedure with either CH_2I_2 or CHI_3.[21]

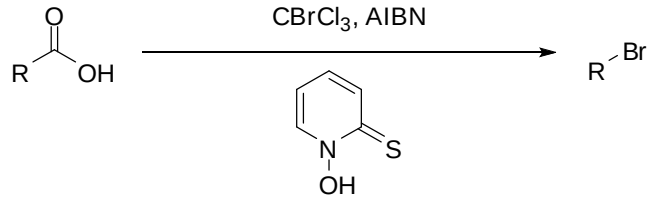


Fig 4.13. *Decarboxylation under Barton's conditions.*

However, although this reaction is an interesting route to prepare halide compounds, initially this did not appear to be the case. This was due to the fact that when α,β-unsaturated carboxylic acids and aromatic carboxylic acid were tested, no conversion was obtained.[21] This problem was overcome by Barton by the replacement of the carboxylic

acids by the corresponding acid chlorides, giving similar results to those obtained with saturated substrates.[21]

A plausible mechanism for this radical decarboxylation has been proposed by Barton (Fig 4.14). The initial step of this reaction is the formation of radical **33** which breaks the C-Br of $CBrCl_3$ homolytically generating the highly reactive $CCl_3^{\cdot}$ radical. This radical may then react with species **34** giving a carboxylate radical which can be broken homoliticaly generating an alkyl radical. In the last step, this radical can react with a molecule of $CBrCl_3$ generating the product, RBr, and regenerating $CCl_3^{\cdot}$.

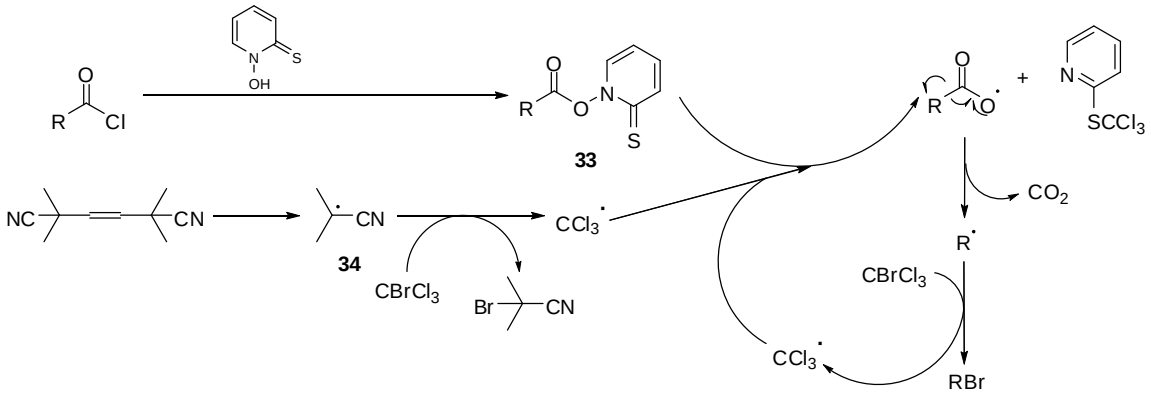


Fig 4.14. *Proposed mechanism for Barton's decarboxylation.*

4.1.2.- Desulfonation.

Sulfonic groups in aromatic compounds are easily formed by the reaction of an aromatic substrate with sulphuric acid (Fig 4.15). The sulfonic group is widely used to block a position on the aromatic ring.[3] It should also be noted that the sulfonic group is a highly electron withdrawing group, which can significantly affect the reactivity of the aromatic ring.

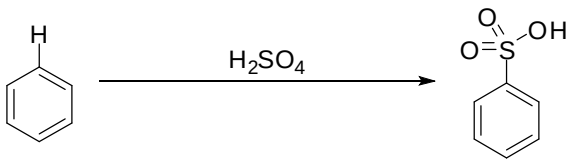


Fig 4.15. *Sulfonation of aromatic rings*

The removal of a sulfonic group, is known as desulfonation (Fig 4.16), and can take place under acidic conditions (H_2SO_4) at high temperatures (135-200ºC). The concentration of H_2SO_4 used was found to be an important variant which must be taken into consideration. The concentration must be low to avoid the reversibility of the reaction. An alternative to the use of dilute sulphuric acid is the use of an alkaline solution of Raney Nickel.[22]

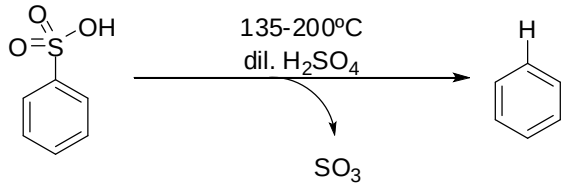


Fig 4.16. *Desulfonation of an aromatic ring.*

An interesting route to the synthesis of aromatic halides was developed by Blum and co-workers.[23] The aromatic halides can be formed by the extrusion of SO_2 from the corresponding sulfonyl halide, catalysed by [RhCl(PPh_3)] (Fig 4.17). This reaction usually gives high conversions in a very short reaction time (~30 min), allowing the preparation of a wide group of aromatic halides including fluorides.

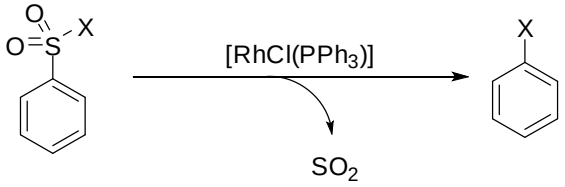


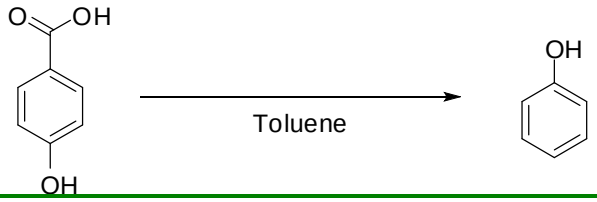
Fig 4.17. *Generation of aromatic halide by extrusion of SO_2 catalysed by [RhCl(PPh_3)].*

4.2.- Results and Discussion.

4.2.1.- Decarboxylation

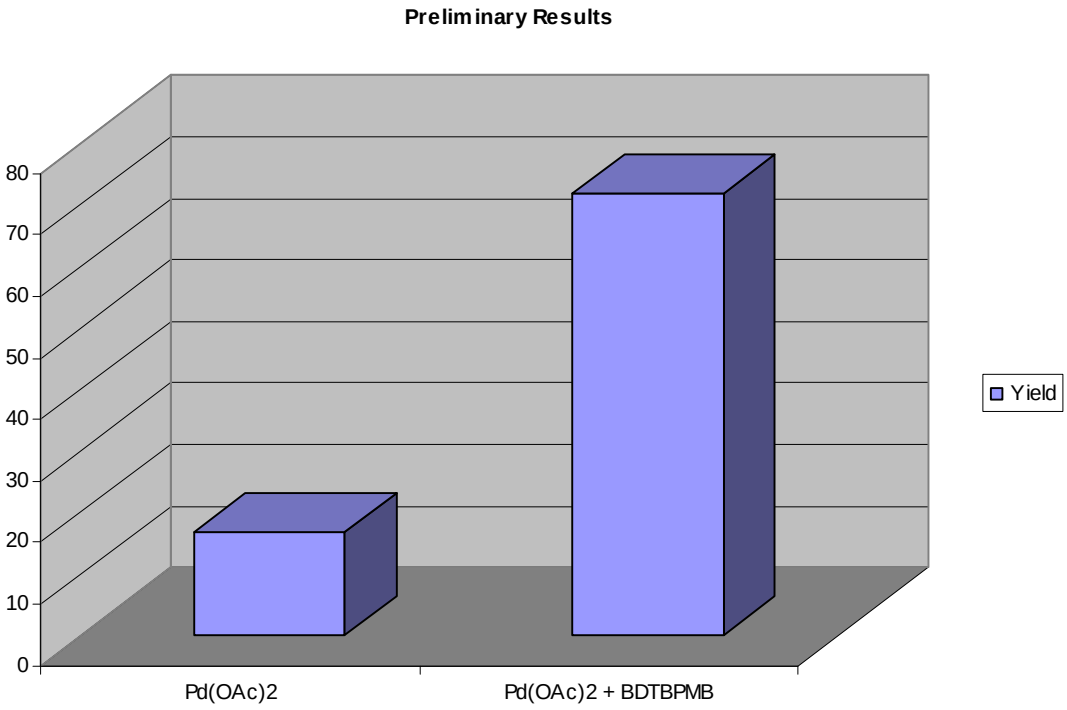
4.2.1.1.- Preliminary Results.

Table 4.2. Preliminary results



Entry	Palladium compound	Ligand	Yield (%)
1	-	-	0
2	$[Pd(OAc)_2]$ (0.5 %)	-	17
3	$[Pd(OAc)_2]$ (0.5 %)	BDTBPMB (1 %)	72

Conditions: 4-hydroxybenzoic acid (2 g, 14.5 mmol), $[Pd(OAc)_2]$ (as described), BDTBPMB (as described), toluene (10 mL), 140ºC, 5 h.



As Section 4.1.1 shows, decarboxylation is an attractive route for the cleavage of a C-C bond. However, nowadays this route still requires harsh conditions to yield high conversion. Thus, it was considered useful to develop a catalytic system which may give high conversion under mild conditions.

The substrate chosen for this study was *p*-hydroxybenzoic acid. This substrate contains a highly electron donating group (the hydroxy group) in the *para* position with respect to the carboxyl group. This hydroxyl group can, therefore donate electrons to the aromatic ring, changing its properties in the decarboxylation reaction. Likewise, *p*-hydroxybenzoic acid is particularly interesting due to its easy formation and the possibility of isotopic labelling.[2]

Initial studies were carried out to test the possibility of the decarboxylation of *p*-hydroxybenzoic acid, catalysed by palladium. No conversion was obtained when the reaction was carried out in the absence of a catalyst at 140ºC (Table 4.2, entry 1). The addition of $[Pd(OAc)]_2$ gave some activity, yielding low conversion (Table 4.2, entry 2). The positive result of the addition of a palladium catalyst to the medium in the presence of a diphosphine, BDTBPMB was moderate conversion (Table 4.2, entry 3).

4.2.1.2.- Mechanism of Decarboxylation.

Pd/BDTBPMB has been proven to be quite active in the decarboxylation of aromatic compounds (see Section 4.2.1.1). Assuming that a palladium complex of the diphosphine BDTBPMB is involved, a mechanism can be proposed.

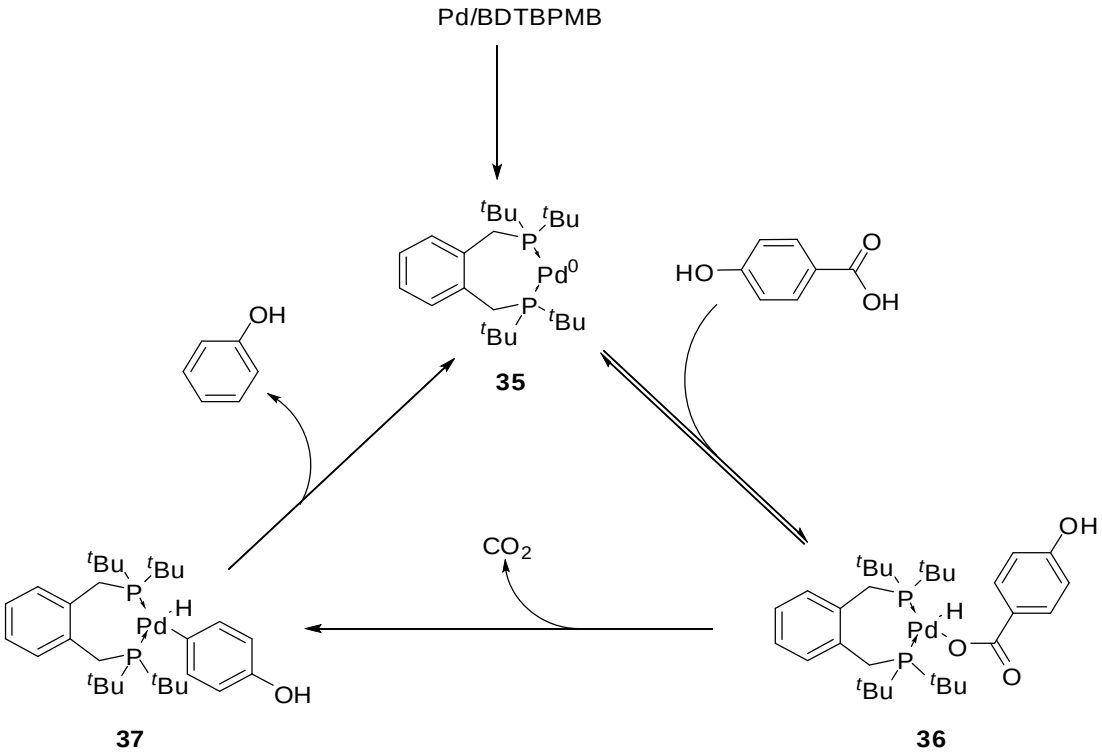


Fig 4.18. *Plausible mechanism of the decarboxylation of aromatic carboxylic acid catalsyst by Pd/BDTBPMB*

We propose that the first step of this mechanism is the formation of the palladium complex **35** from palladium acetate and BDTBPMB. The reaction of this with *p*-hydroxybenzoic acid could generate the hydride complex **36** which, by decarboxylation, can generate the arylspecies **37**. This species could, therefore, give the final product (phenol) by reductive elimination, while regenerating the catalyst **35.**

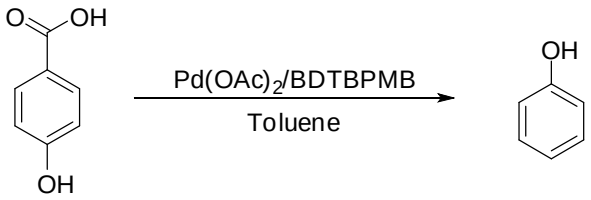
4.2.1.3.- Effect of the Temperature in the Decarboxylation of *p*-Hydroxybenzoic acid.

The initial results mentioned in the Section 4.2.1.1 were very promising. These results proved the high activity of the Pd/BDTBPMB system in the decarboxylation of *p*-hydroxybenzoic acid. However, although the temperature of these experiments was significantly lower than the copper system (See Section 4.1.1), it was still high.

To study the effect of temperature on the decarboxylation of *p*-hydroxybenzoic acid and the possibility of carrying out the experiment under milder conditions, a series of assays was carried out. A range of temperatures between 100ºC and 140ºC was employed and the results are summarised in Table 4.3.

A positive role of increasing temperature was found during this study. When the reaction was carried out at 100ºC no conversion was obtained (Table 4.3, entry 1). An increase of temperature to 120ºC yielded low conversions (Table 4.3, entry 2) while carrying out the reaction at 140ºC gave high conversion (Table 4.3, entry 3). This fact proved that the decarboxylation reaction is highly dependant on the temperature, as a range of 40ºC increased conversion from zero to 70 %. No assays were carried out at temperature above 140 ºC due to the instability of the palladium complex at high temperatures.

Table 4.3. Effect of temperature in the decarboxylation of *p*-hydroxybenzoic acid.



Entry	Temperature	Yield (%)
1	100	0
2	120	17
3	140	72

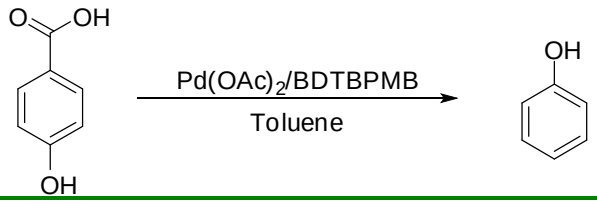
Conditions: 4-hydroxybenzoic acid (2 g, 14.5 mmol), [$Pd(OAc)_2$] (16 mg, 0.07 mmol), BDTBPMB (60 mg, 0.15 mmol), toluene (10 mL), 5 h.

4.2.1.4.- Study of the Effect of the BDTBPMB/Pd Ratio in the Decarboxylation of *p*-Hydroxybenzoic Acid.

Assuming that the good results obtained in the decarboxylation for the Pd/BDTBPMB system (Table 4.2, entry 3) are due to a palladium complex of this diphosphine a study on the effect of the BDTBPMB/Pd ratio in decarboxylation is very attractive.

It should be noted that the formation of a complex is essentially an equilibrium. Therefore, according to *Le Chatelier's* principle, the increase in concentration of the ligand (in this case BDTBPMB) displaces the equilibrium, therefore, increasing the concentration of the complex. Thus, the concentration of the ligand should be as high as possible. However, a high concentration of ligand may play a negative effect in the reaction by formation of other complexes. Likewise, it brings with it an increase in the cost of the process due to the high price of the ligands. Therefore, obtaining the optimum ligand/metal ratio is normally a priority in the design of a process.

Table 4.4. Study of the effect of the BDTBPMB/Pd ratio in the decarboxylation of *p*-hydroxybenzoic acid.



Entry	BDTBPMB/Pd ratio	Yield (%)
1	2	72
2	4	70
3	8	74

Conditions: 4-hydroxybenzoic acid (2 g, 14.5 mmol), [$Pd(OAc)_2$] (16 mg, 0.07 mmol), BDTBPMB (as described), toluene (10 mL), 140ºC, 5 h.

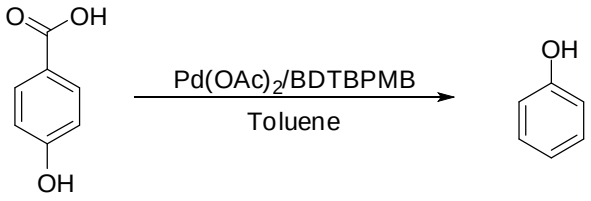
However, this variable was not found to be particularly important. As Table 4.4 shows, when the reaction was carried out using a BDTBPMB/Pd ratio of 2, high conversion was obtained (Table 4.4, entry 1). No significant differences were found in the increase of the BDTBPMB/Pd ratio to 4 (Table 4.4, entry 2). A high excess of BDTBPMB did not result in any notable changes (Table 4.4, entry 3).

4.2.1.5.- Effect of Halides in the Decarboxylation of *p*-Hydroxybenzoic acid.

The addition of halides may play an important role in organometallic catalysis changing the catalyst's properties and reactivities.[14] This effect may be due to the

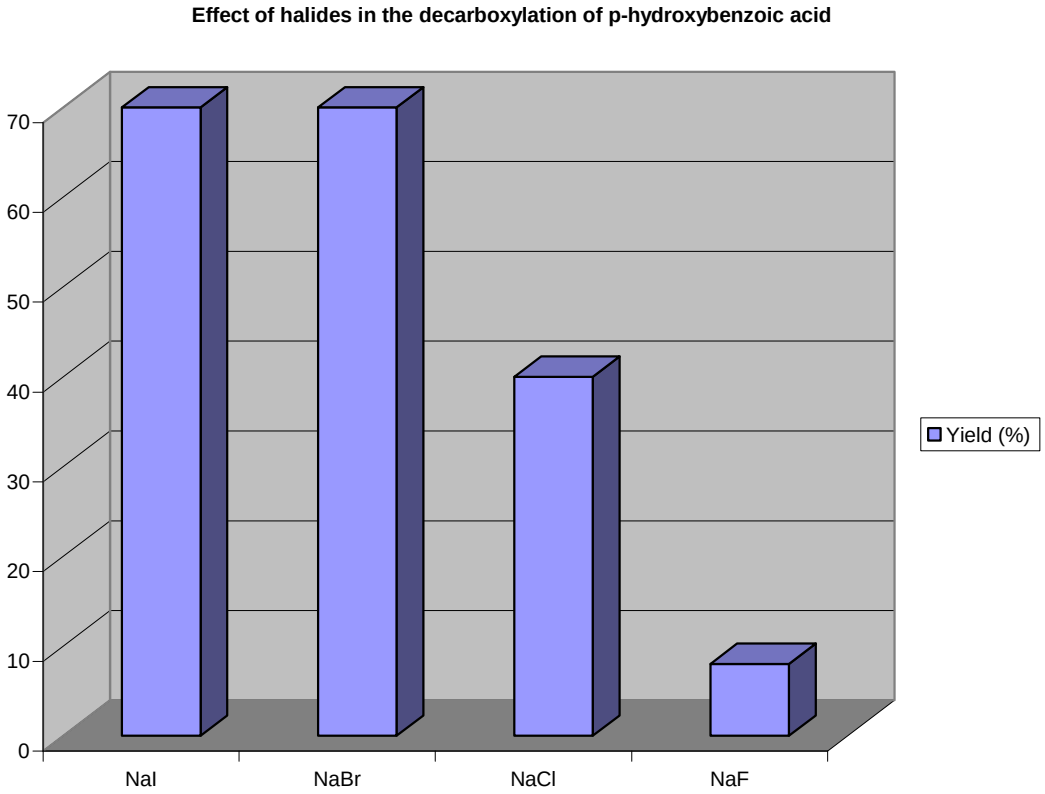
coordination of the halide atom in some part of the catalytic cycle, therefore modifying the electron density of the catalyst probably by either σ or π-donation.

Table 4.5. Effect of halides in the decarboxylation of *p*-hydroxybenzoic acid.



Entry	NaX	Yield (%)
1	NaI	70
2	NaBr	70
3	NaCl	40
4	NaF	8

Conditions: 4-hydroxybenzoic acid (2 g, 14.5 mmol), [$Pd(OAc)_2$] (16 mg, 0.07 mmol), BDTBPMB (60 mg, 0.15 mmol), NaX (0.725 mmol), toluene (10 mL), 140ºC, 5 h.



Therefore, it is interesting to know if the presence of halides in the medium can affect the activity of the Pd/BDTBPMB system in decarboxylation reactions. Hence, a series of experiments under typical decarboxylation conditions in the presence of sodium salts of different halides were carried out. Table 4.5 shows the results obtained.

When the reaction was carried out in the presence of NaI or NaBr, no appreciable differences (Table 4.5, entries 1 and 2) were obtained with respect to the results obtained under normal conditions (Table 4.2, entry 3). However, NaCl lowered the conversion significantly (Table 4.5, entry 3). This result is even more evident when NaF was used (Table 4.5, entry 4).

Therefore, from these results, it can be concluded that σ-donor atoms such as iodine do not result in any effect in the reaction, while π-donor atoms such as fluorine play a notable negative role in the activity of the catalyst. This negative effect is probably due to strong Pd-F bond formation.

4.2.1.6.- Study of the Effect of Base in the Medium of the Decarboxylation Reaction.

According to the proposed mechanism, the addition of base to the medium can generate three acid-base equilibria (Fig 4.19): The formation of benzoates and, depending on the acidity of complexes **36** and **37**, the deprotonation of these complexes. It is plausible to think that these acid-base equilibriums can block the catalytic cycle and therefore, block the synthesis. It should be noted that no equilibria involving the hydroxyl group has been included considering that these equilibrias do not play significant role in the catalysis

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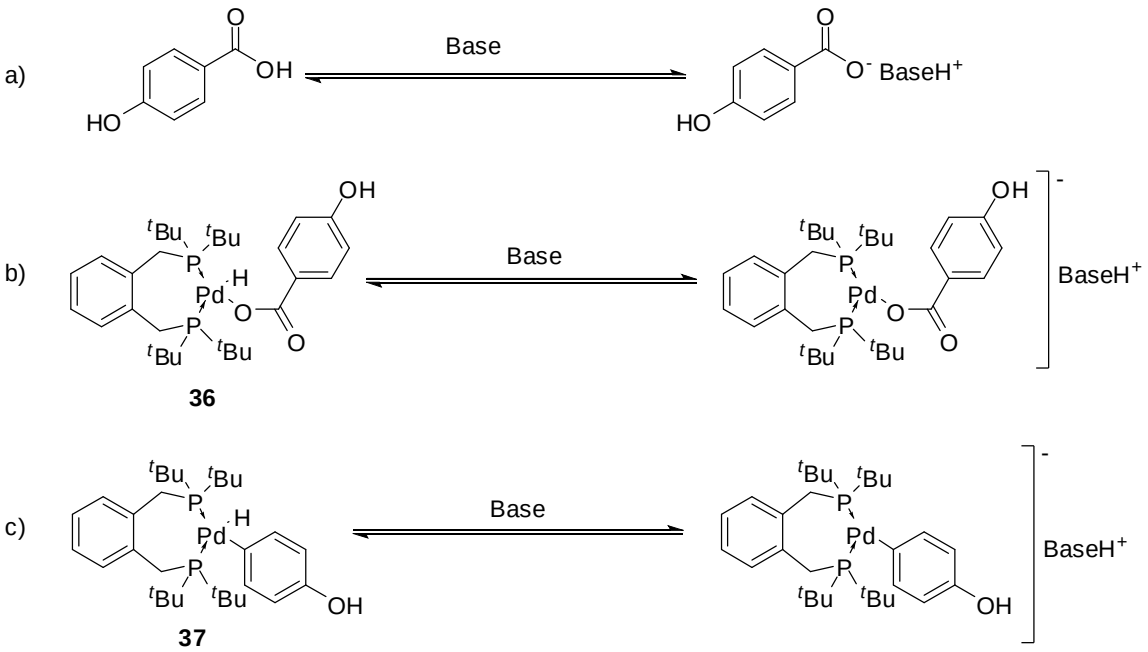
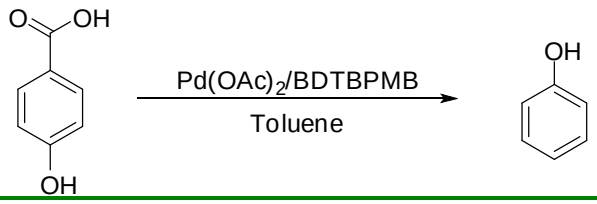


Fig 4.19. *Equilibriums formed in the decarboxylation medium in the presence of base.*

To prove this hypothesis, an experiment under normal conditions in presence of Et_3N (2 equivalents per equivalent of *p*-hydroxybenzoic) was carried out. Unexpectedly, a similar conversion was obtained in this case (Table 4.6, entry 2). This result can be explained considering that BDTBPMB is a highly electron donating phosphine and therefore, its palladium complexes are highly basic. Therefore, although in the presence of a base, these equilibria are present within the medium, the high basicity of the catalyst keeps the equilibrium to the left.

Table 4.6. Study of the effect of base in the medium of the decarboxylation reaction.



Entry	Base	Yield (%)
1	-	72
2	Et_3N (2 equivalent)	75

Conditions: 4-hydroxybenzoic acid (2 g, 14.5 mmol), [$Pd(OAc)_2$] (16 mg, 0.07 mmol), BDTBPMB (60 mg, 0.15 mmol), toluene (10 mL), base (as described), 140ºC, 5 h.

It should be noted that the basicity of a catalyst does not affect the first equilibrium (Fig 4.19a). However, the triethylammonium cation generated by deprotonation of 4-hydroxybenzoic acid may be acidic enough to protonate the catalyst **35,** generating the species **36** (Fig 4.20).

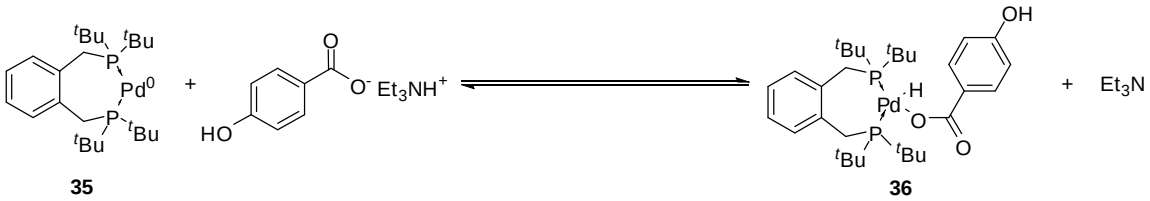


Fig 4.20. *Generation of species **35** by reaction of **36** with triethylammonium-4-hydroxybenzoate.*

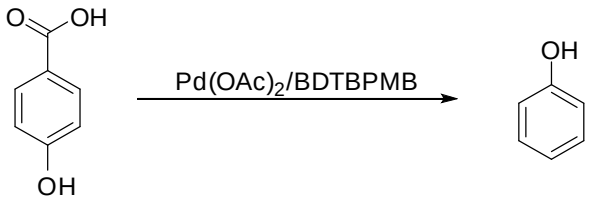
4.2.1.7.- Decarboxylation in Other Solvents.

The decarboxylation reactions described above were carried out in toluene. However, often the properties of the catalyst and its activity depend upon solvent properties such as solvation or polarity. To study this variable the reaction was carried out in other solvents. These chosen solvents were *o*-dichlorobenzene, and two ethereal solvents, THF and diethyl ether.

It is plausible to think that *o*-dichlorobenzene has similar properties to those of toluene. However, the presence of two chlorine atoms gives it a higher polarity than toluene. This increase in polarity may explain why conversion was lower when the reaction was carried out in *o*-dichlorobenzene (Table 4.7, entry 1).

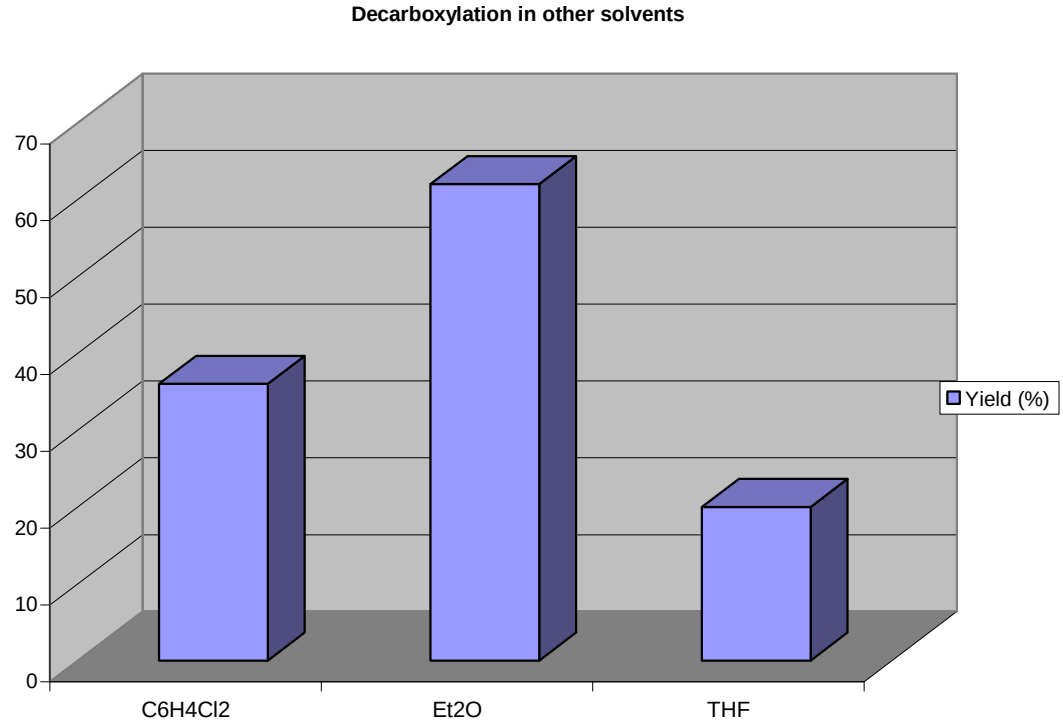
Ethereal solvents are widely used in organometallic catalysis due to their solvation and coordination properties give an optimum medium for the reaction. However, when diethyl ether was used in place of toluene, moderate conversion was obtained (Table 4.7, entry 2). This conversion is notably lower than the one obtained under normal conditions (Table 4.2, entry 3). THF gave only low conversion (Table 4.7, entry 3).

Table 4.7. Decarboxylation in other solvents**.**



Entry	Solvent	Yield (%)
1	$C_6H_4Cl_2$	36
2	Et_2O	62
3	THF	20

Conditions: 4-hydroxybenzoic acid (2g, 14.5 mmol), [$Pd(OAc)_2$] (16 mg, 0.07 mmol), BDTBPMB (60 mg, 0.15 mmol), solvent (10 mL), 140ºC, 5 h.

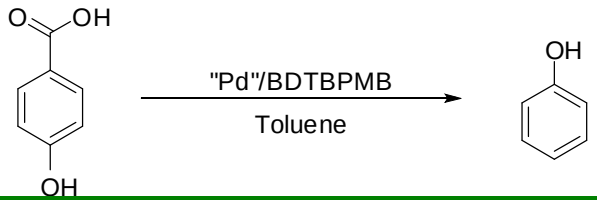


4.2.1.8.- The use of Other Palladium Precursors in Decarboxylation.

Other palladium precursors have been tested under the normal decarboxylation conditions. Using [$Pd(MeCN)_2Cl_2$] as the precursor of the palladium complex of BDTBPMB, the reaction yielded moderate conversion (Table 4.8, entry 1). It should be

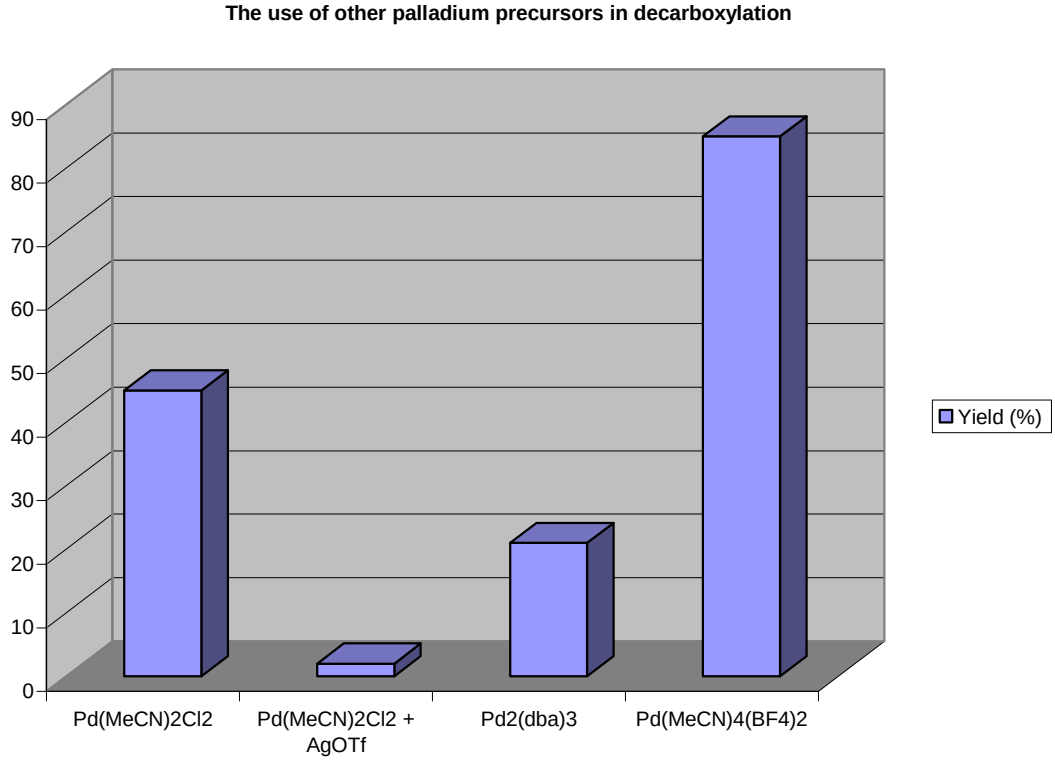
noted that this conversion was significantly lower than that obtained when the reaction was carried out under normal conditions using [$Pd(OAc)_2$] as the precursor (Table 4.2, entry 3). This decrease in conversion can be attributed to the two chlorine atoms present in [$Pd(MeCN)_2Cl_2$]. This result corroborated the negative effect of the presence of chloride in the medium as mentioned in Section 4.2.1.5.

Table 4.8. The use of other palladium precursors in decarboxylation**.**



Entry	Pd precatalyst	Additive	Yield (%)
1	[$Pd(MeCN)_2Cl_2$]	-	45
2	[$Pd(MeCN)_2Cl_2$]	AgOTf (2 %)	2
3	[$Pd_2(dba)_3$]	-	21
4	[$Pd(MeCN)_4$][BF_4]$_2$	-	85

Conditions: 4-hydroxybenzoic acid (2g, 14.5 mmol), palladium compound (0.07 mmol), BDTBPMB (60 mg, 0.15 mmol), toluene (10 mL), 140ºC, 5 h.

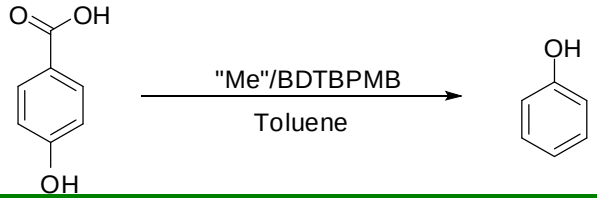


Due to this hypothesis, it was thought that the addition of a chloride scavenger, such as a silver compound, may increased the conversion of the decarboxylation reaction when using $[Pd(MeCN)_2Cl_2]$. However, when silver triflate was added only traces of product were obtained in the reaction (Table 4.8, entry 2), probably due to a decrease in the stability of the catalyst in the presence of silver. The use of a palladium zero precursor, $[Pd_2(dba)_3]$, gave only low conversion (Table 4.8, entry 3). Excellent conversion was obtained when $[Pd(MeCN)_4][BF_4]_2$ was used as a palladium precursor due to the high lability of MeCN, which may make the formation of complex **36** from **35** more facile (Table 4.8, entry 4).

4.2.1.9.- The Use of other Metal Catalysts in Decarboxylation.

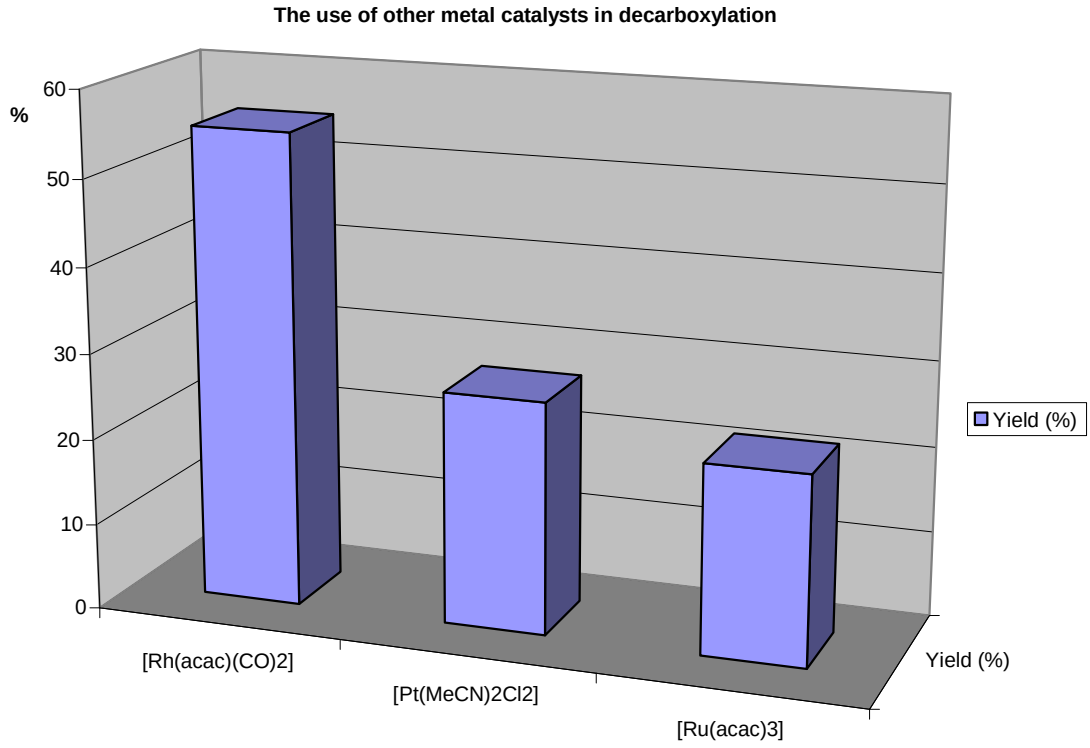
In order to extend this study, a series of experiments with other metal catalysts has been carried out. When the reaction was carried out using a rhodium catalyst ($[Rh(acac)(CO)_2]$) a moderate conversion was obtained (Table 4.9, entry 1). $[Pt(MeCN)_2Cl_2]$ and $[Ru(acac)_3]$ gave low conversions (Table 4.9, entries 2 and 5). Only traces of phenol were obtained when the reaction was catalyzed by copper salts and the iridium complex, $[Ir(acac)(CO)_2]$ (Table 4.9, entries 3,4 and 6). This study confirmed that palladium complexes are the most active in the decarboxylation of benzoic acid under these conditions.

Table 4.9. The use of other metal catalysts in decarboxylation**.**



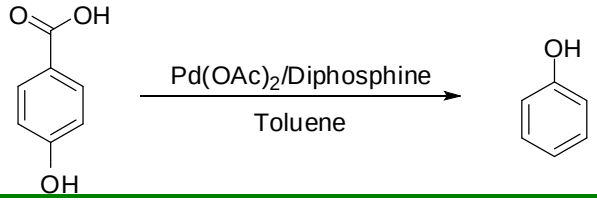
Entry	Metal compound	Yield (%)
1	$[Rh(acac)(CO)_2]$	55
2	$[Pt(MeCN)_2Cl_2]$	27
3	$[Cu(OAc)_2]$	Trace
4	CuI	0
5	$[Ru(acac)_3]$	22
6	$[Ir(acac)(CO)_2]$	Traces

Conditions: 4-hydroxybenzoic acid (2g, 14.5 mmol), metal compound (0.07 mmol), BDTBPMB (60 mg, 0.15 mmol), toluene (10 mL), 140ºC, 5 h.



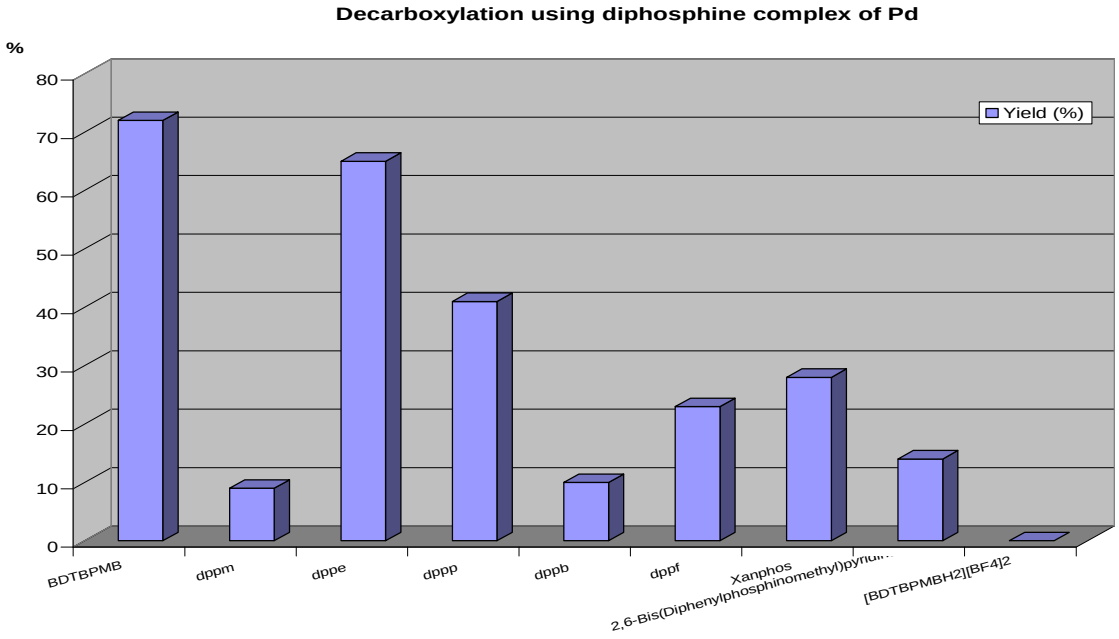
4.2.1.10.- Decarboxylation of *p*-Hydroxybenzoic Acid Using Palladium Complexes of other phosphines.

Table 4.10. Decarboxylation of *p*-hydroxybenzoic acid using palladium complexes of other diphosphines.



Entry	Diphosphine	Yield (%)
1	BDTBPMB	72
2	dppm	9
3	dppe	65
4	dppp	41
5	dppb	10
6	dppf	23
7	Xanphos	28
8	2,6-Bis(Diphenylphosphinomethyl)pyridine	14
9	$[BDTBPMBH_2][BF_4]_2$	0

Conditions: 4-hydroxybenzoic acid (2 g, 14.5 mmol), $[Pd(OAc)_2]$ (16 mg, 0.07 mmol), diphosphine (1.5 mmol), toluene (10 mL), 140ºC, 5 h.



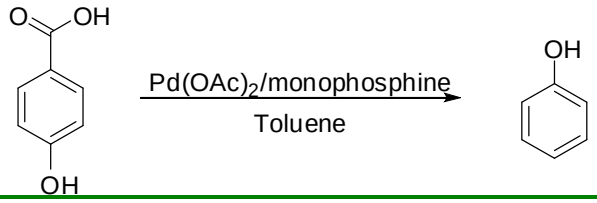
As mentioned in Section 1.2.2.1, phosphines are ligands in which the electronic and steric properties can be modified depending on the substituent on the phosphorus atom. Nowadays, there is a wide pool of different phosphines, where the most important are monophosphines and diphosphines.

To extend this study of decarboxylations catalysed by palladium, a series of assays using different phosphines has been carried out. Due to the different reactivity and properties of monophosphines and diphosphines, this study has been separated into two groups.

Initially, diphosphines were studied (Table 4.10). Using diphosphines with a very small bite angle,[24] such as dppm, the conversion obtained was appreciably lower (Table 4.10, entry 1) than when using BDTBPMB. A significant increase in conversion was obtained when the bite angle of the phosphine (dppe) was increased (Table 4.10, entry 2). Dppp, which has a bigger bite angle than dppe, lowered the conversion of the decarboxylation (Table 4.10, entry 3). This effect was more evident when dppb was used. Only low conversion was obtained under these conditions (Table 4.10, entry 4). Diphosphines with a wide bite angle such as dppf, Xanphos and 2,6-bis(Diphenylphosphinomethyl)pyridine gave low conversions (Table 4.10, entries 5 to 7). Surprisingly, the air stable BDTBPMB analogue, $[BDTBPMBH_2][BF_4]_2$,[25] was not active under decarboxylation conditions (Table 4.10, entry 8).

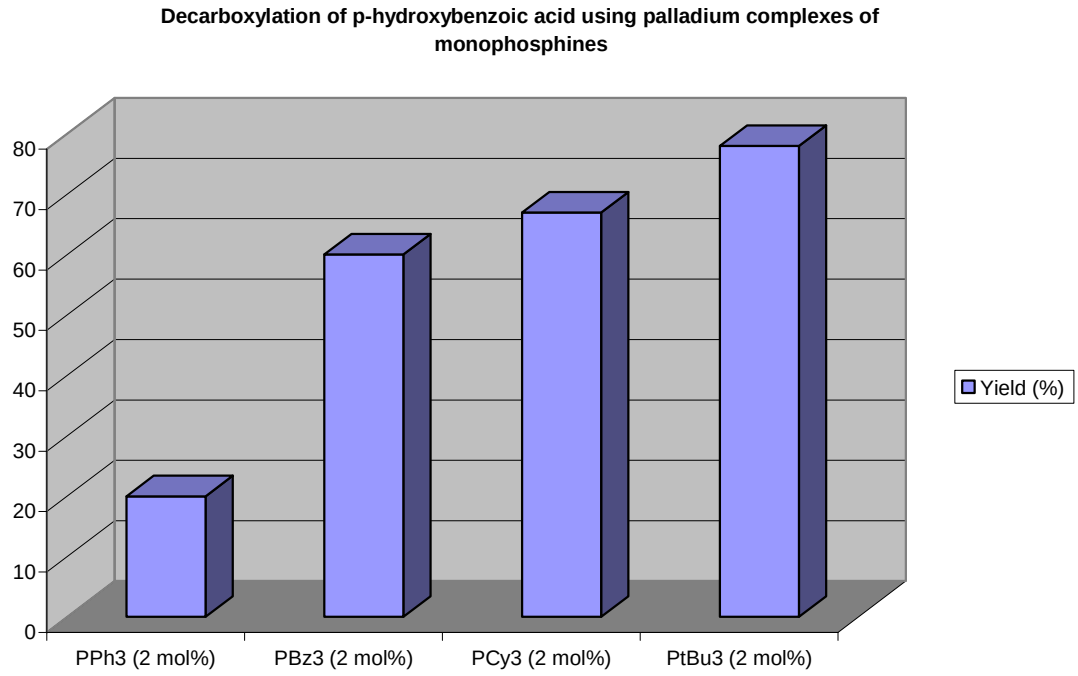
In the case of monophosphines, the common triphenylphosphine gave only low conversion (Table 4.11, entry 1). When the reaction was carried out using PBz_3 or PCy_3, which are notably more electron donating than PPh_3, moderate conversions were obtained (Table 4.11, entries 2 and 3). These conversions are significantly higher than that obtained using PPh_3. Thus, it can be concluded that highly electron donating ligands facilitate the reaction. This was corroborated when P^tBu_3, a highly electron donating phosphine, gave high conversion (Table 4.11, entry 4).

Table 4.11. Decarboxylation of *p*-hydroxybenzoic acid using palladium complexes of monophosphines.



Entry	Monophosphine	Yield (%)
1	PPh_3	20
2	PBz_3	60
3	PCy_3	67
4	P^tBu_3	78

Conditions: 4-hydroxybenzoic acid (2 g, 14.5 mmol), [$Pd(OAc)_2$] (16 mg, 0.07 mmol), monophosphine (3 mmol), toluene (10 mL), 140ºC, 5 h.



4.2.1.11.- The Use of D_2O in Decarboxylation Reactions.

According to the proposed mechanism, and considering the equilibrium that takes place in the presence of deuterated water (D_2O) the formation of d^2-phenol may take place during the decarboxylation.

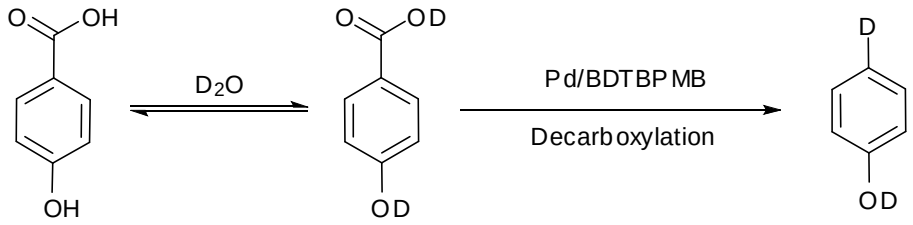


Fig 4.21. *Hypothetical deuteration of the aromatic ring during the decarboxylation reaction in the presence of D_2O*

When the reaction was carried out under normal conditions with 2 mL of D_2O, three or four atoms of deuterium were incorporated into the structure along with the expected d^1-phenol and d^2-phenol (Table 4.12, entry 1). The deuteration was more appreciable when the volume of D_2O was increased to 10 mL. Under these conditions, d^4-phenol was the main product with some d^5-phenol and d^6-phenol also being formed (Table 4.12, entry 2).

Table 4.12. The use of D_2O in the decarboxylation reaction.

Entry	D_2O (mL)	Yield (%)	d^0	d^1	d^2	d^3	d^4	d^5	d^6
1	2	57	4	20	41	32	3	0	0
2	10	24	0	1	10	37	46	5	1
3[a)]	10	-	24	49	22	5	0	0	0

Conditions: 4-hydroxybenzoic acid (2 g, 14.5 mmol), [$Pd(OAc)_2$] (16 mg, 0.07 mmol), BDTBPMB (60 mg, 0.15 mmol), toluene (10 mL), 140ºC, 5 h. a) Blank assay: Phenol (1.4 g, 14.5 mmol), toluene (10 mL), D_2O (10 mL), 140ºC, 5 h.

A possible explanation for this observation may be that non-catalysed H/D exchange occurs into the *ortho* and *para* positions of phenol due to the partial acidity presented in those positions. This may explain the formation of d^1-d^4 phenols. To confirm this hyphotesis a blank assay only with phenol was carried out (Table 4.12, entry 3). Surprisingly under these conditions, the main deuterated product was d^1-phenol, with a small amount of d^3-phenol. Therefore, a catalytic route could be taken into consideration for the generation of the highly deuterated products. It should be noted that Pd/BDTBPMB system has been proven to be active in C-H activation in the position *ortho* to a carbonyl group in an aromatic ring.[26] Therefore, it is plausible to propose C-H activation of the aromatic ring, followed by H/D exchange from D_2O resulting in the formation of species **38,** which can generate a C-D bond in the *ortho* position by reductive elimination (Fig 4.22).

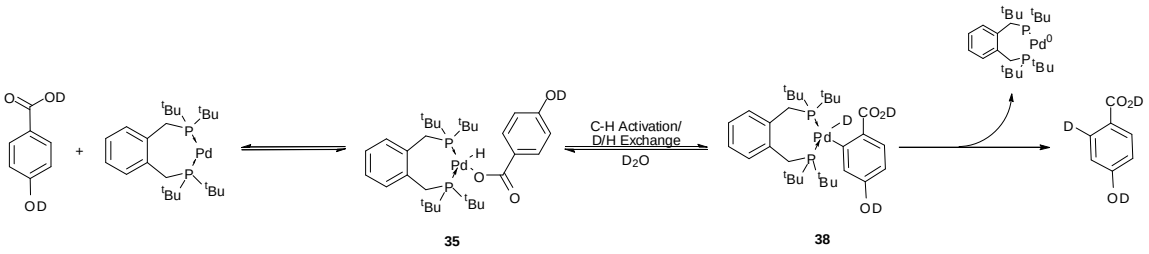


Fig 4.22. *Deuteration of the aromatic ring catalysed by palladium*

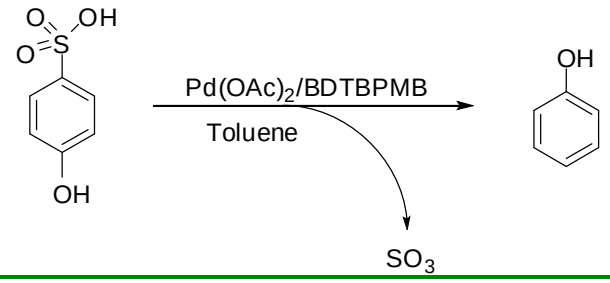
Finally it should be noted that, although the increase of D_2O increased the deuteration of the product, it also significantly lowered the yield of the decarboxylation (Table 4.12, entries 1 and 2). This can be explained by the instability of the catalyst in the presence of water as mentioned in Section 2.2.1.

4.2.2.- Desulfonation .

Some similarities can be found when comparing benzoic acid and benzenesulfonic acid,. Both compounds posess an acidic proton, and the distance between the *ipso* carbon and this proton is two bonds. Thus, it is possible that the promising results obtained in decarboxylation can be extrapolated to desulfonation by synthesising phenol from *p*-hydroxybenzenesulfonic acid.

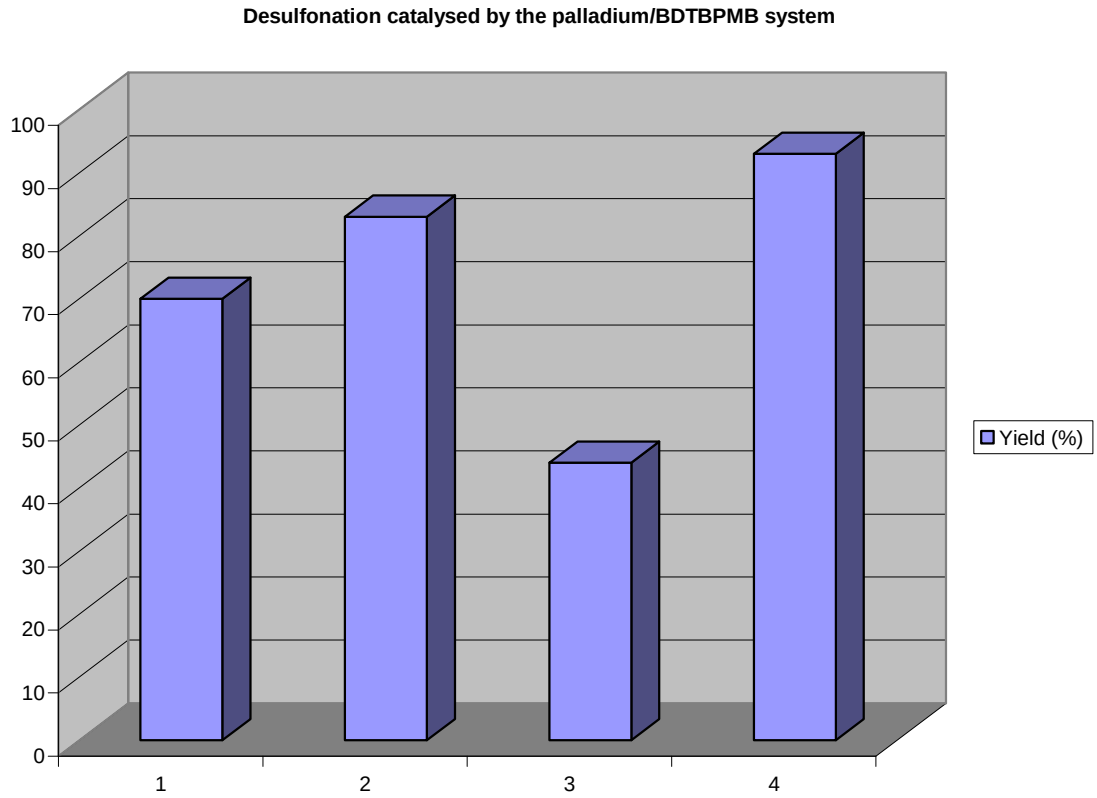
As mentioned in Section 4.1.2., the desulfonation of aromatic sulfonic acid is a difficult process, which usually requires harsh conditions to give good conversion. Hence, the possibility of palladium-catalysed desulfonation was considered to be interesting.

Table 4.13. Desulfonation catalysed by the palladium/BDTBPMB system.



Entry	Palladium compound	Ligand	Yield (%)
1	-	-	44
2	$[Pd(OAc)_2]$	BDTBPMB (1%)	70
3	$[Pd(OAc)_2]$	P^tBu_3 (2%)	83
4	$[Pd(OAc)_2]$	PBz_3 (2%)	44
5	$[Pd(MeCN)_4][BF_4]_2$	BDTBPMB (1%)	93

Conditions: 4-hydroxybenzenesulfonic acid (2.9 mL, 14.5 mmol), palladium compound (0.07 mmol), ligand (as described), toluene (10 mL), 140ºC, 5 h.



For the initial study, a blank assay was carried out. The reaction without any catalyst gave significant conversion (Table 4.13, entry 1). The optimum conditions from

decarboxylation were examined, changing only the substrate to *p*-hydroxybenzenesulfonic acid. After 5 hours, high conversion was obtained (Table 4.13, entry 2). The use of P^tBu_3 in place of BDTBPMB increased the conversion (Table 4.13, entry 3). However, PBz_3 did not present significant activity (Table 4.13, entry 4). Excellent conversion was obtained when $[Pd(OAc)_2]$ was replaced by $[Pd(MeCN)_4][BF_4]_2$ (Table 4.13, entry 5) for a reaction using BDTBPMB as the ligand.

4.3.- Conclusions.

Systems formed from Pd/BDTBPMB have been proven to be highly active in the decarboxylation of benzoic acid. Although the reaction catalysed by Pd/BDTBPMB required high temperatures (~140ºC), this temperature is significantly lower than the temperature required in other catalytic systems such as Cu/Quinoline. Therefore, this study shown that palladium catalysts are an interesting alternative for the decarboxylation reaction.

Different phosphines and conditions were tested. It can be concluded that highly electron donating phosphines such as BDTBPMB or P^tBu_3 are ideal for this reaction. Likewise, $[Pd(MeCN)_4][BF_4]_2$ has been proven to be an interesting alternative as the palladium precursor. The results obtained were significantly higher when this precursor was used.

Palladium catalysts have been proven to be active in the desulfonation reaction by significantly lowering the reaction temperature and giving high conversion in this reaction.

4.4.- References

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Chapter 5: Conclusions and Further work

5.- Conclusions and Further Work.

Carbonylation processes for the generation of acids and amides have been developed catalysed of Pd/BDTBPMB system (see Chapter 2 and Fig 5.1). This homogenous system gave high selectivities and yields under mild conditions. However, although these procedures have been proven active in the preparation of a wide group of products, there are two points which may be improved: the generation of primary amides and the separation of the catalyst from the reaction medium.

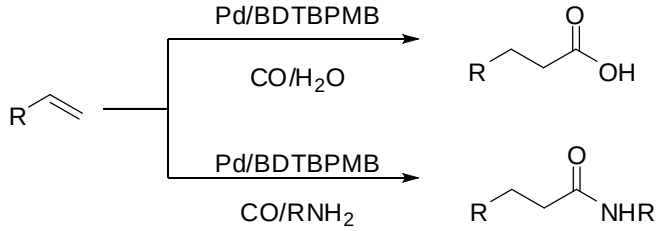

Fig 5.1. *Generation of acids and amides via carbonylation catalysed by the Pd/BDTBPMB system.*

Primary amides are important compounds, which may be considered to be the most important of the amide family. Although some attempts have been carried out to synthesise these compounds via carbonylation of alkenes, only moderate yields were obtained. This problem has been addressed by an alternative route consisting of a two step process: aminocarbonylation and transamidation. This route, although giving high conversion, is more expensive in term of production cost than the hypothetical generation of primary amides via aminocarbonylation. Thus, new processes should be studied for the preparation of these high valuable compounds.

The second point to be developed is the separation of the catalyst from the reaction medium. As previously mentioned in Section 1.2.2, homogeneous catalysts usually give better selectivities and yields than heterogeneous catalysts. However, the separation under homogeneous conditions can be difficult. This fact is particularly important in the generation of acids and amides due to the high boiling points of these products.

Although some attempts have been carried out regarding the immobilisation of the Pd/BDTBPMB system,[1] only one has been reported to be successful in the retention of the catalyst on a solid support.[2,3] This system, developed by Tanaka and co-workers is based on a modified Wang resin which contains sulfonic groups (Fig 1.40).[4] This polar group plays two important roles in the process -the generation of a palladium hydride specie **1** and the linking of Pd/BDTBPMB to the resin.

This system was proven to be active in the carbonylation of vinyl acetate, with the catalyst being recycled up to five times without an appreciable loss of efficieync (no leaching measurements have been reported by Tanaka). Although this immobilisation is an elegant form to link the catalyst, it has been based on electrostatic interactions, which are usually quite weak. Hence, more robust systems must be developed.

To increase the stability of this immobilisation, the preparation of a solid support in which a formal bond with the complex exists must be considered. An interesting route may be the formation of a sulfone link due to the high robustness of this functional group (Fig 5.2). The origin of this route may begin with potassium 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonate (KBDTBPMBS). This phosphine has been successfully synthesized by Parnham by the sulfonation of BDTBPMB.[1] By reaction of this with $SOCl_2$ the corresponding sulfonyl chlorine can be formed. This can react with lithiated polystyrene (formed by Br/Li exchange[5]) generating the sulfone link.

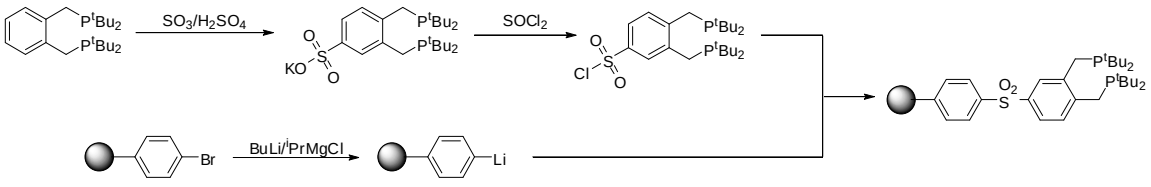

Fig 5.2. *Synthesis of inmobilisation of BDTBPMB in resin by a sulphone link.*

Although the route shown in Fig 5.2. is an attractive route for the separation of catalyst from the reaction medium, polystyrene is not the best support for the catalyst due to the limited conditions in which it is stable. Hence, another interesting immobilisation on silica gel could be proposed (Fig 5.3). Immobilisation in silica allows the catalysed reaction to be carried out under a wide range of conditions. However, this immobilisation requires,

in this case, a synthetic route to the formation of the ligand, due to the fact that no modification of the aromatic ring has been successfully addressed.[1]

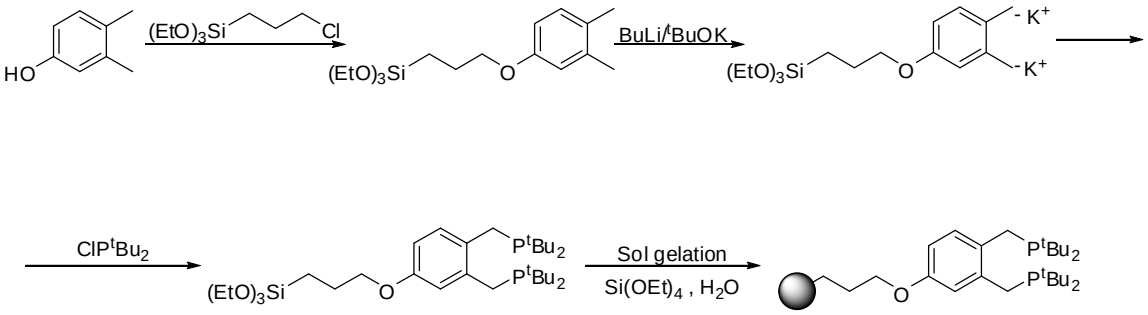

Fig 5.3. *Synthesis of inmobilisation of BDTBPMB in silica.*

The proposed synthetic route may start from 3,4-dimethylphenol. The reaction of this with (3-chloropropyl)triethoxysilane generates the link, for the immobilisation. Deprotonation of the benzilic position and subsequent reaction with di-*tert*-butylclorophosphine may generate the phosphine.[6] The last step of this synthesis will be the formation of silica gel[7] linking BDTBPMB to silica.

As previously mentioned in chapter 3, the hydrogenation of amides (from aminocarbonylation) can be an interesting route for the preparation of highly valuable amines, which are produced on a scale of 100,000 t/a (Fig 5.4).[8] High yield and selectivity were obtained in the hydrogenation of secondary amides. However, low selectivity was obtained when primary amides were examined. This problem was addressed by the addition of ammonia. Under these conditions high conversion and selectivity for the primary amine were obtained.

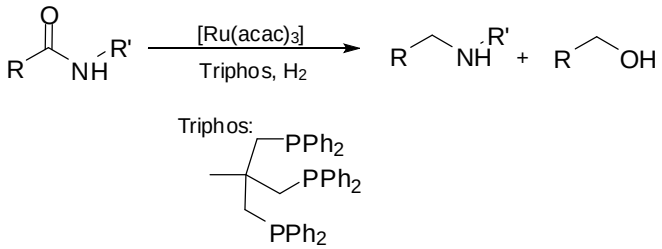

Fig 5.4. *Hydrogenation of amides under homogeneous catalysis using a Ru/Triphos complex*

The preparation of amides *in situ* by the reaction of acids with ammonia was proven to be an alternative route to primary amides. However, this route gave significantly lower selectivities than the hydrogenation of primary amides. Attempts were made to increase the selectivity, by only moderate conversion was achieved.

The origin of this loss in selectivity may be attributed to the slow generation of amides or imines from acids or aldehydes (Fig 3.27). Therefore, further work in this area should be concentrated on improving the generation of these two nitrogen compound *in situ* from acids and aldehydes, which may in turn lead the reaction to higher selectivities.

Another interesting alternative is the use of esters as substrates (Fig 5.5). Esters can react in the presence of water and ammonia to give the corresponding amides, which are transformed into amines *via* hydrogenation. The resulting alcohol can then be recycled to generate esters from alkenes *via* alkoxycarbonylation. This route can therefore, produces primary amines from alkenes, carbon monoxide and ammonia.

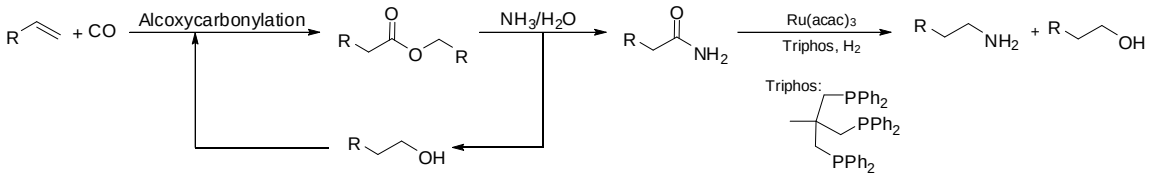

Fig 5.5. *Hydrogenation of amides generated in situ by the reaction of esters with ammonia.*

An interesting decarboxylation of benzoic acids (benzoic acids) catalysed by the Pd/BDTBPMB system has been studied (Fig 5.6). This reaction requires milder condition than those used in the decarboxylation which was catalysed by copper (Section 4.11)

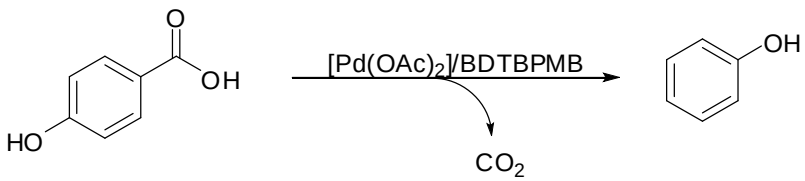

Fig 5.6. *Decarboxylation of benzoic acids catalysed by the Pd/BDTBPMB system.*

According to the proposed mechanism (see Section 4.2.1.2) a Pd-Aryl species is formed in the catalytic cycle. This species is particulary attractive due to its significant role in other transformations such as the Heck[9] or Suzuki reactions.[10]. Hence, it is plausible to think about an alternative route involving decarboxylation to generate the normal Heck or Suzuki products (Fig 5.7).[11,12]

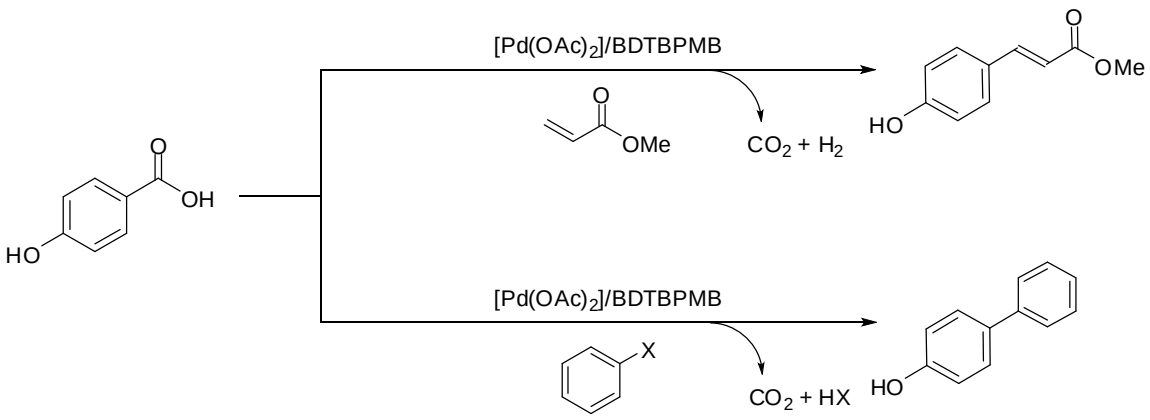

Fig 5.7. *Coupling reaction involving a catalysed decarboxylation.*

The tandem decarboxylation/coupling may form the same product expected from the Heck or Suzuki couplings, but avoiding the use of toxic arylhalides in the case of the Heck reaction, and the expensive boronic acid in the case of the Suzuki reaction.

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Chapter 6: Experimental

6.- Experimental.

All experiments were carried out under dry argon using a standard Schlenk line and catheter tubing techniques. Argon was dried through a Cr(II)/silica packed glass column. Liquids were transferred under inert atmosphere by syringe or cannula though a septum. Solids were transferred directly from one Schlenk tube to another or weighed out in a glove box under argon.

All gases were purchased from BOC gases. Methanol was distilled over magnesium alkoxide under argon and stored under argon over molecular sieves. Diethyl ether, toluene, tetrahydrofuran and petroleum spirit were dried on alumina columns. Dichloromethane was distilled over calcium hydride. Dioxane, DME, acetonitrile and acetone were degassed by the bubbling of argon, and stored over molecular sieves. Dry *o*-dichlorobenzene (Aldrich) was used as received. Water was distilled and degassed by the bubbling of argon, before storing under argon. Deuterated solvents were purchased form Sigma-Aldrich, degassed by the bubbling of argon, and stored under argon over molecular sieves.

The metal complexes $[Pd_2(dba)_3]$, $[Pd(OAc)_2]$, $[Ru(acac)_3]$, $RuCl_3$, CuI, $[Cu(OAc)_2]$, $[Ti(NMe_2)]$, $[Ti(O^iPr)_4]$ and $[Sc(OTf)_3]$ were purchased from Sigma-Aldrich and used as received. $[PdCl_2]$ was purchased from Lancaster and used as received. $[Rh(CO)_2(acac)]$ was purchased form Alfa Aesar and used as received. $[Ru(COD)Cl_2]$ was purchased form Acros and used as received. $[Ir(acac)(CO)_2]_2$ (Lancaster), $[Pd(MeCN)_4][BF_4]$ (Aldrich) and $[Pt(MeCN)_2Cl_2]$ (Aldrich) were stored under argon in a glove box.

1,2-Bis(ditertbutylphosphinomethyl)benzene (supplied by Lucite International), and tritertbutylphosphine (Aldrich) were stored and handled in a glove box. Bis(diphenylphosphino)methane, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 1,1'-Bis(diphenylphosphino)ferrocene, Triphos**,** tribenzylphophine and tricyclohexylphosphine (Aldrich) were used as received. Diphenylphosphine and chlorodiphenylphosphine (Aldrich) were stored under argon.

The substrates 1-octene, 2-octene, 3-octene, 4-octene, methyl oleate, 2-methyl-pent-2-ene, pent-2-enoic, pent-3-enoic, pent-4-enoic, hex-3-enoic and styrene (Aldrich) were

degassed by bubbling argon and stored under argon in the dark. The liquid amines such as butylamine (Aldrich) were degassed by the bubbling of argon, and stored under argon. Solid amines were used as received. Triethylamine (Avocado), 4-hydroxybenzenesulfonic acid (Aldrich) were degassed by the bubbling of argon, and stored under argon. Methanesulfonic acid, hydrobromic acid, nonanoyl chloride, acryloyl chloride, oxalyl chloride, *p*-hydroxybenzoic acid, butanamide, nonanoic acid, adipamide, succinamide, *N*-acetylcaprolactam, lithium aluminium hydride, sodium fluoride, sodium chloride, sodium bromide, sodium iodide, tetrabutylammonium fluoride, tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, *N*-methylimidazol, *p*-cyanophenol, phenol, methyl-3-hydroxy-2-naphthoate, 1,3,5-benzenetricarboxylic acid (Aldrich), 1-naphtol (May and Baker LTC), 2-naphthol (Fisons) and tetrafluoroboronic acid (Alfa Aesar) were used as received.

1,3,5-Tri(hydroxymethyl)benzene,[1] 1,3,5-tri(bromomethyl)benzene,[2] 2,6-bis((diphenylphosphino)methyl)pyridine (BDPPMB),[3] $[Ru(DMSO)_4Cl_2]$,[4] $[Ru_2(Triphos)_2Cl_3]Cl$,[5] and Xanphos[6] were prepared according to the literature.

6.1. Analytical Techniques.

G.C. analysis was carried out using a Hewlett-Packard 5890 series gas chromatograph, equipped with a flame ionisation detector for quantitative analysis and a Hewlett-Packard 5890 series mass selective detector, fitted with a SUPELCO MDN-35 35% phenyl/65% methyl-polysiloxane capillary column for qualitative analysis by G.C.M.S. The temperature programme used was: 50 ºC (4 minutes), Δ 20 ºC / minute to 130ºC (2 minutes), Δ 20 ºC / minute to 220 ºC (15.5 minutes). Helium was used as the carrier gas with an initial flow of 1 mL/ minute.

^{13}C, ^{1}H and ^{31}P spectra were recorded on a Bruker AM 300 NMR spectrometer. Broadband decoupling was used for ^{13}C spectra and ^{31}P spectra. ^{1}H and ^{13}C NMR spectra were referenced internally to deuterated solvent, which were referenced relative to TMS at $\delta = 0$: CD_2Cl_2: ^{1}H, $\delta = 5.35$ ppm, ^{13}C, $\delta = 53.8$ ppm; CD_3OD: ^{1}H, $\delta = 3.35$ ppm, ^{13}C, $\delta = 49.0$ ppm; C_6H_6: ^{1}H, $\delta = 7.16$, ^{13}C, $\delta = 128.39$ ppm; C_7H_8: ^{1}H, $\delta = 2.09$ ppm, ^{13}C, $\delta = 20.4$ ppm; $CDCl_3$: ^{1}H, $\delta = 7.27$ ppm, ^{13}C, $\delta = 77.23$ ppm. ^{31}P NMR and ^{19}F NMR spectra were

referenced externally to 85 % H_3PO_4 and CCl_3F respectively. Coupling constants are given in Hz.

6.2.- Preparation of Solutions for Catalytic Tests.

6.2.1.- Hydroxycarbonylation of Alkenes.

$PdCl_2$ (32 mg, 0.19 mmol) was placed in an autoclave, which was flushed three times with CO. BDTBPMB (83 mg, 0.21 mmol) was dissolved in dioxane (10 cm^3) in a degassed Schlenk flask. 1-Octene (1 cm^3, 6.37 mmol) and water (2 cm^3) were added to the solution, which was transferred to the autoclave via cannula. The autoclave was pressurised with 70 bar of CO and heated at 80 ºC for 5 hours. The autoclave was then cooled and vented. The solution was analysed by GCFID.

6.2.2.- Aminocarbonylation of Alkenes in the Presence of a Promoter.

2-Naphthol (1.4 g, 9.5 mmol) and NaI (9.5 mg, 0.0637 mmol) were placed in an autoclave, which was flushed three times with CO. BDTBPMB (25 mg, 0.0637 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) were dissolved in toluene (10 cm^3) in a degassed Schlenk flask. 1-Octene (2 cm^3, 12.7 mmol), methanesulphonic acid (10 μl, 0.15 mmol) and aniline (1.2 cm^3, 12.74 mmol) were added to the solution, which was transferred to the autoclave via cannula. The autoclave was pressurised with 20 bar of CO and heated at 140 ºC for 1 hour. The autoclave was then cooled and vented. The solution was analysed by GCFID.

6.2.3.- Aminocarbonylation of Alkenes in the Presence of Ammonia.

$Pd(OAc)_2$ (14 mg, 0.063 mmol) and $nHex_4N^+Cl^-$ (247 mg, 0.63 mmol) were placed in an autoclave, which was flushed three times with CO. BDTBPMB (125.49 mg, 0.31 mmol) was dissolved in pentanoic acid (10 cm^3) in a degassed Schlenk flask. 1-octene (1 cm^3, 6.3 mmol) and water (1 cm^3) were added to the solution, which was transferred to the autoclave via cannula. The autoclave was pressurised with 4 bar of NH_3 and 60 bar of CO

and heated at 135 ºC for 17 hours. The autoclave was then cooled and vented. The solution was analysed by GCFID.

6.2.4.- Methoxycarbonylation of Alkenes in the Presence of a Promoter.

2-Napthol (1.8 g, 12.7 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) were placed in an autoclave, which was flushed three times with CO. BDTBPMB (25 mg, 0.0637 mmol) was dissolved in methanol (10 cm^3) in a degassed Schlenk flask. 1-Octene (2 cm^3, 12.7 mmol), and methanesulphonic acid (10 μl, 0.15 mmol) were added to the solution, which was transferred to the autoclave via cannula. The autoclave was pressurised with 20 bar of CO and heated at 140 ºC for 1 hour. The autoclave was then cooled and vented. The solution was analysed by GCFID

6.2.5.- Transamidation of *N*-phenylnonamides.

N-Phenylnonamide (1 g, 4.2 mmol) was placed in a degassed autoclave. $Ti(NMe)_4$ (20 μL, 0.08 mmol) was dissolved in toluene (10 cm^3) in a degassed Schlenk flask. The solution was transferred to the autoclave via cannula. Liquid ammonia (10 cm^3) was introduced into the autoclave which was heated at 120 ºC for 14 hours. The autoclave was then cooled and vented. The solution was analysed by GCFID

6.2.6.- Hydrogenation of Amides.

1 g. of *N*-Phenylnonamide and $[Ru(acac)_3]$ (17 mg, 0.043 mmol) were placed in a hasteloy autoclave, which was flushed three times with H_2. Triphos (54 mg, 0.086 mmol) was dissolved in THF (10 mL) and water (1 mL) in a degassed Schlenk flask. The solution was transferred via cannula. The autoclave was pressurised with H_2 (40 bar) and heated at 164 ºC for 14 hours. The autoclave was then cooled and vented. The solution was analysed by GCFID. Isolation of the product was carried out as follows: solvents from the final solution were removed under reduce pressure. The crude product was purified by column chromatography (hexane/SiO_2). Yield = 70%.

^{1}HNMR (300 MHz, $CDCl_3$, 298 K):[7] 7.15 (t, 2 H, *J* = 8 Hz), 6.65 (t, 1 H, *J* = 8 Hz), 6.52 (d, 2 H, *J* = 8 Hz), 3.08 (t, 2 H, *J* = 7 Hz), 1.5-1.8 (m, 2H), 1.4-1.5 (m, 11 H), 0.75-0.85 (m, 3 H).

6.2.7.- Decarboxylation of Arylcarboxylic Acids.

p-Hydroxybenzoic acid (2 g, 14.5 mmol) and $Pd(OAc)_2$ (16 mg, 0.07 mmol) were placed in a degassed autoclave. BDTBPMB (60 mg, 0.15 mmol) was dissolved in toluene (10 mL) in a degassed Schlenk flask. The solution was transferred to the autoclave via cannula. The autoclave was heated at 140 ºC for 5 hours. The autoclave was then cooled. The solution was analysed by GCFID.

6.3.- Techniques.

6.3.1.- HPNMR.[8]

The high pressure NMR equipment consists of a sapphire and titanium cell, a brass and aluminium housing, two brass fittings, an NMR spinner, a spiral hose, and an extendable clamp. The sapphire titanium cell has been pressure tested to 100 bar and 100 ºC, although the specifications are greater than that. The housing allows the cell to be pressurised, depressurised, and stored under pressure safely. The brass fitting for the housing allows the cell to be pressurised/depressurised, and can be removed so that the cell can be placed in its spinner. Trhe spiral hose connects the cell to a conventional high pressure head/gas cylinder, and the extendable clamp allows the cell to be removed and placed in the cell safely, as well as in the NMR magnet.

The high pressure NMR cell was degassed and the analysed solution was transferred. The high pressure NMR cell was then sealed by means of the screw top.

The cell was placed in the brass aluminium housing with a brass pressurising/depressuring attachment fitted. The spiral hose was attached to the cell via the screw top, and was also attached to a cylinder or autoclave containing the desired gas mixture. The hose was then degassed three times with the gas, and the hose left under a

low pressure atmosphere of the desired gas mixture. The cell was then opened to the gas and pressurised to the desired pressure. The pressure in the hose was then relased and the spiral hose detached from the cell. The cell was removed from its housing with the extendable clamp. This clamp was used to remove the cell from the housing at all times when under pressure as the cell is kept behind a wall of brass within the clamp. The brass fitting which allowed pressuring and depressurising, was then removed from the housing and replaced with the NMR spinner. The cell was then placed in the spinner with the clamp, and pushed down firmly to ensure the cell was tightly held in the spinner. The cell was then released from the clamp and was ready to be placed in the Bruker AM 300 NMR spectrometer.

Fig 6.1. *Brass and aluminium NMR tube protective case, 10 mm high pressure NMR cell and spinner.*

The spinner and the gas uplift for the NMR spectrometer were then turned off. The cell was removed from its housing with the extendable clamp. The bottom of the clamp was fitted to the top of the NMR spectrometer. The cell was then lowered into the NMR magnet with the extendable clamp. The NMR spectrum of the solution was then acquired.

6.3.2.- Procedure for the Charging of the Autoclave with Ammonia Gas.

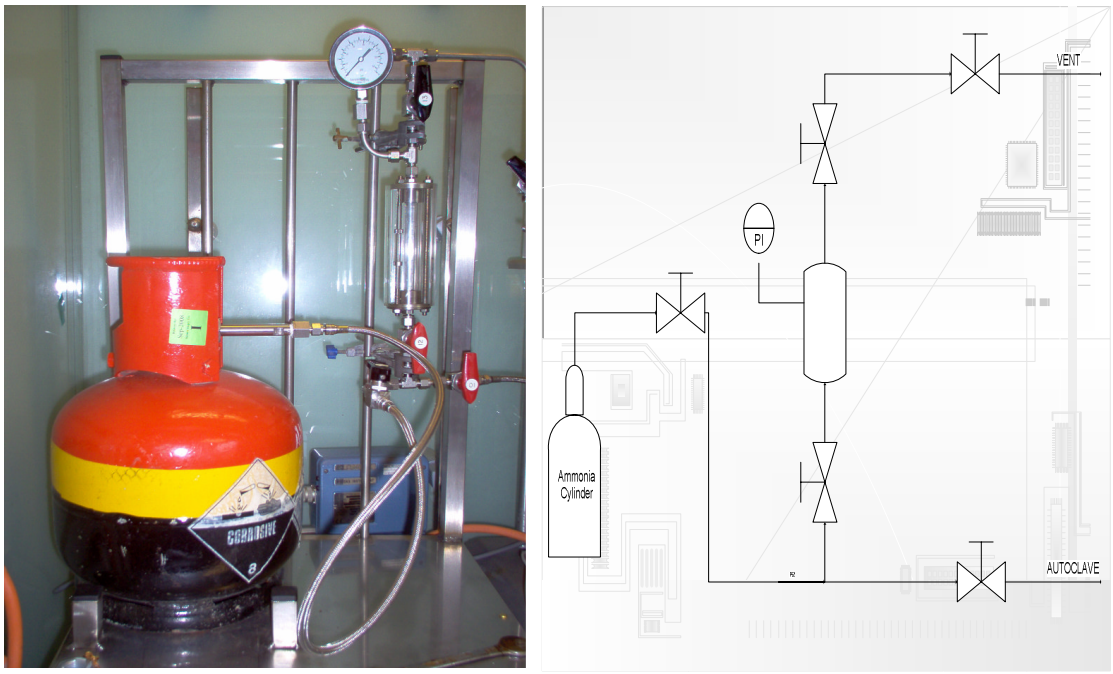


Fig 6.2. *Apparatus to pressurise autoclaves with liquid ammonia.*

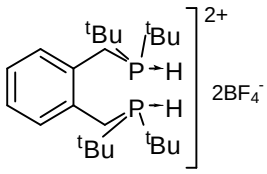
A specially constructed protected glass graduated container fitted with a valve at the top and two valves at the bottom was connected to an upturned ammonia cylinder (pressure = 4 bar). This was achieved using a flexible steel pipe via one of the bottom valves, and also to an autoclave via the other bottom valve (Fig 6.2). With all valves closed, the ammonia cylinder was opened. The vent valve at the top of the glass cylinder was opened, and the valve at the bottom attached to the cylinder gently opened to allow liquid ammonia to pass into the glass vessel. This was carried out until the correct amount of ammonia had been dispensed. The tap between the ammonia cylinder, the glass vessel and the top valve on the glass container was closed followed by closing of the valve on the ammonia cylinder. The valve on the glass vessel leading to the autoclave was opened and the vent from the autoclave was then opened slightly. The valve on the autoclave was opened slowly to allow the ammonia to discharge slowly into the autoclave. The blank on the autoclave was shut, followed by the valve on the autoclave. The vent at the top of the glass

vessel was opened and the autoclave removed for further pressurising/heating. Finally, the glass vessel and attached tubing was allowed to vent residual ammonia into the fume-cupboard.

6.4.- Synthesis.

6.4.1.- Phosphines.

6.4.1.1.- $[BDTBPMBH_2][BF_4]_2$.



BDTBPMB (2 g, 5 mmol) was dissolved in diethyl ether (20 mL) in a degassed Schlenk flask. a solution HBF_4 (10 mL,50% - 54% w/v in diethyl ether) were added. A white solid was formed inmediately. The solution was stirred for 3 hours. The solid was filtered,washed with diethyl ether (3 x 25 mL) and acetone (3 x 25 ml) and dried *in vacuo* (2.8 g, 65%).

^{1}HNMR (300 MHz, d^{8}-DMSO, 298 K): 7.55-7.50 (m, 1 H), 7.43-7.37 (m, 1H), 3.97 (d, J_{PH} = 13.8 Hz, 2 H), 1.37 (d, J_{PH} = 16.3 Hz,18 H).

^{13}CNMR (75 MHz, d^{8}-DMSO, 298 K): 131.81, 131.73, 128.81, 33.47 (d, J_{PC} = 35.8 Hz), 27.32, 18.70 (d, J_{PC} = 38.0 Hz)

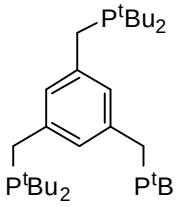
^{31}P{^{1}H}NMR (121 MHz, d^{8}-DMSO, 298 K): 44.70 (bs)

^{19}F{^{1}H}NMR (282 MHz, $CDCl_3$, 298 K): -143.91

m.p.: up to 230 ºC

MS (EI+): Found: 395.2997. Required (M-H^{+}): 395.3007.

6.4.1.2.- 1,3,5-tris((di-tert-butylphosphino)methyl)benzene (TDTBPMB).



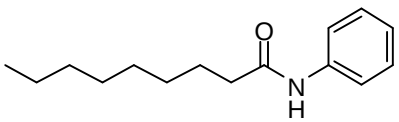
Tri-(bromomethyl)benzene (1 g, 2.8 mmol) was placed in a degassed Schlenk flask and dissolved in methanol (20 mL). The solution was cooled in on ice bath. Di-*tert*-butylphosphine (1.8 mL, 9.7 mmol) was added. The solution was allowed to warm to room temperature and stirred overnight. The solvent was then, removed *in vacuo*. The resulting solid was washed with acetone (3 x 20 mL) and dissolved in MeOH (20 mL). Triethylamine (2 mL, 14.5 mmol) was added. The solvent was removed *in vacuo* and the solid was redissolved in dichloromethane (20 mL). A saturated solution of NH_4Cl in degassed water (20 mL) was added. The organic phase was collected and the aqueous phase extracted with dichloromethane (2 x 20 mL). The organic phases were combined and the solvent removed *in vacuo*. The crude product was recrystallised from MeOH (0.97 g, 63%)

^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 7.05 (s, 1 H), 2.74 (d, J_{PH} = 3.0 Hz, 2 H), 1.04 (d, J_{PH} = 10.8 Hz, 18 H).
^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 141.00 (d, J_{PH} = 28.1 Hz), 127.96 (t, J_{PH} = 8.2 Hz), 31.72 (d, J_{PH} = 77.8 Hz), 29.83 (d, J_{PH} = 42.7 Hz), 28.42 (d, J_{PH} = 64.6 Hz).
^{31}P{^{1}H}NMR (121 MHz, $CDCl_3$, 298 K): 34.0
Elemental analysis: Found: C = 68.29 %, H = 12.00 %. Required for $C_{33}H_{63}P_3 \cdot 2MeOH$: C = 68.11 %, H = 11.60 %

6.4.2.- Synthesis of Aryl Sustituted Nonamides.

A solution of the corresponding amine (22 mmol) and triethylamine (3 ml, 22 mmol) in dichloromethane (50 ml) was cooled to 0 ºC in a water/ice bath. Nonanoyl chloride (4 ml, 22 mmol) was added dropwise over 10 minutes. After this, the solution was warmed to room temperature and stirred overnight. The reaction was then, washed with a solution of 2N HCl (3 x 50 ml) and saturated $NaHCO_3$ (3 x 50 ml). The organic phase was dried ($MgSO_4$) and solvents removed in vacuo to give the crude product.

6.4.2.1.- *N*-phenylnonamide.



Purification: Recrystalation AcOEt/Hex

Appearance: White solid

Yield: 86%

^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 7.63-7.57 (bs, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.21 (dd, *J* = 7.6 Hz and *J*= 8.7 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 1H), 2.26 (t, *J* = 7.6 Hz, 2H), 1.69-1.57 (m, 2H), 1.30-1.14 (m, 10H), 0.84-0.76 (m, 3H).

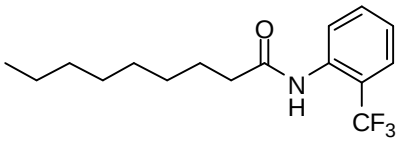
^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 172.21, 138.49, 129.32, 124.51, 120.32, 38.19, 32.24, 29.77, 29.71, 29.58, 26.12, 23.05, 14.52.

Elemental analysis**:** Found 77.34 % C, 11.27 % H and 5.95 % N. Required 77.21 % C, 9.93 % H and 6.00 % N.

MS (EI+): Found**:** 233.1780**.** Required**:** 233.1784**;** Fragmentation: 233.18**,** 149.08, 135.07, 120.05, 94.06, 93.06, 92.05, 65.04.

m.p.: 62-64 ºC.

6.4.2.2.- *N*-(*o*-trifluoromethylphenyl)nonamide.



Appearance: White solid

Yield: 83%

^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 8.18-8.10 (m, 1 H), 7.56-7.44 (m, 2H), 7.38-7.32 (bs, 1 H), 7.15 (t, *J* = 7.7 Hz, 1 H), 2.33 (t, *J* = 7.5 Hz, 2 H), 1.72-1.60 (m, 2 H), 1.36-1.15 (m, 10 H), 0.84-0.78 (m, 3 H).

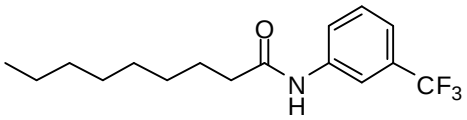
^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 172.03, 135.68, 133.1, 126.26 (q, J_{FC} = 272 Hz), 126.35 (q, J_{FC} = 6 Hz), 125.14, 124.77, 122.64, 38.16, 32.06, 29.66, 29.49, 27.68, 25.20, 23.00, 14.42.

^{19}H{^{1}H}NMR (282 MHz, $CDCl_3$, 298 K): -60.64.

MS (EI+): Found**:** 301.1653**.** Required**:** 301.1646; Fragmentation: 301.16, 282.16, 216.07, 204.06, 203.05, 196.06, 168.02, 161.02, 142.04, 141.03, 134.06, 114.03, 71.08, 69.07.

m.p.: 54-55 ºC.

6.4.2.3.- *N*-(*m*-trifluoromethylphenyl)nonamide.



Appearance: Brown liquid

Yield: 78%

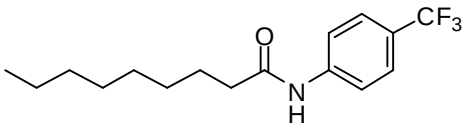
^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 8.15 (bs, 1 H), 7.76 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.30 (t, *J* = 7.8 Hz, 1 H), 7.24 (d, *J* = 7.8 Hz, 1 H), 2.29 (t, *J* = 7.5 Hz, 2 H), 1.68-1.56 (m, 2 H), 1.30-1.10 (m, 10 H), 0.82-0.75 (m, 3 H).

^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 172.81, 139.01, 131.61 (q, J_{FC} = 32.3 Hz), 129.78, 123.41, 123.25 (q, J_{FC} = 272.3 Hz), 121.05, 117.10, 38.00, 32.18, 29.70, 29.63, 29.51, 25.99, 23.00, 14.42

^{19}H{^{1}H}NMR (282 MHz, $CDCl_3$, 298 K): -62.81.

MS (EI+): Found: 301.1653. Required: 301.1645; Fragmentation: 301.16, 282.16, 216.06, 203.05, 188.03, 162.05, 161.02, 160.04, 145.02, 140.03, 114.03, 81.07, 71.08, 69.07.

6.4.2.4.- *N*-(*p*-trifluoromethylphenyl)nonamide.



Appearance: White solid

Yield: 78%

^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 7.71 (bs, 1 H), 7.57 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 8.5 Hz, 2 H), 2.31 (t, *J* = 7.6 Hz, 2 H), 1.70-1.58 (m, 2 H), 1.33-1.14 (m, 10 H), 0.83-0.75 (m, 3 H).

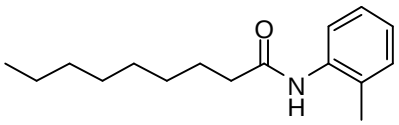
^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 172.45, 141.44, 126.55 (q, J_{FC} = 3.8 Hz), 126.26, 124.46 (q, J_{FC} = 270.0 Hz), 119.78, 38.20, 32.19, 29.71, 29.65, 29.52, 25.92, 23.01, 14.45.

^{19}H{^{1}H}NMR (282 MHz, $CDCl_3$, 298 K): -62.121

MS (EI+): Found: 301.1653. Required: 301.1644; Fragmentation: 301.16, 203.05, 188.03, 162.05, 161.02, 141.12, 140.04, 71.08, 69.07.

m.p.: 88-90 ºC

6.4.2.5.- *N*-(*o*-methylphenyl)nonamide.



Appearance: White solid

Yield: 90%

^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 7.81 (d, *J* = 7.8 Hz, 1 H), 7.25-7.14 (m, 2 H), 7.12-7.03 (m, 1H), 7.05-6.98 (bs, 1 H), 2.39 (t, *J* = 7.5 Hz, 2 H), 2.26 (s, 3 H), 1.80-1.68 (m, 2 H), 1.46-1.22 (m, 10 H), 0.93-0.84 (m, 3 H).

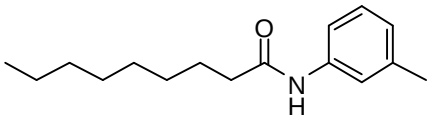
^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 171.79, 136.12, 130.83, 129.31, 127.17, 125.48, 123.58, 38.11, 32.23, 29.75, 29.70, 29.57, 26.26, 23.05, 18.21, 14.51.

Elemental analysis**:** Found: 77.82 % C, 10.19 % H and 5.66 % N. Required: 77.82 % C, 10.83 % H and 4.89 % N.

MS (EI+): Found**:** 248.2014**.** Required ($M+H^+$): 248.2012**;** Fragmentation: 249.21, 248.20, 246.19, 232.17, 214.22, 159.14, 150.09, 107.07

m.p.: 66-68 ºC

6.4.2.6.- *N*-(*m*-methylphenyl)nonamide.



Appearance: White solid

Yield: 98%

^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 7.81-7.63 (bs, 1H), 7.41 (s, 1 H), 7.26 (d, *J* = 7.8 Hz, 1 H), 7.19 (t, *J* = 7.7 Hz, 1 H), 6.86 (d, *J* = 7.7 Hz, 1 H), 2.40-2.30 (m, 5 H), 1.80-1.62 (m, 2 H), 1.40-1.20 (m, 10 H), 0.94-0.87 (m, 3 H).

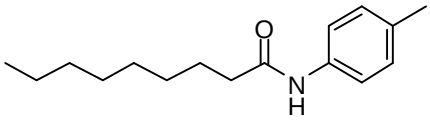
^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 171.85, 138.78, 138.05, 128.71, 124.91, 120.62, 117.03, 37.77, 31.85, 29.40, 29.32, 29.19, 25.76, 22.66, 14.11.

Elemental analysis**:** Found: 77.76 % C, 10.94 % H and 5.54 % N. Required: 77.68 % C, 10.19 % H and 5.66 % N.

MS (EI+): Found**:** 248.2014**.** Required ($M+H^+$): 248.2015**;** Fragmentation: 249.21, 248.20, 246.19, 232.17, 149.08, 107.07

m.p.: 40-42 ºC.

6.4.2.7.- *N*-(*p*-methylphenyl)nonamide.



Appearance: White solid

Yield: 97%

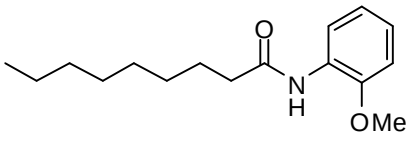
^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 7.42 (d, *J* = 8.1 Hz, 2 H), 7.12 (d, *J* = 8.1 Hz, 2 H), 2.38-2.30 (m, 5 H), 1.78-1.66 (m, 2 H), 1.40-1.24 (m, 10 H), 0.92-0.86 (m, 3H).

^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 171.39, 135.44, 133.74, 129.44, 119.90, 37.80, 31.83, 29.36, 29.31, 29.17, 25.70, 22.66, 20.86, 14.11.

MS (EI+): Found**:** 248.2014. Required ($M+H^+$): 248.2010; Fragmentation: 249.21, 248.20, 246.19, 232.17, 107.07.

m.p.: 72-74 ºC.

6.4.2.8.- *N*-(*o*-methoxyphenyl)nonamide.



Appearance: Orange solid

Yield: 82%

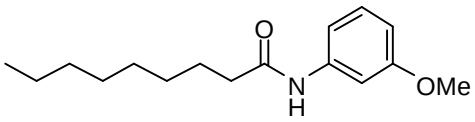
^{1}HNMR (400 MHz, $CDCl_3$, 298 K): 8.42 (dd, *J* = 6.6 and 1.4 Hz, 1 H), 7.8 (bs, 1 H), 7.04 (dt, *J* = 6.3 and 1.4 Hz, 1 H), 6.97 (dt, *J* = 6.3 and 1.4 Hz, 1H), 6.88 (dd, *J* = 6.6 and 1.4 Hz, 1H), 3.89 (s, 3 H), 2.40 (t, *J* = 7.6 Hz, 2 H), 1.80-1.7 (m, 2H), 1.45-1.25 (m, 10 H), 0.95-0.9 (m, 3 H).

^{13}CNMR (100 MHz, $CDCl_3$, 298 K): 171.29, 147.67, 127.81, 123.42, 121.08, 119.72, 109.83, 55.64, 38.11, 31.84, 29.37, 29.27, 29.17, 25.68, 22.66, 14.11.

MS (EI+): Found: 263.1885. Required: 263.1845; Fragmentation: 263.19, 165.08, 124.07, 123.06, 108.04, 80.05.

m.p.: 50-54 ºC.

6.4.2.9.- *N*-(*m*-methoxyphenyl)nonamide.



Appearance: Brown solid

Yield: 75%

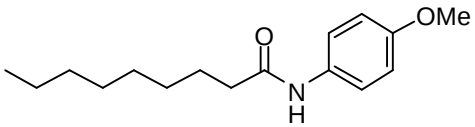
^{1}HNMR (400 MHz, $CDCl_3$, 298 K): 7.82 (bs, 1H), 7.26 (s, 1 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 6.93 (d, *J* = 7.8 Hz, 1 H), 6.55 (dd, *J* = 8.0 and 1.8 Hz, 1 H), 3.67 (s, 3 H), 2.26 (t, *J* = 7.5 Hz, 2 H), 1.68-1.58 (m, 2 H), 1.30-1.10 (m, 10 H), 0.85-0.7 (m, 3 H).

^{13}CNMR (100 MHz, $CDCl_3$, 298 K): 172.04, 160.07, 139.45, 129.45, 112.06, 109.95, 105.59, 55.21, 37.78, 31.84, 29.39, 29.31, 29.18, 25.70, 22.65, 14.10.

MS (EI+): Found: 263.1885. Required: 263.1881; Fragmentation: 263.19, 178.06, 165.08, 161.06, 124.07, 123.06, 105.04, 77.04, 69.07.

m.p.: 42-46 ºC.

6.4.2.10.- *N*-(*p*-methoxyphenyl)nonamide.



Appearance: Purple solid

Yield: 95%

^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 7.41 (d, *J* = 9 Hz, 2 H), 7.12-7.06 (bs, 1 H), 6.86 (d, *J* = 9 Hz, 2 H), 3.90 (s, 3 H), 2.33 (t, *J* = 7.5 Hz, 2 H), 1.78-1.66 (m, 2 H), 1.40-1.23 (m, 10 H), 0.92-0.85 (m, 3 H).

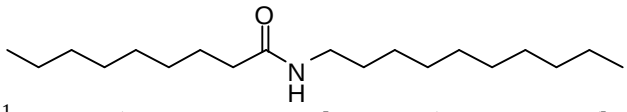
^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 171.64, 156.71, 131.45, 122.09, 114.51, 55.88, 38.10, 32.23, 29.75, 29.71, 29.56, 26.12, 23.05, 14.51.

Elemental analysis**:** Found: 73.25 % C, 10.09 % H and 6.21 % N. Required: 72.96 % C, 9.57 % H and 5.32 % N.

MS (EI+): Found**:** 264.1964**.** Required ($M+H^+$): 264.1959; Fragmentation: 264.20, 263.19, 262.18, 248.17, 123.07.

m.p.: 78-82 ºC.

6.4.2.11.- *N*-(*p*-methoxyphenyl)nonamide.



Appearance: White solid

Yield: 70%

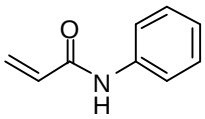
^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 6.92-6.66 (bs, 1 H), 3.18 (t, *J* = 7.2 Hz, 2 H), 2.19 (t, *J* = 7.4 Hz, 2 H), 1.65-1.55 (m, 2 H), 1.55-1.45 (m, 2 H), 1.35-1.15 (m, 22 H), 0.85-0.80 (m, 6 H).

^{13}CNMR (75 MHz, $CDCl_3$, 298 K): 174.55, 40.17, 36.74, 32.23, 32.21, 29.91, 29.82, 29.72, 29.69, 29.64, 29.58, 27.35, 26.42, 23.01, 14.42.

MS (EI+): Found:283.2875. Required: 283.2868; Fragmentation: 283.29, 254.25, 240.23, 226.22, 212.20, 198.18, 185.17, 170.15, 158.15, 142.13, 141.12, 129.09, 115.07, 114.09, 87.06.

m.p.: 43-44 ºC.

6.4.2.12.- *N*-phenylacrylamide.[9]



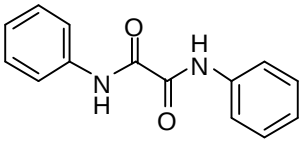
Purification: Recrystalization in AcOEt/Hex.

Appearance: White solid

Yield: 75%

^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 8.43 (br, 1 H), 7.62 (d, *J* = 7.9 Hz, 2 H), 7.30 (m, 2 H), 7.11 (d, *J* = 7.4 Hz, 1 H), 6.46-6.29 (m, 2 H), 5.71 (dd, *J* = 6.5 and 2.5 Hz, 2 H).

6.4.2.13.- *N,N'*-diphenyloxalamide.[10]



Appearance: White solid

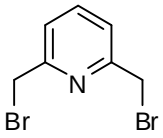
Yield: 52%

^{1}HNMR (300 MHz, d^6-DMSO, 298 K): 10.1 (s, 1H), 8.88(d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 8 Hz, 2H), 7.15 (t, *J* = 7.8 Hz, 1H).

^{13}CNMR (75 MHz, d^6-DMSO, 298 K): 158.95, 138.00, 129.12, 124.98, 120.79, 118.47.

6.4.3.- Other compounds.

6.4.3.1.- 2,6-(bromomethyl)pyridine.[11]

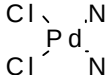


A solution 2,6-(hydroxymethyl)pyridine (1 g, 7.19 mmol) in aqueous 48% HBr (20 mL) was heated under reflux for 3 days. The solution was cooled and neutralised by a saturated solution of $NaHCO_3$. The product was extracted with dichloromethane (3 x 50 mL), and the solvent removed *in vacuo*. The crude product was purified by flash cromatographic (AcOEt/Hex 1:4). (753 mg, 40%).

^{1}HNMR (300 MHz, $CDCl_3$, 298 K): 7.71 (t, *J* = 7.7 Hz, 1 H), 7.39 (d, *J* = 7.7 Hz, 2 H), 4.54 (s, 4 H).

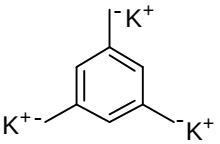
m.p.: 76-78 ºC (lit. 85-87 ºC)

6.4.3.2.- Bis(acetonitrile)dichloropaladium (II).[12]



Palladium (II) chloride (2 g, 1.13 mmol) was stirred in MeCN (40 ml). After 14 hours a bright orange solid formed, which was filtered and dried under vaccum. (2.8 g, 97%).

6.4.3.3.- Mesitylene-α,α',α''-triyl tripotassium [$K_3(C_9H_9)$]



Dry and degassed mesitylene (1 mL, 7.15 mmol) was mixed with petroleum ether (30 mL) in a degassed Schlenk flask before adding by cannula to another degassed Schlenk flask containing potassium *tert*-butoxide. The solution was cooled to -78 ºC and *n*-butyl lithium (2M in hexane, 11 mL) was added slowly. The flask was allowed to warm to room temperature and the solution stirred overnight. The formed bright yellow solid was filtered, and washed with petroleum ether (3 x 20 mL). The solid which was highly pyrophoric, was, then dried *in vacuo* and stored in the glove box (1.3 mg, 77%).

6.5.- References.

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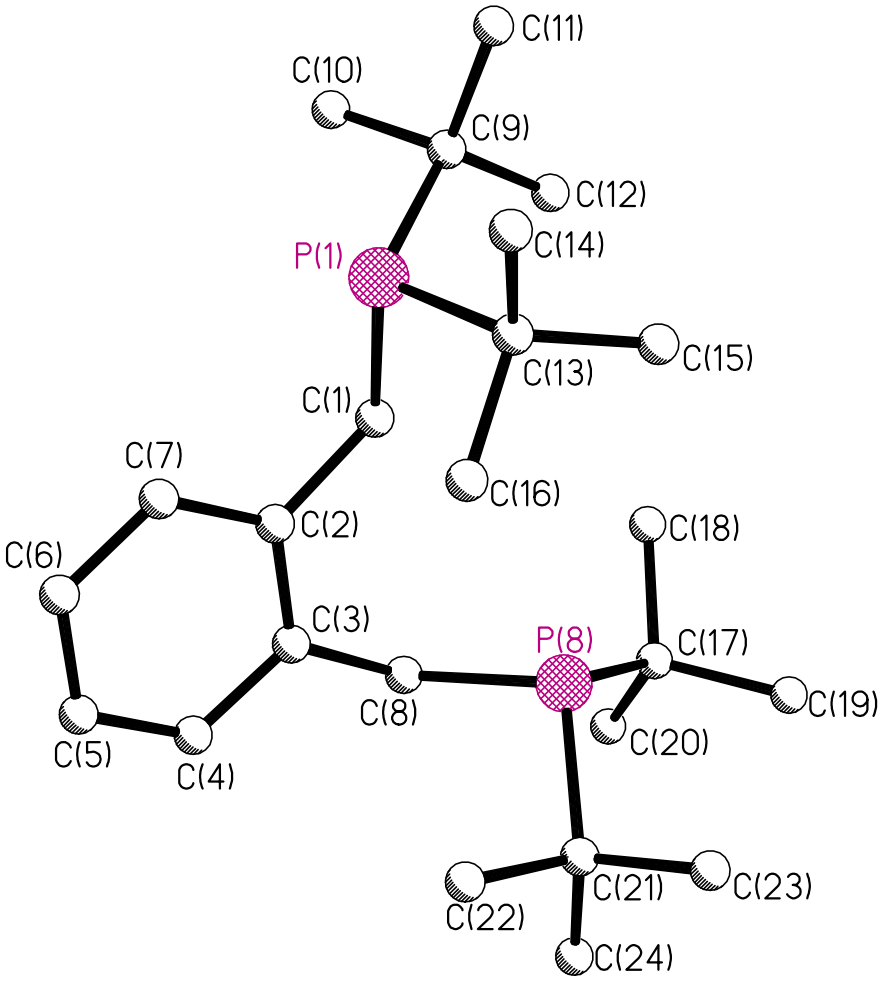
Chapter 7: Appendices

7.- Appendices *(Full details in the attached cd).*

7.1.- Structure of BDTBPMB

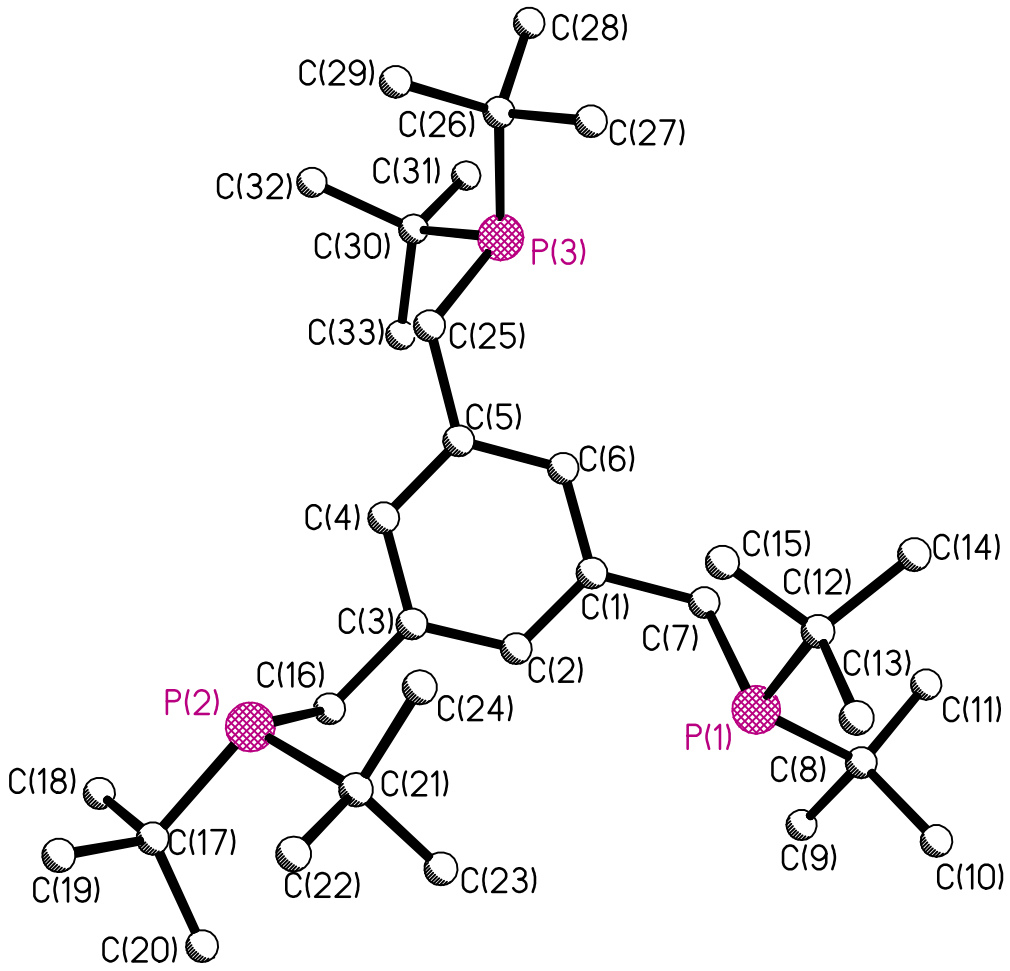


Crystal data and structure refinement

Identification code	aadch1
Empirical formula	C24 H44 P2
Formula weight	394.53
Temperature	93(2) K

Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.9447(19) Å	α= 117.625(6)°.
	b = 11.839(2) Å	β= 92.392(9)°.
	c = 11.991(2) Å	γ = 99.186(8)°.
Volume	1224.0(4) $Å^3$	
Z	2	
Density (calculated)	1.070 Mg/m^3	
Absorption coefficient	0.184 mm^{-1}	
F(000)	436	
Crystal size	0.100 x 0.100 x 0.100 mm^3	
Theta range for data collection	2.00 to 25.35°.	
Index ranges	-9<=h<=11, -13<=k<=13, -13<=l<=14	
Reflections collected	6891	
Independent reflections	4039 [R(int) = 0.0199]	
Completeness to theta = 25.35°	90.3 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.3995	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4039 / 0 / 236	
Goodness-of-fit on F^2	0.493	
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.1105	
R indices (all data)	R1 = 0.0452, wR2 = 0.1214	
Largest diff. peak and hole	0.430 and -0.387 $e.Å^{-3}$	

7.2.- Structure of TDTBPMB

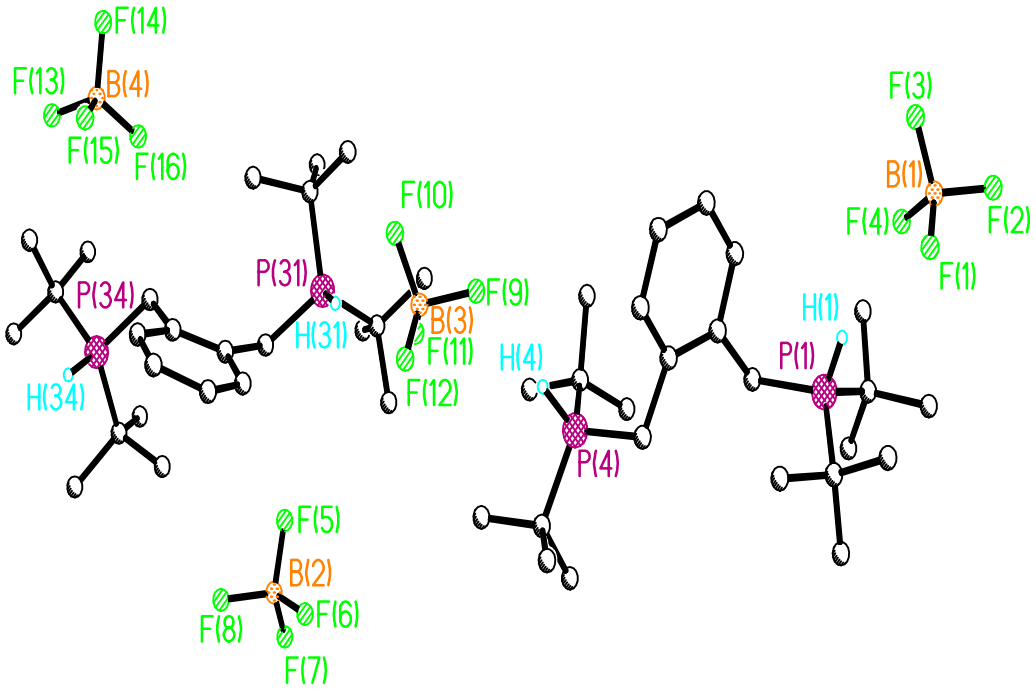


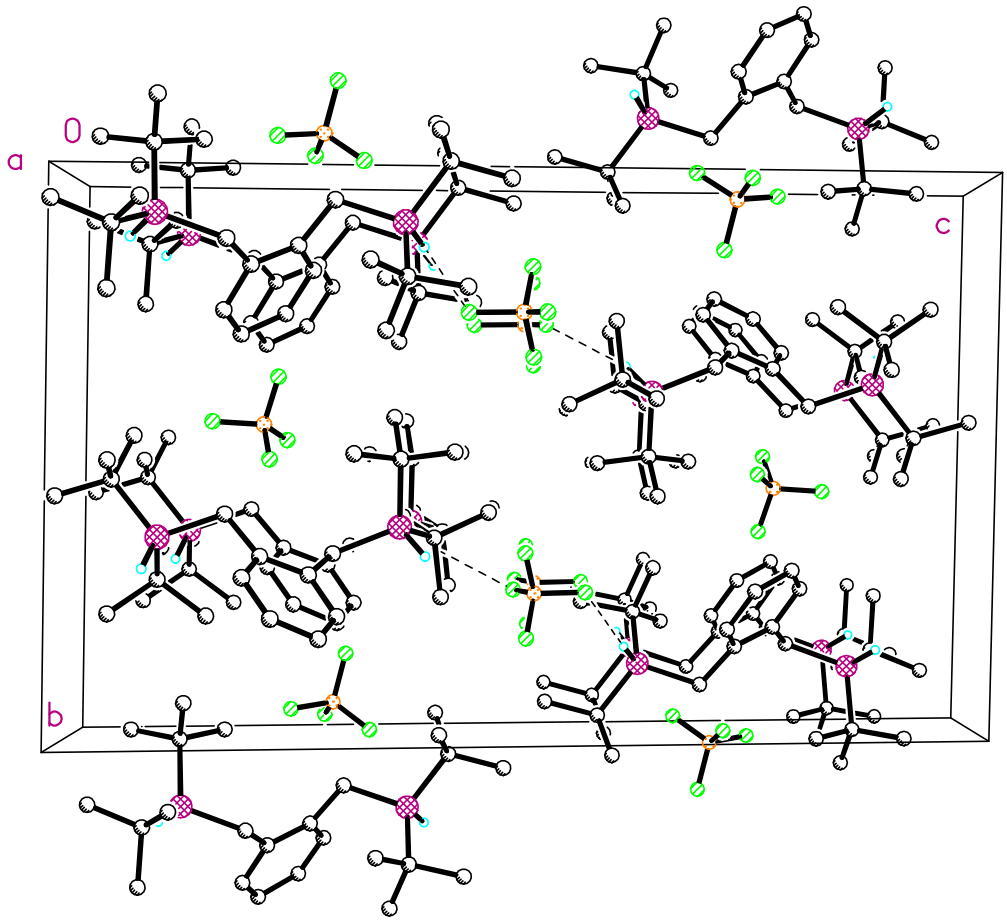
Crystal data and structure refinement

Identification code	aadch5
Empirical formula	C33 H63 P3
Formula weight	552.74
Temperature	93(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c

Unit cell dimensions	a = 19.460(4) Å	α= 90°.
	b = 12.072(3) Å	β= 108.254(9)°.
	c = 15.752(4) Å	γ = 90°.
Volume	3514.3(13) $Å^3$	
Z	4	
Density (calculated)	1.045 Mg/m^3	
Absorption coefficient	0.188 mm^{-1}	
F(000)	1224	
Crystal size	0.100 x 0.100 x 0.100 mm^3	
Theta range for data collection	2.62 to 25.35°.	
Index ranges	-23<=h<=19, -14<=k<=14, -13<=l<=18	
Reflections collected	20416	
Independent reflections	6117 [R(int) = 0.1286]	
Completeness to theta = 25.00°	96.3 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.6333	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6117 / 0 / 326	
Goodness-of-fit on F^2	1.078	
Final R indices [I>2sigma(I)]	R1 = 0.0883, wR2 = 0.1881	
R indices (all data)	R1 = 0.1527, wR2 = 0.2310	
Largest diff. peak and hole	0.637 and -0.483 $e.Å^{-3}$	

7.3.- Structure of $[BDTBPMBH_2][BF_4]_2$



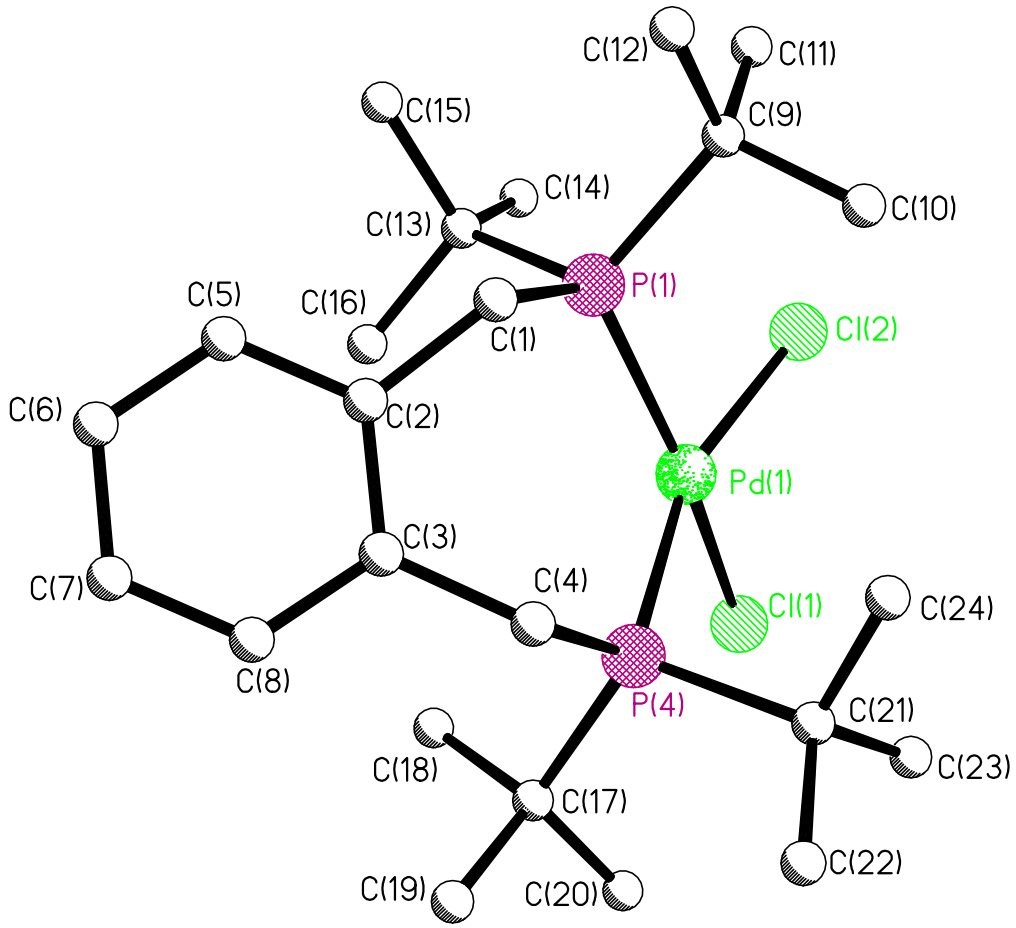


Crystal data and structure refinement

Identification code	aadch11	
Empirical formula	C24 H46 B2 F8 P2	
Formula weight	570.17	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.722(2) Å	α= 90.779(7)°.
	b = 15.101(4) Å	β= 97.485(9)°.

	c = 24.950(7) Å γ = 92.145(10)°.
Volume	2882.0(13) $Å^3$
Z	4
Density (calculated)	1.314 Mg/m^3
Absorption coefficient	0.215 mm^{-1}
F(000)	1208
Crystal size	0.2000 x 0.0300 x 0.0200 mm^3
Theta range for data collection	2.11 to 25.37°.
Index ranges	-9<=h<=7, -18<=k<=18, -30<=l<=24
Reflections collected	17527
Independent reflections	9426 [R(int) = 0.0484]
Completeness to theta = 25.00°	89.9 %
Absorption correction	Multiscan
Max. and min. transmission	1.0000 and 0.5514
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9426 / 4 / 666
Goodness-of-fit on F^2	0.993
Final R indices [I>2sigma(I)]	R1 = 0.0953, wR2 = 0.2107
R indices (all data)	R1 = 0.1119, wR2 = 0.2225
Largest diff. peak and hole	1.433 and -1.039 $e.Å^{-3}$

7.4.- Structure of [Pd(BDTBPMB)Cl_2]

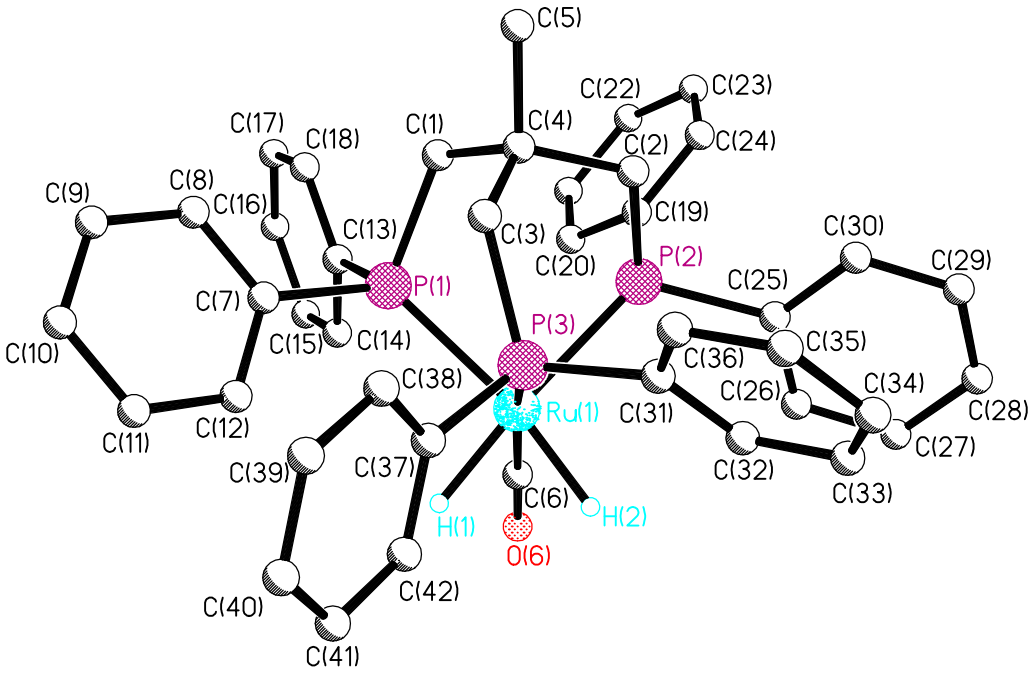


Crystal data and structure refinement

Identification code	aadch8
Empirical formula	C24 H44 Cl2 P2 Pd
Formula weight	571.83
Temperature	93(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c

Unit cell dimensions	a = 9.1553(15) Å	α= 90°.
	b = 19.646(3) Å	β= 101.766(5)°.
	c = 15.159(3) Å	γ = 90°.
Volume	2669.3(8) $Å^3$	
Z	4	
Density (calculated)	1.423 Mg/m^3	
Absorption coefficient	1.025 mm^{-1}	
F(000)	1192	
Crystal size	0.1000 x 0.1000 x 0.0700 mm^3	
Theta range for data collection	1.72 to 25.34°.	
Index ranges	-8<=h<=10, -23<=k<=22, -15<=l<=17	
Reflections collected	14255	
Independent reflections	4316 [R(int) = 0.0241]	
Completeness to theta = 25.00°	89.1 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8170	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4316 / 0 / 263	
Goodness-of-fit on F^2	1.091	
Final R indices [I>2sigma(I)]	R1 = 0.0315, wR2 = 0.0710	
R indices (all data)	R1 = 0.0354, wR2 = 0.0738	
Largest diff. peak and hole	0.785 and -0.633 $e.Å^{-3}$	

7.5.- Structure of [$RuH_2CO(Triphos)$]



Crystal data and structure refinement

Identification code	aadch4	
Empirical formula	C42 H41 O P3 Ru	
Formula weight	755.73	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 20.541(5) Å	α= 90°.
	b = 10.190(2) Å	β= 90°.
	c = 16.712(4) Å	γ= 90°.
Volume	3498.2(15) $Å^3$	
Z	4	
Density (calculated)	1.435 Mg/m^3	

Absorption coefficient	0.619 mm^{-1}
F(000)	1560
Crystal size	0.1000 x 0.0300 x 0.0100 mm^3
Theta range for data collection	1.98 to 25.52°.
Index ranges	-24<=h<=20, -12<=k<=12, -20<=l<=18
Reflections collected	23367
Independent reflections	5386 [R(int) = 0.1201]
Completeness to theta = 25.00°	99.2 %
Absorption correction	Multiscan
Max. and min. transmission	1.0000 and 0.5151
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5386 / 3 / 360
Goodness-of-fit on F^2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0682, wR2 = 0.1260
R indices (all data)	R1 = 0.0968, wR2 = 0.1438
Absolute structure parameter	-0.02(6)
Extinction coefficient	0.00023(19)
Largest diff. peak and hole	1.093 and -0.755 $e.Å^{-3}$