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Synthesis and reactivity of new transition metal-based catalytic systems in carbonylation reactions

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List of Abbreviations

AN: Aniline

BDOMP: 1,3-bis(bis(2-methoxyphenyl)phosphino)propane

BQ :   1,4-Benzoquinone

CHA;   cyclohexylamine

CON: cyclohexanone

COX: cyclohexanone oxime

CPL: Caprolactam

DBU: 1,8-Diazabicyclo(5.4.0)undec-7-ene

Dcypf: 1,1′-Bis(di-cyclohexylphosphino)ferrocene]

DMC: dimethyl carbonate

DPEphos: Bis[(2-diphenylphosphino)phenyl] ether

Dppb :   1,4-Bis(diphenylphosphino)butane

dppBz: 1,2-Bis(diphenylphosphino)benzene

dppe: 1,2-Bis(diphenylphosphino)ethane

dppf: 1,1'-Bis(diphenylphosphino)ferrocene

dppm: 1,1-Bis(diphenylphosphino)methane

dppp_   1,3-Bis(diphenylphosphino)propane

DPU: 1,3-Diphenylurea

Fc: Ferrocene

Fc$^+$:   Ferrocenium

MeO-dppf: 1,1′-Bis[bis(2-methoxy-phenyl)phosphino] ferrocene

NB: nitrobenzene

PCA:	N-phenylcyclohexyl amine
PCNA:	N-cyclohexylideneaniline
PI:	phenyl-isocyanate
PMC:	methyl phenylcarbamate
PPh$_3$:	triphenylphosphine
SDS:	Sodium dodecyl sulfate
SPAN-60:	Sorbitane monostearate
SPANphos:	4,4,4',4',6,6'-hexamethyl-2,2'-spirobi[chroman]-8,8'-diylbis(diphenylphosphane)
TAH:	trifluoacetic hydroxylamine
TBAB:	Tetrabutylammonium bromide
TBAI:	Tetrabutylammonium iodide
TFA:	trifluoroacetic acid
TOF:	turnover frequency
TON:	turnover number
Xantphos:	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Abstract

The aim of this PhD thesis was to explore the activity of new catalytic systems in some carbonylation reactions of organic substrates, like aromatic amines, olefins and/or iodoarenes which are transformed in isocyanates, ureas, esters, amides and polymers, interesting for the chemical industry.

In **Chapter 1** the study of the synthesis of isocyanates and amides of industrial interest is reported. A catalytic system based on [PdCl$_2$(dppf)]/FeCl$_3$/O$_2$ was studied for the synthesis of phenyl isocyanate and N,N diphenyl urea (DPU), by oxidative carbonylation of aniline. Also presented is a study of synthesis of cyclohexanone oxime obtained by reduction of nitrobenzene in the presence of NH$_2$OH·HCl with heterogeneous Pd catalysts, which by Beckmann rearrangement can lead to the formation of Caprolactam. A reactivity study of trifluoroacetate hydroxylamine (NH$_2$OH·CF$_3$COOH) for the synthesis of oximes and amides of industrial interest is also presented.

In **Chapter 2**, a study on the carbonylation of olefins with Pd-based heterogeneous pre-catalysts is presented. Through the study of methoxycarbonylation of cyclohexene these catalysts were compared to the activity of the homogeneous catalyst of [Pd(TsO)$_2$(PPh$_3$)$_2$]. From a study of the reaction mechanism, the possibility of having a mixed homogeneous/heterogeneous catalysis is proposed.
In addition, a study of a new heterogeneous magnetic support obtained by decomposition of Fe(CO)$_5$ is presented, which was suitably coated with a polyketone layer. Such a support was employed for the synthesis of a Pd-based heterogeneous catalyst (Pd/MIM) and successfully employed in methoxycarbonylation reaction of cyclohexene, methoxycarbonylation of iodobenzene and for nitrobenzene reduction reaction.
In conclusion, the hydration of olefins catalyzed by CF$_3$COOH, which is commonly employed as an acidic promoter in palladium-catalyzed carbonylation reactions, was investigated to delineate possible side reactions for olefin carbonylation reactions for industrially employed two-phase systems.

In **Chapter 3**, a study was performed on the carbonylation of iodobenzenes. A new catalytic system based on [PdCl$_2$(Xantphos)] was studied for alkoxycarbonylation reactions. In particular, the effects of some additives on the productivity of the reaction have been studied, defining as the best catalytic system the one formed by [PdCl$_2$(Xantphos)] and the pair ferrocene/ferrocenium.
In addition, a preliminary study of the amino-carbonylation reaction of iodobenzene is presented, the selectivity of the reaction is explored, and the possible competition of the base required for the catalytic cycle and the amine employed as a nucleophile.

In **Chapter 4**, the possibility of employing green surrogates for carbonylation reactions was investigated. A study was carried out on the generation of CO from formic acid, through the Morgan reaction, using heterogeneous acid catalysts. The best setup of the reactor has been studied to optimize the yield of carbon monoxide and avoid the mechanical degradation of acid resins used as catalysts.
A new multi-chamber reactor has also been designed to perform simultaneously several Palladium-catalyzed carbonylation reactions, employing CO generated by formic acid.
Finally, the first example of polymer obtained by catalytic carbonylation of ethylene (PK), employing CO generated by formic acid and acetic anhydride system, is presented. The HCOOH/CH$_3$COO$_2$ mixture plays both the role of solvent and carbon monoxide generator.

Sommario

Lo scopo di questa tesi di dottorato è stato quello di esplorare l'attività di nuovi sistemi catalitici in alcune reazioni di carbonilazione di substrati organici, come ammine aromatiche, olefine e/o iodoareni che vengono trasformati in isocianati, uree, esteri, ammidi e polimeri, interessanti per l'industria chimica.

Nel Capitolo 1 viene riportato lo studio della sintesi di isocianati e ammidi di interesse industriale. Il sistema catalitico basato su [PdCl$_2$(dppf)]/FeCl$_3$/O$_2$ è stato studiato per la sintesi di fenilisocianato e N,N difenilurea (DPU), mediante carbonilazione ossidativa dell'anilina. Viene anche presentato uno studio di sintesi della cicloesanoneossima ottenuta per riduzione del nitrobenzene in presenza di NH$_2$OH·HCl con catalizzatori eterogenei a base di Pd, che per riarrangiamento di Beckmann può portare alla formazione del caprolattame. Inoltre, viene porposto uno studio di reattività dell'idrossilammina trifluoroacetata (NH$_2$OH·CF$_3$COOH) per la sintesi di ossime e ammidi di interesse industriale.

Nel Capitolo 2, viene illustrato uno studio sulla carbonilazione di olefine con pre-catalizzatori eterogenei a base di Pd. Attraverso lo studio della metossicarbonilazione del cicloesene questi catalizzatori sono stati confrontati con l'attività del catalizzatore [Pd(TsO)$_2$(PPh$_3$)$_2$] in fase omogenea. Da uno studio del meccanismo di reazione, viene proposta la possibilità di avere una catalisi mista omogenea/eterogenea.

Inoltre, si riporta lo studio di un nuovo supporto magnetico eterogeneo ottenuto dalla decomposizione di Fe(CO)$_5$, che è stato opportunamente rivestito con uno strato di polichetone. Tale supporto è stato impiegato per la sintesi di un catalizzatore eterogeneo a base di Pd (Pd/MIM) e impiegato con successo nella reazione di metossicarbonilazione del cicloesene, metossicarbonilazione dello iodobenzene e per la reazione di riduzione del nitrobenzene.

In conclusione, l'idratazione delle olefine catalizzata da CF$_3$COOH, che è comunemente impiegato come promotore acido nelle reazioni di carbonilazione catalizzate dal palladio, è stata studiata per delineare le possibili reazioni secondarie per le reazioni di carbonilazione delle olefine per i sistemi bifase impiegati industrialmente.

Nel capitolo 3, è stato eseguito uno studio sulla carbonilazione degli iodobenzeni. Un nuovo sistema catalitico basato su [PdCl$_2$(Xantphos)] è stato studiato per reazioni di alcossicarbonilazione. In particolare, sono stati studiati gli effetti di alcuni additivi sulla produttività della reazione, definendo come miglior sistema catalitico quello formato da [PdCl$_2$(Xantphos)] e la coppia ferrocene/ferrocenio.

Inoltre, viene presentato uno studio preliminare della reazione di amminocarbonilazione dello iodobenzene, viene esplorata la selettività della reazione e la possibile competizione tra la base richiesta per il ciclo catalitico e l'ammina impiegata come nucleofilo.

Nel capitolo 4, è stata studiata la possibilità di impiegare surrogati al CO per le reazioni di carbonilazione. È stato condotto uno studio sulla generazione di CO dall'acido formico, attraverso la reazione di Morgan, utilizzando catalizzatori acidi eterogenei. Il miglior setup

del reattore è stato studiato per ottimizzare la resa di monossido di carbonio ed evitare la degradazione meccanica delle resine acide usate come catalizzatori.

Un nuovo reattore multicamera è stato anche progettato per eseguire simultaneamente diverse reazioni di carbonilazione catalizzate dal palladio, utilizzando il CO generato dall'acido formico.

Infine, viene presentato il primo esempio di polimero ottenuto dalla carbonilazione catalitica dell'etilene (PK), utilizzando il CO generato dall'acido formico in cui la miscela $HCOOH/CH_3COO_2$ svolge sia il ruolo di solvente che di generatore di monossido di carbonio.

Introduction

Historical Overview

About 10% of the carbon in the universe is stored in the form of carbon monoxide (CO).
CO is one of the most common air pollutant gases; more than 60% of emissions come from anthropogenic sources, mainly due to combustion in transport vehicle engines, thermal power plants, incinerators, and industrial processes [1].
Although the first evidence of the existence and toxicity of carbon monoxide date back to ancient Greece (about 300 b.C), it is very probable that the toxicity of carbon monoxide was noticed in prehistoric times by cavemen with the discovery of fire [2].
This molecule was "re-discovered" and studied between the end of 1600 and the beginning of 1700, especially from a toxicological point of view. In 1776 Lassone, a French doctor and chemist, succeeded in synthesizing CO by heating Coke with Zinc oxide, but given the flammable nature of the gas, he deduced it was hydrogen. In 1777, Antoine Lavoisier came to the same erroneous conclusion [3].
It was only in 1800 that chemist W.C. Cruikshank, was able to identify this toxic and flammable gas as a molecule containing only carbon and oxygen.
Systematic study of the reactivity and chemical- physical properties of carbon monoxide was not performed until the late 1890s[4].
L. Mond was the first to discover the possible reaction between carbon monoxide and metals, and this observation is the basis of Mond's process for purifying nickel by thermal decomposition of $Ni(CO)_4$, obtained by heating nickel powder in a CO atmosphere [5].
A little later, about 1897, CO was applied for the first time in organic synthesis by chemists L. Gattermann and J.A. Koch, for the synthesis of aromatic aldehydes, in the presence of HCl and $AlCl_3$ as catalysts [6].
What gave the impetus to the use of CO in industrial processes was the discovery of Fischer and Tropsch (about 1920s) who first observed the reaction between carbon monoxide and hydrogen to produce hydrocarbon mixtures, using heterogeneous catalysts based on iron and cobalt [7].
A substantial evolution of the Fischer-Tropsch process was made by O. Roelen, who based on the results obtained by the two colleagues, was the first to develop a carbonylation of olefins using H_2 and CO, using transition metal catalysts to produce aldehydes (hydroformilation)[8].
A further boost for the use of CO in industrial synthesis was the synthesis of acetic acid obtained by carbonylation of methanol. In 1925, the Swiss chemist H. Drefyus developed the process at pilot plant level. Unfortunately, the strongly acidic conditions combined with the high carbon monoxide pressures were a huge obstacle to the commercialization of the process.
More fortunate was the research of the German chemist Reppe who in 1940 studied the possibility of carrying out the synthesis of acetic acid by carbonylation of methanol in the presence of transition metal catalysts (iron, cobalt and nickel). Despite the severe reaction

conditions (250°C and 690 atm), the process was commercialized by BASF in 1960 using Cobalt as catalyst [9].

Only a few years later Monsanto developed an industrial process for the synthesis of acetic acid obtained by carbonylation of methanol, using rhodium-based catalysts. This process proved to be much more convenient due to both the lighter operating conditions (200 °C, 40 atm) and the high selectivity of the system (99%). This process remained the most convenient until 1996, when the BP Chemicals company developed the Cativa process, which used iridium as a catalyst, less expensive than the rhodium-based catalyst [10].

In the same years, alternative strategies were developed for the synthesis of acids by carbonylation. For example, in 1955 was developed the Koch reaction, which by means of carbocatonic intermediates allows to obtain acids from olefins or tertiary alcohols in acid catalysis. Although this type of process is problematic from an environmental point of view because of the production of large quantities of waste, currently about 150'000 tons per year of organic acids are produced by the Koch reaction [11].

What represented the breakthrough in the use of carbon monoxide at both laboratory and industrial scales was the development around the 1970s of palladium-catalyzed cross-coupling reactions, which represent a powerful route for the synthesis of new C-C bonds. Pioneer was Heck, who, along with Suzuki and Negishi, won the Nobel Prize in chemistry for " *palladium-catalyzed cross couplings in organic synthesis*" [12].

 In 1974, he and his collaborators performed the first carbonylative cross-coupling reaction. From that moment on, due to the continuous effort of academic and industrial research, CO represents a very important building block for the synthesis of a wide range of products both of fine and bulk chemistry, such as esters, amides, aldehydes, ketones, uree, polymers etc.

Metal-catalyzed carbonylation reactions have attracted the attention of academia and industry for several important reasons. Most notable among them are the milder reaction conditions and the tolerance of a wide range of functional groups.

Another reason why metal-catalyzed reactions represent a powerful synthetic means is related to their versatility, indeed by modifying the operating conditions or the ligands based on P, N, S, O etc. it is possible to improve the selectivity and the productivity of the catalytic system.

In literature it is possible to find an innumerable amount of carbonylative reactions that can be obtained with metal catalysts.

Industrially, carbon monoxide is produced mainly through two different processes.
In the first case, a mixture of CO and N_2 is obtained by direct combustion in oxygen-deficient of coke at 800 °C. Initially this process leads to the synthesis of CO_2 which reacts with carbon and is subject to a disproportion equilibrium reaction, known as the Boudouard reaction (scheme 1)[13] At high temperatures this equilibrium reaction is shifted towards the formation of CO, making it the major product.
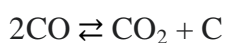
$$2CO \rightleftarrows CO_2 + C$$
Scheme 1. Boudouard Reaction

Another important industrial process to produce CO is *Steam-reforming* (scheme 2)[14]. This process allows to obtain as a product a gaseous mixture, consisting mainly of H_2 and CO.

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This process consists in reacting steam at high temperature with natural gas (CH$_4$, *Syngas*) or with Coke (*water gas*).

$$CH_4 + H_2O \rightleftarrows CO + 3\ H_2$$
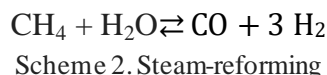
In some cases, when high purity of carbon monoxide is required, it can be synthesized from formic acid (FA) by the Morgan reaction (scheme 3) [15].

$$HCOOH \xrightarrow[\text{- }H_2O]{H_2SO_4} CO$$
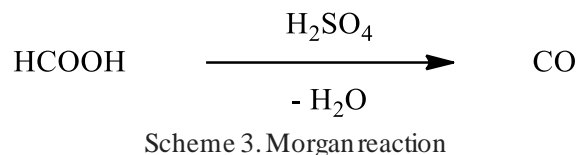
This reaction consists of a dehydration of FA catalyzed by concentrated sulfuric acid. Although it is a synthetic route with some obvious industrial limitations (waste production and reconcentration of exhausted sulfuric acid), this strategy is used for some carbonylations aimed at the production of organic acids (Kock-Haaf reaction) [16].

Carbonylation Reaction

The term "carbonylation," coined by W. Reppe at BASF in the early 1940s, refers to all reactions in which a carbon monoxide molecule is incorporated into organic substrates.[17] Since then, transition metal-catalyzed carbonylations of olefins, alkynes, halides, alcohols, amines, and nitro compounds have become a very important tool for organic synthesis on both industrial and laboratory scales.

Due to the low cost of the C1 source and the wide range of products that can be obtained, research aimed at improving existing catalytic systems and the identification of new reactive pathways is still a very active branch of scientific research.

Primarily, research focuses on identifying new transition metals that are cheaper than those currently used, or on activating less reactive (and less expensive) substrates to make these reactions more attractive for industrial applications.

Olefins carbonylation

Carbonylation of olefins is an important synthetic means available to industrial and organic chemists to produce a wide range of carbonyl compounds such as carboxylic acids, anhydrides, esters, amides, amino acids etc. (Scheme 4)
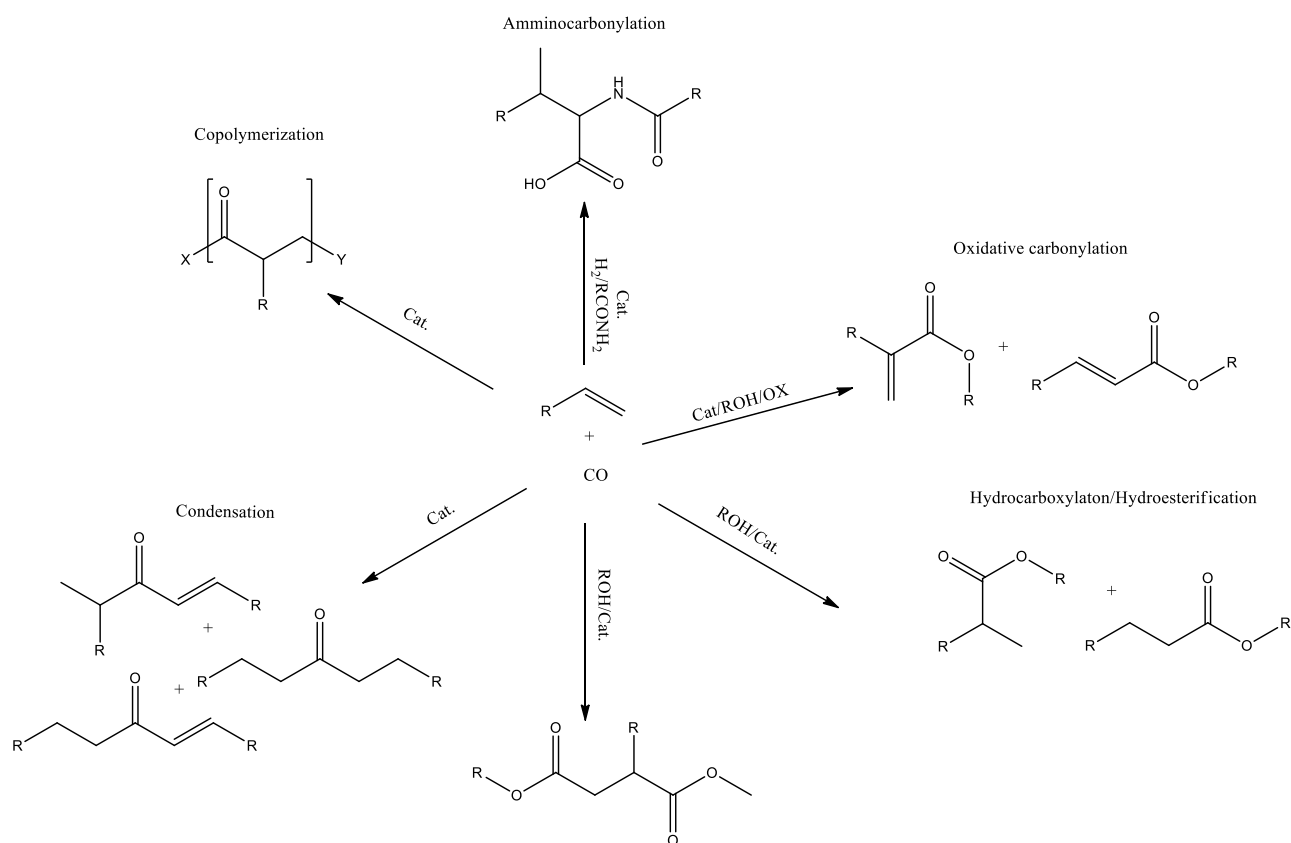
Scheme 4. Different type of Carbonylation of Olefins

Hydroxycarbonylation and hydroesterification reactions of alkenes, also called Reppe carbonylation, has attracted particular attention from chemists since the 1980s, who identified transition metals such as Co, Pd, Pt, Ni, Rh, and Ru as the most promising catalysts[18] (Scheme 5). To date, the main goal of research remains to develop catalytic systems capable of achieving regioselectivity of the reaction; palladium takes a privileged place in this class of reactions because of its versatility that allows to selectively incorporate CO into acyclic and cyclic compounds under mild temperature and pressure conditions.

(NuH= H₂O, ROH
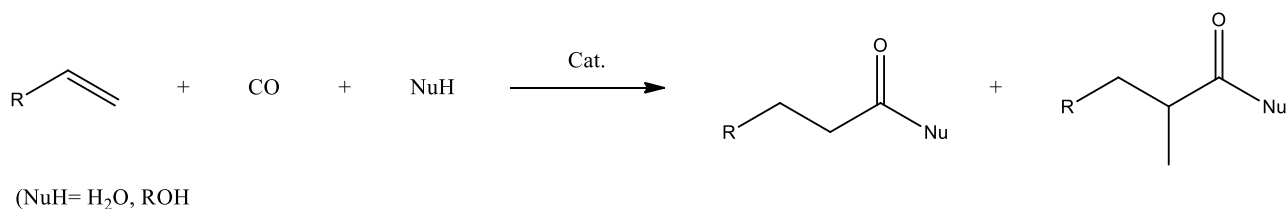
Scheme 5. Hydroxycarbonylation and hydroesterification reaction

Because of the many areas of application of esters, and because of the simplicity of purification of reaction products, academia has focused primarily on alkoxycarbonylation reactions, which reaction parameters similarly affect the hydrocarboxylation reaction in the same way.

In addition, the synthesis of esters by hydroesterification of 1-alkenes often leads to quantitative conversions, such that olefins can be used as solvents. This makes this type of

reaction very interesting, both for the synthesis of high value products and from the point of view of economic and environmental sustainability of the syntheses[19,20].

For olefin carbonylations catalyzed by Pd(II) complexes, there are mainly two reaction mechanisms proposed and most accepted.
The first (Scheme 6, Pd-Hydride mechanism) involves the insertion of olefins into the palladium-hydride species Pd-H with the formation of the palladium-alkyl species, which undergoes the insertion of CO to form the palladium-acyl species. The nucleophilic attack of alcohol, (or alcoholysis) on the Pd-acyl species leads to the formation of the ester and the Pd-Hydride species again, which restart the cycle.
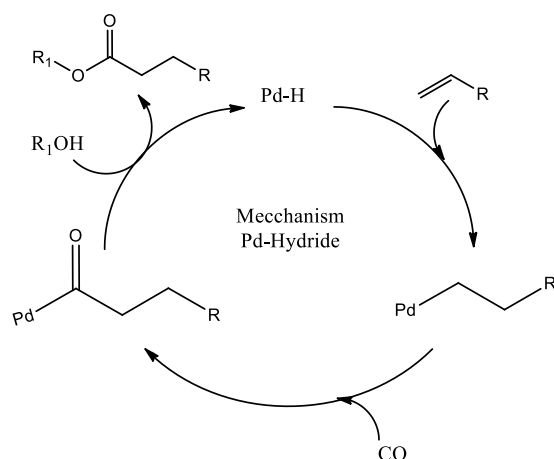
Scheme 6. Schematic representation of the Pd-hydride Mechanism for alkoxycarbonylation of olefins

The second mechanism (Pd-alkoxy, Scheme 7), involves the initial nucleophilic attack of alcohol on Pd(II) to form the Pd-alkoxy species, which undergoes the insertion of carbon monoxide to form the Pd-acyl species, then there is the coordination of olefin that insert into the Pd-acyl species, which is attacked again by an alcohol molecule to give the ester product and again form the Pd-Alkoxy species, which restart the cycle[21].
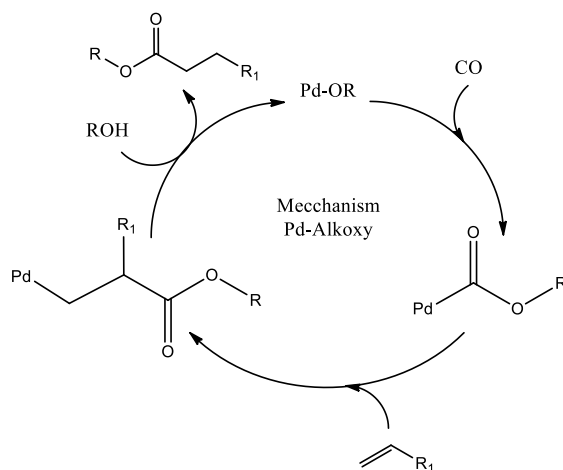
Scheme 7. Schematic representation of the Pd-Alkoxy Mechanism for alkoxycarbonylation of olefins

The regioselectivity of these reactions is not very high and is attributed to the low selectivity of olefin in the coordination and insertion into the Pd complex. Typically, catalytic systems that give linear esters as the main product are proposed to operate via mechanism Pd-H. In contrast, mechanism Pd-OR is often invoked for those systems that give branched products. Although there are many different catalytic systems proposed in the literature, all in addition to the Pd(II) precursor need the presence of ligands, and acid additives.

Typically, the acid additives are strong Bronsted acid HA, which A is a weakly coordinating anionic ligand, usually p-TsOH or CF_3SO_3H. The main roles of such additives are therefore both to give to the Pd-center a weakly coordinating ligand, which favor the reaction, and to avoid the catalyst deactivation due to formation of inactive Pd-black[22]. The strong acid can react with Pd(0) species leads to the formation of Pd(II)-H species, which turns out to be one of the possible active species of the catalyst.

$$Pd^0 + HX \rightarrow HPdX$$
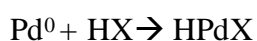
The concept that the active species for this catalysis is Pd (II) is also supported by the fact that the nature of the counterion of the cationic species affects both the conversion and selectivity of the hydroesterification reaction. For example, Tsuji [23], working on the hydroesterification of butadiene, concluded that the presence of strongly coordinating anions does not allow the formation of the Pd-allyl intermediate and this favors the hydroesterification reaction at the expense of oligomerization or thalomerization. Other work, focusing on the use of $[PdX_2(P-P)]$ (P-P = bidentate phosphine ligands), has shown that with strongly coordinating anionic ligand (X^-) such as chlorides, they turn out to be inactive when compared to the corresponding complexes with weakly coordinating anions. In the hydroesterification of styrene with $[PdX_2(PPh_3)_2]$ the activity varies with $X=Cl<BF_4<CF_3SO_3<TsO$ [24].

With $[Pd(OAc)_2L_2]$ the presence of strong acids allows the acetate ions to be replaced by more labile anions, and sometime such ligands are so weakly coordinating that are replaced by solvent itself (scheme 8). Apparently, this allows to have coordination sites on the metal center much more accessible for substrates, allowing to start more easily the catalytic cycle.

$$[Pd(OAc)_2L_2] + 2HX + 2S \rightleftarrows [PdL_2S_2]^{+2}2X^- + 2HOAc$$
$$L = \text{phosphine ligand}$$
$$HX = \text{strong acid with weakly coordinating anion}$$
$$S = \text{solvent}$$
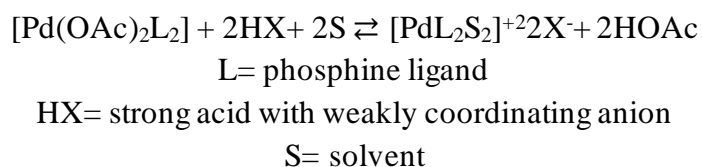
Scheme 8. Replacing labile anions on catalyst

For these syntheses, the reaction rate varies greatly depending on the structure of the olefin[25]. Although it is difficult to give univocal values, it is possible to determine a qualitative trend in which a maximum of the reaction speed for the linear olefins of the C3-C20 fraction is observed for the C5-C7 cut, while for cyclic olefins the speed of hydroesterification turns out to be much higher than for linear olefins[26-27].

For branched olefins the reaction rate is at least an order of magnitude slower than for linear olefins.

Depending on the reaction conditions, the carbonylation of dienes can lead to obtaining unsaturated and/or saturated mono- and/or dicarboxylated products, and in some cases, it is possible to observe the formation of isomers related to the isomerization of carbon-carbon double bonds.

BASF, to produce an intermediate for manufacturing of Nylon 6-6, has developed a process for the synthesis of adipic acid that involves the hydrolysis of dimethyl adipate obtained from butadiene (scheme 9)[28].
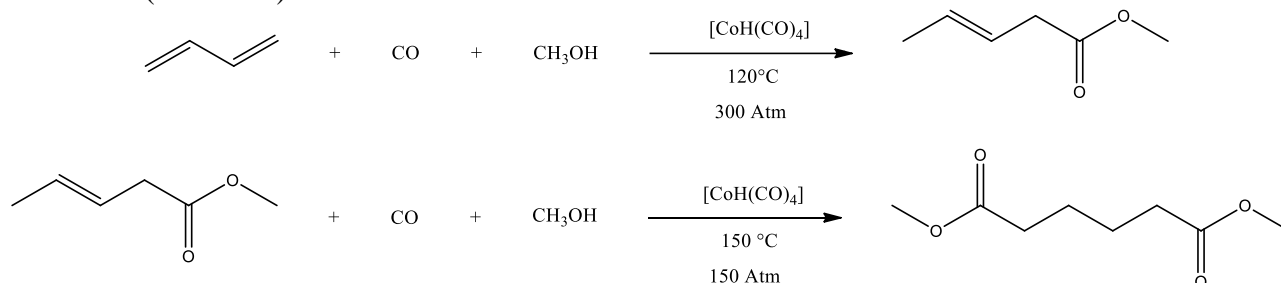
Scheme 9. BASF process for dimethyl adipate synthesis

The use of phosphine ligands can significantly affect the activity and selectivity of the catalyst. It is not possible to define "the best ligand", often the choice of ligand is a function of the substrate on which the reaction will be performed. For example, it has been observed that the selectivity towards the formation of linear alkyl esters is enhanced by using very bulky chelating phosphines, such as bis(phosphaadamantyl)diphosphines[29] or bis(di-tert-butylphosphinomethyl) benzene[30-31] (figure 1), which achieve selectivity towards linear ester isomers more than 95% for terminal olefins.
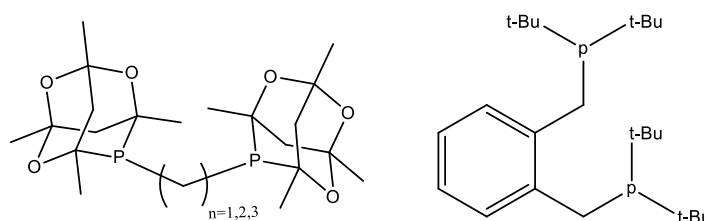
Fig.1.bis(phosphaadamantyl)diphosphines and 1,2-Bis(di-tert-butylphosphinomethyl)benzene

In 1969, BASF patented the hydroxycarbonylation of terminal olefins using palladium complexes using phosphine ligands[32]. Later a more detailed study was performed by Fenton who starting from the $PdCl_2/PPh_3$ catalytic system optimized the reaction parameters (T=150°C, P_{CO} 5-55 atm) to obtain high conversions with an n/iso ratio of 3.5 for the hydroxycarbonylation of 1-octene [33].

Alper, working on the carbonylation of a series of linear and non-linear olefins, showed that the addition of $CuCl_2$ a HCl to the Pd(II)/PPh_3 catalytic system can allow to vary the selectivity towards the formation of the branched isomers, working at very mild reaction conditions (room temperature, P_{CO}= 1 atm)[34].

Hydrocarboxylations of aromatic olefins are also of great interest, as they allow the direct synthesis of 2-aryl propionic acids. Unlike the products obtained from the carbonylation of linear olefins, whose most interesting products are linear, for aromatic olefins the desired isomer is the branched isomer.

Alper studied the possibility of performing enantioselective carbonylations starting from prochiral terminal alkenes, going to use chiral ligands such as (R)- or (S)- 1,1-binapthyl-2,2-diylhydrogenophosphate (BNPPA) (Fig. 2), obtaining an enantiomeric excess of more than 90% [35].
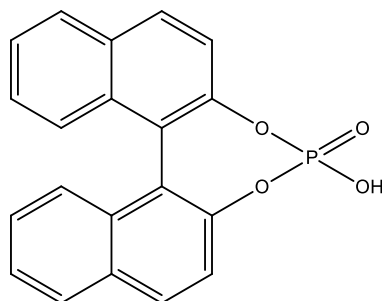
(BNPPA)

Fig.2 1,1-binapthyl-2,2-diylhydrogenophosphate

This work laid the foundation for the possible industrial application of the synthesis of non-steroidal anti-inflammatory products such as (S)-ibuprofen and (S)-naproxen (Figure 3) by enantioselective carbonylation.

(S)-Ibuprofen   (S)-Naproxen
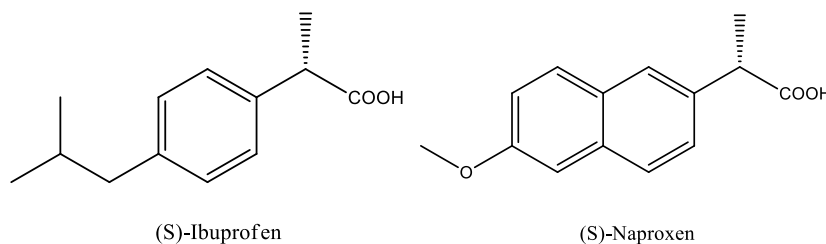
Fig. 3. (*S*)-ibuprofen and (*S*)-naproxen

On the other hand, for linear aromatic acids, it has been observed that by employing $Pd(OAc)_2$, 1,4-bis(diphenylphosphino)butane (dppb), and formic or oxalic acid, at 7 atm CO and 150°C, high yields and selectivity can be obtained from styrenic substrates[36].

With the aim of verifying the possibility of recycling the catalytic system, several studies have been performed on the possibility of performing hydrocarbonylation in two-phase systems, employing water-soluble mono- or di-phosphine ligands. For example, employing sodium salt of trisulfonated triphenylphosphine (TPPTS) (Figure 4), some works are reported in which an effective carbonylation of light olefins is obtained [37, 38] which do not show problems related to mass transport phenomena between the organic and aqueous phases.

(TPPTS)
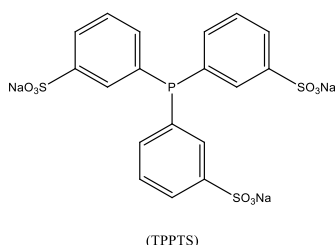
Fig.4. 3,3′,3″-Phosphanetriyltris(benzenesulfonic acid) trisodium salt

The ligands used for carbonylation reactions, in addition to influencing the n/iso selectivity, can also be decisive on the type of product that can be obtained, for example PPh_3 favors the hydroesterification of ethylene in the presence of CO and MeOH (forming methylpropionate, MP), while in the same reaction conditions, with 1,3-Bis(diphenylphosphino)propane (dppp) reaction leads to the formation of CO/ethene copolymer (polyketone, PK) [39-40]

In addition to factors related to the steric bulk of the ligands, it has been observed that their electronic structure can affect the productivity of the catalytic system. For example (2-pyridyl)diphenylphoshine ($2PyPPh_2$) lead to ten times higher catalytic activity in olefin hydroesterification than triphenylphopshine (PPh_3)[41].

Polymerization of olefins and CO: synthesis of Polyketones

The first perfectly alternating CO-ethene polyketone, patented by the BASF company in 1951, was obtained using $K_2Ni(CN)_4$ as catalyst [42] Since then, several academic research groups have made continuous improvements in the synthetic procedures for producing PK.
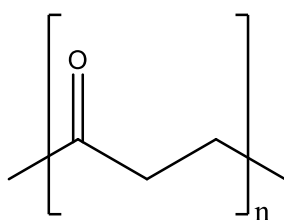
PK-E

The attractive characteristics of this class of semi-crystalline thermoplastic polymers, such as high temperature, acid and solvent resistance, prompted Shell Chemicals to set up the first commercial PK-EP alternate polyketone plant in 1966, (7000 t/year)[43], which was closed in 2001 due to changing business strategies. However, in 2015, Hyosung Corporation set up its first PK-E(alt-poly-1-oxotrimethylene) plant in Korea with a production capacity of 50 kt/year[44].

Numerous studies have shown that the reaction rate and molecular weight of the polymer are related to the reaction conditions, in particular the type of catalyst, chelating ligands, counter-anions and solvent.

The catalysts commonly employed for the synthesis of these 1-alkene/CO copolymers are Pd(II) complexes of the type $[PdX_2(L)]$ where L is a diphosphinic ligand and X is a weakly

coordinating anion; for arylolefin/CO copolymers, on the other hand, the chelating ligands typically employed are bidentate nitrogen molecule.

As for any polymer, the reaction mechanism for the synthesis of PKs (scheme 10) can be schematized into three important steps: initiation, propagation, and termination.

$$n \; \text{CH}_2{=}\text{CH}_2 \quad + \quad n\,CO \quad \xrightarrow{\text{Cat.}} \quad \text{PK-E}$$
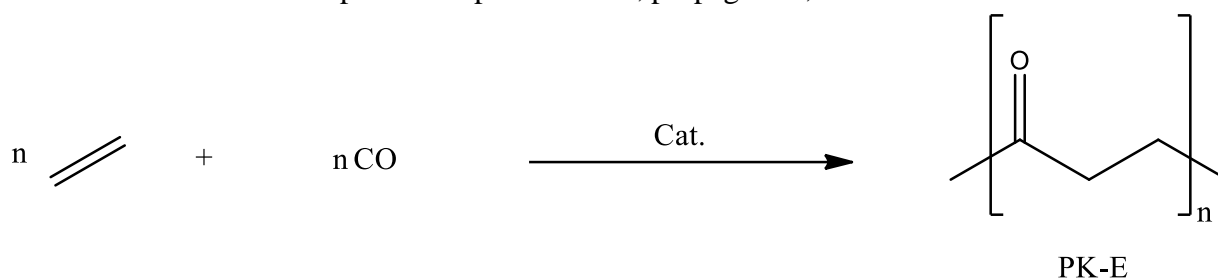
Scheme 10. Syntesis polyketone CO/ethene (PK-E)

From the analysis of the end groups of polyketones synthesized in MeOH as solvent, it has been possible to identify ester ($-COOCH_3$) and ketone ($-COCH_2CH_3$) functionalities. This provided a basis for hypothesizing the mechanism of initiation of catalytic polymerization. The presence of two types of end-groups can be explained by considering the two catalytic cycles also commonly accepted for alkoxycarbonylation reactions of olefins. The ester functionality may be due to an initiation with a Pd-Alkoxy species (Scheme 7) [45-50].

The second possibility of initiation is due to insertion of the olefin into a palladium (II) hydride species [48,50] (Scheme 6). While the insertion of both CO and ethene on the Pd-hydride species appears to be reversible, the insertion of olefin on the palladium acyl species is thought to be irreversible and this initiates the propagation step of catalytic polymerization. Polyketone (PK-E) chain growth occurs through the perfectly alternating incorporation of CO and ethene. It has been observed from some studies that the perfectly alternating sequence of the two monomers can be attributed to thermodynamic and kinetic reasons [51-53]. Although it has been shown that similar catalytic systems can promote the formation of dimers or polyolefins, in the presence of CO, it turns out to be very rare. This may be related to the differences in the energy barriers of insertion of the two monomers and the different affinities in coordination towards the metal center. CO, compared to ethene, has a higher affinity in coordination toward the metal center, to which it binds more strongly also due to retro-donation. Therefore, after olefin insertion, the competition for the free site is dominated by CO. Kinetic studies have revealed that, under typical conditions, a double ethylene insertion occurs only after every ~ 105 CO insertion in the Pd-alkyl bond [54-59]. In addition to these factors, it has also been considered that polymerization the chain can interact with the metal center through the so-called "back-biting effect" [60-63].

It is possible that the carbonyl oxygen in the polymer chain can coordinate the metal center (back biting), going on to form a 5-membered species (β-chelate), which can only be opened due to the coordination of a strongly coordinating speciation such as CO (Scheme 11). The subsequent formation of a second chelate second cycle (γ-chelate), due to the insertion of another ethene molecule, can also be opened only by the coordination of CO.
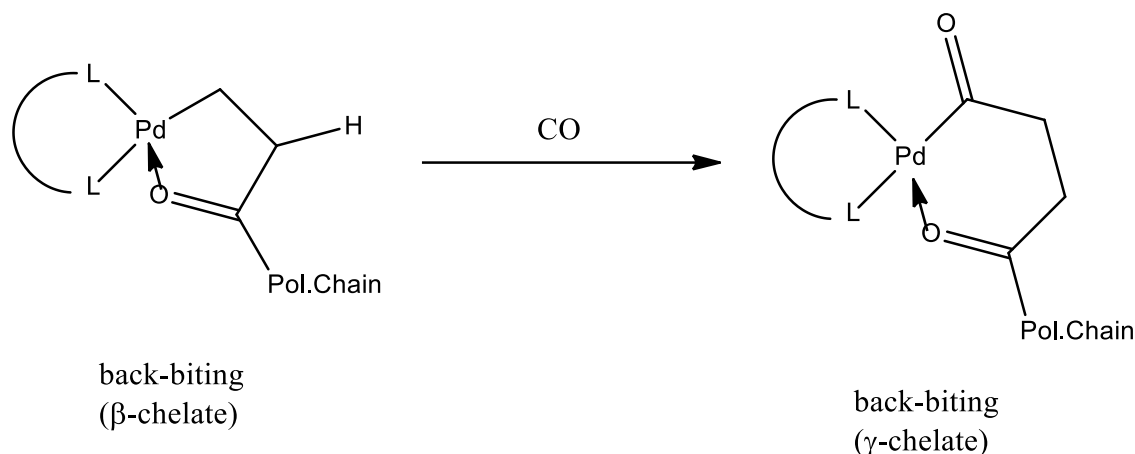
Scheme 11. Back biting effect in the CO-ethene copolymerization

This mechanism, repeating itself, leads to the growth of the perfectly alternating polymer chain. In addition, the "back-biting effect", prevents the elimination of the β-hydride.
Concerning the termination phase instead, three mechanisms have been accepted in which , in the first one it is assumed to occur by protonolysis of the Pd-alkyl species (ketone terminal group); in the second case instead it is assumed to occur by alcoholysis of the palladium-acyl species(ester terminal group); and the third mechanism involves the β hydride elimination from the growing polymeric chain, but this mechanism can be observed only with higher olefins.

In CO/ethene copolymerization catalyzed by Pd(II) complexes, the nature of the chelating phosphine plays a key role [64-66]. Indeed, only by changing is possible to obtain a wide range of different products, from perfectly alternating PKs to MP[67-69].
As reported in many theoretical studies, it has been observed that Pd(II)-based catalysts with cis-diphosphonic ligands (such as dppp, 1,3- bis(diphenylphosphino)propane) provide higher productivity than Pd-Monophosphine catalysts. The motivation is due to geometric factors; indeed, the cis coordination of the ligand also forces the other two free coordination sites to be in Cis, which is the optimal configuration to promote chain growth(scheme 12).
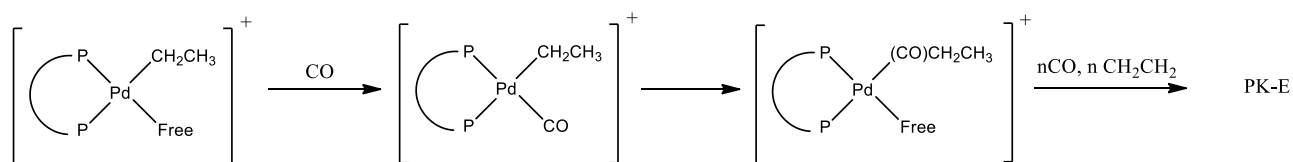
Scheme 12. Cis-configuration of Pd(II) catalyst

For this reason, numerous ligands and their characteristics have been studied with the aim of optimizing catalyst productivity and selecting polymer molecular weight [70-74]. It has been shown that the best cis- planar square configuration of the homogeneous catalyst is obtained with ligands with bite angles around 90◦.
In addition to the bite angle, the steric bulk of the ligand appears to be crucial for the chain growth rate, in fact increasing the bulk of the substituents present on the diphosphine, an

increase in the kinetics of the termination phase at the expense of the propagation phase is observed [75-77].

As with the alkoxycarbonylation reactions of olefins, in the synthesis of polyketones, the catalytic system requires the presence of promoters such as H_2O or protic acid.

Again, their purpose is to promote the initiation step and avoid catalyst deactivation (Pd-Black), in fact, Pd(II) complexes find a highly reducing reaction medium (MeOH and CO). Pd(II) species can be easily transformed into less active or inactive Pd(0).

The acid prevents the formation of inactive Pd(0) from the active Pd(II)-H species by shifting the equilibrium (Scheme 13) to the left:

$$\text{Scheme 13} \qquad [Pd(II)\text{-}H]^+ \rightleftharpoons Pd(0) + H^+$$
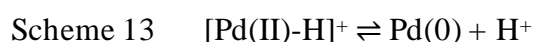
In addition, the presence of weakly coordinated strong acids makes it easy to obtain cationic Pd(II) species , in which the active sites are readily accessible from the monomers [78-79].

Clearly, in addition to the catalytic system, the productivity and molecular weight of polymers is also related to reaction conditions, such as temperature and monomer pressure.

Usually, decreasing the temperature leads to obtain polyketones with higher molecular weight, but of lower productivity due to the decrease in the overall kinetics of the reaction [80]. Pressure also affects both the average molecular weight and productivity of the catalyst.

As gas pressure increases, there is an increase in productivity, due to an increase in the amount of monomers dissolved in the solvent (Henry's law [81-84]). Thus, higher monomer concentration increases the kinetics of the polymer propagation step.

Furthermore, due to mechanistic studies carried out by studying the structure of polymers, and thus the catalytic cycle, it has been observed that the optimal ratio of the two monomers must be 1:1 (of dissolved gases), and under these conditions both the productivity and the average molecular weight increase linearly with increasing total pressure.

Oxidative carbonylation

Palladium-catalyzed oxidative carbonylations are an important class of reactions that allow the introduction of carbonyl groups to various organic nucleophiles or electrophiles in the presence of oxidizing agents.

One milestones for the palladium-catalyzed oxidative carbonylation is the well-known Wacker process, in which ethylene is oxidized to acetaldehyde using a combination of Pd(II) and Cu(II) salts.

Although it is not possible to speak of "carbonylation" for this process (it does not employ CO), the catalytic process of reoxidation of the catalyst is the basis of many oxidative carbonylation reactions.

In this process, the active Pd (II) species is regenerated from Pd(0) using $CuCl_2$, which in turn is regenerated by molecular oxygen.

This strategy has been adopted in many palladium-catalyzed oxidative carbonylations of alkenes for the synthesis of unsaturated esters or diesters (depending on the catalyst system and the reaction conditions, Scheme 14)

Scheme 14. Palladium-catalyzed oxidative carbonylation of olefins
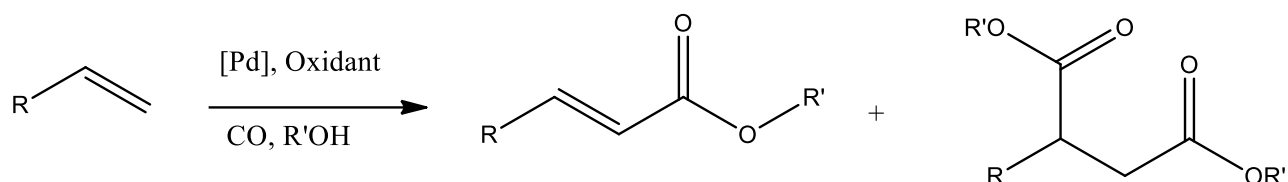
A typical example of a catalytic cycle for these reactions involves two key steps:
(i) palladium (II)-mediated oxidation of the organic substrate.
(ii) regeneration of the oxidized catalyst by molecular oxygen
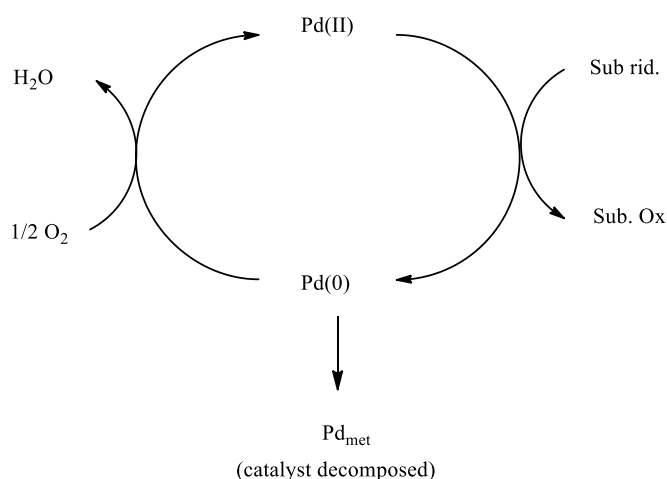
Scheme 15. General proposed mechanism for Palladium-catalyzed oxidative carbonylation

Although very attractive, the direct oxidation of Pd (0) to Pd (II) with molecular oxygen is not very easy to perform. First because the reoxidation of Pd (0) by O_2 is not a process that occurs very efficiently. There are also problems related to the safety of the reaction, because in some compositions CO/O_2 lead to form explosive mixtures.

For these reasons, most palladium-mediated oxidative carbonylation are not performed in the presence of oxygen, but stoichiometric oxidants (to the starting reagent) are used, such as benzoquinone, alkyl nitrite, or metal salts of copper or iron. In some cases, the possibility of employing mediators has been studied to exploit a redox chain with oxygen to regenerate Pd (II) species.

Independently, in the late 1960s, Fenton and Medema reported the first catalytic dialkoxycarbonylation of olefins [85-86], using a catalytic amount of palladium together with an equivalent amount of $CuCl_2$, with high CO pressures and high temperatures (120-150°C).

As demonstrated by Heck a few years later, at lower temperatures $CuCl_2$ is unable to reoxidize inactive Pd(0) species[87].

In 1972, Fenton and Steinwand reported the synthesis of succinates by oxidative carbonylation of olefins, employing an oxidizing system consisting of iron (III) chloride, copper (II) chloride, and oxygen, to reoxidize Pd(0)[88].

Using a catalytic system composed of $PdCl_2$, $CuCl_2$, $MgCl_2$ and NaOAc, Cometti and Chiusoli published interesting results on the oxidative carbonylation of styrene, for the synthesis of methylcinnamates[89].
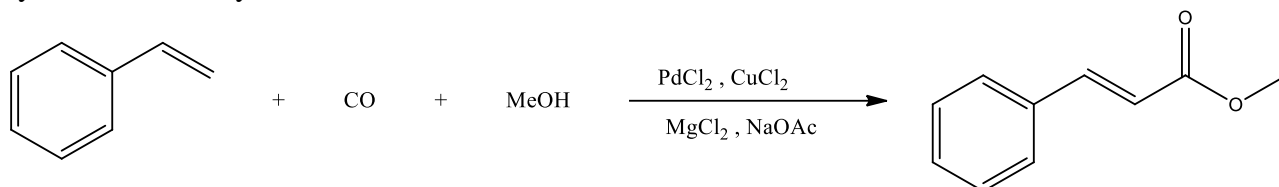
Scheme 16 Oxidative carbonylation of Styrene

From the oxidant aspect for catalyst regeneration, in addition to the use of high oxidation state salts, numerous works have focused on identifying alternative oxidative systems.

$$2\ CO\ +\ 2\ ROH\ +\ 1/2\ O_2 \xrightarrow{PdCl_2/CuCl_2}$$
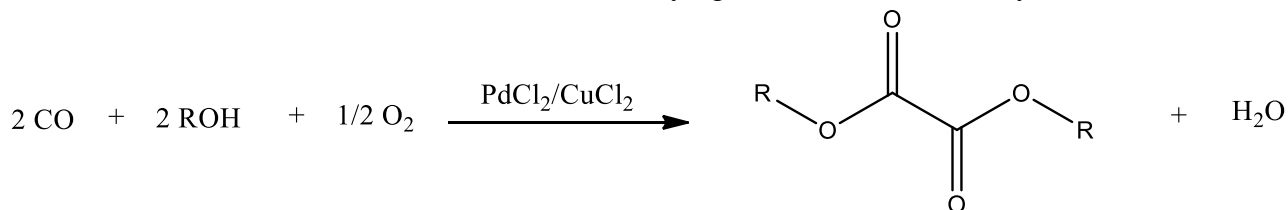
Scheme 17 Synthesis dialkyloxalate by oxidative carbonylation of alchols

For example, Fenton, in studying the oxidative carbonylation of ethanol for the synthesis of diethyloxalate, with a catalytic system like that employed in the Waker Process, observed that the use of oxygen was problematic. In fact, the use of oxygen leads to the formation of water, which can often lead to problems during the oxidation of organic substrates[90].

Initially, the addition of dehydrating agents, such as alkyl orthoformates, was shown to increase the productivity of the catalyst system. But this option is not readily available on an industrial scale due to increased process costs. A substantial improvement has been going to use butyl nitrite as an oxidizer[91].

But even in this case, butyl nitrite is not free from problems, mainly related to toxicity and safety measures required for its use.

From many studies, a valid alternative has been found in Benzoquinone (BQ). In fact, Consiglio, reporting the bis-alkoxycarbonylation of alkenes, observed that BQ can be used as an oxidizing agent, leading to higher conversions than in the case of using O_2 or alkyl nitrite. In addition, water formation is avoided with this system due to the conversion of BQ to H_2BQ.

In the literature it is possible to find numerous examples of application of the Pd(II)/BQ catalytic system applied in many reactions such as oxidative carbonylation of styrenes and alkynes, and oxidations of conjugated dienes, diols and terminal olefins[92-95].

Palladium-catalyzed oxidative carbonylations can also be employed to transform amines to ureas and oxamides, and the first example was proposed in 1966 by Tsuji and Iwamoto in 1966.

Given the enormous industrial and application interest in the products that can be obtained from this type of carbonylation, such as ureas, carbamates, and isocyanates, there are several studies aimed at determining the best catalytic system and operating conditions.

These efforts outlined two possibilities for carbonylation of nitrogen compounds: oxidative carbonylation of amines and reductive carbonylation of nitroderivatives.

Since then, it has been observed that a wide variety of transition metals involving Au, Co, Ni, Mn, Ru, and main group elements (such as S and Se) can be employed as catalysts [96-99]. Unfortunately, most of these catalytic systems provide a lower TurnOver Frequency (TOF) than palladium catalysts. Pd complexes have been the most effective of these catalyst systems, however, most of these methods require a large excess of promoter (NaI, KI, or I_2) [100-102].

Recently, Xia and co-workers reposted that oxidative carbonylations of amines to ureas can be catalyzed by palladium complexes with N-heterocyclic carbene ligands [103], showing that the palladium-carbene complex containing both an aniline and an N-heterocyclic carbene (NHC) ligand was the active species for this oxidative carbonylation of amines.
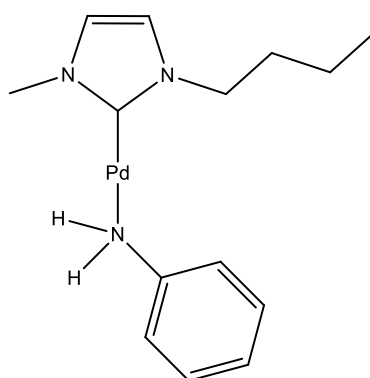
Schema 18. Pd-(NHC) Complex

Without the use of any promoter, this catalytic system allows for a range of ureas in discrete (46-99 %) yields.

Giannoccaro and co-workers reported the possibility of performing oxidative carbonylation on α,ϖ-Amino alcohols effectively at symmetric N,N-bis(hydroxyalkyl)uree or at Oxazolidinones using Pd(II) as catalytic systems and molecular oxygen as an oxidant[104-105].

$NH_2(CH_2)_nOH$ + CO + $\xrightarrow[O_2]{Pd(II), L/Et_3N/HI}$

L= dipy, PN,PPh$_3$,CH$_3$CN

$NH_2(CH_2)_nOH$ + CO + $\xrightarrow[O_2]{PdI_2, KI}$
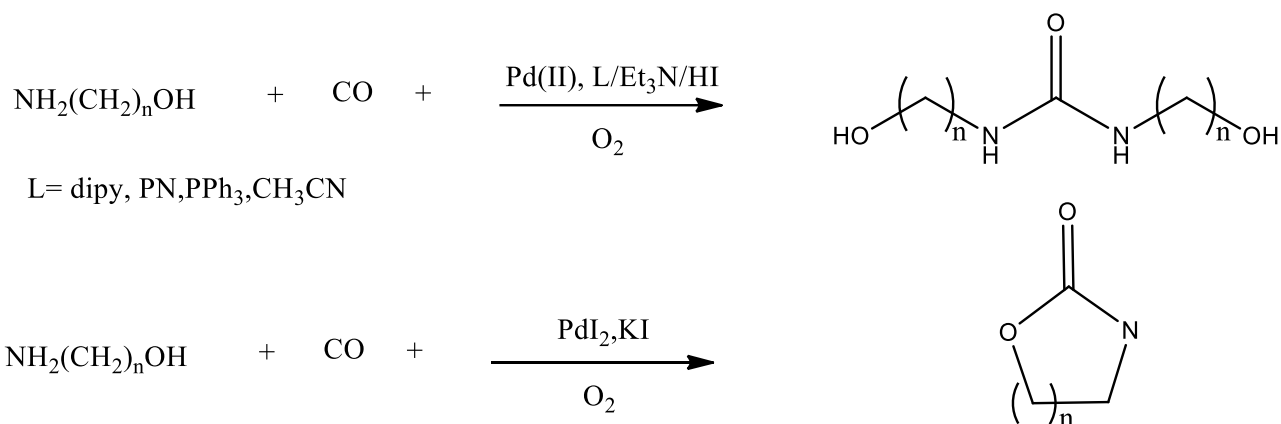
Excellent yields of the corresponding products were achieved with reactions condition relatively mild, at 100°C using an optimized mixture of CO/O$_2$/air (1:6:5; 60 atm total).

With similar systems, it is also possible to produce a range of organic carbonates by performing oxidative carbonylation of alcohols. For example, the system Pd(OAc)$_2$/BQ/Co(acac)$_3$/dmphen (2,9 dimethyl-1-10 Phenantroline), in combination with tetrabutylammonium bromide TBAB as a surfactant agent is an efficient catalyst for the oxidative carbonylation of phenol to diphenyl carbonate (DPC)[106]

+ CO + 1/2 O$_2$ $\xrightarrow{Pd(OAc)2/BQ/Co(acac)3/dmphen}$
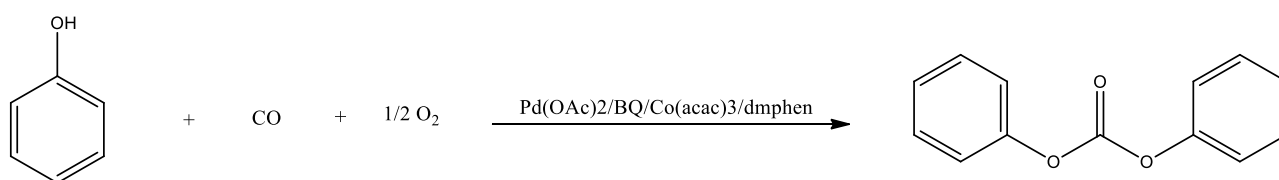
Schema 19 synthesis of DPC

To date, research on this type of reaction is still very active, both to outline new catalytic systems and ligand, more efficient and economical, and to find catalytic systems capable of using air, oxygen or hydrogen peroxide as *Green* oxidants.

Alkynes Carbonylation

The same catalysts used for carbonylations of alkenes can be conveniently used also for the carbonylation of alkynes as demonstrated by Reppe's work in 1938 for the industrial preparation of acrylic acid from acetylene[107]. This process foresaw drastic operating conditions (T>200°C, P$_{CO}$= 100 atm), and because of the cost of acetylene this process is now destined to die. In fact today, for the synthesis of acrylic acid, it is more economically viable to start from propylene [108].

A few years later, Alper reported the possibility of performing the hydroxycarbonylation of alkynes under mild conditions (90°C, 1 atm of CO), using a biphasic system with a phase transfer agent. Starting from Ni(CN)$_2$, in the presence of cetyltrimethylammonium bromide

(CTAB), it is possible to convert various alkynes into the corresponding unsaturated carboxylic acids.

In addition to alkynes, the same carbonylation can also be extended to allenes and alkinols to produce β,γ-unsaturated acids and unsaturated diacids.

The reactivity of alkinols in nickel-catalyzed carbonylation involves three steps: (i) carbonylation of the triple bond leading to the formation of an acid containing one part allyl alcohol; (ii) second carbonylation of the double bond to provide a hydroxydehyde; and (iii) a dehydration that gives the corresponding unsaturated diacid (Scheme 20).
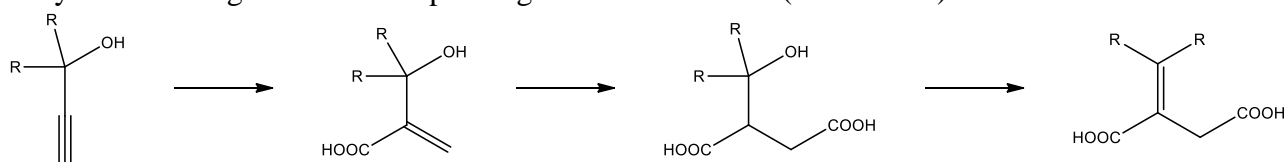
Scheme 20 Formation of a *β,γ*-unsaturated diacid from an alkynol

The most important aspect of the work focused on the carbonylation of alkenes is focused on the regio- and stereoselectivity of the catalytic systems. In this case, it has been observed that the phase transfer agent greatly influences the stereochemistry observed in the final product, in fact, E unsaturated diacids can be selectively produced in the presence of polyethylene glycol (PEG-400), while Z isomers can be obtained by employing quaternary ammonium salts [109]

Alper also demonstrated that the cationic Pd-hydride complex $[Pd(H)(H_2O)(PCy_3)_2][BF_4]$ is capable of catalyzing the hydroxycarbonylation of triple bonds scheme 21 [110].
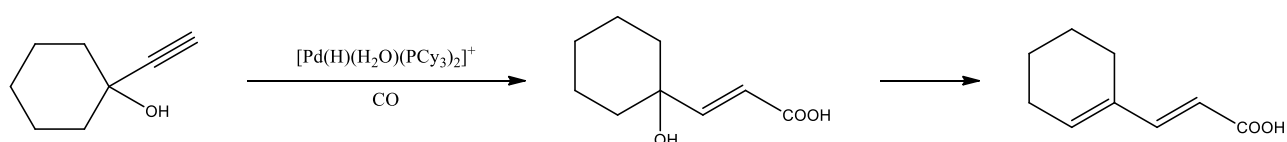
Scheme 21 Hydroxycarbonylation of alkynols followed by a dehydration step

Using the same catalytic system, he performed carbonylations on α-allene molecules to provide dienoic acids with the COOH group in the branched position (Schema 22) [111]
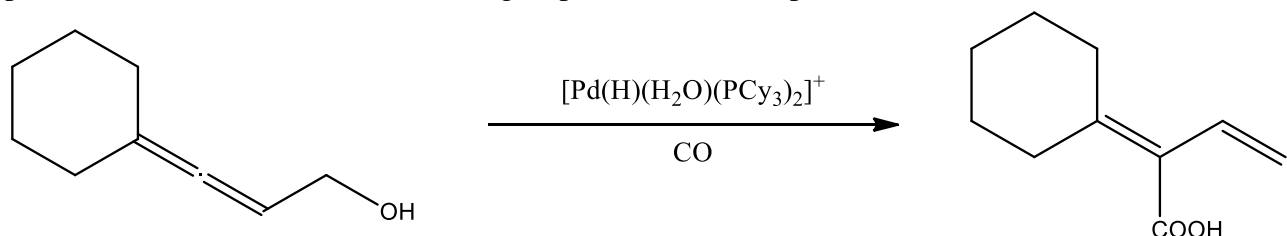
Scheme 22 Hydroxycarbonylation of allenes

In the late 1990s, reductive carbonylation of alkynes from the CO/H_2O pair performed with PdI_2/KI catalysts was reported, in which terminal alkynes were selectively converted to furan-2-(5H)-ones or anhydrides when a high CO_2 concentration is maintained (scheme 23).

Two CO molecules can be incorporated through a series of metal-catalyzed cascade reactions leading to cyclization along with the formation of an oxygen-carbon bond [112,113].
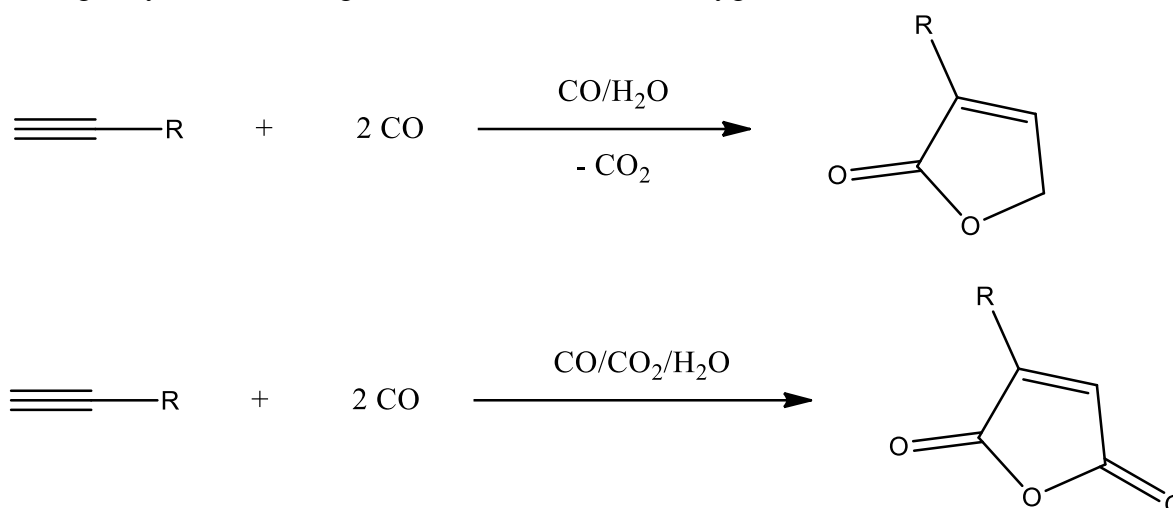
Scheme 23 Synthesis lactones and anhydrides by carbonylation of terminal alkynes

In this case, the use of KI as a promoter avoids the use of stoichiometric oxidizing agents such as $CuCl_2$ or BQ.

In 1995, Scrivanti reported the hydrocarboxylation of phenylacetylene using a catalyst of Pd(II) and 2-pyridyl phosphine as a ligand, obtaining selectivity higher than 98% towards 2-phenylpropenoic acid with a TOF of 3000 h^{-1}, working at relatively mild reaction conditions (P_{CO} 30 atm, T= 50°C). [114]

A few years later, Reetz and co-workers report, that with the same catalytic system it is possible to perform methoxy carbonylation of internal alkynes with TOFs greater than 7000 h^{-1}.
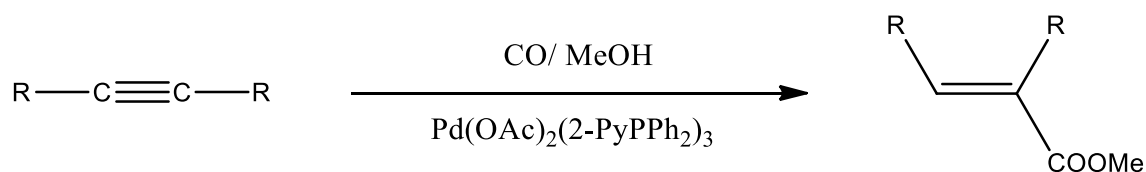
Scheme 24 Carbonylation internal alkynes

Chaudhari also reported the possibility of performing carbonylations of terminal or internal alkynes at low CO pressures (2 atm) by employing a Pd(OAc)$_2$-based catalyst with a ligand system consisting of picolinic acid (pyridine 2-carboxylic acid pyca) and PPh$_3$, achieving a selectivity of over 98% and TOF of 2500 h^{-1} toward branched products. In addition to performing an in-depth study of the effect of phosphines with electron attractor groups, he also reports the need to employ an acidic promoter such as p-TsOH. With this work, it is shown that the acid concentration is important for the formation of the active Pd-hydride species, increasing the reaction rate when employing an optimal p-TsOH/Pd ratio of 10:1.

It is also hypothesized that the synergistic effect of phosphines and pyca helps stabilize the intermediate Pd-hydride species, which are recognized as the active species for this type of catalysis[115].

Carbonylation of CX compounds

For bulk chemistry, the use of organic halides for the synthesis of benzoic acid derivatives, which are commonly obtained by oxidation of toluene, are not very attractive.

In fact, their use is limited to the synthesis of high-value fine chemistry products, obtained through the work of Heck, who during the mid-1970s, studied aryl and vinyl-X carbonylations (Heck's carbonylation) [116].

Based on his work, interest has focused on the development of catalytic systems capable of achieving high regio- and stereo- selectivity, while maintaining the efficient atom-economy that characterizes these reactions.

Despite the great potential, to date, none of the methods described in the literature has found application at the industrial level, and this is mainly due to the low activity of the catalysts (TOF below 20 h^{-1}) and the high cost of raw materials.

Most of the works that can be found in the literature report the study of this reaction on aryl halides, in particular bromides and iodides, and as complex catalysts based on Pd, Co and more rarely based on Ni [117] (scheme 25).

This reaction has also been studied for reagents pseudo-aryl halides, diazonium compounds[118], triflates or alkyl/aryl-sulfonates [119].
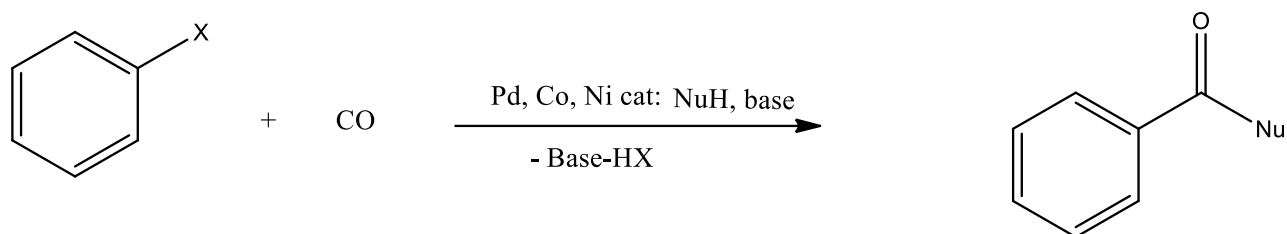
Nu= OH, OR, NR$_2$, halides

X= I, Br, Cl, N$_2$, CF$_3$SO$_3$, ecc

Scheme 25 Carbonylation aryl halides

By varying the reaction conditions, it is possible to synthesize a wide range of carboxylic acids [120] and derivatives, such as esters [121-122] amides [123] and carboxyamides, and acyl acid halides[124-126].

The reaction mechanism for these carbonylations has been studied in detail by considering the alkoxycarbonylation of iodo or bromine derived compounds (Scheme 26).
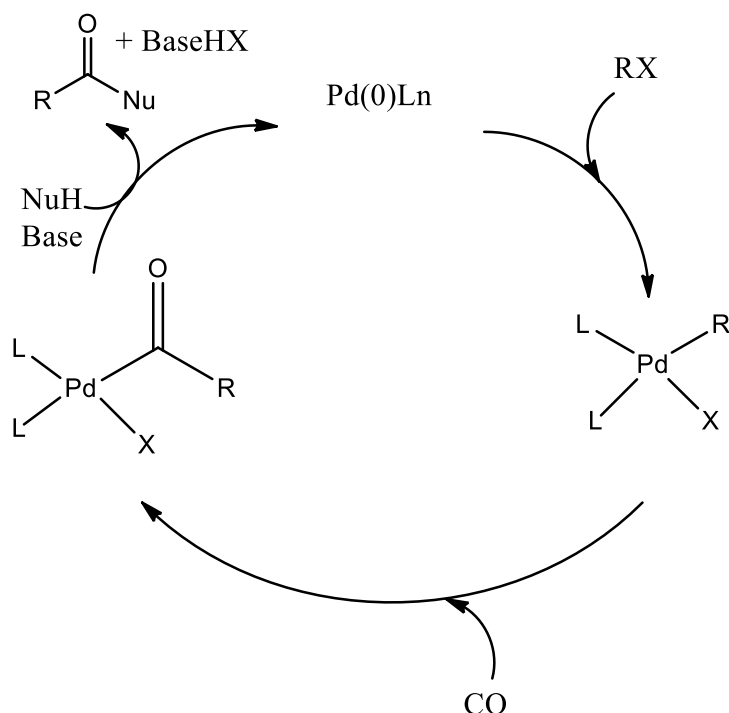
Scheme 26 Proposed reaction mechanism of carbonylation aryl halides

It has been observed from mechanistic studies that even when operating at high alcohol concentrations, the dominant Pd species is the one derived from the oxidative addition of the halide to the Pd(0) species.

The catalytic cycle most widely accepted by academia involves:
(1) The oxidative addition of the aryl halide to a Pd(0) species to form a Pd(II) intermediate.
(2) Coordination of carbon monoxide and migratory insertion of carbonyl to form a Pd(II)-acyl species
(3) Nucleophilic attack at the acyl complex resulting in the final product and regeneration of the Pd(0) species by reductive elimination.

Alkoxycarbonylations catalyzed by Pd complexes have also been applied to aromatic halides for the synthesis of polyesters/polyamides/polyesteramides (scheme 27) with very interesting technological properties (e.g., Kevlar) [127].

X= I, Br
Y= NH₂, OH
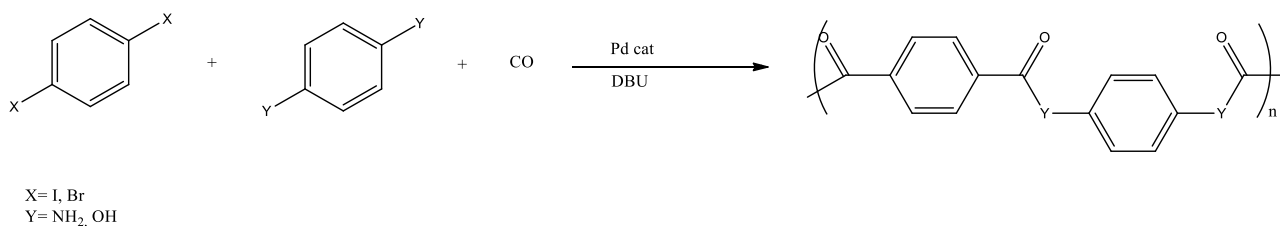
Scheme 27 Synthesis polyesters/polyamides by carbonylation reaction

To obtain a catalytic system, it is necessary to employ a base that sequesters the HX that is released from the nucleophile and aryl halide. Commonly, organic bases such as trialkyl amines (Et$_3$N) or sodium acetate (NaOAc) are used. For the synthesis of polymeric materials, however, these bases lead to low yields in the desired product. In this case, stronger bases such as 1,5-diazabicyclo(5.4.0)undec-7-ene (DBU) are required, which drastically increase the yield and reaction rate [128].It has been hypothesized that this base allows for greater solubility of the polymers in the reaction medium, allowing for a homogeneous reaction condition and thus higher performance.

From an industrial point of view, the use of aryl chlorides for carbonylation reactions is attractive due to the lower price of the starting material.

Unfortunately, the oxidative addition of aryl chlorides to the Pd(0) species is the limiting step in the reaction. For this reason, much effort has been expended in trying to overcome this limited reactivity of oxidative addition.

To make this reaction possible, it is possible to employ aryl halides with electron-attracting groups (such as CF$_3$) to labilize the C-Cl bond, or to employ electron-rich phosphine ligands to be able to increase the electron density on the metal and promote oxidative addition of the halide.

For example, Milstein describes the reactivity of complexes of palladium and electron-rich chelating diphosphine ligands such as 1,3-bis(diisopropylphosphino)propane (dippp)[130] (Figure 5).
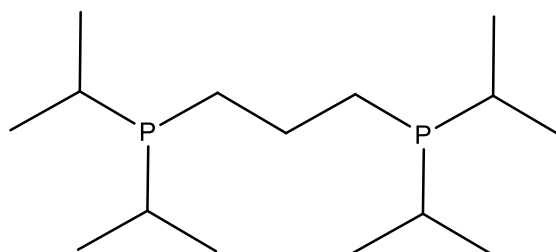
Figure 5. 1,3-bis(diisopropylphosphino)propane

Subsequently, Osbom and Alper, obtained appreciable results in the carbonylation of the CH$_2$Cl$_2$ and chlorobenzene using a complex of palladium and tricyclohexylphosphine (PCy$_3$) as ligand [131,132].

Than was observed that some N-heteroaromatic chlorides can be carbonylated much more easily because of the lower electronic density of the aromatic ring and a greater polarization of the C-Cl bond [133]
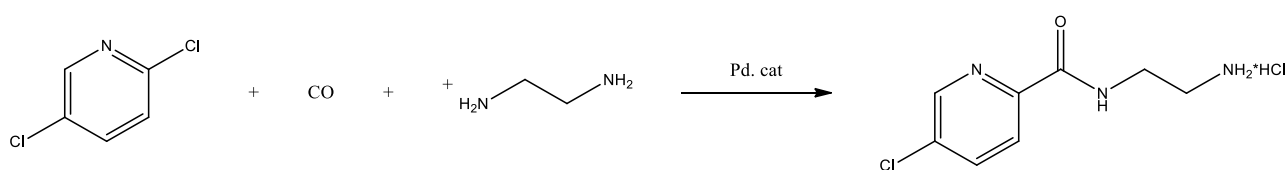
Scheme 28. Aminocarbonylation 2-chloropyridines

For amino-carbonylations it has been observed that the high CO pressure conditions can yield double carbonylation products (ketoamides). Depending on the catalyst system and reaction conditions, especially at high CO pressures, double carbonylation reactions to 1-keto carboxylic acid derivatives can be obtained (Scheme 29) [134-135]
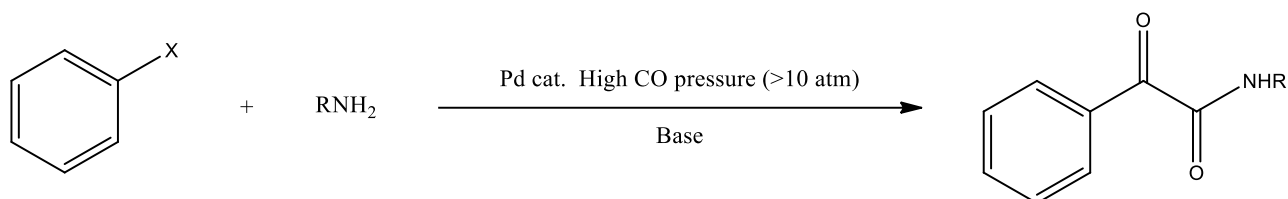
Scheme 29. Double carbonylation reaction

Mechanistic investigations have shown that the double carbonylation product does not occur by a double CO insertion in the Pd-C bond, but is obtained by a coupling reaction between two palladium-bonded acyl groups [136].

By means of this reaction, it is also possible to perform intermolecular carbonylations on reactants that contain both halide functionality and a group that can function as a nucleophile. For example [137] with the 2-aloanilines it is possible to obtain the intramolecular double carbonylation products (isatin, scheme 30)[138].
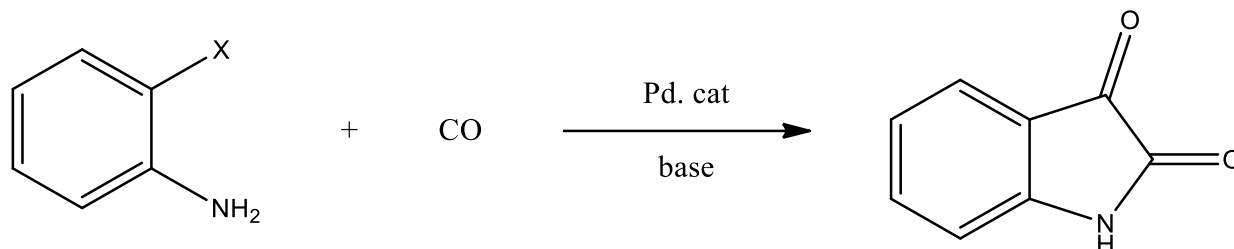
Schema 30 Synthesis isatin by carbonylation of 2-haloaniline

The synthetic power of this reaction is very broad, and with simple variation in the reactants a wide range of cyclic products can be obtained, for example from the carbonylation reaction of 2-halophenols, in the presence of alkynes have been used for the synthesis of derivatives of aurones [139] (scheme 31) and furanones [140].
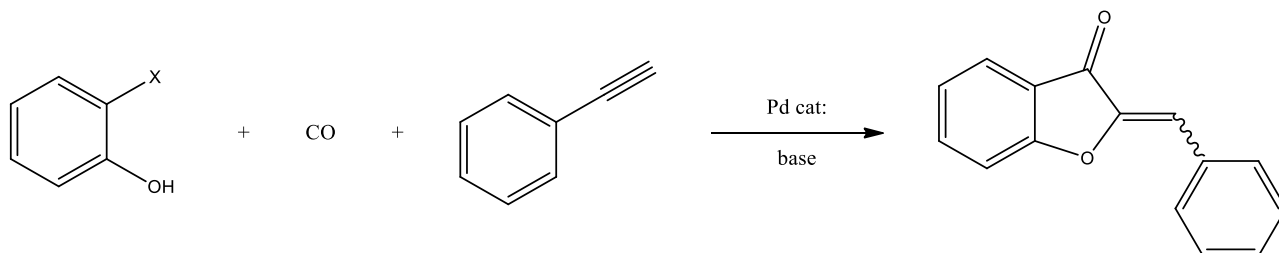
Scheme 31 Synthesis Aurones by cascade carbonylation reaction of 2-halophenols

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Chapter 1:
Alternative synthesis of isocyanates and amides of industrial interest

Isocyanates have applications in crucial industrial sectors, ranging from pharmaceutical chemistry to the synthesis of polymeric materials.

In addition to the classical synthesis involving the use of phosgene, isocyanates can be synthesized by safer catalytic syntheses consisting of carbonylation of nitrogen derivatives.

A study of the oxidative carbonylation of aniline is presented in this chapter. In particular, the new catalytic system composed of [PdCl$_2$(dppf)]/Fe(III)/O$_2$ has been studied, verifying the effect of the operating conditions on the selectivity and productivity of the reaction.

In this chapter, the synthesis of caprolactam from nitrobenzene is also discussed.

One of the most important amides for bulk chemistry is caprolactam, although it is used as a starting material for the synthesis of some drugs, such as meptazinal and laurocapram, it is mainly used for the synthesis of Nylon 6 by Ring-Opening Polymerization.

About 90% of the world production of caprolactam is based on the reaction between cyclohexanone and hydroxylamine which leads to the formation of the corresponding cyclohexanone oxime, which by Beckmann rearrangement gives caprolactam.

Here, a study is presented aimed at obtaining cyclohexanone oxime from the reduction of nitrobenzene in the presence of hydrogen and hydroxylamine hydrochloride ($NH_2OH \cdot HCl$), using heterogeneous Palladium-based catalyst.

In addition, the reactivity of hydroxylamine trifluoroacetate with aldehydes and ketones was studied for the synthesis of caprolactam and other amides of industrial interest.

1.1 *The [PdCl₂(dppf)]/FeCl₃/O₂ system efficiently catalyzes the oxidative carbonylation of aniline to phenyl isocyanate*

1.1.1 Introduction

In recent years, both academia and industry are focusing on the development of new processes that are more sustainable from an environmental and economic point of view. One of the most important challenges remains that of moving away from production processes linked to the use of phosgene. In fact, despite its extreme toxicity and dangerous nature, its use is increasingly limited by safety measures to be adopted during production, transport and storage processes. However, phosgene is still one of the most important building blocks for industrial synthesis. It is used for the large-scale production of carbonates, isocyanates, ureas and carbamates which are important starting materials for the synthesis of products for the pharmaceutical, agrochemical, pesticides [1-5], polymer industries [6] and so on. The extreme versatility and success of isocyanates, ureas and carbamates is also because they are chemically related compounds, indeed, in function of reaction condition they can be easily converted to each other. (Scheme 1.)
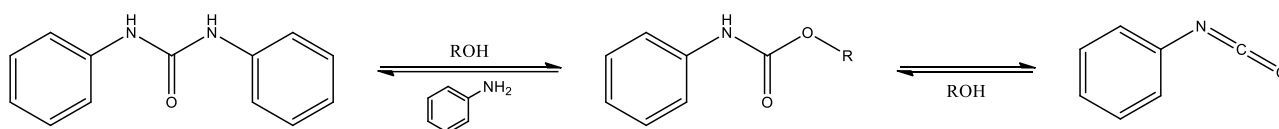
Scheme 1. Chemical conversion of DPU, Carbammate and isocyanate

Thus, it is not surprising that there is still an immense effort aimed at developing phosgene-free pathways for production of these starting materials [7-8]. Noteworthy is the Enichem process of 1983, which by oxidative carbonylation of methanol, catalyzed by copper salts, allows the production of dimethylcarbonate (DMC) while avoiding the use of phosgene [9-15]. For the synthesis of isocyanates, ureas and carbamate, on the other hand, several alternative routes to arylamine phosphenation have been explored and developed over time [16-19]. Among these, however, reductive carbonylation of nitro aryl compounds [20] and oxidative carbonylation arylamines, catalyzed transition metals appear to be the most promising [21-23]

Reductive Carbonylation of Nitroarenes

Reductive catalytic carbonylation represents the simplest possible route to form aromatic isocyanates. But the direct carbonylation of nitro compounds, due to the extreme reactivity of the isocyanates, presents problems related to the selectivity of the reaction.

$$ArNO_2 + 3CO \rightarrow ArNCO + 2CO_2$$
$$ArNO_2 + ROH + 3CO \rightarrow ArNHC(O)OR + 2CO_2$$
$$ArNO_2 + ArNH_2 + 3CO \rightarrow ArNHC(O)NHAr + 2CO_2$$
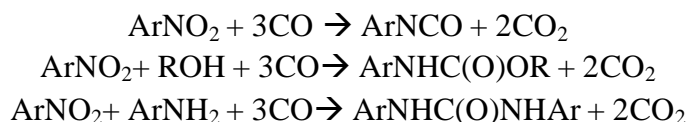
Scheme 2. Reductive carbonylation of nitroarenes to produce isocyanates, carbamates and ureas

Typically, carbonylation of nitroarenes is catalyzed by transition metals of groups 8-10, particularly Rh and Pd. The generally accepted mechanism involves the formation of a metal-cycle that is formed by the coordination of the nitro group on a metal-carbonyl species. This intermediate species, after decarboxylation, leaves a nitrous group bound to the metal[24]. Subsequently, after a further cycle of CO insertion and decarboxylation, the formation of an M-nitrene species is assumed, which due to a subsequent coordination of CO to the metal center, leads to the formation of isocyanate[25].
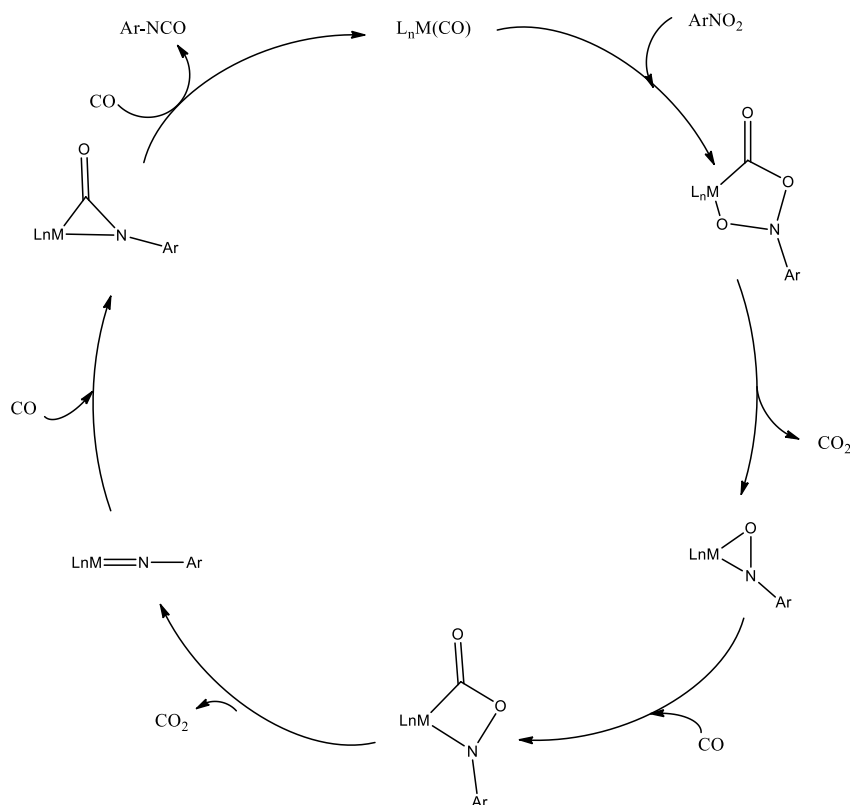
Scheme 3 Proposed Reaction Mechanism for reductive carbonylation nitroarenes

When the reaction is carried out in the presence of amine or alcohol, it is generally accepted that the corresponding carbamate or urea occurs by reaction between the isocyanate and the nucleophile, outside the coordination sphere of the metal.

However, with a Ru-based catalyst and Et_4NCl as the cocatalyst, a slightly different mechanism for the formation of carbamates has been described, in which the M-nitrene species plays a key role. It is hypothesized that an alkoxycarbonyl species can couple with the nitrene species, which after protonation leads to the formation of carbamate.

It has been observed that in some cases, reductive carbonylations require the use of some cocatalysts, such as some oxides or chlorides of Fe, Mo or V, which allow the reactions to be carried out at milder conditions with excellent yields. Although the effect of these promoters is not yet well defined, it has been hypothesized that their acidity may promote coordination of the nitro group towards the metal center favoring reduction or accelerate the insertion of carbon monoxide into the M=N bond of the nitrene species.

Generally, the ligands employed for reductive carbonylation are pyridines, quinolines, and phenanthrolines. The catalytic activity was observed to increase with donor electron substitutes. (2,9-dimethyl-1,10-phenanthroline < 1,10-phenanthroline (phen) < 3,4,7,8-tetramethyl-1,10-phenanthroline (TMphen).

A problem that could limit this synthesis for possible industrial applications is that reductive carbonylation can be applied only to nitroarenes, in fact aliphatic nitro compounds, due to their *aci* form, show a completely different reactivity, and moreover they are not as easily available as the corresponding aromatic compounds.

Nitromethane   *aci*-Nitromethane
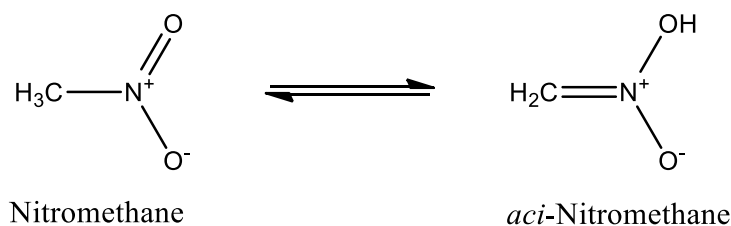
Fig 1 Resonance of Nitromethane

In addition, the synthesis of diisocyanates like toluene diisocianate (TDI) and 4-4' diphenylmethane diisocyanate (MDI), obtained by carbonylation of dinitroarenes requires very long reaction times, since it is a consecutive carbonylation reaction and the second carbonylation is slower than the first.

Oxidative carbonylation of Amines

The drawback of reductive carbonylation of nitroarenes can be overcome by oxidative carbonylation of amines, which can be obtained by simple reduction of the corresponding nitroderivates. (scheme 4)

$$RNH_2 + CO + \tfrac{1}{2}\,O_2 + ROH \;\rightarrow\; RNHCOOR' + H_2O$$

$$2RNH_2 + CO + \tfrac{1}{2}\,O_2 \;\rightarrow\; RNHC(O)NHR + H_2O$$
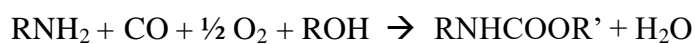
Scheme 4 oxidative carbonylation of aromatic amines to produce carbamates and ureas

The problem with this type of carbonylation is related to the use of CO/O_2 mixtures, which requires careful safety measures to avoid explosive mixtures.
Although there are many examples of catalysts based on Co [26], Ni[27],Mn[28],Rh[29], and Ru, the most promising are homogeneous catalysts based on Pd (II).
The reaction mechanism is complicated and there are still some doubts about some steps, but it is commonly accepted that the oxidative carbonylation of amines is obtained towards Pd(II) species, which are reduced to inactive Pd(0) species, and that is why the catalysis needs the addition of an oxidizing agent to obtain the active species again.
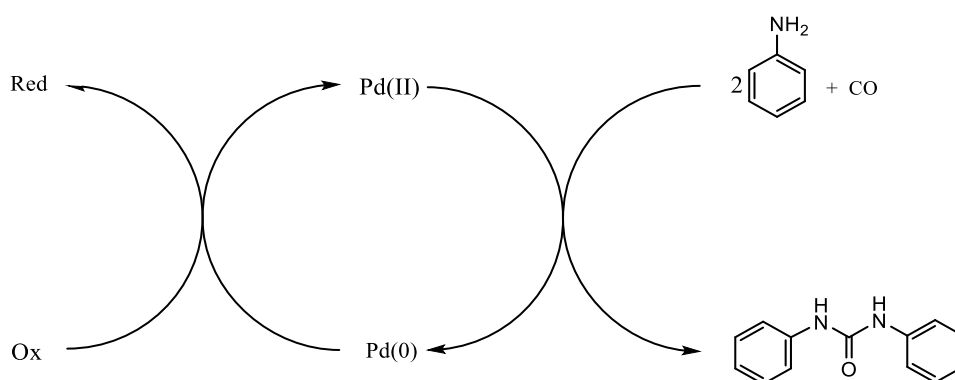
Scheme 5 General reaction mechanism for oxidative carbonylation of aniline

Of all the oxidants that can be effectively used, molecular oxygen appears to be the most attractive from a green point of view, indeed for this type of carbonylation the only by-product is the reduced form of oxidant (H_2O). However, the reoxidation of Pd(0) complexes with oxygen is almost always so slow that competitive decomposition to inactive Pd metal is favored. It is plausible that Pd-metal nanoparticles are formed at first, but they easily agglomerate into macroparticles[5], which precipitate as palladium black at the end of the reaction. The formation of a Pd-black is considered one of the most plausible causes of the loss of activity, as it is not readily reoxidized under the reaction conditions. Thus, to circumvent this problem, an interesting method is undoubtedly to promote the most rapid reoxidation of Pd(0) complexes (or Pd metal nanoparticles) to avoid the precipitation of Pd black. It has been observed that the addition of iodide ions is able to avoid deactivation of the catalyst due to iodine-iodide redox[16]. Examples of oxidative carbonylation performed in the presence of phosphine, nitrogen or carbene ligands can be found in the literature, but they do not seem to bring substantial differences in the selectivity of the reaction, compared to the PdI_2 and KI system.
It has also been observed that several metal cocatalysts working as electron transfer mediators (ETMs) between Pd(II) and oxygen as the terminal oxidizing agent, are able to prevent the formation of inactive Pd(0) species. Interesting results are obtained with pairs

using $PdCl_2$ (or $Pd(OAc)_2$) together with a metal salt, e.g. Cu(II), Cu(I), Fe(II), Fe(III), Ag(I) salts [30-33]

For example, recently, it has been reported that the $Pd(OAc)_2/FeCl_3/O_2$ system efficiently catalyzes the oxidative carbonylation of aniline to bring 1,3-diphenylurea (DPU) with a selectivity of 88% and TOF of 1667 h^{-1}[34].

In the present chapter, is proposed a more efficient catalytic system for such a reaction based on Pd(II) diphosphine complexes. In particular, the multistep electron transfer system $[PdCl_2(dppf)]/FeCl_3/O_2$ used together with LiBr as a promoter agent leads to the best results in terms of TOF and selectivity to phenylisocyanate (4500 h^{-1}, Sel. 90%). In the absence of O_2, the system catalyzes the formation of 1,3-diphenylurea with 100% selectivity.

1.1.2. Results and discussion

1.1.2.1 Preliminary results

The palladium catalyzed oxidative carbonylation of aniline has been preliminary carried out using both $PdCl_2$ and $Pd(OAc)_2$ as catalysts coupled with the co-catalysts listed in Table 1. All such experiments have been carried out in absence of oxygen to find the redox couple which leads to the highest catalytic activity. As a matter of fact, by using the couple $PdCl_2/FeCl_3$, the 1,3-diphenylurea (DPU) has obtained with a TOF of 40 h^{-1} and 85 % selectivity (at 393 K, Table 1 entry 10) (according to [34]).
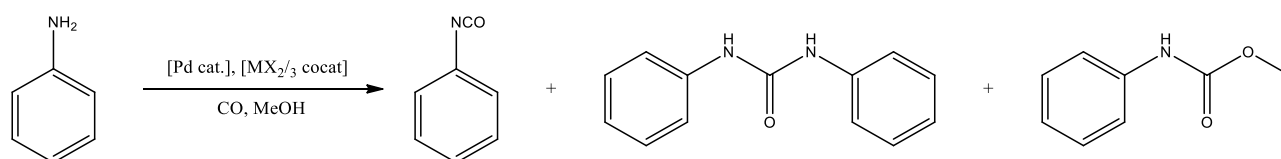
At the end of each reaction, however, it has been found palladium black suggesting that the rate of the Pd(0) re-oxidation step is not fast enough compared to Pd metal agglomeration (see introduction).
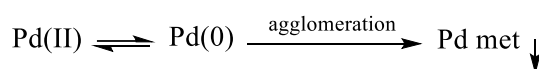
Therefore, with the aim to increase the performance of the $PdCl_2/FeCl_3$ system, avoiding Pd metal formation [30], was carried out some reaction by substituting the $PdCl_2$ salt with a preformed Pd(II)-diphosphine complex.

Table 1 Catalytic activity of Pd(II)-based redox couples in the oxidative carbonylation of aniline.

entry	T	Catalyst	TOF	selectivity		
	K		h^{-1}	PI[a]	DPU[b]	PMC[c]
				%	%	%
1	373	$PdCl_2/CuCl_2$	9	2	90	8
2	373	$PdCl_2/FeCl_3$	26	8	70	22
3	373	$Pd(AcO)_2/FeCl_3$	22	2	78	20
4	373	$PdCl_2/NiCl_2$	12	4	75	21
5	373	$PdCl_2/CeBr_3$	5	18	50	32
6	373	$PdCl_2/Mn(AcO)_2$	10	2	80	18
7	373	$Pd(AcO)_2/Co(AcO)_2$	7	8	85	7
8	373	$Pd(AcO)_2/NiCl_2$	11	/	88	12
9	393	$PdCl_2/CuCl_2$	16	/	95	5
10	393	$PdCl_2/FeCl_3$	40	5	85	10
11	393	$Pd(AcO)_2/FeCl_3$	38	10	80	10
12	393	$PdCl_2/NiCl_2$	23	2	86	12
13	393	$PdCl_2/CeBr_3$	8	11	63	26
14	393	$PdCl_2/Mn(AcO)_2$	12	/	82	18
15	393	$Pd(AcO)_2/Co(AcO)_2$	15	3	90	7
16	393	$Pd(AcO)_2/NiCl_2$	22	/	88	12

Run conditions: $PdX_2 = 2.725\ 10^{-3}$ mmoli (X=Cl, OAc), co-catalyst/Pd(II) = 200/1 (mol/mol), CO = 5.0 MPa, Aniline = 1.50 mL (1.530 g, 16.43 mmol), NaI = 81.70 mg (NaI/Pd = 200/1), CH_3OH = 18.5 mL, time = 3 h.
[a] PI = Phenylisocianate, [b] DPU = 1,3-diphenylurea, [c] PMC = N-phenyl-methylcarbamate

1.1.2.2 Influence of chelating diphosphine ligands on the catalytic activity of the Pd(II)/FeCl₃ system

All the complexes tested (see Table 2) efficiently catalyze the reaction in the presence of $FeCl_3$, leading to a TOF higher than by using $PdCl_2$ as precursor (entry 1). Some experiments (entries 4-8) lead to 1,3-diphenylurea (DPU) with 100% of selectivity, greatly reducing or completely avoiding the deposition of Pd black (see notes in Table2). According to similar carbonylation reactions [35], also in the present case the catalytic activity increases with the bite angle of the P-P ligands (dppm<dppe<dppp<dppb<dppf) reaching the highest value with the [PdCl₂(dppf)] complex (at 393 K: TOF = 180 h^{-1}, entry 7).

Table 2. Influence of different Pd(II)-catalyst precursors on the activity.

entry	Pd-Catalyst	TOF	selectivity			Notes:
		h^{-1}	PI	DPU	PMC	
			%	%	%	
1	$PdCl_2$	40	5	85	10	Pd black
2	$[PdCl_2(PPh_3)_2]$	60	/	95	5	traces of Pd black
3	$[PdCl_2(dppm)]$	65	/	96	4	traces of Pd black
4	$[PdCl_2(dppe)]$	71	/	100	/	Pd black: not observed
5	$[PdCl_2(dppp)]$	90	/	100	/	Pd black: not observed
6	$[PdCl_2(dppb)]$	120	/	100	/	Pd black: not observed
7	$[PdCl_2(dppf)]$	180	/	100	/	Pd black: not observed

Run conditions: $[PdCl_2(P-P)] = 2.725\ 10^{-3}$ mmoli (P-P = diphosphine ligands), $FeCl_3/Pd(II)$ = 200/1 (mol/mol), CO = 5.0 MPa, T = 393 K, Aniline = 1.50 mL (1.530 g, 16.43 mmol), CH_3OH = 18.5 mL, time = 3 h.

Table 3 shows the influence on the TOF of the $FeCl_3$/[$PdCl_2$(dppf)] molar ratios, temperature, and pressure of the [$PdCl_2$(dppf)]/$FeCl_3$ catalytic system. The TOF linearly increases by increasing the $FeCl_3$ concentration (entries 1-5), raising to a plateau for Fe(III)/Pd(II) molar ratios higher than 1000/1 (637 h^{-1}, entry 5). By increasing the CO pressure (entries 5-9) the TOF linearly increases (up to 757 h^{-1}, at 6.0 MPa (entry 5), whereas by increasing the temperature (entries 5, 10-12) it reaches a maximum value of 637 h^{-1} at 393 K (at 5.0 MPa, entry 5).

Table 3. influence on the TOF of the $FeCl_3$/Pd molar ratios, temperature, and pressure of the catalytic system.

entry n°	T K	CO MPa	$FeCl_3$/Pd mol/mol	TON h^{-1}
1	393	5.0	100	95
2	393	5.0	200	180
3	393	5.0	500	480
4	393	5.0	800	596
5	393	5.0	1200	637
6	393	2.0	1200	225
7	393	3.0	1200	350
8	393	4.0	1200	498
9	393	6.0	1200	757
10	373	5.0	1200	320
11	383	5.0	1200	455
12	415	5.0	1200	233

Run conditions: [$PdCl_2$(dppf)] = 2.725 10^{-3} mmoli, Aniline = 1.50 mL (1.530 g, 16.43 mmol), CH_3OH = 18.5 mL, time = 1 h.

1.1.2.3 Influence of promoters

The addition of a promoter strongly influences the catalytic activity of the [$PdCl_2$(dppf)]/$FeCl_3$ system. As an example, the Figure 1 shows that LiBr and TBAB have a very different influence which is also function of the amount of promoter added. Both the salts lead to a plateau value for a specific promoter/Pd molar ratio (in any case > 200/1).
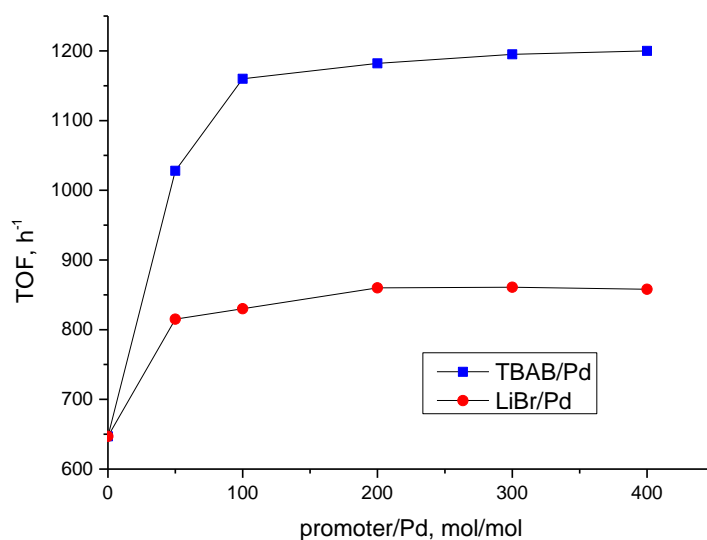
Fig.1 Influence of Promoter/Pd ration on TOF.

On the bases of the data reported in Figure 1 we tested the influence on TOF of several salts using 200/1 constant promoter/Pd molar ratio.

The Table 4 shows that the LiBr appears as the most efficient as the TOF increases from 637 h^{-1} (without promoter, entry 1) up to 1177 h^{-1} with LiBr (entry 5). All the experiments reported leads to the formation of 1, 3- diphenylurea with a 100% of selectivity.

Table 4. Influence of the promoter on the TOF

entry	promoter	TOF h^{-1}
1	/	637
2	NaI	695
3	KI	700
4	TBAI	733
5	LiI	815
6	LiBr	1177
7	TBAB	882
8	LiCl	760
9	TBAC	807

Run conditions: [PdCl$_2$(dppf)] = 2.725 10^{-3} mmoli, FeCl$_3$/Pd(II) = 1200/1 (mol/mol), CO = 5.0 MPa, T = 393 K, Aniline = 1.50 mL (1.530 g, 16.43 mmol), promoter/Pd = 200/1, CH$_3$OH= 18.5 mL, time = 1 h.

Furthermore, the results suggest that both the nature of the anion and the cation have an influence on the TOF: For instance, the TOF increase in the order $Cl^-<I^-<Br^-$ (entries 8, 5 and 6, respectively for Li salts) and $Li^+>TBA^+>K^+>Na^+$ (entries 5, 4, 3, and 2 respectively for the iodide salts). It is plausible that the anionic influence is relate to the in situ formation of Pd - active species containing ligands weakly coordinating than the chloride. On the other hand, the influence played by the nature of cations could be related to its possible role as protective stabilizers for the Pd metal nanoparticles as reported in literature [36]. In fact, it is widely reported that Li and TBA salts form layers of anions and counter-cations on the surface of metal nanoparticles (see Figure 2), generating in such a way a combination of electrostatic and steric effects which preserve they from the agglomeration and from the irreversible precipitation of Pd black[37].
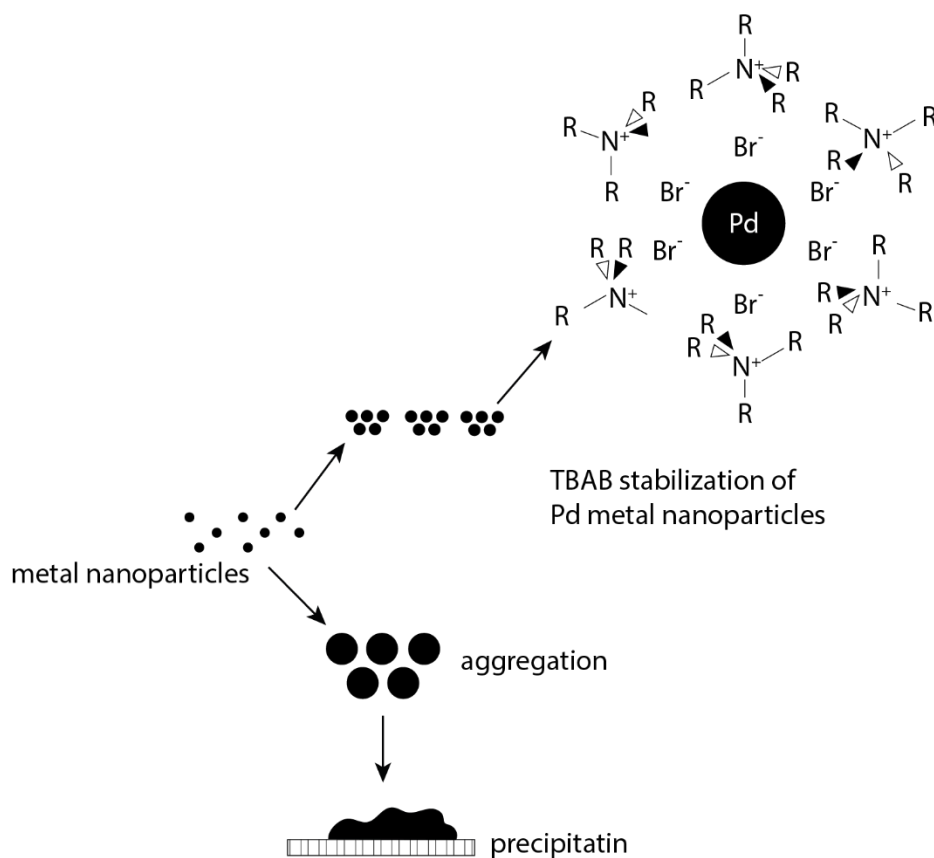
Fig.2 Pattern of nucleation or stabilization of metal nanoparticle

1.1.2.4. Influence of oxygen as terminal oxidant

The carbonylation of aniline has been carried out by using the catalytic system $[PdCl_2(dppf)]/FeCl_3/LiBr = 1/1200/200$ (mol/mol) in the presence of O_2, as terminal oxidating agent.
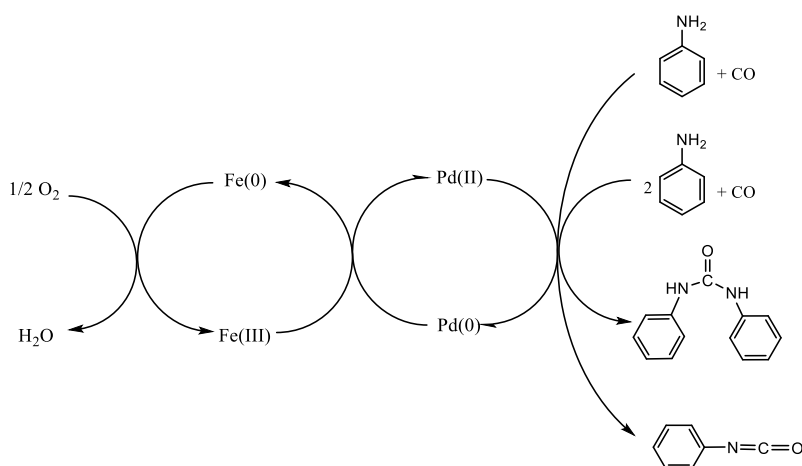
Fig.3 proposed mechanism for oxidative carbonylation of aniline with [Pd(Cl)$_2$dppf]/FeCl$_3$/O$_2$

The Table 5 shows that the TOF linearly increases by increasing the oxygen pressure and reaches the value of 4500 h^{-1} at partial pressure of 0.4 MPa, which is a TOF value four times higher than the value reported in literature for the system [PdI$_2$]/FeCl$_3$/O$_2$ [34].

Under such reaction conditions, however, the phenylisocyanate (PI) was the main product and the selectivity towards PI increases with the increase of oxygen pressure. In the experiments reported the selectivity raises the value of 90% at O$_2$ = 0.4 MPa, which is the safety limit chosen to avoid forming explosive mixtures.

Table 5

O$_2$ MPa	TOF h^{-1}	DPU mol %	PIC mol %
0	1400	100	0
0.05	1900	90	10
0.10	2150	70	30
0.20	3120	45	55
0.25	3500	35	65
0.30	3930	22	78
0.40	4500	10	90

Run conditions: [PdCl$_2$(dppf)] = 2.725 10^{-3} mmoli, FeCl$_3$/Pd(II) = 1200/1 (mol/mol), CO = 5.0 MPa, T = 393 K, Aniline = 1.50 mL (1.530 g, 16.43 mmol), promoter/Pd = 200/1), CH$_3$OH= 18.5 mL, time = 1 h.

1.1.3 Conclusions

The aniline carbonylation has been efficiently carried out by using the catalytic system formed by [PdCl$_2$(dppf)]/FeCl$_3$/LiBr = 1/1200/200 (mol/mol) which results more active than the catalytic systems reported in the literature. In particular, as can be seen by comparing entry 1 of Table 5 and entry 2 of Table 6, at 393 K, 1,3-diphenylurea was selectively formed (100%) with a TOF of 1400 h^{-1}, without the addition of O$_2$ as an external oxidant.

Moreover, with the addition of oxygen, the system achieves a TOF value four times higher than that reported in the literature for the [PdI$_2$]/FeCl$_3$/O$_2$ system (4500 h^{-1} vs 1120 h^{-1} with 0.4 MPa of partial pressure of O$_2$) with a selectivity that reaches 90% towards the formation of phenyl isocyanate. It is plausible to hypothesize that an increase in the oxygen concentration in the reaction environment could further increase the selectivity toward PI, but this has not been studied to avoid reaching explosive CO/O$_2$ mixtures.

Table 6

entry	Catalyst	CO/O$_2$ MPa	TOF h^{-1}	selectivity		
				PI %	DPU %	PMC %
1	PdCl$_2$/CuCl$_2$/NaI [30]	4.5/0.5	96	traces	5	95
2	PdI$_2$/FeCl$_3$ [34]	4.5/0.5	1120	traces	88	12
5	[PdCl$_2$(dppf)]/FeCl$_3$/LiBr	4.6/0.4	4500	90	10	

1.1.4 Experimental

Reagents

Aniline, palladium(ii) chloride, palladium(ii) acetate, bis(triphenylphosphine)palladium(ii) dichloride, 1,1-bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe), 1,3-bis(diphenylphosphino)propane (dppp), 1,4-bis(triphenylphosphine)butane (dppb), 1,1'-bis(diphenylphosphino)ferrocene (dppf), sodium iodide, potassium iodide, lithium iodide, lithium bromide, lithium chloride, copper(ii) chloride, iron(iii) chloride, cerium(iii) bromide, manganese(ii) acetate, cobalt(ii) acetate, nickel (ii) chloride hexahydrate, tetrabutylammonium iodide (TBAI), tetrabutylammonium bromide (TBAB), tetrabutylammonium chloride (TBAC) were all Aldrich products and employed without any purification and all solvent are ACS reagent supplied by Aldrich.
Carbon monoxide and Oxygen were supplied by SIAD Company Italy('research grade', purity >99.9%)

Equipment and characterization

The catalyst precursor was weighted on a Sartorious Micro balance (precision 0.001 mg). High-performance liquid chromatography (HPLC) analyses were carried out by a Perkin Elmer 250 equipped with a diode array LC-235 detector and a Lichrosphere 100 (RP-18, 5 μm) column employing water acetonitrile mixtures as eluent, the concentrations of the reagent and products were calculated by calibration with standard solution.

Gas-chromatographic (GC) analysis was performed on a Hewlett Packard Model 5890, Series II chromatograph fitted with a HP1, 30 m × 0.35 mm × 0.53 μm column (detector: FID; carrier gas: N_2, 0.2 ml/min; oven: 45 °C (3 min) to 250 °C at 15 °C/min).

GC/MS analyses were performed on a MS Agilent apparatus 5975C Model, interfaced with an Agilent chromatograph 7890 A Model equipped with a HP1 column (30 m × 0.25 mm × 0.25 μm, oven: 45 °C (3 min) to 250 °C at 15 °C/min).

Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Magna 750 instrument in KBr powder. All the NMR spectra were recorded on a Brucker Avance 400 II spectrometer.

Catalyst Synthesis

All complex was prepared as reported in literature [38] with slight variations. The synthesis of [PdCl$_2$(dppf)] is shown as an example: 0.3 mmol of PdCl$_2$ is placed in a mixture of 5 mL toluene and 1 mL acetonitrile and refluxed into a two-neck flask. Once the palladium salt is dissolved, 0.3 mmol of dppf in toluene was added dropwise. After 1 h of reaction, the resulting mixture was cooled to room temperature. The resulting solid was filtered with the

minimum amount of cold toluene, and left to dry overnight (yields 60-90%). All complexes were characterized by FT-IR and NMR.

Catalytic reactions

The catalysis was carried out in a batch reactor of *ca*. 100 mL provided with a magnetic stirrer. In a typical experiment, $2.7\ 10^{-3}$ mmol of Pd(II) complex, together with 16.43 mmol of aniline (1.5 mL), were added to methanol (20 mL total volume) in a glass tube to prevent any contamination due to the internal walls of the reactor. To avoid catalyst deactivation the reactor was carefully flushed with CO at room temperature with stirring and then pressurized with 0.5 MPa of CO and heated up to 393 K in *ca*. 10 min without stirring. The pressure was then adjusted to the desired value (typically 5.0 MPa total pressure) and, while stirring, maintained constant throughout the experiment. At the end of each experiment the autoclave was quickly cooled and carefully depressurized.

The reaction products were detected and quantified by the HPLC and GC-MS analysis.

1.1.5 References

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1.2 Pd/C Catalyzed selective hydrogenation of nitrobenzene to cyclohexanone oxime in the presence of NH₂OH·HCl: Influence of the operative variables and insights on the reaction mechanism

1.2.1 Introduction

Nitro-derivates reductions are important and useful reactions for several industrial processes [1-4]. Among them, nitrobenzene hydrogenation to aniline is one of the most important reaction, since the latter is used as an intermediate in many fields of application, for instance, in the production of isocyanates, rubber processing chemicals, dyes and pigments, agricultural chemicals and pharmaceuticals [1]. Industrial hydrogenation methods employ several types of catalysts [5] But typical catalyst used for this reduction are based on Pt, Ni, Pd [6].

The reduction of the nitro-group involves several steps following the well-known Haber reaction path, where nitro-group is reduced step by step to the amine together with the formation of condensation products between nitrosobenzene and phenyl hydroxyl amine (see Scheme 1) [7].
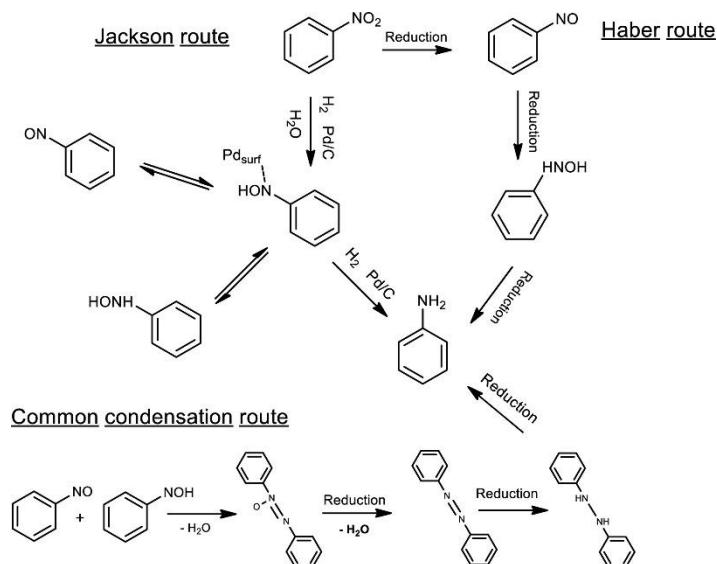
Scheme 1. Haber and Jackson Nitrobenzene reduction/hydrogenation mechanism.

Recently, for the catalytic hydrogenation mechanism, it has been suggested a similar path, but the formation of nitrosobenzene has been related to a surface equilibrium phenyl hydroxylamine/nitrosobenzene rather than the formation of an actual reaction intermediate (see Scheme 1 Jackson route). Condensation of nitrosobenzene and phenyl hydroxyl amine occurs in the same way of the Haber scheme [8,9]. This has been clearly pointed out by the study of Jackson and co-workers on the kinetics of the nitrosobenzene hydrogenation, they demonstrated indeed a different reaction path for nitrosobenzene hydrogenation with respect to that of nitrobenzene [8].

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The complexity of the reaction scheme of nitrocompounds reduction allows to take into consideration (see Scheme 1) the possibility of designing catalyst or processes that gives, under experimental conditions, quite selectively a particular intermediate [9]. For instance, formation of azo-compounds can be achieved by combining the partial reduction of nitrobenzene condensation and dehydration in basic media [16].

The further reduction of the aromatic amines and of aniline, is relatively less studied compared to the hydrogenation of the nitro-aromatic compounds [21-33]. Hydrogenation of aniline to the cyclohexylamine, particularly, has been investigated from long time, and the best catalytic system is mostly Ru supported catalysts at quite high temperature and pressure (373−473 K, 1−10 MPa) [22-26]. Even though, less studied than that of nitrobenzene reduction, the mechanism of this reaction has been already proposed by Greenfield in the early sixty. Taking into consideration that in the reduction reaction of aniline to cyclohexylamine, the corresponding imine is a key intermediate (Scheme 2), it has been hypothesized that due to its high reactivity, it can undergo easy condensation reactions with all nucleophiles present in solution [21]. The reactivity of such an intermediate drive the selectivity toward the formation of cyclohexyl amine, di-cyclohexyl amine, and, in the presence of water, to cyclohexanone and cyclohexanol [21,28-31]. The highly reactive imine intermediate has been never isolated in the hydrogenation medium, however, the final products observed strongly supports the goodness of such a hypothesis .
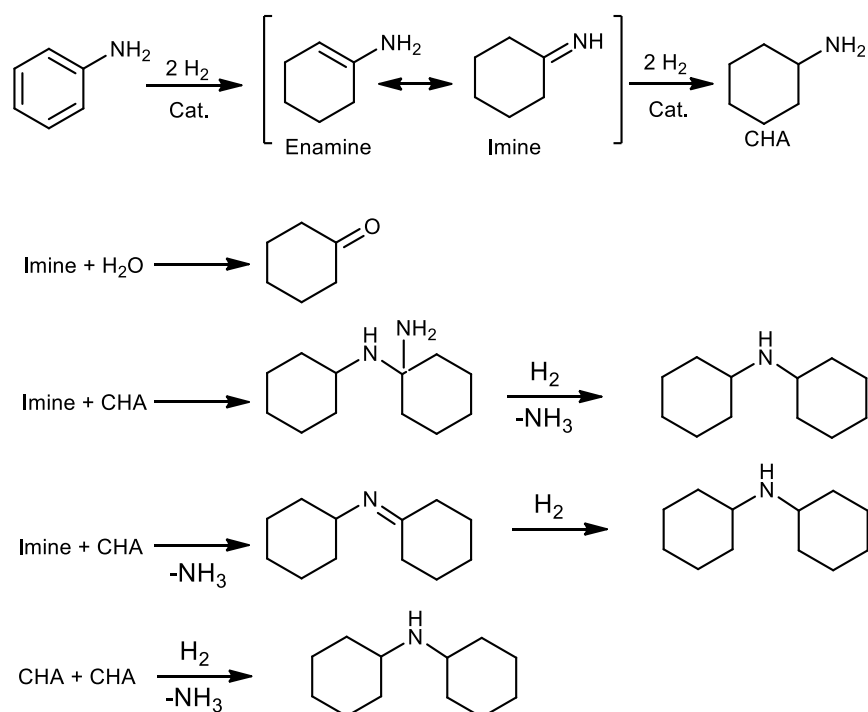
Scheme 2. Reaction mechanism of aniline hydrogenation suggested by Greenfield [21].

This mechanism suggests of using the reactivity of the imine intermediate towards nucleophiles; for instance, the substitution with water gives cyclohexanone, a fundamental intermediate, in the production of nylon-6 and in several fine chemistry synthesis [18,31-33]. In fact, recently, appears some patents claiming a direct route from nitrobenzene to cyclohexanone oxime by hydrogenation and direct oximation [34,35]. Corma and coworkers

have carried out the hydrogenation of nitrobenzene to cyclohexanone oxime in the presence of hydroxyl amine hydrochloride, in multiphase systems, catalyzed by Pd and Au supported catalysts [35,36]. These authors have claimed that the presence of the two types of catalyst allows high selectivity in the cyclohexanone oxime. The highest selectivity towards the oxime is achieved in the presence of a physical mixture of the two catalysts with respect to the single catalytic system Pd/C or Au/C, moreover, the latter leads to aniline only. Finally, the bimetallic Pd-Au/C catalyst is less selective than the physical mixture of the two catalysts, as well [36]. The mechanism suggested (see Scheme 3) is based on the hypothesis that cyclohexyl amine is in dehydrogenative equilibrium with the cyclohexyl imine, which undergoes to the nucleophilic attack of the aniline, thus forming N-cyclohexylideneaniline. In turn, the latter may undergo nucleophilic attack of the hydroxylamine, or the hydrogenation to phenyl cyclohexyl amine and finally to dicyclohexyl amine. From a mechanistic point of view, the Authors have suggested the involvement of the gold catalyst in the transformation the N-cyclohexylideneaniline, which determines the overall selectivity to the various products [36].
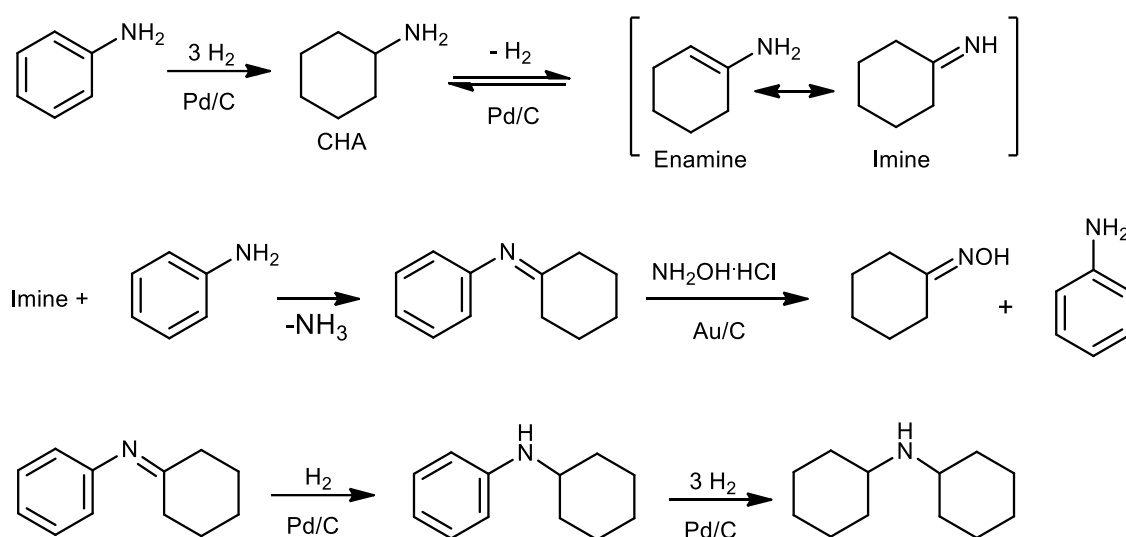
Scheme. 3. Mechanism of nitrobenzene hydrogenation to cyclohexanone oxime suggested by Corma [36].

In fact, the nucleophilic attack of NH_2OH catalyzed by Au/C catalyst to N-cyclohexylideneaniline leads to cyclohexanone oxime and finally its hydrolysis can give cyclohexanone if water is present [36]. In addition, Pd/C is responsible for the formation of di-cyclohexylamine by the sequential hydrogenation of N-cyclohexylideneaniline to N-cyclohexyl aniline, which is finally hydrogenated to di-alkylamine [36]. In any case, in agreement with the mechanism suggested by Greenfield, the formation of the imine intermediate is, again, an important step, since its reactivity leads to the formation of N-cyclohexylideneaniline recognized by these authors as the effective intermediate, whose Au-catalyzed reactivity determines the high selectivity in cyclohexanone oxime.
In this part of the work, the selective hydrogenation of nitrobenzene to cyclohexanone oxime with different solvents, in the presence of various hydroxylammonium salts, and catalyzed by a commercial Pd/C catalyst was studied. In addition, the influence of the operating variables

(pressure, temperature and type of solvent), the amount and type of catalyst on the selectivity to oxime and various by-products has been investigated. In addition, special attention was paid to the study of probable intermediates present in trace amounts in the reaction medium and to the parallel $NH_2OH \cdot HCl$ reduction reaction whose products favor the selectivity in the oxime of cyclohexanone.

1.2.2 Results and discussion

1.2.2.1. Preliminary results and Choice of the catalytic system

The main results of some supported precious metal hydrogenation catalysts employed under mild conditions (333 K 0.8 MPa), are reported in Table 1 in presence of $NH_2OH \cdot HCl$, necessary for achieving a selectivity to the cyclohexanone oxime (COX).
In terms of nitrobenzene conversion, the best performing catalysts were Pd- and Pt-based catalysts. The reason of this behavior is likely related to the specific activity of each catalyst, however, the high activity of Pd/C in nitrobenzene (NB) hydrogenation is well known from the beginning of the studies in catalysis, while other metals are active only in more severe conditions [21-27]. As regard the selectivity in COX, only Pd shows a clear selectivity to this compound. This is related to its high activity in the hydrogenation reactions, since the formation of COX must proceed via the reduction step of aniline which is indeed a harsh substrate to be reduced [21-27].

Table 1. Influence of the catalyst on the conversion and selectivity of nitrobenzene hydrogenation. Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, hydrogen Pressure 0.8 MPa, $NH_2OH \cdot HCl$ 30 mmol, T 333 K, catalyst 50 mg, time of reaction 20 h, solvent diethyl ether.

Catalyst	Conversion	Selectivity					
		AN[a]	COX[b]	CON[c]	CHA[d]	PCA[e]	Others[f]
	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Pd/C (5%)	>99	30	64	1	1	2	2
Pd/Al₂O₃ (5%)	99	70	29	traces	traces	traces	traces
Pt/C (3%)	>99	>99	/	/	traces	traces	traces
Pt/Al₂O₃ (5%)	90	>99	/	/	traces	traces	traces
Au/C (0.5 %)	1	99[c]	/	/	/	/	/
Au/SBA (2 %)	1	99[c]	/	/	/	/	/
Ru/C (5%)	5	>99	/	/	/	/	/
Rh/C (5%)	10	>99	/	/	/	/	/

[a]AN=aniline, [b]COX=cyclohenxanone oxime, [c]CON=cyclohexanone, [d]CHA=cyclohexylamine, [e]PCA=N-phenylcyclohexylamine [f]GC-MS reveals traces of condensation products and N,N-dicyclohexylamine and others not identified.

1.2.2.2 Influence of solvent type, hydrogen pressure and temperature

The solvent plays a fundamental role for driving selectivity toward COX, this is evident from the results of Table 2, in which nitrobenzene is in practical quantitatively hydrogenated in all the solvents, but low or no selectivity to COX is achieved by using ethanol (EtOH), acetonitrile (ACN) and toluene (Tol). The highest selectivity in COX is obtained by using THF as the solvent. The reason is not easy to explain because of the different nature of these solvents (chemical and/or physical). As can be observed in Table 2 there are no evident relationships between solvent dielectric constant and selectivity to COX.

This suggests that the solvent may influence the selectivity in one of the many equilibria involved in the mechanism, although it is difficult to identify which one it is. However, tetrahydrofuran (THF) seems to be the best solvent followed by diethyl ether (Et_2O), dichloromethane (DCM) and dimethyl carbonate (DMC). Due to lower cost issues, it was chosen to study the reaction parameters using Et_2O as solvent.

Table 2. Influence of the solvent on conversion and selectivity. Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, hydrogen Pressure 0.8 MPa, NH$_2$OH·HCl 30 mmol, T 333 K, Pd/C 50 mg, time of reaction 20 h.

Solvent	ε	Conversion	Selectivity					
		(%)	AN[a] (%)	COX[b] (%)	CON[c] (%)	CHA[d] (%)	PCA[e] (%)	Others (%)
EtOH	24,6	> 99	52	< 1	/	/	/	47[f]
CH$_3$CN	35,9	97	50	22	/	/	/	38[f]
CH$_3$NO$_2$	35,9	> 99	58	/	< 1	/	/	41[f]
CH$_3$(CO)CH$_3$	20,7	> 99	45	/	/	/	/	55[f]
Tol	2,38	95	99	< 1	/	< 1	< 1	< 1[g]
THF	7,58	> 99	24	71	< 1	< 1	3	1[g]
THF/H$_2$O[h]	42,8	> 99	98	< 1	< 1	/	/	1
Et$_2$O	4,34	> 99	32	64	< 1	< 1	2	1[g]
Et$_2$O[i]	4,34	> 99	64	32	< 1	< 1	2	1[g]
iPr$_2$O	8,31	> 99	73	21	< 1	< 1	5	/
DMC	3,07	> 99	55	40	< 1	< 1	3	1[g]
DCM	8,93	> 99	40	55	< 1	< 1	3	1[g]

[a]AN=aniline, [b]COX=cyclohexanone oxime, [c]CON=cyclohexanone, [d]CHA=cyclohexylamine, [e]PCA=N-phenylcyclohexylamine, [f]Products of aniline alkylation [45]. [g]Condensation products and N, N-dicyclohexylamine.[h]THF/H$_2$O = 1/1 wt. [46]. [i]In the presence of 200 mg of molecular sieve 4A.

Table 3 shows the influence of hydrogen pressure and temperature on conversion and selectivity. As it is possible to observe, hydrogen pressure does not affect the conversion of nitrobenzene, which in 20 h, is quantitative. However, an influence of the selectivity towards the formation of cyclohexanone oxime (COX) can be observed, which reaches its maximum in the H$_2$ pressure range of 8-10 bar. Reasonably, as the H$_2$ pressure increases, the rate of aniline hydrogenation is expected to increase, but looking at Table 3, the selectivity towards

cyclohexylamine formation varies little, only in the range of 0.1-1%. *Vice versa*, with increasing hydrogen pressure, an increase in selectivity towards the N-phenylcyclohexyl amine (PCA) can be observed, suggesting competition between COX and PCA formation.

Table 3 Influence of the hydrogen pressure and temperature on selectivity (quantitative conversion). Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, NH$_2$OH·HCl 30 mmol, T 323-353 K, Pd/C 50 mg, time of reaction 20 h.

Entry	Pressure	Temp.[a]	Selectivity					
			AN[b]	COX[c]	CON[d]	CHA[e]	PCA[f]	Others[g]
	(Bar)	(K)	(%)	(%)	(%)	(%)	(%)	(%)
1	5	333	48	49	< 1	< 1	1	< 1
2	8	323	59	40	< 1	< 1	< 1	< 1
3	8	333	31	64	1	1	2	1
4	8	343	27	67	1	1	2	2
5	8	353	42	51	1	1	3	2
6	10	333	32	62	1	1	3	1
7	20	333	42	53	traces	1	3	< 1

[a]Temp. = Temperature, [b]AN=aniline, [c]COX= cyclohenxanone oxime, [d]CON= cyclohexanone, [e]CHA= cyclohexylamine, [f]PCA=N-phenylcyclohexyl amine, [g]Condensation products and N,N-dicyclohexylamine

In the tested temperature range, there are no variations in nitrobenzene conversion (quantitative), but it is possible to notice an influence in the selectivity towards the formation of cyclohexanone oxime, which has a maximum at the range of temperature 333−343 K. At the highest temperature, likely, the reaction is less selective because of an increase of the rate of side of reactions.

1.2.2.3 Influence of the catalyst amount on conversion and selectivity

The selectivity in COX decreases as the catalyst amount increase (Fig. 1). The explanation of this fact is not easy, but it is likely that key intermediate determining the selectivity in COX is on catalyst surface. The presence of a reactive surface intermediate derived from aniline hydrogenation also explains the increase of byproducts with catalyst amount, thus suggesting all intermediates and byproduct derive from aniline hydrogenation. This is clear, since nitrobenzene, under the reaction conditions, is readily and quantitatively hydrogenated to aniline (AN), while the hydrogenation of the AN ring is not easy. As a matter of fact, it is probably that AN has the tendency of being strongly adsorbed on catalyst surface, since stable aniline-Pd(II) complexes are well known and characterized thus justifying strong interaction between the surface Pd atoms and the AN molecule [47].
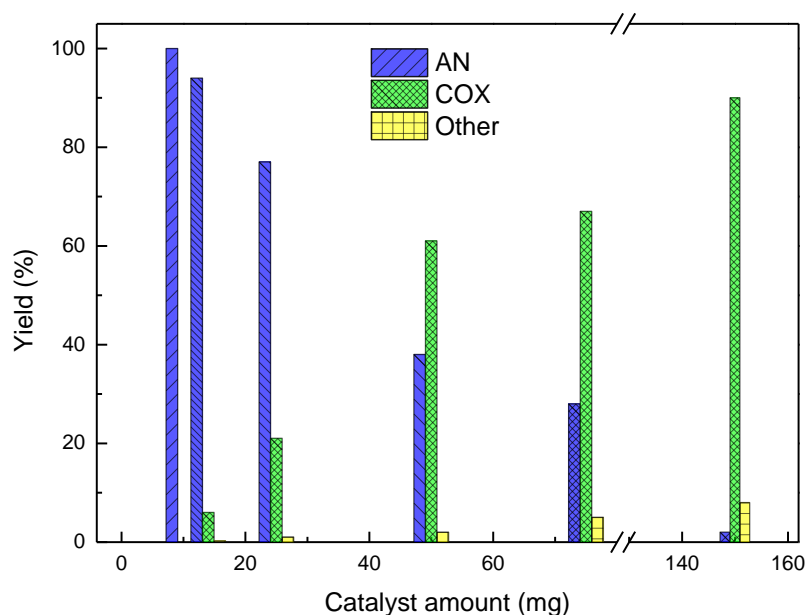
Fig. 1. Influence of the catalyst amount on the yield of aniline and cyclohexanone oxime. Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, NH$_2$OH·HCl 30 mmol, T 333K, Pd/C 50 mg, time of reaction 20 h.

1.2.2.4. Time vs concentration profiles, hydrogen consumption and mass balance

Fig. 2 shows the reaction profile of a typical experiment. During the first few hours of the reaction, a rapid conversion of nitrobenzene is observed, and only later is the formation of COX and other byproducts observed.
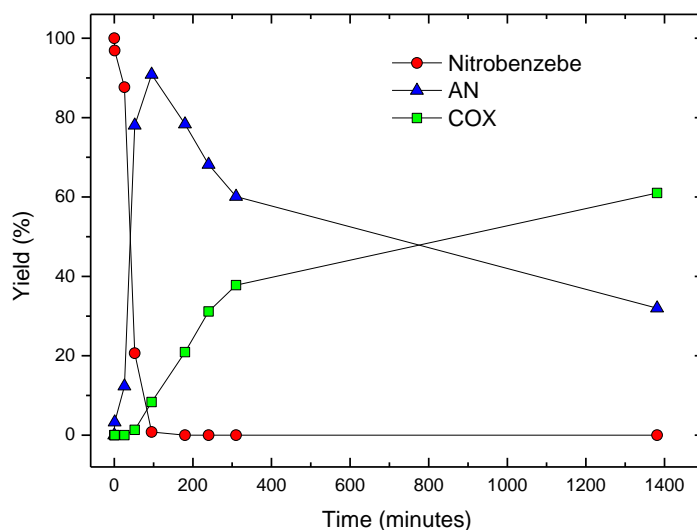
Fig. 2. Hydrogenation profile. Run conditions: reaction volume 75 mL, nitrobenzene 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, NH$_2$OH·HCl 75 mmol, T 333 K, Pd/C 60 mg, time of reaction 20h.

The determination of the hydrogen consumption profile (Fig. 3) allows to verify if this trend is compatible with the one in Fig. 2.
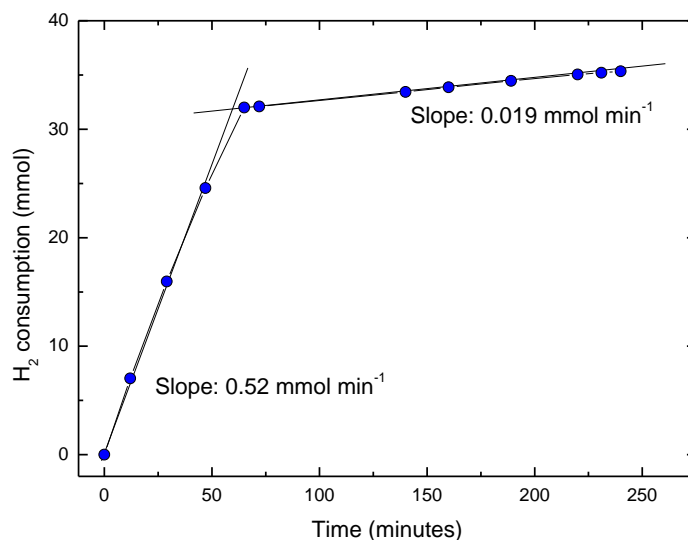
Fig. 3. Hydrogen consumption profile of nitrobenzene hydrogenation. Run conditions: reaction volume 20 mL, nitrobenzene 0.5 mol L^{-1}, Hydrogen Pressure 0.8 Mpa, NH$_2$OH·HCl 30 mmol, T 333 K, Pd/C 50 mg.

In the first 60-80 min, the H$_2$ consumption agrees with the hydrogenation of nitrobenzene to aniline, whose reaction rate is fast and shows virtually a linear trend. It is noteworthy that the second part of the nitrobenzene hydrogenation (see Fig. 2) also appears as a straight line, but its slope is lower than that of the first part (Fig. 3, 0.019 mmol min-1 versus 0.52 mmol min^{-1}, respectively).

This behavior confirms the low activity of the catalyst in the hydrogenation of AN.

After about 70 min, the H$_2$ consumed is about 35 mmol (30 mmol required to reduce nitrobenzene to aniline), suggesting the presence of possible reactions resulting in the formation of byproducts. From the various tests conducted, it has been observed that NH$_2$OH·HCl in the presence of the amount of water, normally produced by the reduction of nitrobenzene, leads to the formation of the corresponding ammonium salt.

$$NH_2OH \cdot HCl \; + \; H_2 \quad \xrightarrow{Pd/C} \quad NH_4Cl \; + \; H_2O \qquad \text{Scheme 4}$$

Besides, the reaction rate is not influenced by the hydroxylammonium concentration (it results as a pseudo zero order in the salt concentration) thus suggesting a strong adsorption on the catalyst surface. Form Fig.4 it is possible to observe that the NH$_2$OH·HCl solution adsorbs after 4 h, 7 mmol of hydrogen, which agrees with the conversion of the NH$_2$OH·HCl to NH$_4$Cl measured by titration of the solution obtained by extraction with water of the inorganic salts present into the reaction environment.
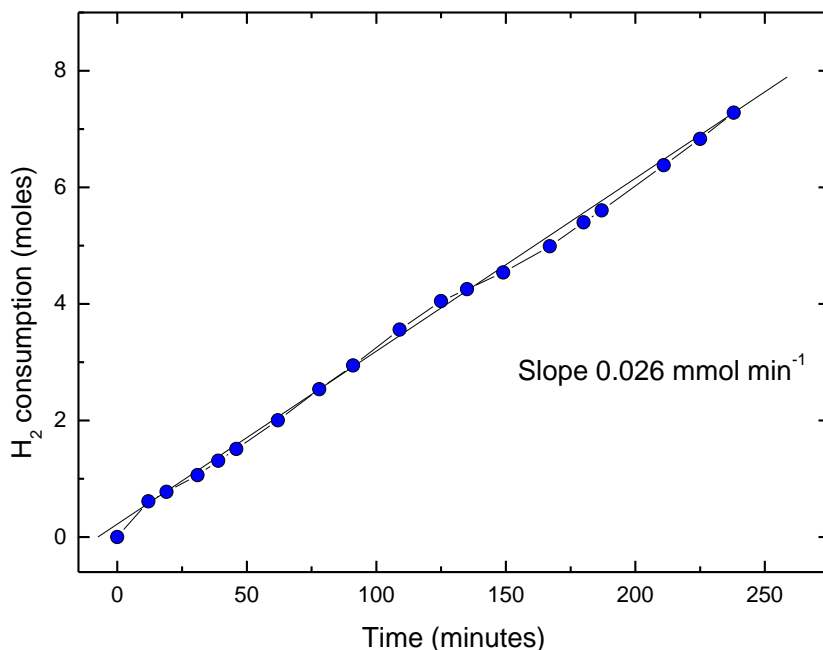
Fig. 4. H_2 consumption profile for NH_2OH hydrogenation. Run conditions: reaction volume 20 mL, Hydrogen Pressure 0.8 Mpa, $NH_2OH \cdot HCl$ 30 mmol, H2O 20 mmol, T 333 K, Pd/C 50 mg.

1.2.2.5. Aniline hydrogenation to COX

Studying the hydrogenation reaction profile of aniline (Fig. 5) shows that the initial reaction rate is slower than that of nitrobenzene, since AN is a more difficult substrate to hydrogenate[22-26]. After 20 h it proceeds to 47 % aniline conversion with a very high cyclohexanone oxime selectivity (COX selectivity > 96 %). But on balance, the overall COX yield is lower (45 %) than that found in nitrobenzene hydrogenation (62 % yield). Thus, it is possible to speculate that the different initial conditions and hydrogenation course may result in a lower COX yield, due to a different reactive pattern. When starting with nitrobenzene, water is obtained as a byproduct of hydrogenation, this could change both the reaction environment and catalyst reactivity thus likely inducing the higher final yield.

In addition, the reaction studied from aniline, does not lead to the formation of the same by-products obtained in the case of nitrobenzene, this is a further suggestion that supports the possibility of having a slightly different reaction mechanism.
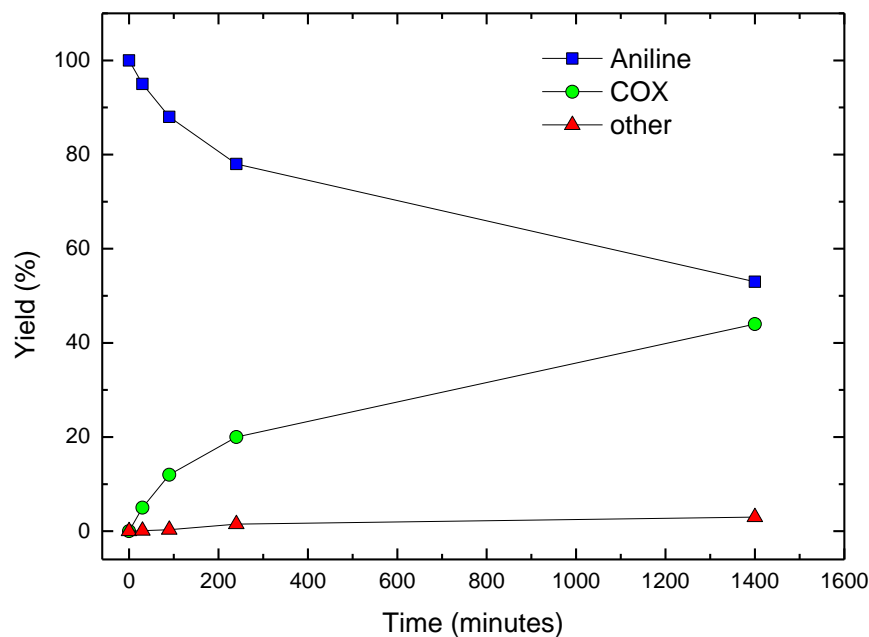
Fig. 5. Reaction profile of aniline hydrogenation. Run conditions: reaction volume 80 mL, aniline $0.5 \, mol \, L^{-1}$, H_2O 20 mmol, hydrogen Pressure 0.8 MPa, $NH_2OH \cdot HCl$ 75 mmol, T 333 K, Pd/C 50 mg.

The importance of the presence of water in the reaction environment is evident by observing the results shown in Fig. 6. It appears that the amount of water, up to 80 mmol, promotes COX formation, probably because it affects the availability of NH_2OH in the reaction environment, increasing its solubility. The reaction, however, also occurs in the presence of 5A molecular sieves, but in lower yield (about 13%), suggesting that NH_2OH also exists in solution in the organic solvent due to complicated acid-base equilibria.

Above 80 mmol of water there is a decrease in the overall yield of cyclohexanone oxime. This agrees with what has been observed using an H_2O/THF mixture as a solvent (see Table 4 entry 5) where aniline conversion is negligible at very high-water concentrations.
This could be due to several competitive causes. It is possible that the increase in the amount of water can lead to the formation of a two-phase system when the reaction progresses, which leads to a decrease in the hydrogenation of AN, or that the solvent can interfere with the active sites of the catalyst, decreasing its activity.
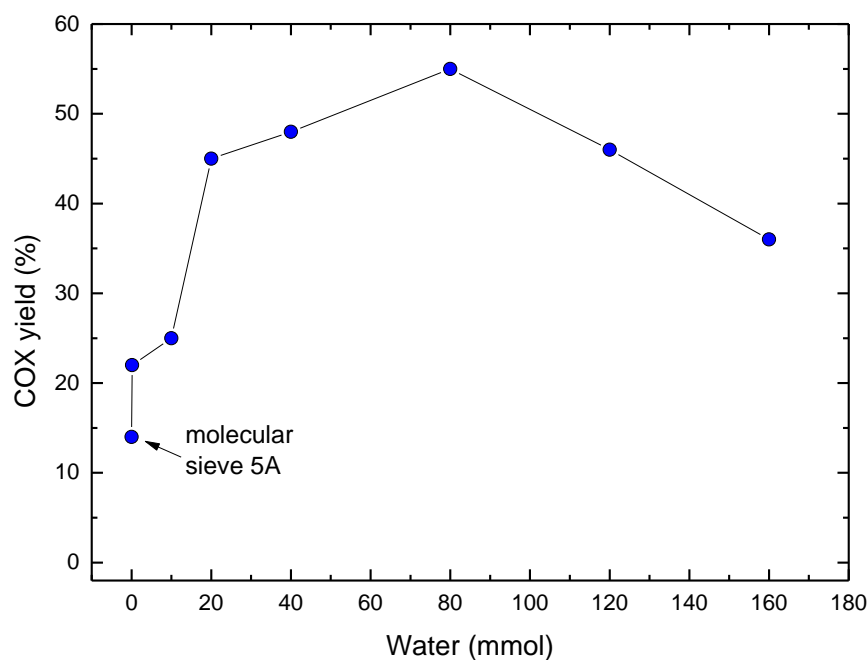
Fig. 6. Influence of H_2O on COX yield. Run conditions: reaction volume 20 mL, AN 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, $NH_2OH\cdot HCl$ 30 mmol, T 333 K, Pd/C 50 mg, time of reaction 20 h.

Table 4. Reactivity of AN. Run conditions: reaction volume 20 mL, AN 0.5 mol L-1, $NH_2OH\cdot HCl$ 30 mmol, H2 pressure 0.8 MPa, H_2O 20 mmol, T 333 K, Pd/C 50 mg, time of reaction 20 h.

Entry	Solvent	Conversion	Selectivity				
			COX[a]	CHA[b]	CON[c]	PCA[d]	Others
		(%)	(%)	(%)	(%)	(%)	(%)
1	Et$_2$O	47	98	0,3	0,2	1	0,5
2	THF	49	97	0,3	0,3	1,5	0,9
3	EtOH	12	95	0,3	0,3	0,4	4
4[e]	CH$_3$CN	100	20	0,5	0,5	1	78
5[f]	THF/H$_2$O	2	/	/	/	/	100
6[g]	Et$_2$O	8	/	14	/	48	38

[a]COX= cyclohenxanone oxime, [b]CHA= cyclohexylamine, [c]CON= cyclohexanone, [d]PCA=N-phenylcyclohexyl amine, [e]Other is mainly AN alkylation. [f]Reaction carried out phase in great excess of water: THF/H$_2$O = 1/1 wt. [g]Reaction carried out without NH_2OH

Further consideration must be done on the presence of the ammonium salt. In fact, its presence is not unbiased for the reactivity of the system, since it may influence all equilibria, and then, the overall COX yield. It appears from Fig. 7 that the trend of the influence of NH_4Cl amount on the COX yield have a maximum at 10 mmol (COX yield 65 %). This behavior suggests that ammonium salt favors the formation of the oxime by decreasing the reduction of hydroxylamine hydrochloride. But by increasing the amount of NH_4Cl, a decrease in the yield of cyclohexanone oxime is observed. It is possible to speculate that the

presence of some subproducts, such as cyclohexylamine, may release NH_3 and compete with NH_2OH for the synthesis of the desired product.
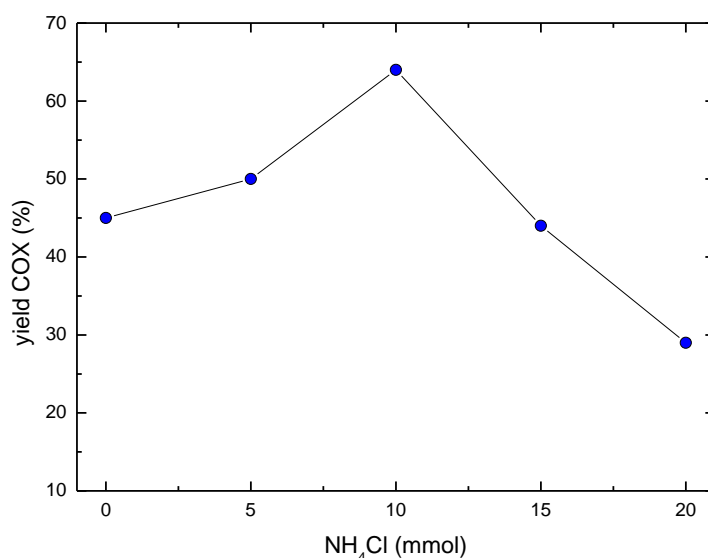
Fig. 7. Influence of NH_4Cl amount on COX yield. Run conditions: reaction volume 20 mL, AN 0.5 mol L^{-1}, Hydrogen Pressure 0.8 MPa, $NH_2OH \cdot HCl$ 30 mmol, H_2O 20 mmol, T 333 K, Pd/C 50 mg, time of reaction 20 h.

After this discussion, it is quite evident the first part of the reaction, that is the hydrogenation of NB to AN influence the reactivity of the system, mainly for the coproduction of water and ammonium salt, the latter deriving from the parallel reaction of $NH_2OH \cdot HCl$ reduction. Both byproducts promote the yield in COX.

1.2.2.6. Influence of the intermediates and possible reaction path

The side-products (cyclohexylamine, cyclohexanone and N-phenylcyclohexylamine) are in low concentrations and no other products are observed. To determine their importance in the catalytic cycle, their reactivities are shown in Table 5 and 6.

Table 5. Reactivity of CHA. Run conditions: reaction volume 20 mL, substrate 0.5 mol L^{-1}, $NH_2OH \cdot HCl$ 30 mmol, H_2O 20 mmol, T 333 K, Pd/C 50 mg, time of reaction 20 h.

Entry	Substrate	Pressure	Conversion	Selectivity			
				COX[a]	CON[b]	PCA[c]	Others
		(Bar)	(%)	(%)	(%)	(%)	(%)
1	CHA	5 (N_2)	1	/	/	/	100[d]
2	CHA	8 (H_2)	1	/	/	/	100[d]
3[g]	CHA + AN	8 (H_2)	4	/	/	5	95
4[g]	CHA+ AN	5 (N_2)	1	/	/	/	100

[a]COX= cyclohenxanone oxime, [b]CON= cyclohexanone, [c]PCA=N-phenylcyclohexylamine, [d]Other mainly products of CHA alkylations. [g]CHA/AN = 1/1 conversion on aniline.

As can be seen from Table 5 (entries 1, 2) cyclohexylamine does not lead to the formation of cyclohexanone oxime either in the presence or absence of hydrogen and aniline. This suggests that it is a by-product due to the hydrogenation of aniline, rather than a reaction intermediate.

It can be seen from the results that cyclohexanone (CON) reacts with $NH_2OH \cdot HCl$ quite easily, such that the conversion of cyclohexanone after 0.5 h is equal to that obtained after 20 h (70 % conversion entries 1-4). The selectivity is higher without any catalyst (94 % in COX entry 2)[53].

From entry 5 of Table 6, it is observed that from PCA, the formation of cyclohexanone oxime is not observed, suggesting that it is a reaction by-product.

N-cyclohexylideneaniline (PCNA) was observed in solution during the reaction, only in trace amounts (from careful GC-MS analysis) but we synthesized the compound and tested its reactivity. Indeed, it reacts with virtually all nucleophiles giving a fast substitution, with aniline as the outgoing group. However, in the presence of hydrogen, NH_2OH and Pd/C catalysts, PCNA gives COX in high yield (93 % entry 6).

Table 6. Reactivity of CON, PCA and PCNA. Run conditions: reaction volume 20 mL, Et_2O as a solvent, substrate 0.5 mol L^{-1}, $NH_2OH \cdot HCl$ 30 mmol, H_2O 20 mmol, T 333 K, catalyst 50 mg.

Entry	Sub.	Catalyst	Time	Pressure	Conversion	Selectivity				
						COX[a]	CHA[b]	CON[c]	PCA[d]	Others
			(h)	(Bar)	(%)	(%)	(%)	(%)	(%)	(%)
1	CON	/	20	5(N$_2$)	70	89	/	/	/	11
2	CON	/	0,5	5(N$_2$)	70	94	/	/	/	6
3	CON	Pd/C (5%)	20	8 (H$_2$)	72	88	/	/	/	12
4	CON	Pd/C (5%)	0,5	5(N$_2$)	70	91	/	/	/	9
5	PCA	Pd/C (5%)	20	8 (H$_2$)	6	/	/	/	/	100[f]
6	PCNA[e]	Pd/C (5%)	20	8 (H$_2$)	>99	93	/	3	3	1
7	PCNA	Pd/C (5%)	20	5(N$_2$)	>99	46	/	2	2	50[g]
8	CON	/	20	5(N$_2$)	>99	48	/	2	2	48[g]
16	PCNA[h]	Pd/C (5%)	20	8 (H$_2$)	98	/	/	10	72	10[f]
17	PCNA + CHA[h]	/	20	8 (H$_2$)	>99	/	/	8	/	92[i]
18	PCNA + CHA[h]	Pd/C (5%)	20	8 (H$_2$)	>99	/	8	8	4	80[j]

[a]COX= cyclohenxanone oxime, [b]CHA= cyclohexylamine, [c]CON= cyclohexanone, [d]PCA=N-phenylcyclohexyl amine, [e]PCNA= N-cyclohexylideneaniline, [f]Other is mainly N, N-dicyclohexylamine. [g]Mainly AN. [h]Reaction carried without NH_2OH. [i]Mainly a mixture AN and N, N-cyclohexyliden-cyclohexane. [j]Mainly a mixture AN and N, N-dicyclohexylamine.

Hydrogenation in the presence of Pd/C of PCNA without NH_2OH shows the formation of PCA and di-cyclohexyl amine (entry 16). Entries 17 and 18 show the facile nucleophilic substitution of CHA toward aniline giving N,N-cyclohexylen-cyclohexylamine in the absence of Pd/C or, in the presence of the Pd catalyst, N,N-dicyclohexylamine as a result of the

hydrogenation of N,N-cyclohexylen-cyclohexylamine. Comparable results were observed with CON and COX suggesting facile nucleophilic substitution due to CHA .

Despite the complexity of the reaction and the large number of equilibria and reactions, we can try to suggest a probable reaction pathway (Scheme 5). All evidence suggests that the first step is hydrogenation of NB to AN. Probably, the second step is the partial hydrogenation of AN and the formation of an imine surface intermediate, which reacts readily with all nucleophiles in solution giving products signed by the dotted lines. The role of water here is not only that of nucleophile, which allows the formation of cyclohexanone, but it also promotes multiphase equilibria that give NH_2OH thus favoring the formation of COX. In fact, the product that is obtained in greater quantity is COX because of the greater nucleophilicity of NH_2OH than that of H_2O and AN [54]. Moreover, all products obtained from the nucleophilic reaction are in equilibrium (molecules circled with the dotted line). In contrast, irreversible hydrogenation reactions (under the conditions investigated) occur giving the molecules circled by the solid line; i.e. CHA, PCA and N,N-dicyclohexylamine. Under the conditions studied CHA and N,N-dicyclohexylamine are observed in low concentration (maximum 1%), and the latter only after a long reaction time. The formation of CHA is very slow and if added in relevant amounts it completely changes the distribution of the products. In fact, if CHA in the presence of CON, COX and Dicyclohexylamine (DCHA) easily gives nucleophilic substitution, thus forming N, N-cyclohexylenecyclohexanamine, which is, in turn, hydrogenated to N, N-dicyclohexylamine .
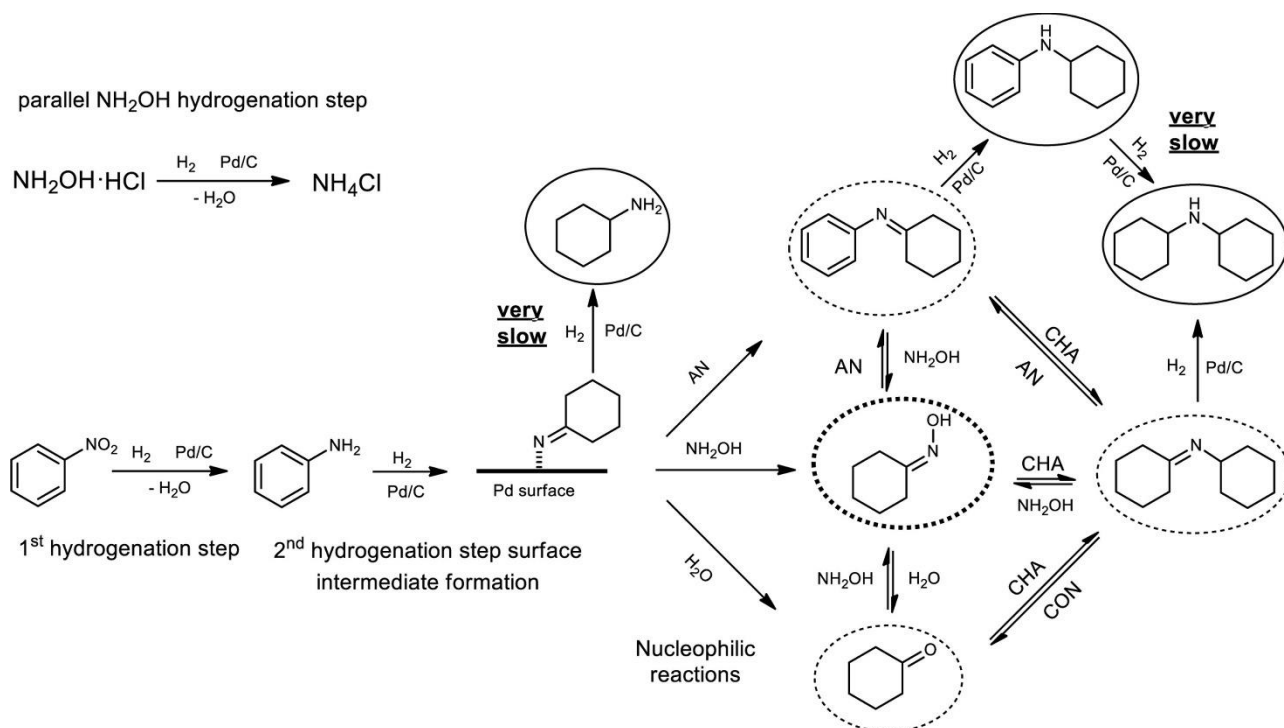
Scheme 5. Proposed reaction path for the direct synthesis COX via nitrobenzene hydrogenation

1.2.3. Conclusions

All results state the complexity of the reaction path and the large number of factors it is necessary to consider for optimizing the yield in COX. The new insights for this process are the importance of the secondary reactions that is the reduction of $NH_2OH \cdot HCl$ and all nucleophiles equilibria. In fact, its reduction gives NH_4Cl and water, which, both, influences the selectivity towards COX. Aniline is the key intermediate and at first sight, its hydrogenation gives a lower yield in COX compared to that obtained using nitrobenzene as a substrate. This evidence is, however, apparent since the addition of a proper amount of water and NH_4Cl shows an increment of the yield at the level of that observed for nitrobenzene. In this way, it has been possible to recognize the role of secondary reactions, which determine the overall selectivity to COX. In fact, the nucleophilic addition to the imine surface intermediate of AN, H_2O and NH_2OH, gives PCNA, CON and COX, respectively, whose equilibria in solution displace to a higher selectivity in COX. It appears that all the nucleophilic reactions are not influenced by the presence of metal catalysts. Pd/C catalyst seems to be the best catalytic system, other supported metal catalyst does not give comparable results, and mixed catalysts gives, in any case, lower selectivity in COX. The selectivity increases as the amount of Pd/C, in agreement with the formation of a surface intermediate determining the selectivity. Besides, it suggests that the mass transfer on catalyst surface may have a role on the overall selectivity in COX, but a detailed kinetic study is beyond the scope of the present work.

The role of solvent is of paramount importance and the best results are achieved by using oxygenated non hydroxylated solvents, preferably ethers. Hydrogen pressure influences the selectivity in the range investigated 0.5−2 MPa, and the best interval of pressure is comprised between 0.8 Mpa and 1 Mpa. Temperature of reaction has been varied between 323 K and 373 K and the highest selectivity has been observed in the range 333−343 K. Some experiments with the likely intermediates and byproducts of the reaction show that both CON and PCNA are intermediate while CHA and PCA are irreversible byproducts.

1.2.4 Experimental

Reagents

Nitrobenzene, aniline, cyclohexylamine, dicyclohexylamine and N-phenylcyclohexylamine (PCA) were all Aldrich products, their purity were checked by the usual methods (melting point, TLC, HPLC, GC and GC–MS) and employed without any purification, acetonitrile HPLC gradient grade was supplied by BDH, 1,4-dioxane, methanol, nitromethane, diethyl ether, dioxane, tetrahydrofuran, dimethylformamide and dimethyl sulfoxide are ACS reagent supplied by Aldrich. N-cyclohexylideneaniline (PCNA) was synthesized by following the procedure of literature and the characterization was carried out by GC–MS, ^{1}H and ^{13}C NMR [37]. Catalysts used were commercial materials supplied by Engelhard (now Basf Catalysts): Pd/C 5% Escat 10, Pt/C 3%, Ru/C 5% Escat 40 and Rh/C 5%. Au/SBA 2% and Au/C 0.5 % were gently furnished by Proff. M. Signoretto and F. Menegazzo; synthesis and characterization of these catalysts has been reported elsewhere [38,39].

Equipment

Products were identified by gas chromatography (GC) gas chromatography coupled mass spectrometry (GC–MS) and high-performance liquid chromatography (HPLC). GC and GC–MS analysis were carried out with an Agilent 7890A equipped with FID or MS detector (Agilent 5975C and a HP 5 column (I.D. 320 μm 30 m long). Helium was employed as carrier in the GC–MS analysis, while nitrogen in the GC ones, in both cases the conditions were the following: injector 523 K, detector 543 K, flow 1 mL min^{-1}, oven 333 K for 3 min 523 K 15 K min^{-1} and 523 K for 15 min. In order to check the thermal stability of the products, some analysis were carried out by HPLC (Perkin Elmer 250 pump, LC 235 diode array detector and a C 8, 5 μm, 4 mm i.d. 25 cm long column) analysis were carried out with CH$_3$CN-H$_2$O as mobile phase in isocratic 70 % of CH$_3$CN at 1 mL min^{-1}. The comparison of GC and HPLC analysis shows a good agreement suggesting both technique gives reliable analytical data. After the test of the analytical reliability, conversion yield and selectivity are calculated by calibrations of the GC analysis obtained by standard solutions of the pure products. ^{1}H and ^{13}C NMR. were carried out in a Brucker Avance 400 II at 400 MHz and 100 MHz, respectively and using CDCl$_3$ as a solvent.

Catalyst characterization

Catalysts employed are commercial catalysts (except Au ones) whose characterization has been already described in previous papers [38], [39], [40].

Hydrogenation of nitrobenzene

The reactions have been carried out in several solvents (1,4-dioxane CH_3NO_2, CH_3OH, $(CH_3)_2NCHO$ and $(CH_3)_2SO$) in an AISI 316 autoclave (80 mL internal volume) equipped with a PTFE insertion (to avoid metal contamination), and a pressure regulator to maintain constant the reaction pressure. A circulation bath ensures a stable temperature in the range $323-353$ K (± 0.5 K). Catalyst activations were preliminarily carried into the autoclave at the running temperature and pressure ($0.3-2$ MPa of H_2), without reagents. Blank reactions in the absence of nitrobenzene and hydroxylamine have been carried out to verify the stability of the solvent. Solvents employed showed no relevant products of reduction at GC analysis. A detailed description of hydrogenation apparatus has been described elsewhere [41]. In a typical experiment 20 mL of solvent with suspended the Pd/C catalyst (typically 50 mg) and $NH_2OH \cdot HCl$ (2.7 g), was introduced into the reactor. After that, the reactor was closed, purged before with nitrogen and then with hydrogen, pressurized at 0.2 MPa, finally heated at $323-353$ K under stirring for 1 h to activate the catalyst. The reactor was left to stabilize at the temperature of reaction ($323-353$ K), than the preheated solution of nitrobenzene (c.a. 2.5 mL, concentration of nitrobenzene 4 mol L^{-1}) was added to the reactor. After the addition of this solution, the computing of the reaction time starts, and the liquid phase analysis is by GC after 20 h of reaction. An electronic pressure transducer monitors hydrogen consumption, which measure the pressure drop in a reservoir at known volume. The reaction environment, at initial stage of the reaction, is a complex mixture composed of a gas phase (mainly hydrogen and solvent), a liquid phase (solvent and nitrobenzene) and two solid phases: hydroxylamine hydrochloride and the catalyst. Both solid are not soluble (negligibly soluble) in the solvent, however, during reaction the formation of water, due to nitrobenzene hydrogenation to aniline, may cause an increase of the solubility of the hydroxyl ammonium salt, or of other salts present and/or produced in the reaction vessel.

In all the experiments at the opening of the reactor, we found a solid mixture crust on the bottom of the reactor made of the catalyst and various salts, strong agitation needs for restoring the homogeneity, it is necessary to carefully verify the agitation of the system in order to avoid reproducibility problems.

Some kinetic profiles has been obtained by using a 250 mL autoclave employing 80 mL of volume under the same concentration of reagent and at 0.8 MPa of hydrogen pressure the apparatus has been detailed described elsewhere [41].

Determination of residual $NH_2OH \cdot HCl$

The residual hydroxyl ammonium salt employed in the reaction has been quantified after filtration and washing of the solid with diethyl ether. Then the salt is dissolved in water diluted, added to an almost equimolar solution of ferric sulfate, left to react for 30 min, and the excess of Fe (III) titrated directly with a solution of $KMnO_4$ (0.05 mol L^{-1}) [42]. The method has been checked by ionic chromatographic analysis, showing equivalent results. In some sample a residual percentage of CHA has been observed after extraction with CH_2Cl_2 of

the KOH basified solution to pH > 12, in any case, the amount is generally lower than 1%, except in those experiments where the CHA was added in high concentration as a reagent.

1.2.5 References

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1.3 Trifluoroacetic Acid Hydroxylamine System as Organocatalyst Reagent in a One-Pot Salt Free Process for the Synthesis of Caprolactam and Amides of Industrial Interest

1.3.1 Introduction

Caprolactam is a chemical whose importance raises continuously being the monomer of the important polyamide nylon 6 [1]. Problems of coproduction of side products of low economic value affects current industrial processes [2]. Recently, salt free processes are running in the Far East by employing a step of cyclohexanone amoximation and a second step of Beckmann rearrangement in gas phase [1]. The Eni amoximation step and the Sumitomo gas phase rearrangement are the core of this salt free processes. More recently, Sinopec has claimed similar route employing both an amoximation step and a gas phase rearrangement [3]. In both cases, however, a complete transformation of the traditional plants, based on liquid phase reactions, needs for running this type of process. In fact, the revamping of existing plant in Europe and USA could be a more economically and environmentally sustainable way, since the demand caprolactam in the western regions does not growth as in the Far East [1, 4–6]. For this reason, the research in this field is in continuous development and only in the last two years has appeared several papers and, in addition, two comprehensive reviews on the argument [7, 8]. The oximation step occurs generally in high selectivity but in the presence of a stoichiometric amount of a base, which leads to the formation of the salt deriving from neutralization of the acid of the hydroxylammonium salt, which is the main byproduct and issue of the whole process [1, 2]. Recently, literature have reported new methodologies giving good yields in ketones oximation carried out in ionic liquids, so that avoiding the neutralization [9]. Besides organocatalysts improves such a step by increasing the yield in the oximes formation, particularly useful for ketones with low reactivity, especially for those with steric hindrance at the carbonyl[10]. Recently, the chemistry of trifuoroacetic acid as organocatalyst has been suggested for the synthesis of the caprolactam, of other amides as well as to several other reactions of industrial interest [7–16]. For instance, some authors proposed the direct oximation and rearrangement of ketones and, of the cyclohexanone, to the corresponding amides [15–20]. The second important process in term of amide produced is the Hoechst-Celanese process for the synthesis of the N-acetyl-4-aminophenol (acetaminophen)[21]. The existing processes are based on several type of reactions, one of the most employed is the Hoechst-Celanese process where 4-hydroxy acetophenone reacts with hydroxylamine giving the corresponding oxime, which rearranges to the N-acetyl-4-aminophenol in the presence of thionyl chloride [22]. In this case, two steps are necessary to carry out the synthesis: an oximation stage and the Beckmann rearrangement [22]. A simplification of the process can be attained by carrying out these two latter stages in one-pot [23]. During the last decade, several papers have been published by independent research

groups in which Beckmann oxidation and rearrangement occur in high-throughput one-pots [15-19, 23]. The kernel of the process is using a mixture of trifuoroacetic acid and acetonitrile, which allows high yield in the amides [15–18, 23]. More recently, we pointed out that the two reactions, when the temperature is increased over 383 K, proceeds also in absence of trifuoroacetic acid (though in lower yield) and the reaction is self-catalyzed by the hydroxylammonium salt [24].

Starting from these considerations, the main concern of the whole one-pot process is strictly related to the hydroxylamine in the reaction environment, in fact, hydroxylammonium salt are sparingly soluble. For this reason, the oximation process are slow, thus needs quite high temperature in order to achieve partial dissolution, for increasing formation of free oxime, and fnally to speed up reaction rate [25]. Furthermore, it is necessary to take into account that the use of liquid hydroxylamine is not industrially desirable due to the intrinsic instability of the compound [26]. Nowadays, the industrial production of hydroxylamine arises mainly from three processes: all based on the reduction of nitrites, NOx and nitric acid in solution of mineral acids, the latter stabilize the hydroxylamine produced to the corresponding hydroxyl ammonium salt [27]. The direct formation of hydroxylamine from ammonia oxidation is practicable by the direct amoximation of ketones by following the abovementioned Eni process [1]. In this case, ketone consumes immediately the hydroxylamine produced by the oxidation reaction thus directly forming the oxime. Furthermore, the reaction occurs in an aqueous solution of isopropyl alcohol, which reduces the risk of decomposition and explosion of the hydroxylamine eventually in solution [1]. The use of such a solvent, however, in the amoximation process does not allow a further Beckmann rearrangement, particularly, by using the trifuoroacetic acid (as organocatalyst) in a onepot process [15–18]. Then under such conditions, the recovery of the oximes from the solvent became necessary for the further step of Beckmann rearrangement. This further step diminishes the sustainability of the rearrangement catalyzed by trifuoroacetic acid in combination with an amoximation stage. Starting from this evidence, it appears that oximation of ketones is the weak stage of an all-liquid phase synthesis of amides in one-pot. In fact, either direct oximation of ketones with a hydroxylammonium salt of a mineral acid, or their amoximation, do not let a direct Beckmann rearrangement step, but separation and purifcation step needs. In this paper, we want to show some results on the synthesis and use of the ionic liquid hydroxylammonium trifuoroacetate as oximation agent for ketones in very mild condition. We want to show also the complete compatibility with a further step of Beckmann rearrangement catalyzed by trifuoroacetic acid. Finally, a very preliminary result on a modifed HPO process for the synthesis of such an ionic liquid is also given. The final aim of this preliminary work is that of proposing a practical liquid phase salts free synthesis of caprolactam and amides in general.
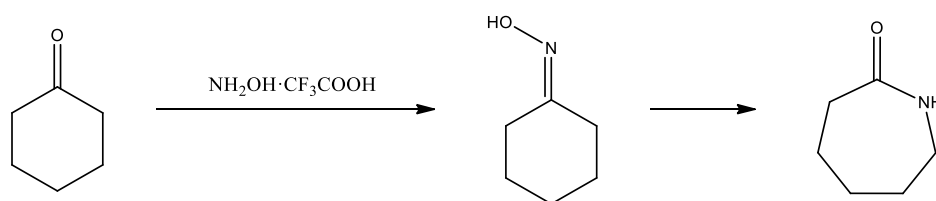
1.3.2 Results and Discussion

1.3.2.1 Infuence of the Oximation Agent in the Cyclohexanone->Cyclohexanane oxime->Caprolactame Process

Oximation reaction is a nucleophilic one and the actual reagent is the NH_2OH. In the usual organic synthesis the use of a strong base, such KOH or NaOH, it allows the neutralization of the acid of the hydroxylammonium salt, and the formation of free NH_2OH with the consequent formation of a stoichiometric amount of the sodium or potassium salt of the acid. The high reactivity of the free NH_2OH, though hydroxylammonium salt are sparingly soluble in non-aqueous organic solvent, allows the formation of the oxime. However, it arises at quite high temperature or long time of reaction.

Table 1 Reactivity of diferent oximation agents toward CON

Oximantion agent	Time (h)	TFA (TFA/CON) mol/mol	Conversion (%)	Selectivity	
				COX (%)	Others (%)
/	1	0	0	0	0
TAH	1	0	99	99	1
HCl	1	0	32	89	11
H_2SO_4	1	0	24	87	13
H_3PO_4	1	0	18	85	15
TAH	20	0	99	97	3
HCl	20	0	78	91	9
H_2SO_4	20	0	79	87	13
H_3PO_4	20	0	65	84	16
/	1	3	3	0	100
TAH	1	3	99	98	2
HCl	1	3	30	88	12
H_2SO_4	1	3	24	82	12
H_3PO_4	1	3	18	79	14
TAH	20	3	99	96	4
HCl	20	3	78	91	9
H_2SO_4	20	3	77	85	13
H_3PO_4	20	3	65	83	15

Run conditions: T 298 K, reaction volume 12 mL, CON 0.8 mol L−1, hydroxyl amine/CON=3, CH_3CN as the solvent 1 Other are mainly cyclohexanone condensation products

Table 1 shows the reactivity of different oximation agent on cyclohexanone (CON) conversion to cyclohexanone oxime (COX) in acetonitrile as the solvent. Only trifluoro acetic hydroxylamine (TAH) achieves quantitative conversion after 1 h of reaction, either in the presence of trifluoroacetic acid (TFA) or in its absence (at longer time of reactions a very small increase of the condensation byproducts is observed about 2%). With other hydroxyl ammonium salts, reactions have shown lower conversion and selectivity. Only the reaction with HCl has reached 78% of conversion after 20 h of reaction. It is noteworthy the presence of TFA is mandatory to have in the second step, that is the Beckmann rearrangement of the oxime, high conversion and selectivity in caprolactame (CPL), for this reason were tested the reactivity of the various oximation agent in the presence of TFA in the optimal concentration for the Beckmann rearrangement [15–18].

The presence of TFA with the others oximation agents causes a slightly reduction of the selectivity in COX, probably because of the increases of the condensation products of CON catalyzed by TFA (Table 1).

The Trifluoro acetic hydroxylamine (THA) gives the best result in terms of conversion and selectivity probably due to its complete solubility in acetonitrile or in the mixture acetonitrile TFA. In addition, just the selectivity is unaffected by the presence of the TFA, while with other oximes decreases.

Table 2 Reactivity of the second step in Beckmann rearrangement in the presence of diferent oximation agent

Oximation Agent	Time	TFA	Conversion	Selectivity	
		(TFA/COX)		CPL	Others[1]
	(h)	mol/mol	(%)	(%)	(%)
/	20	0	3	0	100
TAH	20	0	5	2	98
HCl	20	0	6	2	98
H_2SO_4	20	0	4	2	98
H_3PO_4	20	0	3	2	98
/	1	3	8	0	100
TAH	1	3	99	97	3
HCl	1	3	30	88	12
H_2SO_4	1	3	24	34	66
H_3PO_4	1	3	18	51	49
TAH	20	3	99	98	2
HCl	20	3	98	95	5
H_2SO_4	20	3	77	50	50
H_3PO_4	20	3	65	48	52

Run conditions: T 383 K, reaction volume 12 mL, CH_3CN as the solvent, COX 0.8 mol L−1 [1]Other are mainly cyclohexanone condensation products

Table 2 reports the reactivity in the second step of the process that is the Beckmann rearrangement catalyzed by TFA or, eventually, by the acid deriving from the

hydroxylammonium salt. It appears that only in the presence of an excess of TFA conversion to CPL occurs in practical interesting yield. As a matter fact, in the presence of TFA/COX=3 it achieves practically quantitative conversion and selectivity of 97–98% in CPL after one hour of reaction only in the presence of TAH. In other cases, reactions appear incomplete (even though quite good results it is achieved after 20 h of reaction with Cl–H) and several condensation products of CON are in the reaction mixture after 20 h of reaction.

The formation of such condensation products can be explained by the presence of unreacted CON, which causes these unwanted condensation reactions at the increasing of the temperature to 383 K, necessary to achieve a quite fast Beckmann rearrangement of the COX [15–18]. This agrees with the results of the control reactions carried out without oximes, in which CON condensations products are the only molecules detected. Besides, these side-reactions favors COX hydrolysis further, because of formation of water and alcohols, thus determining an extra reduction of the selectivity in CPL. The formation of condensation products are parallel reactions, since CON in the presence of TFA after 1 h of reaction at 383 K gives, a conversion of 8% to such condensation compounds. In addition, in the presence of hydroxylammonium salts and no TFA, COX forms mainly CON and its condensation products, while, if TAH is in reaction medium, it minimizes hydrolysis to CON together with its condensation products.

1.3.2.2 Infuence of solvents and of the operative variables on oximation of CON with TAH followed by Beckmann rearrangement to CPL

Table 3 Reactivity of TAH toward CON oximation and Beckmann rearrangement in the presence of various solvents

Solvent	Oximation			Beckmann rearrangement		
	CON Conv.(%)	COX Sel. (%)	Other Sel. (%)	COX Conv. (%)	CPL Sel. (%)	Other[1] sel. (%)
CH_3CN	99	99	1	99	97	3
Toluene	92	98	1	98	96	3
Dioxane	99	97	3	8	89	11
THF	99	98	2	7	90	10
EtOH	99	99	1	5	45	55
DMC	99	95	5	2	2	98
Et_2O	99	94	6	2	5	95

Run conditions oximation step: T 298 K reaction volume 12 mL, CON 0.8 mol L−1, hydroxylamine/CON=3, time of reaction 1 h. Beckmann rearrangement step T 383 K, time of reaction 1 h, TFA/CON= 3, [1]Cyclohexanone and cyclohexanone condensation products

Table 3 shows the infuence of various solvents on the reactivity of the TAH in the CON oximation and Beckmann rearrangement. CH_3CN as a solvent gives the best results, since in such a solvent both the oximation and the rearrangement steps occur easily. In the other tested solvents, the oximation takes place in high conversion and selectivity in COX, but the second step occurs in much lower conversion and selectivity. For instance, toluene, dioxane

and THF shows a quite high selectivity in CPL, but conversion of COX is very low, while in EtOH, DMC and Et$_2$O CPL is formed only in few percent of yield. Toluene as the reaction solvent gives lower oximation yield (conversion 94% selectivity 98%), but it appears to be a good solvent for the second step where 96% selectivity to CPL is achieved. Actually, CH$_3$CN appear to be however, the best solvent for such a process, this is in agreement with previous results in which specifcally this solvent was recognized as the best solvent for the Beckmann rearrangement catalyzed by TFA [15–18].

1.3.2.3 Reactivity of TAH towards different ketones

TAH shows high reactivity toward all ketones in the oximation reaction, in fact in all cases high conversion and selectivity is achieved in 1 h at 298 K. As expected, 2,4,6 trimethyl acetophenone (2,4,6-TMA) does not react since the nucleophile does not approach to the carbonyl because of the steric hindrance of the methyl group in 2- and 6- position of the phenyl. This effect on the reactivity of the TAH is the same for the reactivity of the free hydroxylamine in aqueous solvent, in which the same steric effect with ortho- substituents were observed [29].

Table 4 Reactivity of TAH in the oximation of several ketones

Ketone	Time	TFA (TFA/CON)	Conversion	Selectivity	
				Oxime	Other
	(h)	mol/mol	(%)	(%)	(%)
CON	1	0	99	99	1
ACP	1	0	99	99	1
2,4,6-TMA	20[1]	0	0	0	0
4-OH-ACP	1	0	99	99	1
4-Me-ACP	1	0	98	97	3
2-Me-ACP	1	0	77	95[2]	5
2-Me-ACP	20	0	77	95[2]	5
4-NO$_2$-ACP	1	0	96	96	4
CON	1	3	99	98	2
ACP	1	3	99	97	3
2,4,6-TMA	20[1]	3	0	0	0
4-OH-ACP	1	3	99	96	4
4-Me-ACP	1	3	98	96	4
2-Me-ACP	1	3	75	94[2]	6
2-Me-ACP	20	3	77	95[2]	5
4-NO$_2$-ACP	1	3	94	96	4

Run condition: T 298 K, reaction volume 12 mL, Ketone 0.8 mol·L^{-1}, TAH/Ketone=3, CH$_3$CN solvent.
[1]Preparation of 2,4,6,-trimethyl acetophenone oxime requires very long reaction time, but under this condition no reaction has been observed after 30 days[29]. [2]Selectivity is the sum of the two isomers

Such a behavior of the hydroxylamine as nucleophile suggests that the role of the trifuoroacetate is not determining the reactivity of the hydroxylamine itself, but, likely, it acts on the solubility of the ionic specie. In fact, a single phase is achieved with TAH while with the other hydroxylammonium salts a solid phase is always present. From practical point of view, it is noteworthy the high conversion and selectivity for the 4-OH-acetophenone (4-OHACP) would suggest a new route for the synthesis of acetaminophen (N'acetyl-4-aminophenol) in a waste free process and in one pot reaction [23]. In fact, the use of TAH will allow the synthesis of such a compound without salts coproduction and with a complete reuse of solvent and TFA. In this table for the sake of clearness we report the reactivity of only the 2-MeACP since both E and Z oximes are obtained and the reason of this difference with respect to the other ketones is beyond the aim of the present work and it needs further investigations (Table 4).

1.3.2.4 Preliminary results on HNO₃ hydrogenation in TFA for the direct synthesis of TAH

The use of TAH, as oximation agent for cyclohexanone as intermediate in the caprolactam production, is interesting, if it is available an easy way to obtain such a reagent without using complex procedure or multistep process. The HNO_3 hydrogenation DSM-HPO process directly gives hydroxylamine phosphate salt, now we try to verify the feasibility of a modifcation of such a process in order to obtain directly the TAH by hydrogenation of the nitric acid [27].
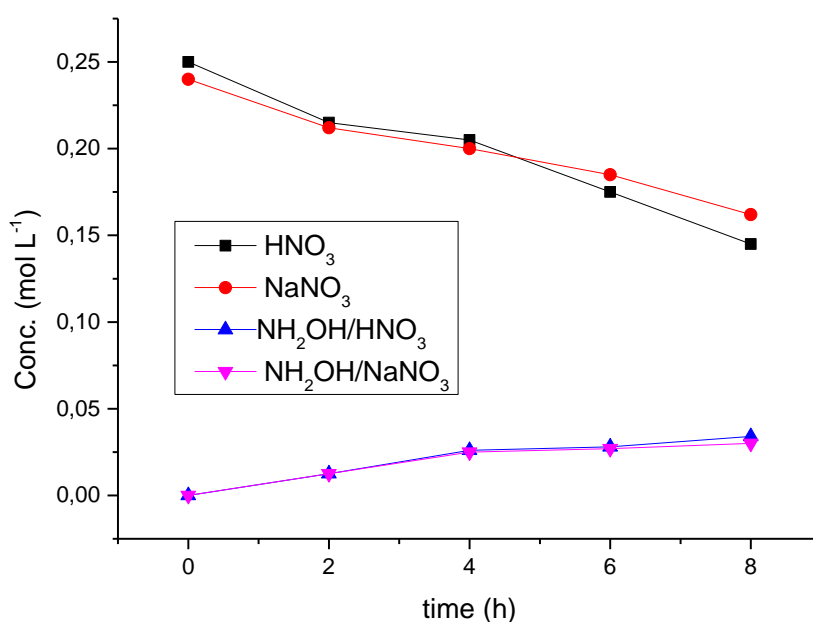

Fig. 1 Reaction profile of Nitric acid hydrogenation. Run conditions: Catalyst Pd/C 10% 50 mg, solvent aqueous TFA 10%, pressure 1 bar, hydrogen flow 20 mL min^{-1}, substrate concentration 0.25 mol L^{-1} reaction volume 20 mL

In Fig. 1 a reaction profile of nitric acid hydrogenation is reported. It is noteworthy that there is a negligible diference in the reactivity of HNO_3 or its sodium salt, suggesting sodium cation does not infuence the overall reactivity. Conversion does not reach completeness after 8 h of reaction however at higher temperature and pressure a complete conversion is reached but at lower overall yield of TAH. As a matter of fact, complete hydrogenation of hydroxylamine to ammonium hydroxide occurs at higher temperature and pressure.

1.3.3 Conclusions

The reactivity of TAH and that of TFA for an integrated process from ketones to amides has been verifed. It appears that TAH as oximation agent results generally more active than the mineral acid oxime salts. In fact, almost all the ketones undergo oximation in 1 h at room temperature. The reason of such a behavior it has been ascribed mainly to the complete solubility of the compound in the various solvents employed for the reactions rather than to a specifc reactivity of the ionic liquid. The more useful behavior of the compound in these consecutive reactions is however, the formation of TFA after the oximation step, which is necessary for the further step of Beckmann rearrangement. Furthermore, TFA does not negatively affect the oximation step and it can be added in quite large excess directly in the first stage of the process. The Beckmann rearrangement however occurs easily in the same reaction environment, but temperature must be raised at 383 K to achieve complete conversion in 1 h of reaction. Finally, the possibility of the synthesis of the TAH via a modifed HPO process in which the ionic liquid can be obtained directly from HNO_3 hydrogenation in the presence of TFA has been preliminarily demonstrated. Reuse of solvent and trifuoroacetic acid is easily achieved by distillation.

1.3.4 Experimental sections

Reagents

All solvents and reagents were employed as received without further purification. trifluoroacetic acid 98% (TFA) Carlo Erba, cyclohexanone 99% (CON), acetophenone 99%, 4-Hydroxyacetophenone $\geq$ 98%, 2-hydroxyacetophenone $\geq$ 95%, 2-methyl-acetophenone $\geq$ 98%, 4-Br-acetophenone 98%, 4-NO_2-acetophenone 98%, 2,4,6-trimethyl-acetophenone $\geq$ 98%, cyclohexanone oxime (COX), acetanilide, N-acetyl-4-aminophenol, caprolactam (CPL), trifluoroacetic acid (TFA) 99%, hydroxylamine hydrochloride (Cl–H) 99%, hydroxylamine Sulfate 99% (SO_4-2H), hydroxylamine phosphate 99% (PO_4-3H), diethyl ether (Et2O), acetonitrile, ethanol (EtOH), dimethyl carbonate (DMC), dichloromethane, tetrahydrofuran (THF), and dioxane were all Merck solvent grade products. Deuterated chloroform and deuterated acetonitrile were Merck products.

Equipment

Analyses of the reactions were carried out with gas chromatograph (GC) an Agilent 6890 equipped with FID or on chromatograph coupled mass spectrometer (GC–MS) Agilent 7890A equipped with a MS detector (Agilent 5975C) both instruments with a HP 5 column (I.D. 320 μm, 30 m long, same column in both the). Calibration with standard solutions of the pure products allows the calculation of yield and selectivity. To verify the presence of thermo-labile substances some samples were analyzed by HPLC (Perkin Elmer 250 pump, LC 235 diode array detector and a C 18, 5 μm, 4 mm i.d. 25 cm long column, using CH_3CN-H_2O as mobile phase, in isocratic CH_3CN 70%, at 1 mL min^{-1}). ^{1}H and ^{13}C NMR measurements were carried out in a Brucker Avance 400 II at 400 MHz and 100 MHz, respectively, in $CDCl_3$, CD_3CN or D_2O as the solvent.
DSC-TGA measurements were carried out on a Linseis TGA1000 in an aluminum crucible under an air fow of 100 mL min^{-1} and a temperature ramp of 10 K min^{-1}.

Synthesis hydroxilamine trifluotoacetate

Hydroxylamine trifluoroacetate were synthesized by an exchange procedure in aqueous solution. A typical preparation was carried out as follow: hydroxylamine sulfate was dissolved in water (c.a. 10 wt. %). A solution of $Ba(OH)_2$ 5% is neutralized with TFA plus an addition of a small excess of TFA until pH=3, this is useful to complete the exchange of the sulfate ions in the second step. The slowly addition of the hydroxylammonium sulfate solution allow the precipitation of $BaSO_4$ and in solution remains $NH_2OH \cdot CF_3COOH$ (TAH). The separation of the surnantant solution by centrifugation it allows recovering TAH after the evaporation of the water in a rotary-evaporator at 343 K under vacuum (mechanical pump 1000 Pa). The resulting viscous oil is then left at 343 K under higher vacuum (0.2 Pa) for 2 h.

TAH is a viscous colorless oil and it was characterized by TGA–DSC, NMR, and electric conductivity.

Fig. 2 shows DSC/TGA characterization of TAH an exothermic decomposition peak is detected at 430K and a second peak at 580K which cause the complete loss of mass in the sample.
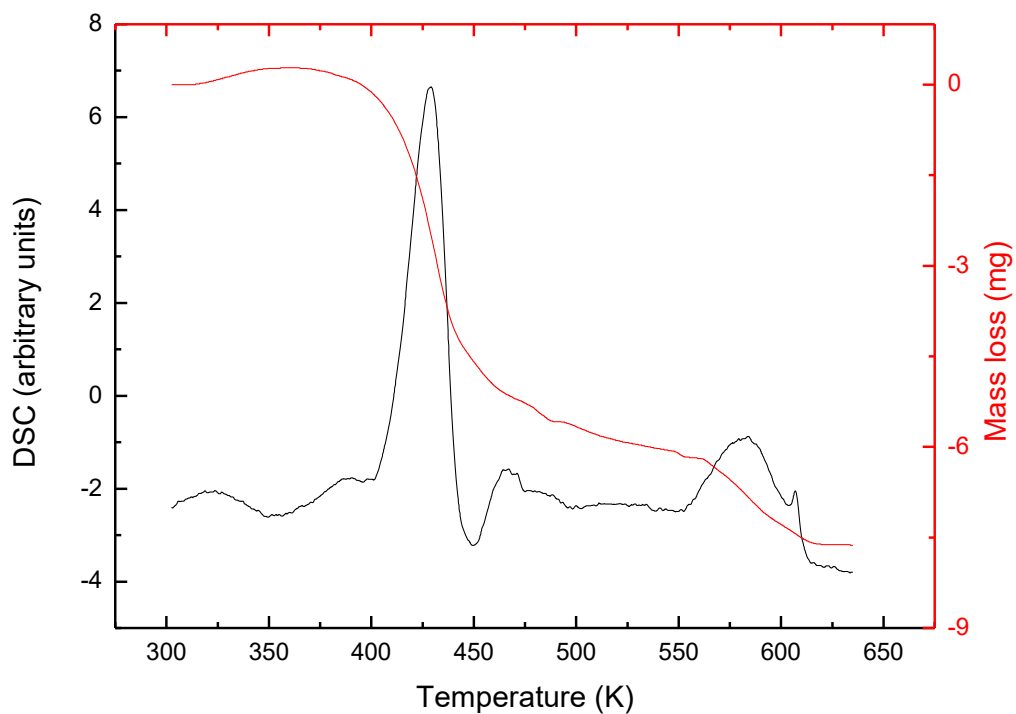

Fig. 2. DSC/TGA measurements of TAH in air (non-corrected). Run conditions: sample 9.28mg, air flow 100mL mim^{-1}, temperature ramp 10 K min^{-1}, crucible aluminum, Linseis tga 1000

The ^{1}H NMR spectrum reported in Fig. 3 shows only a broad signal at 7.34 ppm, which collects all the protons exchanged in the compound.
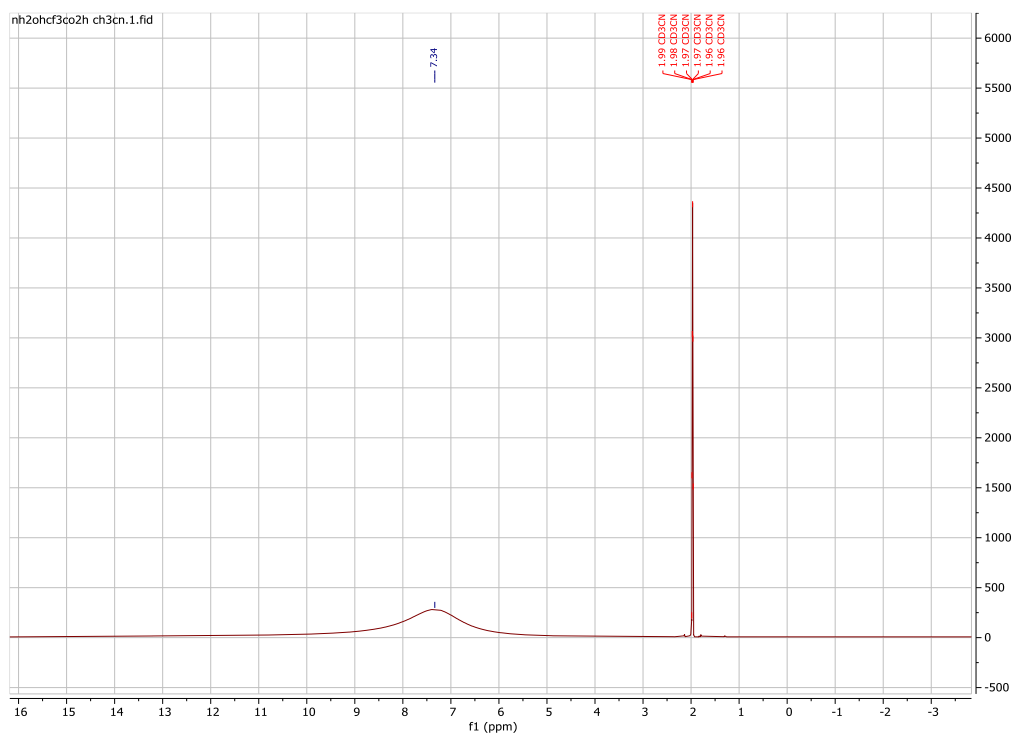

Fig. 3 ^{1}H-NMR CF$_3$COOH*NH$_2$OH (400 MHz,CD$_3$CN): *δ 7,34 broad peak of hydroxyl protons*

Fig. 4 shows the ^{13}C NMR spectrum where only the trifluoroacetate anion is detected.
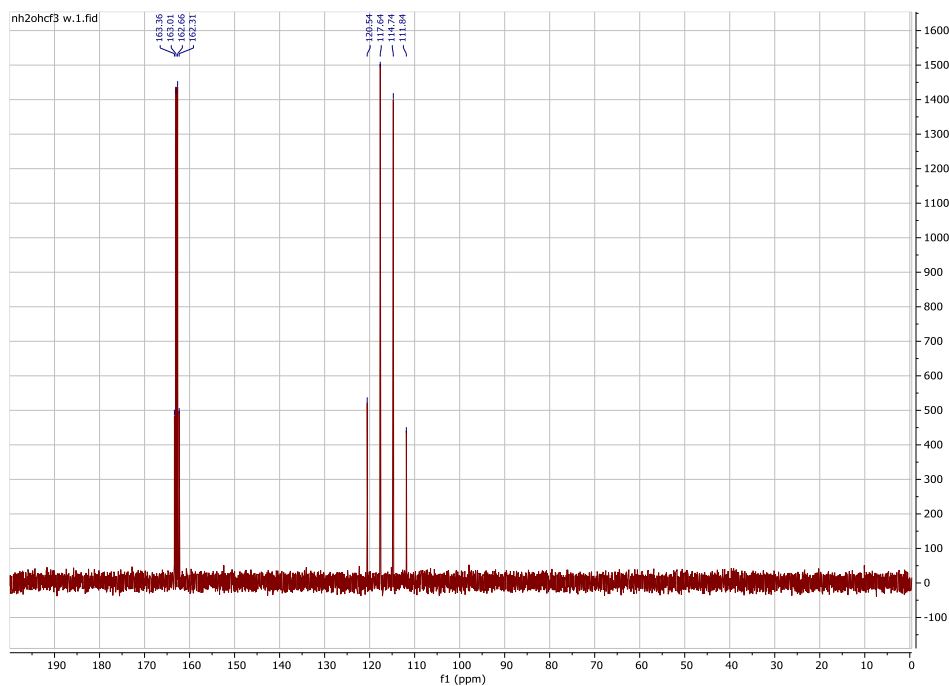

Fig. 4. ^{13}C-NMR CF$_3$COOH*NH$_2$OH (100MHz D$_2$O): δ 116,2 (q, J C-F 35 Hz), δ 162,8 (q, J C-F 290 Hz) spectrum of the trifluoroacetate anion.

Impedance spectra show a typical ionic behavior in water with a conduction typical of a charge transport with very low phase rotation no capacitive effect occurs (see Fig. 5 and 6). Similarly, in ACN as the solvent, the conduction is ionic at low frequency (until 100000Hz) but with a higher resistive impedance with respect of the measurements in water because of cluster aggregation (see Fig. 7 and 8), which reduce ionic mobility. At high frequency (above 100000 Hz) impedance decrease but phase rotation suggests a typical capacitive nature of the transport.
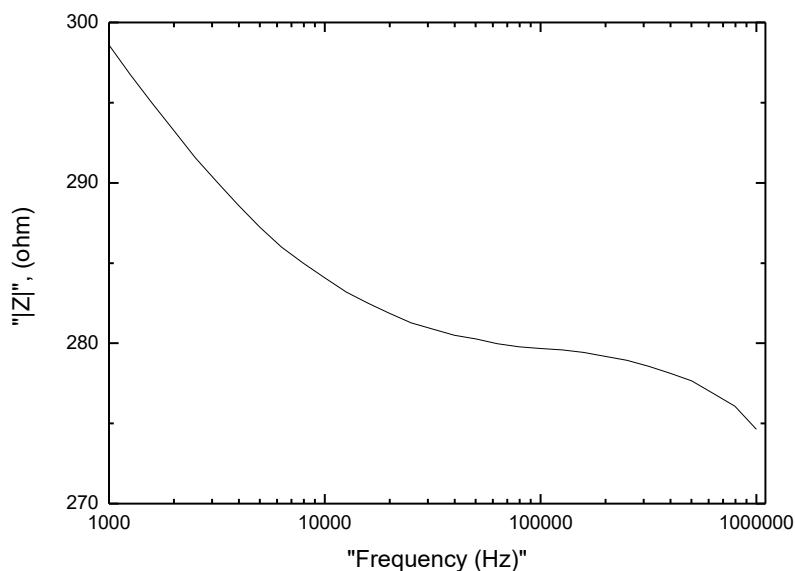

Fig. 5. Impedance spectrum of the aqueous solution of TAH, impedance modulus vs frequency. Run conditions: concentration 0.05 mol L^{-1}, Platinum cell constant 1 cm^{-1}.
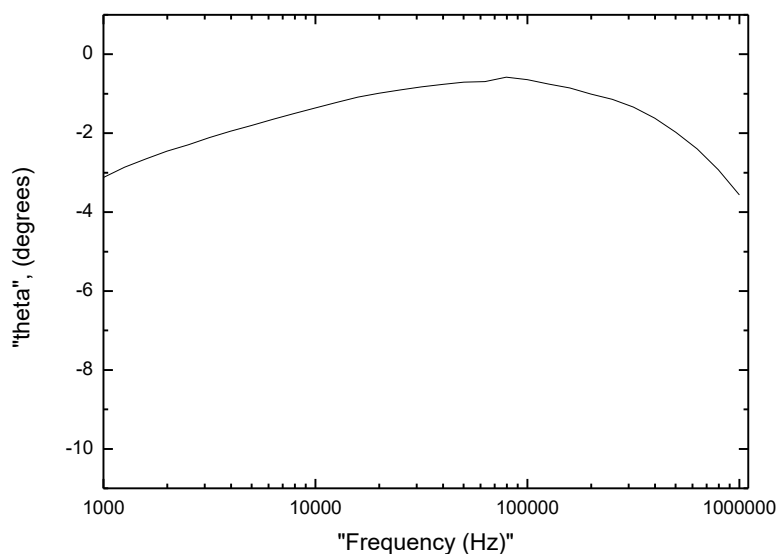

Fig. 6. Impedance spectrum of the aqueous solution of TAH, phase vs frequency. Run conditions: concentration 0.05 mol L^{-1}, Platinum cell constant 1 cm^{-1}.
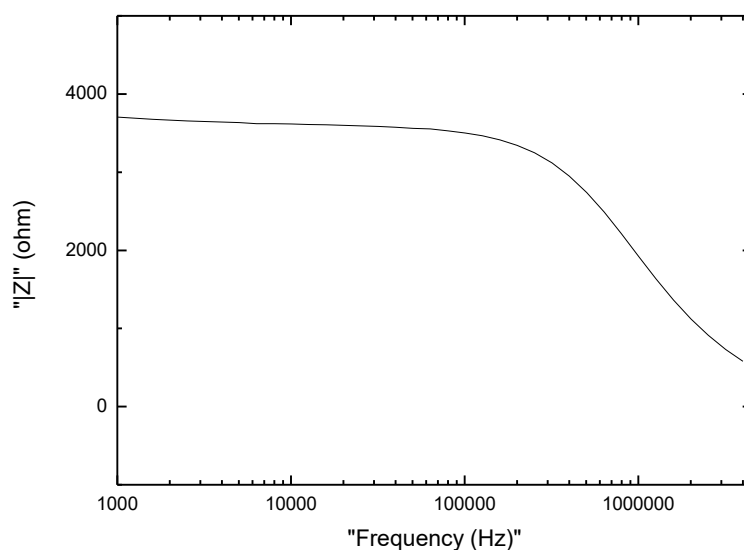
81

Fig. 7. Impedance spectrum of the ACN solution of TAH, impedance modulus vs frequency. Run conditions: concentration 0.05 mol L^{-1}, Platinum cell constant 1 cm^{-1}.
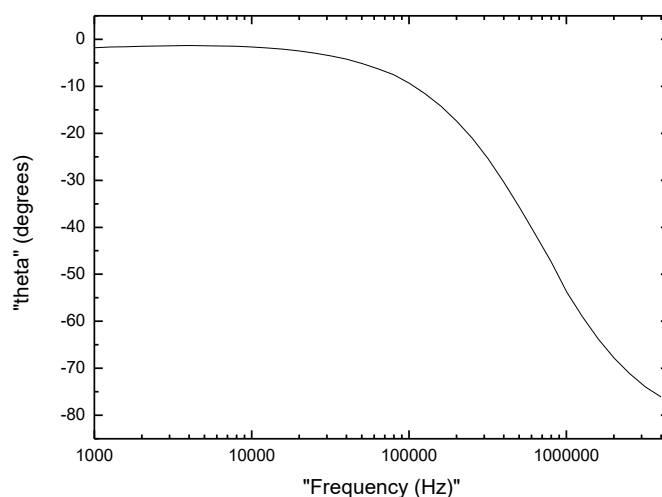

Fig. 8. Impedance spectrum of the ACN of TAH, phase vs frequency. Run conditions: concentration 0.05 mol L^{-1}, Platinum cell constant 1 cm^{-1}.

Reaction Set-up

All the reactions were carried out in a well stirred glass reactor thermostated at temperatures comprised between 298 K and 318 K, containing weighed samples of the solvent and reagents. In a typical experiment was loaded 10 mmol of the selected ketone, 30 mmol of $NH_2OH \cdot X$ (where X= CF_3COOH, HCl, H_2SO_4, H_3PO_4), 10 mL of solvent (CH_3CH_2OH, CH_3CN, DMC, CH_2Cl_2), and, if required, 30 mmol of TFA, reaching the final volume of reaction of about 12 mL. The Beckmann rearrangement step were carried out in the same

reactor used for the oximation plugged into a 20 mL autoclave to accomplish Beckmann rearrangement at temperature of 383 K, which is higher than that of the boiling point of the solvent (acetonitrile 355 K). In the selectivity calculations TFA peak has not been considered, while the traces amount of the ester COX-TFA is added to the COX peack. Preliminary experiments of nitric acid hydrogenation in aqueous TFA as a solvent (12 mL of HNO_3 0.25 mol L^{-1} in aqueous TFA at 10%) were carried out in an agitated glass reactor at 308 K for 8 h, at atmospheric pressure under hydrogen fow of 30 mL min^{-1}. Nitric acid conversion and hydroxyl amine formation are measured by spectrophotometric analysis [28].

1.3.5 References

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Chapter 2:
Olefins Carbonylation

2.1 Olefins carbonylation supported palladium metal as heterogeneous catalyst precursor of the methoxycarbonylation of cyclohexene

2.1.1 Introduction

The carbonylation reactions of alkenes and alkynes has been known since the work of Reppe at BASF reported in 1953, on the carbonylation reaction between acetylene, carbon monoxide and water, catalyzed by $Ni(CO)_4$ for the synthesis of acrylic acid[1] . Since then, hydrocarboxylations and hydroesterifications have attracted much interest in academia and industry, because they represent one of the exemplary cases of use of "green", one-step, atom-economic, environmentally friendly catalysts to obtain a variety of products.

Indeed, carboxylic acids and their derivatives (mainly esters) are a class of highly versatile compounds from a chemical point of view and are used to produce drugs, perfumes, surfactants, plasticizers, additives in the food industry, for the agricultural and textile industry and much more [1-8].

Also the hydrocarboxylation of cyclohexene to produce cyclohexylcarboxylates appears to have an interesting attraction from the commercial point of view, since cyclohexylcarboxylates are used both in massive industry (for example as plasticizers [6]) but also in fine chemistry (from the use as pharmacological and cosmetics intermediates to the production of liquid crystals)[8].

One of the examples of large-scale industrial of Carbonylation of olefins is related to the production of methyl methacrylate (MMA) which is one of the most important monomers in the world, produced annually on a scale of millions. This process involves the methoxycarbonylation of ethylene to produce methylpropionate, which is then reacted with formaldehyde to produce MMA. This synthetic route allows for milder operating conditions, no by-product formation and cuts production costs by at least 40%.[9]
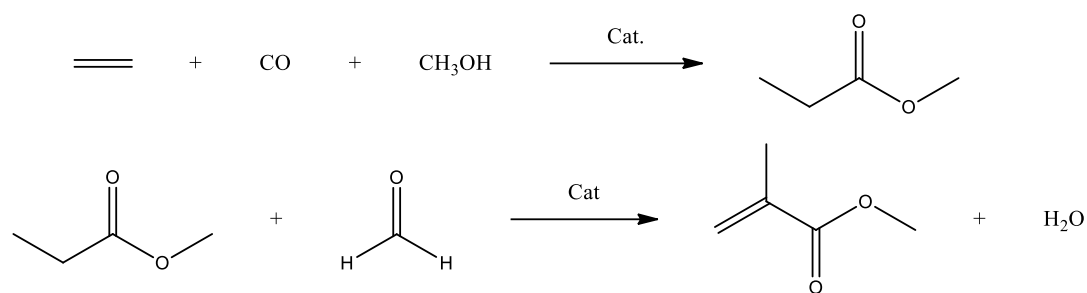
Fig. 1 Synthesis of MMA from Methylpropionate

Typically, carbonylation reactions are performed using homogeneous transition metal catalysts such as Co, Pd, Pt, Ni, Rh, and Ru [10].

The most commonly used catalysts are Pd(II) based, which show the highest catalytic activity. Moreover, the catalytic system requires the use of monodentate phosphine ligands (such as PPh$_3$) or bidentate ligands (P-P, such as dppb), which have been extensively studied in order to determine the best selectivity for the linear/branched ratio.

In addition, catalysis requires the use of an acidic co-catalyst whose purpose is to lead to the formation of the Pd-H species, which represents one of the two active species (along with the Pd-acyl species) currently most accepted for the catalytic cycle, and avoids the formation of metallic Pd, inactive for the reaction.

Although there are some exceptions, these reactions have little space in an industrial landscape because of the homogeneous nature of the catalysts involved, indeed the difficulty of recovering Pd catalysts from the reaction products represents a non-negligible cost.

To solve this problem, the academic world has spent a lot of effort defining some interesting strategies, which however still present some limitations.

For example, water-soluble phosphines such as tri(m-sulfophenyl)phosphine (TPPTS) and bis(SO$_3$Na)-Xantphos have been widely studied for hydrocarboxylation reactions and are already used in the Ruhrchemie/Rhône-Poulenc oxo process (hydroformylation of olefins with rhodium catalysts in a biphasic system). It is clear that this strategy is limited exclusively to the production of carboxylic acids[11]. Another possibility that has been extensively studied is to anchor homogeneous palladium complexes on clays or resins. For example, the methoxycarbonylation of substituted styrenes using Pd(OAc)$_2$ immobilized on montmorillonite (Pd-clay) and PPh$_3$ has been successfully carried out [12]. Although the system was very satisfactory in terms of yield and selectivity, the catalyst is not satisfactorily recyclable. On this example, homogeneous Pd(II) catalysts have been anchored on various supports such as silica, ion exchange resins, chitosan, etc. But in these various cases the problem of metal leaching or change in reaction selectivity after some recycling has been highlighted.

Very recently, a new class of materials, porous organic polymers (POPs), have emerged on the topic of industrial research. Due to their high surface area, variable porosity and high

thermal stability, they are used in various fields, such as in the field of superabsorbent materials.

Depending on the type of monomers used to synthetize these materials, it is possible to obtain more or less inert polymers. For example, in the field of catalysis, research is focusing on POPs obtained by polymerization, through Friedel-Craft alkylation (typically with 1,2-dichloroethane and $FeCl_3$), of triphenylphosphine (PPh_3). Due to the large number of anchor sites, various transition metals can be supported on these polymers by the formation of metal-coordination bonds.

Such catalytic systems have been successfully employed for the hydroesterification of a number of both aliphatic and aromatic olefins using Pd(II) anchored on PPh_3-POPs. These new heterogeneous catalytic systems show high reusability as the leaching is almost zero.

The fundamental problem for this new class of materials is that the synthetic methods used are complicated and lead to the formation of partly unknown Pd(II) species, which are therefore less active but also more unstable (reduction inactive Pd(0) or Pd metal species)[13].

An alternative may be the use of precatalysts of Pd metal deposited on inert solids, going on to synthesize the catalytically active Pd(II) species in situ. This could be attractive from an industrial point of view, as the substrates used may already be in the industrial background.

In the present chapter, the methoxycarbonylation of cyclohexene is presented employing metal Pd supported on a substrate as a heterogeneous precursor to the catalyst.

The catalytic productivity of this new catalytic precursor was compared with that obtained with homogeneous catalysts, such as $[Pd(TsO)_2(PPh_3)_2]$, in methanol as a solvent and in the presence of PPh_3 and a Bronsted acid (such as p-TsOH) as a promoter.

Among them Pd on Amberlyst IRC 50 resulted in the best catalytic activity, comparable homogeneous system $[Pd(TsO)_2(PPh_3)_2]$[30,31]. The leaching of the palladium was negligible, and the catalyst was efficiently recycled at least three times. A reaction mechanism was also proposed and discussed.

2.1.2 Results and Discussion

As a test reaction, the methoxycarbonylation of cyclohexene (figure 2) was performed employing a heterogeneous catalyst precursor based on Pd metal deposited on a insoluble support (Tables 1 and 2). Although it is reported in many works that the hydroesterification reaction is not catalyzed by metal Pd [2-5,31-38], it has been observed that the addition of free ligand (PPh_3) and a source of hydrides (p-TsOH), can lead to the formation of the catalytically active species (Pd-H) and as in the case of homogeneous catalysts[31-38], allows to obtain methyl cyclohexyl carboxylate in high yield.
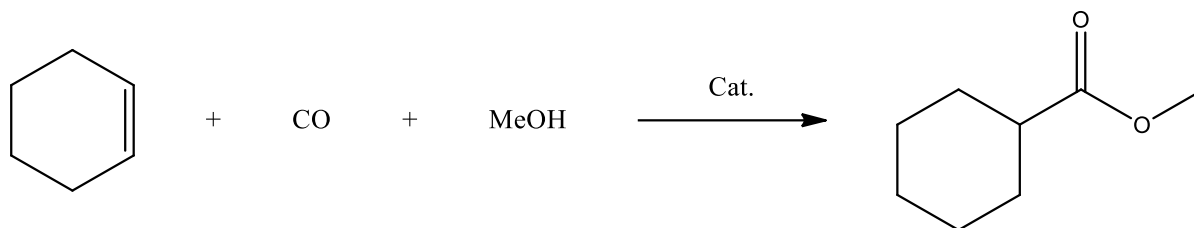
Fig. 2 Hydroesterification cyclohexene as model reaction

2.1.2.1 Influence of different supports on the catalytic activity

The activity of several heterogeneously supported Pd-metal precatalysts was compared with the activity of homogeneous systems, taking [Pd(PPh$_3$)$_2$(TsO)$_2$]/PPh$_3$/TsOH (1/50/60)[35,36] as a References (Table 1).

Table 1. Influence of different heterogeneous catalyst precursors on the methoxycarbonylation of cyclohexene.

entry	Catalyst	Specific Area (m^2/g)	Average porous diameter (nm)	Conv. (%)	TOF[a] (h^{-1})	Leachig of Pd (w/w %)
1	[Pd(PPh$_3$)$_2$(TsO)$_2$][b]	/	/	93	646	100
2	Pd/C (3%)	842	6	83	577	6
3	Pd/PK (3%)[c]	40	20	81	563	5
4	Pd/cellulose	2	20	82	570	6
5	Pd/Amberlyst IRC 50 (3%)	2	6	92	649	0,3
6	Pd/Amberlyst 15 (3%)	40	30	91	643	0,1
7	Pd/Dowex 1-X8 (3%)	0,3	11	42	292	12

Run conditions: Pd/Support = 50 mg (Pd 3 %, 0.014 mmol); Pd/PPh$_3$/TsOH = 1/50/60; Cyclohexene=19.7 mmol (2 mL), solvent = MeOH (8.0 mL, 197.7 mmol); T=120 °C; t = 2 h; P$_{CO}$ = 50 atm.
[a] [mol ester/(molPda * h^{-1})] is the total Pd metal present in the support before the reaction.
[b] homogeneous catalyst Pd/PPh$_3$/TsOH = 1/50/60 (mol/mol/mol) [35,36].
[c] PK = poly(1-oxotrimethylene), named polyketone [61,62].

The activities of the supported pre-catalysts lead to good conversions that are uncorrelated with the surface area and pore size of the heterogeneous supports.

Some of these systems lead to results very close to those obtained with homogeneous catalysis (conversions between 81-83%), especially with Pd/C, Pd/polyketone (Pd/PK), Pd/Cellulose. (items 5-7).

Other supported pre-catalysts have led to a wide range of results, especially Pdmetal supported on ion exchange resins.

Pdmetal on Dowex 1-X8 leads to the worst conversion (42 %, entry 5), while Pdmetal on Amberlyst IRC 50 and Pdmetal on Amberlyst 15 lead to the best conversions (92-91 %,

entries 5, 6), which are almost comparable to the conversion obtained using the homogeneous catalyst (93 %, entry 1).

As can be observed, the worst result was obtained using an anion exchange resin, Dowex 1-X8, characterized by the presence of quaternary amine groups. Probably in this case the formation of the catalytically active Pd-H species is hindered, or there is the formation of Pd(II) species less active for alkoxycarbonylation, but more soluble in the reaction medium, confirmed by the consistent phenomenon of metal leaching (item 7).

In addition to the possibility of recovering the catalytic system by simple filtration, the possibility of employing media recoverable by an external magnetic field was investigated. In the case of using metallic Pd deposited on a ferromagnetic (magnetite) Fe_3O_4 support, a decrease in cyclohexene conversion is observed. Moreover, at the end of the reaction, the total disappearance of the initial magnetic properties is observed. (Table2)[46]

Table 2. Influence of different heterogeneous catalyst precursors on the methoxycarbonylation of cyclohexene.

entry	Catalyst	Conv. (mol%)	sel. Ester% (mol%)
1	Pd/C (3 %)	83	100
2	Pd/PK (3 %)	81	100
3	Pd/Amberlyst IRC 50 (3 %)	92	100
4	Pd/Fe$_3$O$_4$ (3 %)	80	8
5	Pd/[C + Fe$_3$O$_4$ 5%] (3 %)	69	30
6	Pd/[C + Fe$_3$O$_4$ 15%] (3 %)	58	16
7	Pd/[C + Fe$_3$O$_4$ 25%] (3 %)	55	12
8	Pd/[PK + Fe$_3$O$_4$ 15%] (3 %)	65	25
9	Pd/[Amberlyst IRC50 + Fe$_3$O$_4$ 15%](3 %)	77	11

Run conditions: Pd/support =50 mg (Pd 3%, 0,014 mmol); Pd/PPh$_3$/TsOH=1/50/60; Cyclohexene= 19,7 mmol (2 mL), solvent MeOH= 8 mL, 197,75 mmol; T= 120°C, t= 2h; P$_{CO}$ = 50 atm

In the light of the screening results it was decided to optimize and study the reaction conditions on the precursor Pd/amberlyst IRC 50 which led to the best initial results in terms of productivity and Pd leaching.

2.1.2.2 Influence of PPh$_3$ and p-TsOH on the catalytic activity and on the leaching of palladium

As mentioned above, it is widely reported in the literature that metallic Pd is inactive for this type of catalysis.

In Figure 3 it is evident that the reaction conducted in the absence of free ligand (PPh$_3$) and in the presence of the acidic promoter p-TsOH does not turn out to be catalyzed by the Pd$_{Metal}$/Amberlyst IRC 50 precatalyst. However, by increasing the PPh$_3$/Pd molar ratio the

catalyst becomes active and the conversion goes through a maximum of 92% when it is about 50/1.

At PPh_3/Pd below about 45/1, the measured Pd leaching was less than 5% of the initial metal deposited on the support. On the other hand, at PPh_3/Pd higher than 45/1, the metal loss increases rapidly, reaching about 15% when PPh_3/Pd is about 120/1 (conversion of about 50%).

This trend appears to be in accordance with what has been reported for homogeneous catalysis, in fact it is plausible to assume that the metal palladium supported on the surface can form soluble Pd(0) complexes when the PPh_3/Pd ratio turns out to be higher than 45/1. These complexes are then transformed into the active species (Pd(II)-H) by reaction with acidic promoter, increasing the catalytic activity of the system (see Fig. 5).

But as in the case of homogeneous catalysis, increasing the amount of free PPh_3 leads to increased stabilization of Pd(0) species, which are inactive for catalysis, at the expense of Pd(II)-H species, causing a decrease in catalytic activity and an increase in leaching (see Fig. 4 and Fig.8).
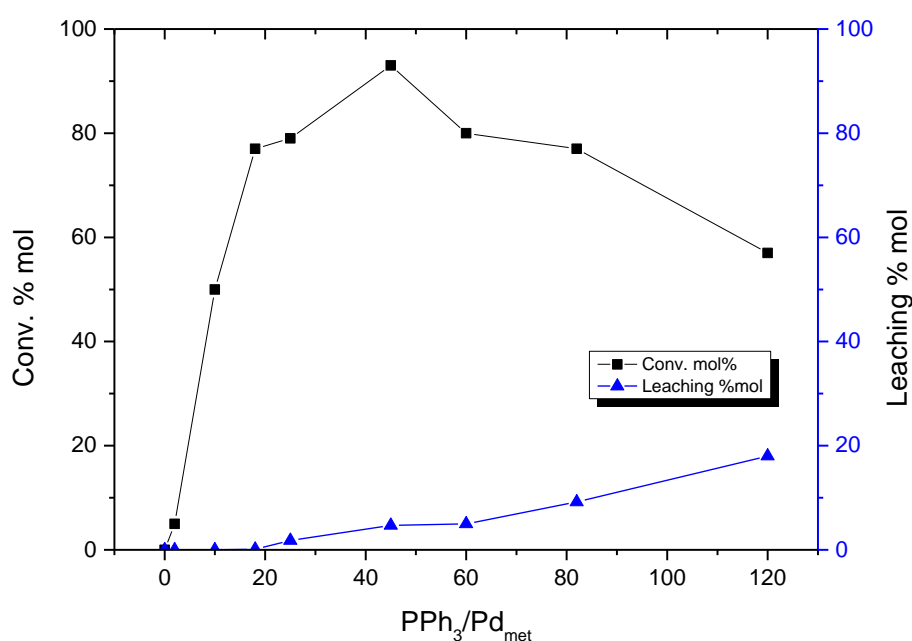

Fig.3. Influence of PPh_3 on the catalytic activity of Pd/Amberlyst IRC50(3%).
Run conditions: Pd/Amberlyst IRC50=50mg (Pd 3% w/w); Pd/TsOH=1/60mol/mol; Cyclohexene= 19.7mmol (2mL), solvent=MeOH (8.0mL); T=120°C; t=2h; P_{CO}= 50atm. TOF=moles of ester/[(moles of Pd in the solid before reaction)*(reaction time)].

Similarly to PPh$_3$, the presence of the acid turns out to be indispensable for the formation of the Pd(II)-H species, this is corroborated by Fig. 4 in which it shows a linear increase in the productivity of the catalytic system with increasing p-TsOH concentration (constant PPh$_3$ concentration, PPh$_3$/Pd=50/1).

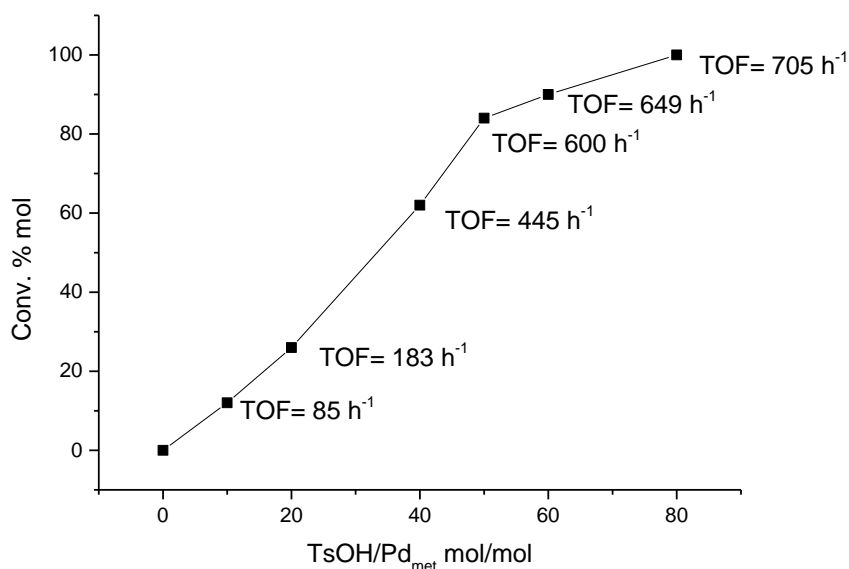
Fig.4. Influence of TsOH on the catalytic activity of Pd/Amberlyst IRC50(3%).
Run conditions: Pd/Amberlyst IRC50 =50mg (Pd3%,w/w); Pd/PPh$_3$=1/50mol/mol; Cyclohexene=19.7mmol (2mL), solvent=MeOH (8.0mL);T=120°C; t=2h; P$_{CO}$=50atm. TOF=moles of ester/[(moles of Pd in the solid before reaction)*(reaction time)]

2.1.2.3 Influence of temperature on the catalytic activity of Pd/Amberlyst IRC 50 (3%)

The temperature trend supplies further indication of the possible formation of the catalytically active species inside the pores or on the surface of the heterogeneous support. Indeed, it is possible to observe the increase in productivity with the increase of the reaction temperature, going to a maximum at 120°C (Fig. 5). Above this value, a drastic decrease in conversion is observed. As in the case of homogeneous catalysis, this is due to the decomposition of the catalytically active Pd(II) species towards the formation of Pd(0) or Pd metal. It is interesting to note that at temperatures above 120°C the leaching phenomenon does not increase significantly (in all tests it always remains below 3%), which may indicate that the decomposition of the active species occurs on the support, redepositing the palladium on its surface.
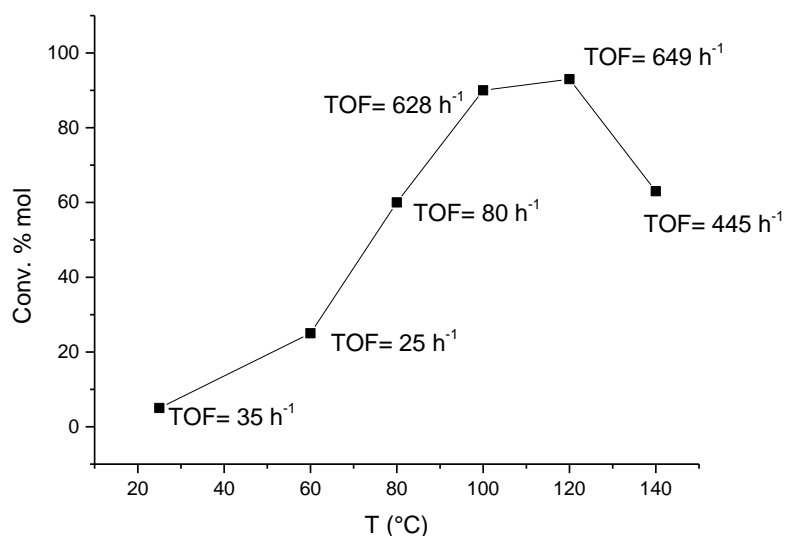
91

Fig.5. Influence of temperature on the catalytic activity. Run conditions: Pd/Amberlyst IRC 50=50mg (Pd 3 %, w/w); Pd/PPh₃/TsOH=1/50/60 (mol/mol/mol); Cyclohexene =19.7 mmol (2mL), solvent=MeOH(8.0mL);T=120°C;t=2h;P_CO=50atm.

2.1.2.4 Catalyst Recycle

To verify the reusability of the catalytic precursor deposited on a heterogeneous support, this was recovered by simple filtration, washed and recycled. To ensure that the recovered solid does not contain traces of complex and free palladium species, a series of thorough washings are performed. The solid is then dried and reweighed prior to each recycling. In addition, leaching tests, performed on both the liquid phase and the solid, confirm the material balance relative to palladium.
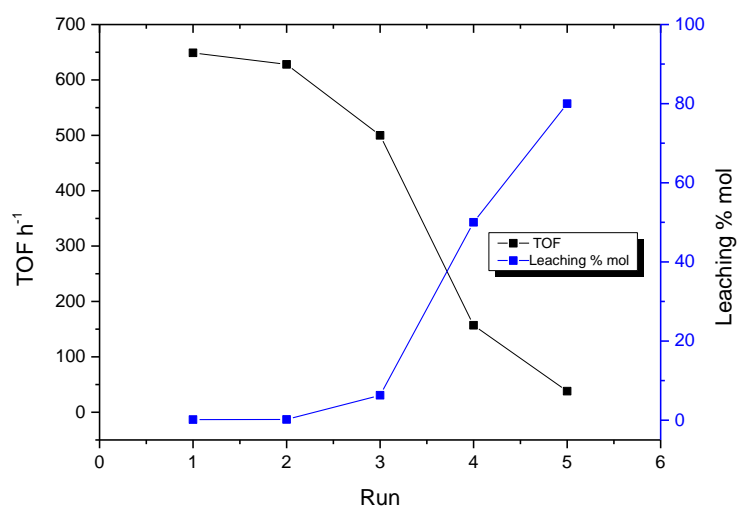

Fig. 6. Influence of catalyst recycling on the catalytic activity and on the leaching of Pd.
Run conditions: Pd/Amberlyst IRC 50=50mg (Pd 3 % ,w/w); Pd/PPh₃/TsOH= 1/50/60 mol/mol/mol; Cyclohexene=19.7mmol (2.0mL), solvent= MeOH(8.0mL); T=120°C; t=2h; P_CO=50atm.

The precursor can be used without significant loss in catalytic activity due to leaching at least twice (leaching less than 0.2%). At third reuse, however, a discrete catalytic decrease and an increase in leaching up to 6.3% is observed (Fig. 6).

In the present case, with the use of resins, this can be explained due to a mechanical degradation of the support, indeed after the second reaction macrostructural changes of the heterogeneous support were observed. Due to the stirring, performed with a magnetic stir bar, the spherical granules in the size range of 0.5-1 mm degrade in the form of powder. This degradation exposes the metallic palladium more to the reacting environment which, due to the formation of soluble Pd(0) or Pd(II) species, leads to increased leaching.

This degradation can be avoided using a special batch reactor setup, in fact with the use of baskets in which to confine the heterogeneous catalyst, it is possible to ensure adequate magnetic stirring without incurring the structural collapse of the support.

2.1.2.5 On the reaction mechanism

The results obtained in the study of Pdmetal-supported heterogeneous precatalysts suggest that the active species for catalysis are formed in situ from the reaction between PPh3, TsOH, and metallic Pd, similarly to what has been reported for homogeneous catalysis [2-5,31-38]. Accordingly, the proposed mechanism is the same as that reported in the case of using soluble Pd complexes in Fig. 7.
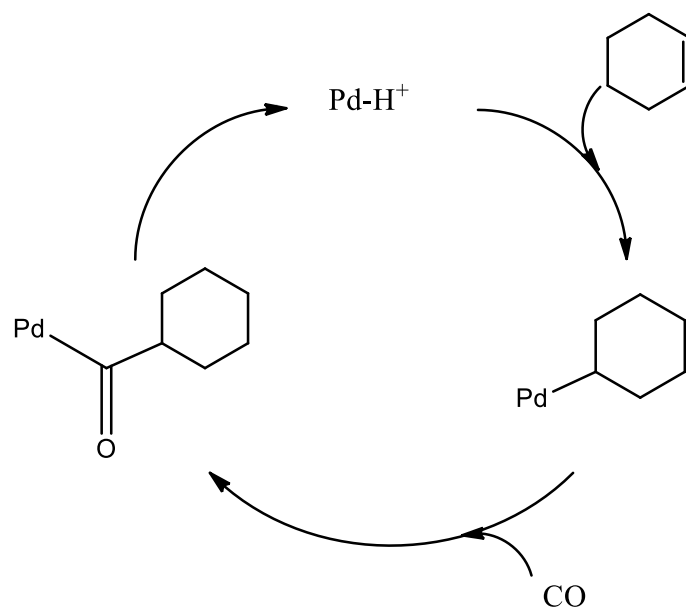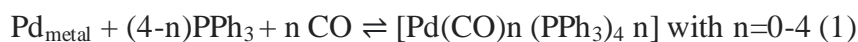

Fig.7. Scheme of the proposed reaction mechanism.

The soluble Pd-hydride species is formed in situ from the Pd metal deposited on the solid surface (or inside the pores) and the free CO, PPh_3 and TsOH, present in solution, for example following reactions 1 and 2.

$$Pd_{metal} + (4-n)PPh_3 + n\ CO \rightleftharpoons [Pd(CO)n\ (PPh_3)_4\ n]\ \text{with}\ n=0\text{-}4\ (1)$$

$$[Pd(CO)(PPh_3)_3] + TsOH \rightleftharpoons [PdH(CO)(PPh_3)_2]+(TsO)^- + PPh_3\ (2)$$

Since the formed Pd(0) and/or Pd(II) complexes are soluble in the reaction medium, it is plausible to assume that they are also the result of the observed leaching. This is confirmed by the increase in leaching, and decrease in catalytic activity, as the concentration of free PPh_3 increases Fig.3.

As reported for homogeneous catalysis, a high amount of free ligand becomes competitive in the formation of the catalytically active species.

But under the optimal conditions of PPh_3/Pd ratio (less than 45/1), in which there is high conversion and low leaching (Table 1), it is possible to hypothesize that this reaction occurs faster than diffusion to the bulk of the solution, retaining the active species within the solid.

Table 3 Effect of addition of a pyridine-based metal scavenger.

entries	metal scavenger	catalyst	conv. (mol %)	TOF (h^{-1})
1		[a]Pd/IRC 50 (3%)	92	649
2		Pd/IRC 50 (3%) recycled from exp 1	89	627
3	[b]PVPy	Pd/Amb IRC 50 (3%)	3	21
4	[c]PVPy-co-Sty	Pd/Amb IRC 50 (3%)	5	35
5		Pd/IRC 50 (3%) recycled from exp 3	n.d	-

Run conditions: Pd/Amberlyst IRC 50 (3%)=50 mg; Pd/PPh$_3$/TsOH=1/50/60; Cyclohexene=19.7 mmol (2 mL), solvent=MeOH (8.0 mL); T=120 °C; t=2 h; PCO=50 atm.
[a] Pd/IRC 50 = Pd/Amberlyst IRC 50 (3%).
[b] PVPy=Poly(4-vinylpyridine) average Mw ~60,000=150 mg.
[c] PVPy-co-Sty=Poly(4-vinylpyridine-*co*-styrene) powder=150 mg

Therefore, it is plausible that the catalytic reaction starts near the surface (in particular inside the pores) and that once the catalytic cycle is over, the soluble palladium species, in particular Pd(II)-H easily decompose to form Pd metal which is deposited back onto the support.

On this basis, Fig.5 shows that by increasing the temperature (> 120 °C) the conversion decreases suggesting a thermal decomposition of the catalyst, while keeping the Pd leaching low (< 0.12%), and this agrees with the hypothesis that a re-deposition of Pdmetal on the substrate surface occurs easily. This is further supported by the observation that the leaching is not affected by the reaction time (Fig. 8 shows that at 7 h it is very low, <0.12%) but only by the concentrations of PPh$_3$ and TsOH (Figs. 3 and 4).
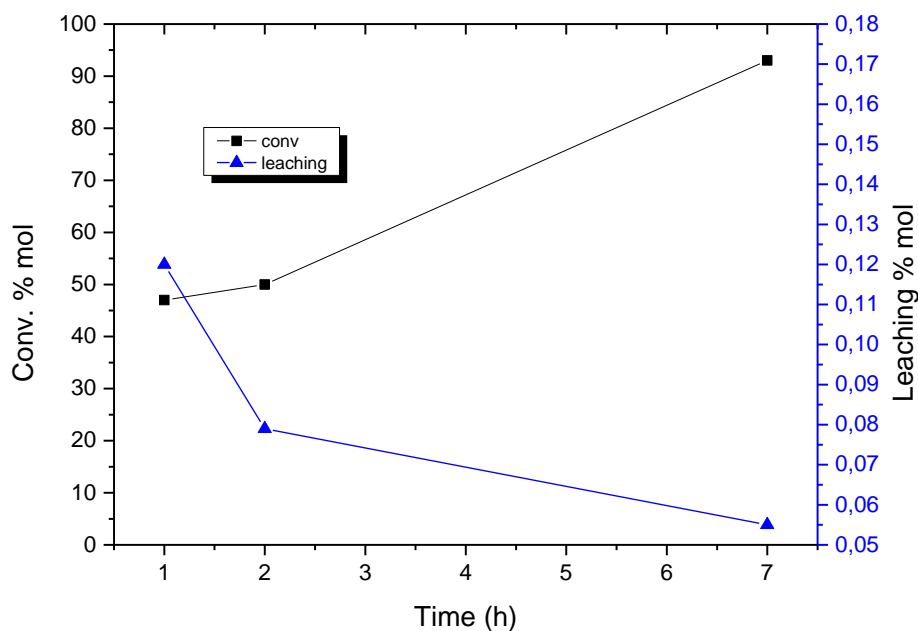
Fig.8. Influence of reaction time on the catalytic activity and on the leaching of Pd. Run conditions: cat: Pd/Amberlyst IRC50= 50mg (Pd 3%,w/w); cat/PPh$_3$/pTsOH= 1/50/60 (mol/mol/mol); Cyclohexene (2.0 mL, 19.7 mmol); MeOH= 8.0mL; T= 120°C; P$_{CO}$= 50atm.

It is clear from Table 1 that leaching is also related to the type of heterogeneous support used, in fact it is very low in the case of cation exchange resins (entries 5 and 6).

This is due to a possible interaction of the carboxylate groups present in Amberlyst IRC 50 (sulfonated in Amberlyst 15) with the cationic Pd(II) species formed in situ. This phenomenon could allow the metal, or soluble Pd(II) cationic species to remain confined within the support and prevent their diffusion to the bulk of the reaction.
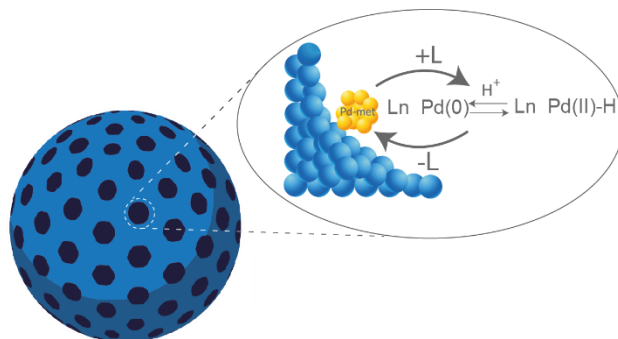
As in some examples reported in the literature (PPh$_3$-POPs), it is plausible to assume that the functional groups of the support act as "heterogeneous" coordinating ligands and/or as a cation-exchange resin between H$^+$ and the [Pd(II)]$^+$ cationic species formed during the catalytic cycle .

To verify the possible homogeneous nature of the catalyst confined in heterogeneous media, reactions were performed in the presence a pair of metal scavengers [68-75].

In partitular, polymers containing pyridine monomers (polypyridine PPy and poly(pyridine-co-styrene) PPy-co-Sty,) which are shown to be effective scavengers of soluble Pd salts or complexes (see Table 3) were used [63-75].

With the introduction of such metal scavengers, a drastic decrease in the catalytic activity is noticed, probably functioning as a driving-force to extract the soluble Pd species from the heterogeneous support. Table 3 (entries 3, 4), turns out to be in agreement with the hypothesis that the catalysis is due to the formation of soluble Pd speciations within the heterogeneous support (mixed homogeneous/heterogeneous catalysis). Furthermore, performing a recycling test with Pd/Amberlyst IRC 50, after being reacted the first time in the presence of the metal scavenger, did not lead to the formation of the ester.

2.1.3 Conclusions

Hydroesterification reactions of cyclohexene can be carried out efficiently using alcohol (methanol) as a solvent, employing precatalysts based on metallic Pd deposited on heterogeneous supports, especially ion exchange resins.

Although the formation of catalytically active Pd(II) species, and thus the catalytic activity, depends on the presence of adequate concentrations of free ligand (PPh$_3$), the presence of an acidic promoter (p-TsOH) and temperature, the best results in terms of productivity and metal leaching have been obtained using cation exchange resins as supports.

The results obtained from this homogeneous/heterogeneous system result in a sustainable alternative for olefin hydroesterification reactions, compared to homogeneous catalysis, which is however comparable in terms of conversion.

First because the heterogeneous nature of the support allows to easily recover the catalyst by simple filtration, with a metal leaching <1%, moreover it allows to easily weigh a low quantity of active metal for catalysis (3% Pd w/w dispersed on a heterogeneous support), and it can be reused for at least two times without significant loss of productivity.

2.1.4 Experimental Section

Reagents

Methanol, cyclohexene, Palladium(II) acetate, triphenylphosphine (PPh$_3$), p-toluenesulfonic acid monohydrate (p-TsOH), Amberlyst IRC 50, Dowex 1-X8, Amberlyst 15, Cellulose MFC (Type 101), Poly(4-vinylpyridine) average Mw ~60,000, and Poly(4-vinylpyridine-co-styrene) powder were purchased from Sigma-Aldrich; Polyketone was synthesized from CO and ethene (supplied by SIAD Company with 'research grade', purity>99.9 %) as described in literature [63].

Equipment

The catalyst precursors were weighted on a Sartorious Micro balance (precision 0.001 mg). Gas-chromatographic (GC) analysis was performed on a Hewlett Packard Model 7890, Series II chromatograph fitted with a HP5, 30m ×0.35mm ×0.53 μm column (detector: FID; carrier gas: N2, 0.2 ml/min; oven: 45 °C (3 min) to 250 °C at 15 °C/min).

GC/MS analyses were performed on a MS Agilent apparatus 5975C Model, interfaced with an Agilent chromatograph 7890 A Model equipped with a HP5 column (30m ×0.25mm ×0.25 μm, oven: 45 °C (3 min) to 250 °C at 15 °C/min).

The ICP-OES (Inductively Coupled Plasma optical emission spectrometry) analyses, to identification and detection of trace metals, were performed by using the PerkinElmer ®Optima 7300 DV ICP-OES instrument.

The specific surface area of the powders was measured by Micromeritics Instrument Inc. USA apparatus, ASAP 2010 model.

Syntesis of Pd-metal supported pre-catalst

Supported Pd-metal precatalysts were synthesized by the standard wet impregnation method [54,65].

As an example: 1 g of support was added, at room temperature and under vigorous stirring, to a freshly prepared solution of Pd(OAc)$_2$ in 50 mL of methanol, the amount of which was adjusted to eventually obtain the desired amount of Pd (ca. 3 %, w/w). The reaction mixture was kept at reflux and stirred for two hours to ensure complete reduction of Pd(II) to Pd-metal.

The catalyst was then filtered and washed 5 times with methanol to remove any reduced palladium not deposited on the support and washed twice with water (to avoid pyrophoric phenomena) and then dried under vacuum.

The amount of Pd-metal deposited on the support was determined by ICP analysis (confirmed as about 3%, within 1% error); the specific surface area of each solid was measured using the N_2 physisorption-BET technique

Synthesis of magnetic supports

The synthesis of magnetic supports was performed by deposition of Fe_3O_4 nanoparticles on support surface [45] (see Table 2). In a typical procedure, 0.115 g of Fe_3O_4, suspended in 5 mL of methanol, was added under vigorous stirring to 1 g of support (carbon black or PK) suspended in 20 mL of methanol. The mixture has refluxed for 1 h and then the solid has separated by a permanent magnet, washed with fresh methanol, and dried under vacuum. The specific surface area has measured by using the N_2 fisi-sorption-BET technique

Experimental setup

All the experiments were carried out in a stainless-steel batch reactor of ca. 50 mL of capacity, provided with a magnetic stirrer and a temperature control system (±0.5 °C). Carbon monoxide was supplied from a gas reservoir (260 mL) connected to the reactor through a constant pressure regulator.

Experimental procedure

In a typical experiment, known quantities of the pre-catalyst, PPh_3 and TsOH along with 8 mL of methanol and 2 mL of cyclohexene were charged into the reactor. The reactor was purged twice with carbon monoxide at room temperature with stirring, pressurized with a low CO pressure (ca. 5 atm) and then heated up (without stirring). At the working temperature the pressure was adjusted to the desired value (typically 50 atm total pressure) and maintained constant throughout the experiment (i.e. 2 h) by continuously supplying the carbon monoxide from the reservoir. At the end of each experiment the reactor was quickly cooled to room temperature and vented. The solid was recovered by filtration, washed and dried under vacuum. To determinate the amount of leaching it has been measured the amount of Pd on the solid before and after the reaction by using the ICP technique (the % of leaching has been expressed as [[(g of Pd in the solid before reaction) - (g of Pd in the solid after reaction)]/(g of Pd in the solid before reaction)]x100. The qualitative and quantitative analysis of the liquid was performed by using the GC–MS and GC technique. The conversion has been expressed as: [(initial moles of cyclohexene – final moles of cyclohexene)/ initial moles of cyclohexene] * 100; In all experiments the material balance has been verify and the selectivity to ester was 100 %

Recycling experiments

The pre-catalyst was recovered from the reaction solution through a simple filtration. It was thoroughly washed many times with methanol and acetone and then dried under vacuum. The solid was weighted and reused in the next reaction. In this case we prefer to evaluate the catalytic activity in term of TOF (Turnover Frequency: moles of ester/ (moles of Pd*h))

which was calculated by considering that all the amount of metal deposited on the surface was active in the catalysis. This is because during the recycling operations part of the catalyst (usually<2 %) could be lost. The leaching in the successive reactions was measured through the ICP analysis of the liquid phase and on solid. The next reaction was carried out following the same procedures above described.

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2.2 Synthesis of heterogeneous magnetic polyketone-coated catalysts for carbonylation reactions

2.2.1 Introduction

Heterogeneous catalysis represents one of the most important aspects of industrial processes, and it is for this reason that academic and industrial research, aimed at outlining new and more efficient heterogeneous catalysts, is still very fervent [1-3].

Recently, the possibility of using magnetic supports has attracted a lot of attention as a possible solution to lower costs in the recovery phase of heterogeneous catalysts. In fact, the magnetic separation results to be a simple, robust and fast system for the recovery in comparison to the classical systems of catalyst isolation (like filtration, centrifugation, extraction etc) [4].

Numerous materials can be prepared from ferromagnetic metals such as Fe, Ni and Co. They can be prepared either as metal nanoparticles or as oxides (e.g., Fe_3O_4), whose particle size properties can be varied to control the reaction parameters [5].

Ideally, like any other type of support for heterogeneous catalysts, these materials should be stable and inert under the reaction conditions. Magnetic nanoparticles can be uncoated or coated with a protective layer. There are numerous examples of transition metal-catalyzed reactions supported on uncoated magnetites, but typically these heterogeneous catalysts are not very stable over time, due to slow oxidation in air, or due to incompatibility with strongly acidic reaction environments [6-10].

For this reason, numerous strategies have been structured to preserve the magnetic characteristics of these materials by coating them with inert coatings. Besides ensuring the protection of the magnetic properties, this approach allows to facilitate the immobilization of the active phase of the metal and to increase the surface area of the catalyst.

Typically the silica coating is obtained by means of the sol-gel process, which consists in the formation of a silica layer due to the hydrolysis of TEOS in water in basic environment. [11-12]

Carbon coating, on the other hand, has attracted particular interest because of the high thermal stability and inertness of carbon. This type of coating is often applied to cover nanoparticles in the metallic state and is typically obtained by spraying the precursor (e.g. iron stearate) and pyrolyzing it at high temperatures, but unfortunately the size of the nanoparticles is difficult to select and the layer of coverage is not always homogeneous [13-17].

The possibility to coat magnetic nanoparticles with polymers is becoming more and more popular due to a series of chemical surface modifications that can be made to the particles [18-20].

Polymers can be physiosorbed or chemisorbed onto the metal surface, and by intervening on the functionalities present on the polymer, it is possible to coat the particles with one or more layers.

These magnetic materials with polymer coatings can be used as supports for heterogeneous catalysts. But even in this case it is necessary to consider some critical aspects related to the use of polymers as coatings, such as their thermal stability and their resistance to solvents. Considering these aspects, a new material has been synthesized with magnetic properties such as to be used as a support for palladium-based magnetic catalysts. Specifically, carbon-coated magnetic iron material (MIM) have been obtained by thermal decomposition of iron(0) pentacarbonyl ($Fe(CO)_5$) in an inert atmosphere using a flow reactor[21-22].

The material consists of a series of dentrites whose core is composed of iron, covered with a layer of carbon. The optical characterizations showed that the layer of protective carbon is not always homogeneous, then was covered with a second layer of poly(1-oxo-trimethylene) (polyketone, PK) obtained by carbonylative polymerization of CO / ethene [23]. The chemical and physical characteristics of the polymer, such as high resistance to temperature and solvents, make it suitable for coating the material and preserving its magnetic properties.

This catalyst has been successfully used in olefin carbonylation reactions, iodoarene carbonylation and nitroarene reduction reactions [24-27].

2.2.2. Results and discussion

2.2.2.1 Synthesis and characterization of Magnetic Iron Material

The magnetic properties of the material synthesized by pyrolytic degradation of $Fe(CO)_5$ (Figure 1) with the flux reactor, are currently in progress, but preliminary results obtained by SQUID analysis suggests that it is a soft magnetic material, a hypothesis supported by XRD analysis (Figure 2) in which it emerges that the core of this material consists primarily of Iron(0).

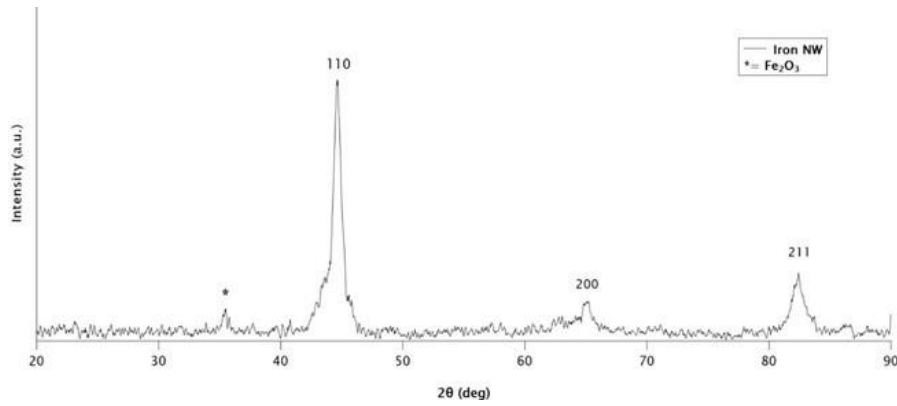Fig. 1. Macroscopic appearance of MIM obtained by decomposition of $Fe(CO)_5$

Fig. 2. XRD spectrum of MIM

As it is possible to observe from Figure 3 the MIM presents a dendritic morphological structure. The filaments are mainly composed of an iron core, covered by a layer of carbon, but as it is possible to observe the coating is not always homogeneous, which makes the material susceptible to oxidation by air (which justifies the presence of traces of iron oxides determined by XRD analysis).
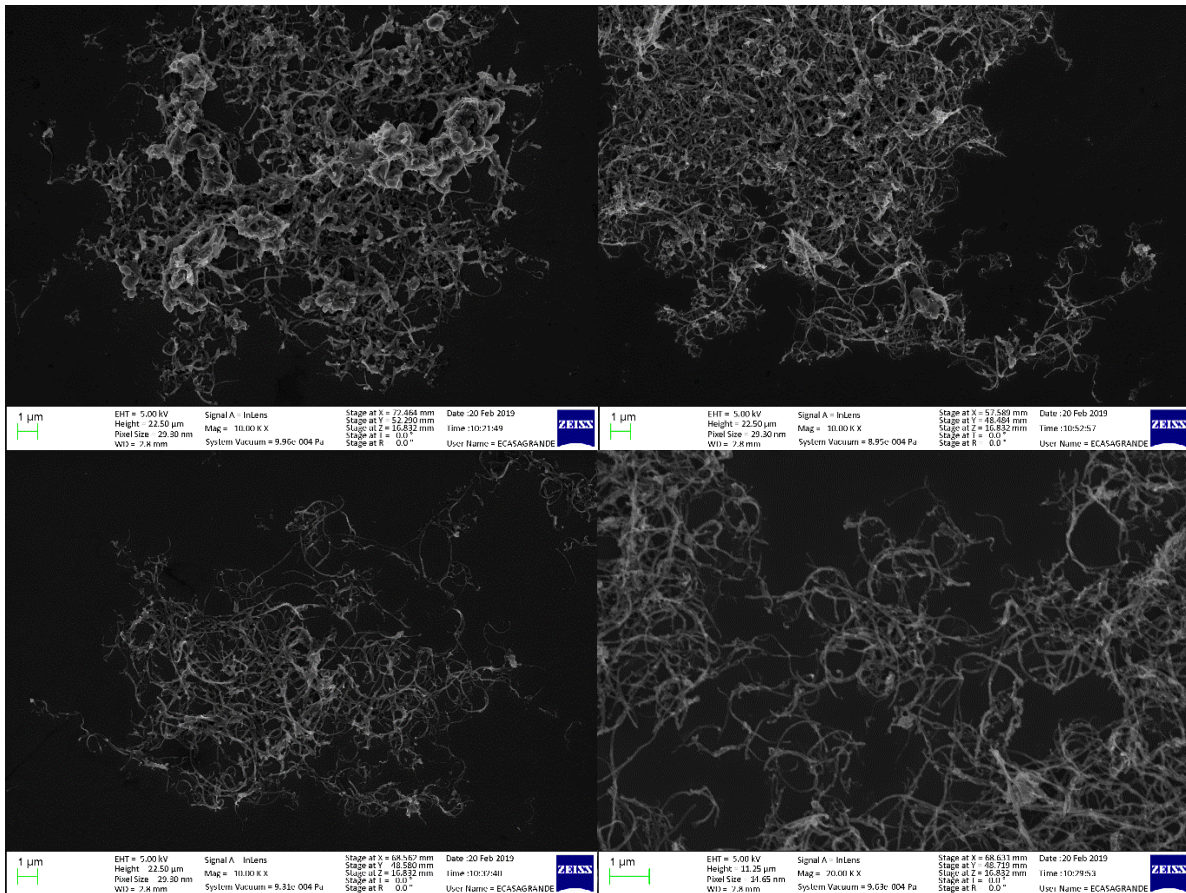

Fig. 3. SEM of surface morphology of MIM.

2.2.2.2 Pd/MIM heterogeneous catalysis

As can be seen from Figure 4, in the synthesis of the Pd-based heterogeneous catalyst, although the magnetic properties of the material are preserved, there is a collapse of the dendritic structure of the support, with the formation of a particulate material. This is probably due to the mechanical agitation that tends to break the filamentous components of the material. Specific surface area analysis gives a value of 3.7 m²/g and this is compatible with a non-porous material.

From SEM-EDX mapping, the distribution of iron, carbon and palladium, appears to be quite homogeneous.
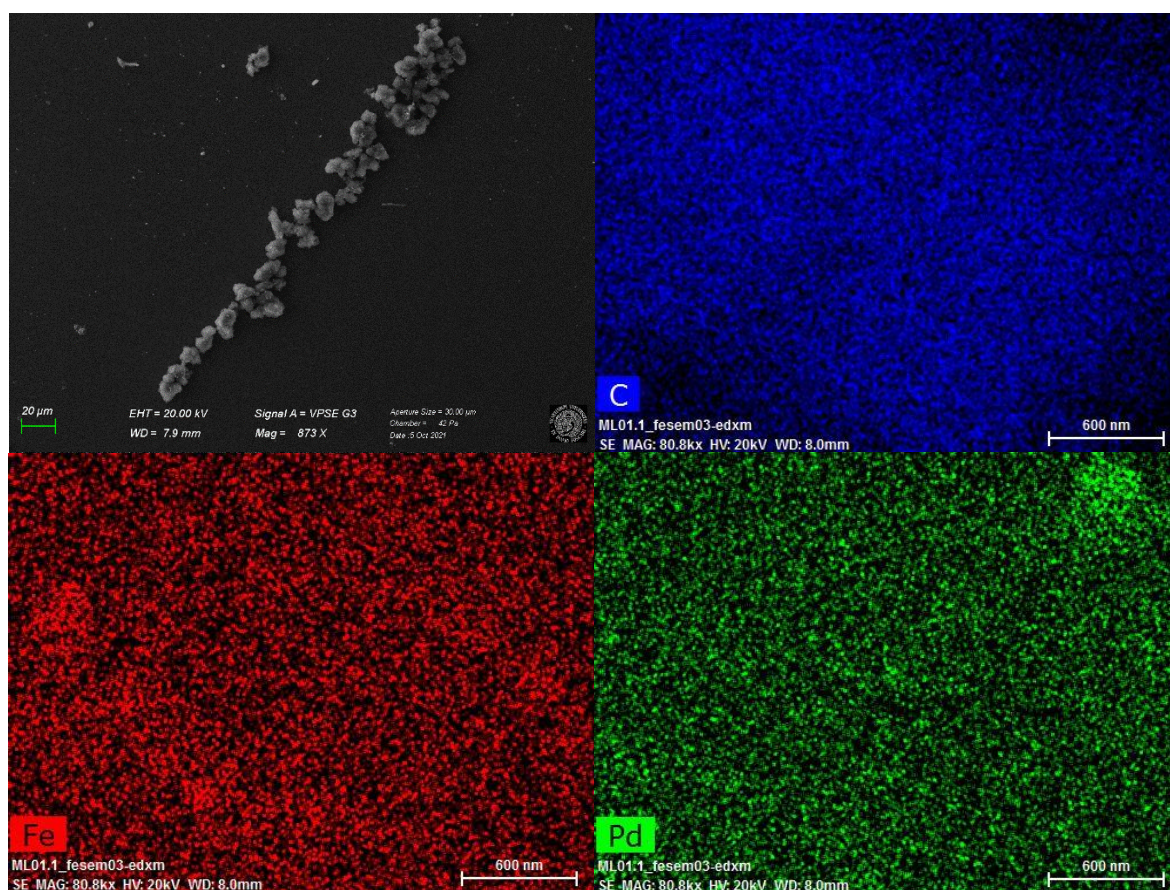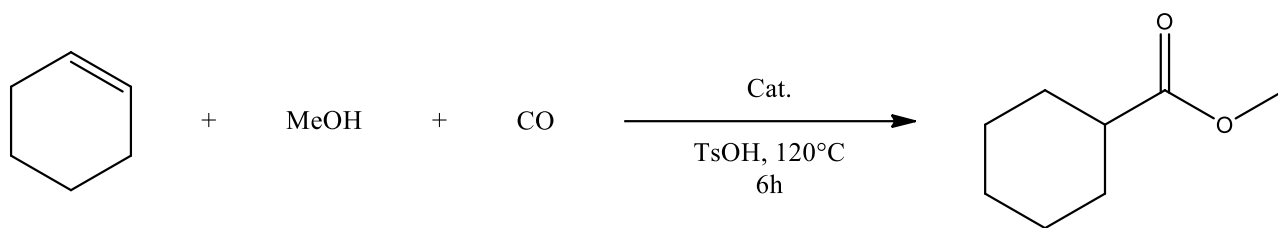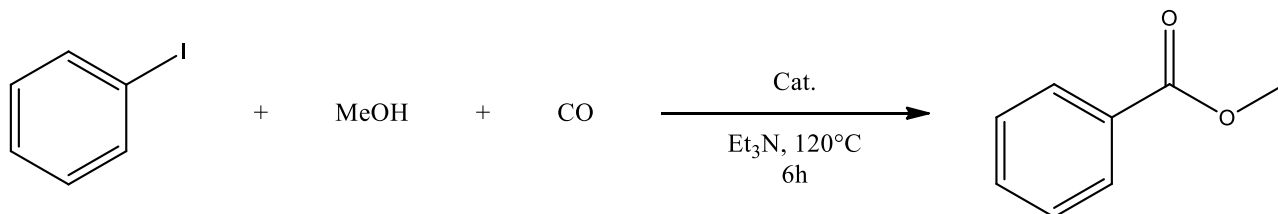

Fig. 4 SEM and SEM-EDX mapping of Pd/MIM

Based on previous work (Chapter 2.1) hydroesterification reactions of cyclohexene and methoxycarbonylation of iodobenzene (Chapter 3) were performed as catalytic tests using Pd/MIM 1% (Schemes 1 and 2)

Scheme 1 Hydroesterification of Cyclohexene

Scheme 2 Methoxycarbonylation Iodobenzene

Table 1 Catalytic Test of Pd/NDs on carbonylation reaction

| entries	Catalyst	Specific Area (m^2/g)	Substrate	Conv.(%)
1	[a]Pd/MIM (1%)	3,7	Cyclohexene	100
2	[a]Pd/MIM (1%) 1° recycle	-	Cyclohexene	21
3	[b]Pd/MIM (1%)	3,7	Iodobenzene	98
4	[b]Pd/MIM (1%) 1° recycle	-	Iodobenzene	34

Run condition: a: Cat= 10 mg (Pd 1 %); Pd/PPh$_3$/TsOH = 1/50/60, Temperature=120°C, PCO= 5MPa, reaction time=6h, Cyclohexene= 0,5 mL (4,9 mmol), solvent: MeOH= 20 mL
b: Cat= 10 mg (Pd 1 %); NEt$_3$=5.2 mmol, Temperature= 120°C, PCO= 5Mpa, reaction time=6h, Iodobenzene= 0,5 mL (4,5 mmol), solvent: MeOH= 20 mL

These reactions were also carried out in the presence of only magnetic support, to exclude that iron could intervene in the catalysis. As it is possible to observe from table1, both for the hydroesterification reaction and the methoxycarbonylation reaction (entries 1 and 4) the catalyst allows to obtain very good conversions, but already at the first recycling of the catalyst a drastic decrease of conversion is observed. The low surface area limits the diffusion problems, since the active metal species is very superficial, but it is possible that the Pd uniformly distributed externally on the particles of the support (Fig.4) undergoes the phenomenon of leaching that leads to lose a large part of the active metal for catalysis, already in the first reaction. In addition, in the case of the hydroesterification reaction, performed in the presence of an acidic cocatalyst (TsOH), the loss of the magnetic characteristics of the catalyst is observed, probably due to a coating of the carbon covering the particles of the support non-homogeneously.

2.2.2.3 Polyketone-coated Pd/MIM preparation and tests in heterogeneous catalysis.

Based on the results obtained from the catalytic tests performed with the 1% Pd/MIM heterogeneous catalyst, it was hypothesized that the loss of the magnetic characteristics of the material is attributable to the non-inertness of the support towards the reaction environment. For this reason, a second coating of the material was performed. In previous works, the possibility of coating magnetic substrates such as Magnetite (Fe_3O_4) by coating a polyketone layer, obtained by emulsion polymerization of CO and Ethene, using the $Pd(OAc)_2$dppp system and TsOH as a catalyst has been verified[6]. Also in 2009 JinTang Guo, presented the possibility of employing Pd/C , Bypy as a free ligand, in the presence of TsOH heterogeneous system for the synthesis of CO/styrene polyketones, soluble in methanol[28].

Given the insolubility of the CO/ethene polyketone in common solvents and the high thermal-mechanical resistance, the coating of the catalyst has been performed through the direct polymerization of CO/Ethene on the particles using palladium present on the support in the presence of dppp and TsOH.
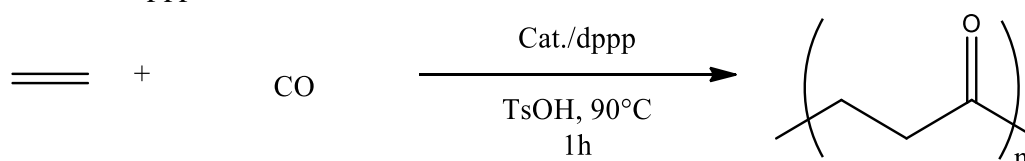
From the FT-IR analysis of this composite material we observe typical Polyketone signals at 1690 and 2912 cm^{-1} related to the presence of the carbonyl and methylene groups of the repeating units. As can be observed from Fig.5 the structure of the PK-coated material does not appear to vary appreciably, remaining particulate.
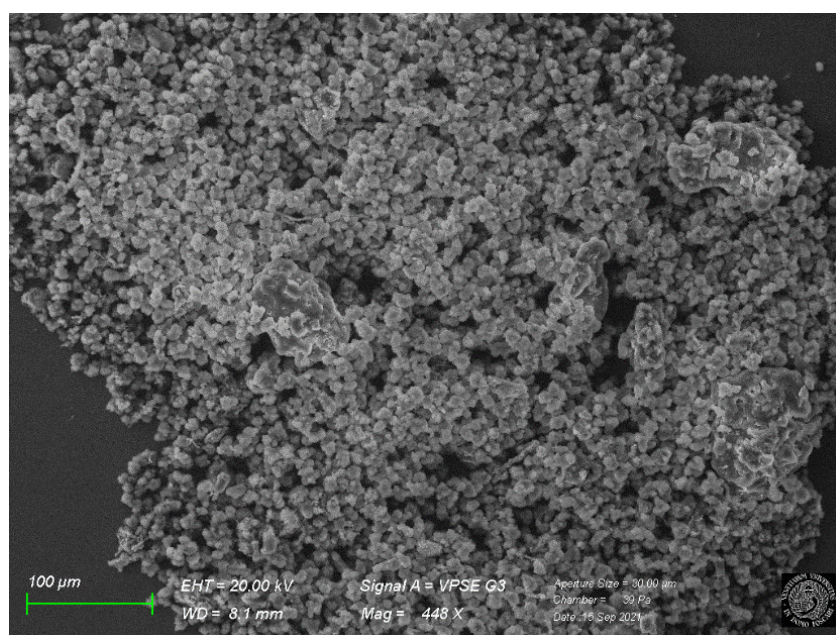
Fig. 5. SEM of surface morphology of Pd/MIM/PK

But as observed by SEM-EDX mapping, the signal related to iron turns out to be less intense than in the catalyst not covered by PK. Unexpectedly, it turns out to be interesting distribution of palladium on the catalyst surface is uniformly deposited. It is possible that the polymeric coating favors the immobilization of Pd that is lost due to the phenomenon of leaching from the surface of the particles of the starting material, remaining rather superficial, or that the soluble palladium species that led to the synthesis of polyketone, due to the reducing environment (CO and MeOH), re-precipitate on the outer surface of the polymer. The final amount of Pd, determined by ICP, turns out to be compatible with the amount present in the starting material.
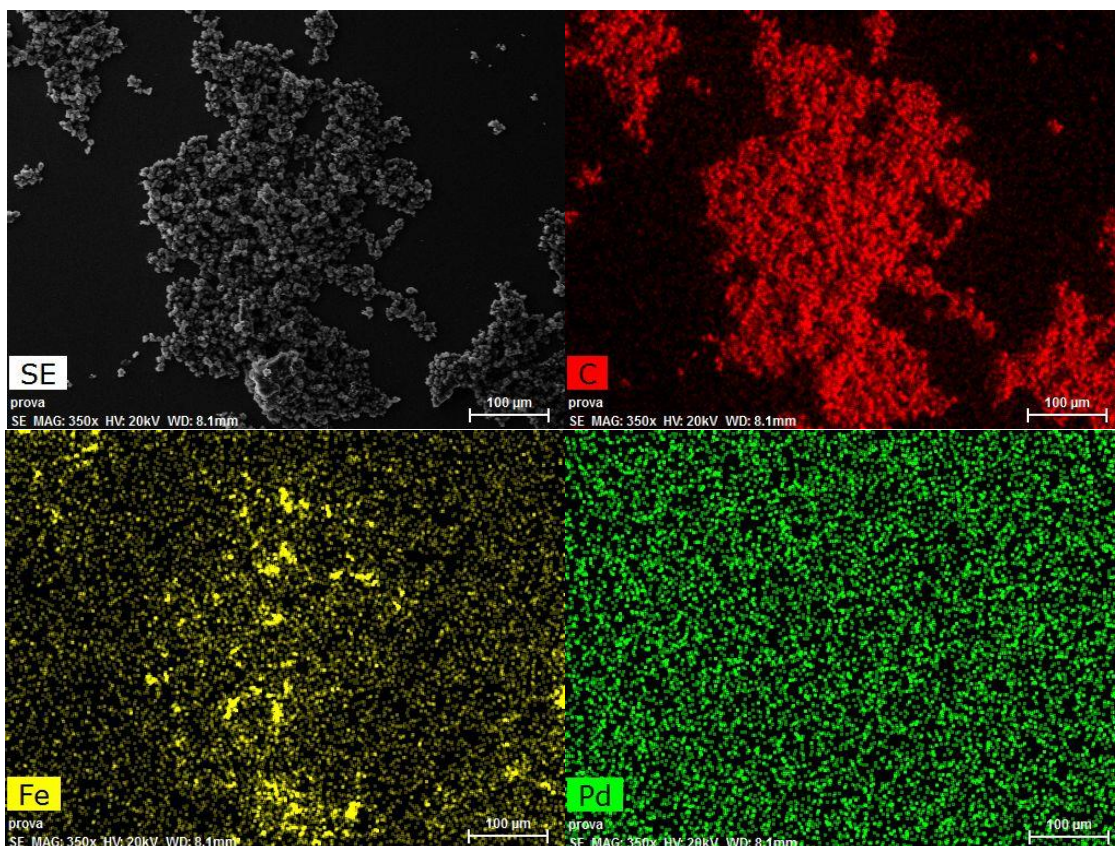

Fig.6 SEM and SEM-EDX mapping of Pd/MIM/PK

This heterogeneous composite catalyst has been tested in the hydroesterification reactions of cyclohexene and methoxycarbonylation of iodobenzene and the reduction of nitro benzene to aniline. Again, this catalyst leads to quantitative conversions, with 100% selectivity. Moreover, at the end of the reaction, it maintains the starting magnetic characteristics of the support.

In fig. 7 it can be observed that the catalyst is recyclable at least 5 times, without a significant loss in conversion. As for the hydrogenation reaction of nitrobenzene, on the other hand, a drastic decrease in conversion is observed as the number of recycles increases. This is probably due to the possible coordination of aniline on the active metal centers, resulting in the formation of soluble species and therefore leaching, or due to the formation of polymeric products of aniline, which can poison the catalyst.
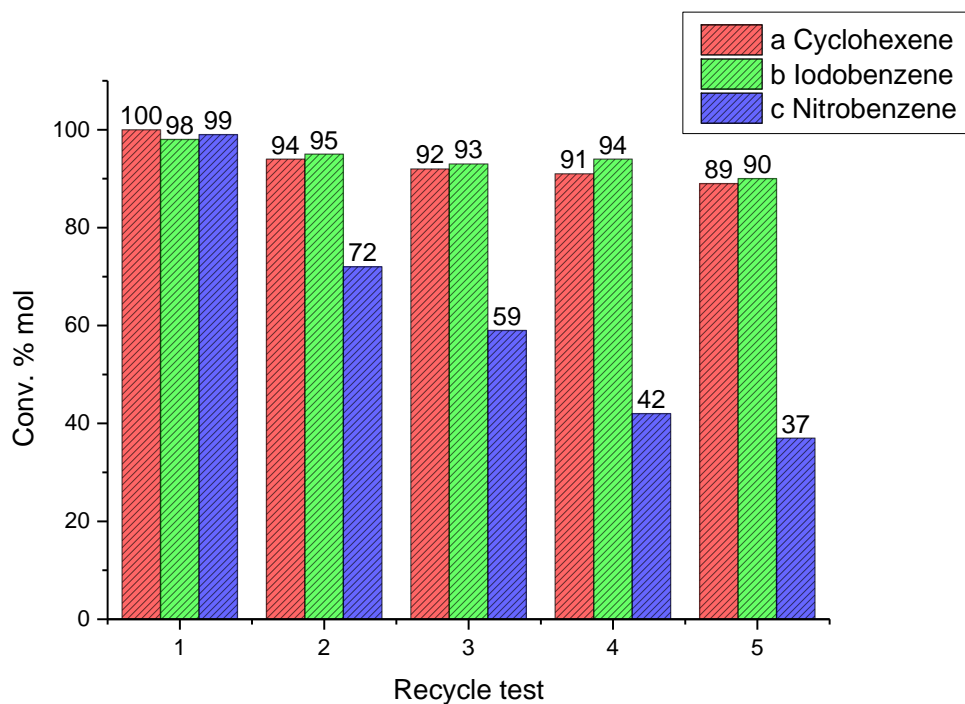
Fig 7. Recycling test: Run condition: a: Cat=10 mg; Pd/PPh₃/TsOH= 1/50/60, Temperature=120°C, PCO= 5MPa, reaction time=6h, Cyclohexene=0,5 mL (4,9 mmol), solvent: MeOH=20 mL
b: Cat=10 mg; NEt₃=5.2 mmol, Temperature=120°C, PCO=5Mpa, reaction time=6h, Iodobenzene=0,5 mL (4,5 mmol), solvent: MeOH=20 mL
c: Cat=10 mg; Temperature 120°C PH2=5 MPa, reaction time=1h, Nitrobenzene=0,5 mL (4,9 mmol), solvent; MeOH=20 mL
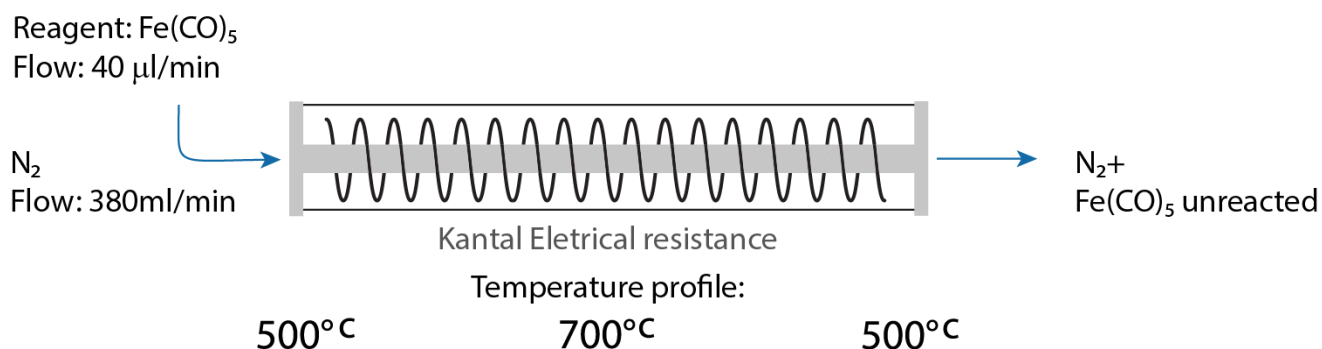
2.2.3. Conclusions

In summary, a new heterogeneous magnetic support was synthesized by thermal decomposition of Fe(CO)₅, leading to the formation of a material consisting of an iron core and coated with carbon. This coating, not being completely homogeneous, was again coated with a polyketone layer, obtained by direct polymerization on the surface of the particles. The polymeric layer seems to favor the immobilization of Pd on the external surface of the material. This heterogeneous Pd-based catalyst was used for carbonylation reactions in both basic and acidic environments and recycling tests were performed. After about 5 recycling tests, it appears to still be active and the magnetic properties appear to be unaltered.

2.2.4. Experimental section

Magnetic Iron Material (MIM) was synthesized by thermal decomposition of $Fe(CO)_5$ within a flow reactor. The Iron (0) pentacarbonyl was pumped inside the reactor (flow 40 $\mu L/min$) under a nitrogen flow (380 mL/min). Decomposition was carried out on Kantal® resistance wire (FeCrAl alloy) wrapped in a quartz tube placed in the center of the reactor, which by applying 30 V and 3 A with a power supply unit (PSU), reached temperatures of 700°C (in the center of the reactor), determined with a thermocouple placed inside the quartz tube. $Fe(CO)_5$ was introduced once the system reached thermal equilibrium, where there is a temperature profile of 450°C at the reactor edges and 700°C at the center.

The morphology of the resulting material was analyzed with an SEM microscope, XRD measurements were performed with a Thermo ARL X'TRA powder diffractometer equipped with a Cu-anode X-ray source with a solid-state cooled Peltier Si(Li) detector. The TGA was recorded with a STA PT 1000 Linseis instrument in a nitrogen atmosphere from 25 to 850 °C with a heating rate of 10 °C/min.

Reagent: $Fe(CO)_5$
Flow: 40 µl/min

N$_2$
Flow: 380ml/min

Kantal Eletrical resistance

Temperature profile:

500°C   700°C   500°C

N$_2$+
$Fe(CO)_5$ unreacted

Synthesis heterogeneous Pd/MIM catalyst

The heterogeneous Pd metal catalyst was supported on MIM by a metal adsorption-reduction procedure. In a typical synthesis, 500 mg of magnetic support was added to a solution $Pd(OAc)_2$ [Pd(II) acetate] in methanol under mechanical stirring. The suspension was refluxed for 1–2 h. After this reaction the magnetic catalyst was separated by magnetic separation, washed with methanol and dried in a vacuum overnight. The amount of Pd on magnetic support was determined by ICP (1% Pd w/w%) and the specific surface area was determined by using the physisorption-BET technique, in addition, the distribution of Pd was observed with SEM-EDX mapping.

Synthesis Pd/MIM/ coated with PK

In a typical procedure 100 mg of Pd/NDs are mixed in 40 mL of MeOH, with 4 mg (9.7 mmol) of dppp, 15 mg of TsOH (78.9 mmol). The reaction solution was mechanically stirred at 600 rpm for 1 h, under 5MPa of a 1:1 CO/ethene mixture at 90°C. At the end of the

reaction, the Pd/MIM/PK particles were separated using a magnet, washed with methanol and water, and dried in a vacuum desiccator.

Catalytic Reaction

Typically, 10 mg of heterogeneous catalyst, the appropriate amount of reagent and co-catalyst, are introduced into a Batch reactor, inside a glass beaker to avoid any contamination of the reactor inner walls. 0.1-0.2 MPa of gas (CO or H_2) are loaded and then vented; this operation is repeated 3 times conditioning the reactor and at the end 0.5 MPa of gas are introduced. Once the reaction temperature is reached, the pressure is adjusted to 5 MPa and stirring is started. At the end of the reaction, the catalyst is recovered using a permanent magnet, washed and dried. The conversion is determined by GC.

2.2.4 References

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2.3   Trifluoroacetic acid promoted hydration of styrene catalyzed by sulfonic resins: Comparison of the reactivity of styrene, n-hexene and cyclohexene

2.3.1 Introduction

As is well known, the hydroesterification of olefins are catalyzed by transition metals. Typically, palladium-based catalysts are employed with the aid of acidic co-catalysts. The use of acids with weakly coordinating anions, such as Trifluoro Acetic Acid (TFA), para-toluenesulfonic (TsOH) acid and trifluoromethanesulfonic acid (triflic acid), is advantageous for carbonylation reactions, as a decrease in the formation of metallic palladium is achieved, which is the first cause of degradation of catalyst.

The selectivity of such reactions is not only related to the type of catalytic system and reaction conditions, but also to the nature of the substrate. One of the main problems observed in the carbonylation of long-chain olefins is the isomerization of the double bond from the terminal and the internal carbons, which leads to the loss of selectivity in the formation of carboxyl or ester groups. For example, in the alkoxycarbonylation of 1-Decene, the presence of 2-ethylnonanoate, due to the migration of the double bond, is not negligible [1].

An additional side reaction which depends on olefin reactivity is related to the formation of addition products of alcohol or water to the double bonds, or the formation of homo-olefinic polymers, favored by the acidic reaction environment.

For example, in the case of hydroesterification of 2-vinyl-6-methoxynaphthalene (VMN), in addition to the formation of linear and branched esters (naproxen esters), also leads to the non-negligible production of double bond addition products (ether product) and poly(VMN) (MW 12500 g/mol) [2].
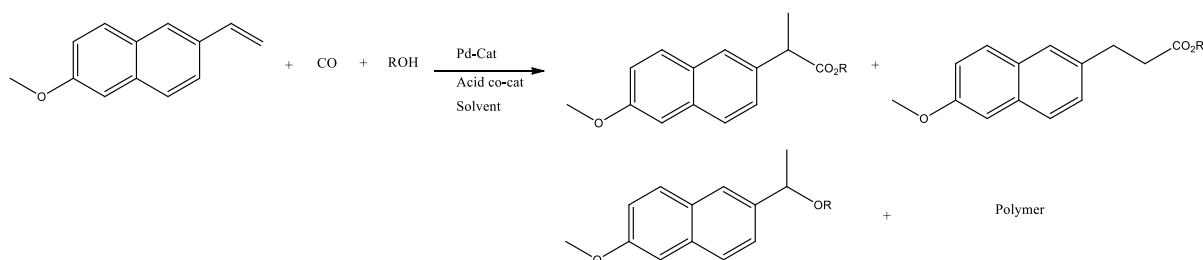
Hydroesterification of 2-vinyl-6methoxynaphthalene

Liquid/liquid biphasic reactions in the presence of an aqueous phase and an organic phase are well-known reactions employed in various industrial processes, nitrations, hydrogenations, carbonylations and hydroformylations [3-9].

In carbonylation reactions, the presence of an aqueous phase allows some interesting features[6].

Indeed, both the limitation of the use of organic solvents and the obtaining of high molecular weight polymers are important purposes that the presence of an aqueous phase can allow to achieve [6].

Hydrocarboxylation of olefins performed in a biphasic water/organic solvent system turns out not to be very different from the hydration and/or emulsion polymerization conditions commonly used in industry, where the organic phase is represented by the olefin itself [10-11]

The hydration of olefins is an apparently simple reaction; however, its practical application at the industrial level is not without some problems [11-17]. The key intermediate in the acid catalytic reaction of olefin, is an attack by nucleophilic molecules on a positively polarized species, in some cases a carbonium ion [18,19].

Typically, in olefin hydration, the presence of a concentrated aqueous mineral acid (usually 70% sulfuric acid) allows high alcohol yields. The reaction proceeds through an alkyl sulfate intermediate, which is hydrolyzed after dilution [20-22].

An important intermediate for polymers and chemicals, is cyclohexanol, which is usually obtained by hydrogenation of phenol or by oxidation of cyclohexane [23].

Among alcohols, interesting intermediates are phenylcarbinols, these compounds are commonly found in nature as fragrances but are also synthesized from bulk chemicals and have applications in many areas of fine chemistry [24-25].

Styrene hydration could be an interesting route being this compound a commodity available in very large quantities (the annual production of styrene in the world is close to 20 million tons) [26].

Currently, Styrene hydration is carried out at high acid concentration (40-50% $HClO_4$), low temperature (283-298 K) and at a concentration of 10-4-10-5 mol L^{-1}, to avoid polystyrene formation [27]. However, starting from another point of view, and taking into consideration the large production and various types of polystyrene, a small co-production (in terms of percentage) of alcohol could be of industrial interest if obtained as a by-product of polymerization.

Many gas-phase and liquid-phase hydration methods catalyzed by a solid acid are widely reported in the literature, and sulfonated resins are important materials for these reactions as well as in carbonylation reactions [28-33, 37-40].

In this Chapter the study of the hydration reaction of olefins in a biphasic system is illustrated, where the olefin forms one phase and the water-TFA solution another, and their reactivity is studied using different solid and three olefins, that is n-hexene, cyclohexene and styrene. In the case of styrene, TFA-initiated polymerization occurs in high yields, but 1-phenyl-ethanol is also formed (4-8%). The addition of TFA to olefin and the formation of the corresponding ester promotes the formation of the alcohol, thus increasing the yield compared to reactions carried out in the absence of TFA. The use of various sulfonated resins was investigated for its ability to interact with the oxygenated compound by promoting hydration and saponification reaction.

2.3.2. Results and discussion

In the first part of the study, the screening of acid in the aqueous phase, the type of heterogeneous catalyst and their combination in the liquid phase hydration reaction of olefins is presented. In the second section, the study on the rate of cyclohexene hydration reaction in the presence of an aqueous solution of TFA and an acidic resin (Amberlyst 36) as a heterogeneous catalyst is presented. All reactions are carried out in a large amount of water, and the concentration of the acid is less than 0.3-1.6 mol L^{-1}, at this concentration the acid is solvated and the aqueous phase can be considered as an aqueous solution [41].

2.3.2.1 Styrene Hydration

The results of acid-promoted hydration of styrene in the liquid phase are shown in Table 1.

Table 1 Styrene hydration promoted by homogeneous acid systems. Run conditions: T 393K, P autogenous pressure of the system, styrene, 2.62 mmol water 2 mL, acid 1 mmol, time of reaction 4 h.

Entry	acid promoter	Conversion (%)	1-phenylethanol (%)[a]	Styrene dimers (%)[a]	Condensation products (%)[a,b]	Polymer (solid) (%)[a,b c]
1	/	95	/	5	/	95
2	TFA	87	10	7	3	80
3	H_2SO_4	87	1	30	9	60
4	TsOH	86	2	5	2	91
5	CH3COOH	85	/	4	1	95

[a]Selectivity. [b]Oxygenated compounds observed by GC–MS. [c]Calculated by weighing the solid.

As can be seen from entry 1, in the absence of the acid promoter, a high polystyrene yield is observed together with the formation of trace of oligomers due to thermal polymerization, and a small amount of unreacted styrene [42].

The presence of organic acids decreases the amount of solid polymer recovered at the end of the reaction. This may be due to an increase in the solubility of styrene in the aqueous phase. Hydration is probably initially due to catalytic protonation of olefin and subsequent nucleophilic attack, which could be both other olefin molecule (oligomer production) or water (alcohol product). Substrate oligomerization is clearly favored in the case of sulfuric acid as a promoter, thus causing low selectivity for the hydration reaction, which also occurs, although to a minor degree, with acetic acid.

Although the main product is polystyrene, TFA allows a remarkable selectivity for alcohol thus suggesting a different reaction path in the presence of this acid. The reaction selectivity could be driven by the addition of TFA to the double bond, with a consequent hydrolysis of

the 1-phenylethyl trifluoroacetate ester to give 1-phenyl-ethanol [29,30] with a selectivity of 10% (entry 2). Table 2 shows the hydration of styrene catalyzed by some solid acids.

Table 2 Styrene hydration promoted by homogeneous acid systems and catalyzed by solid acid. Run conditions: T 393 K, P autogenous pressure of the system, styrene 2.62 mmol, water 2 mL, acid 1 mmol, catalyst 40 mg, and time of reaction 4 h

Entry	Catalystic System	Conversion (%)	1-phenylethanol (%)[a]	Dimers (%)[a]	Condensation products (%)[a,b]	Polymer (solid) (%)[a,c]
1	Amb.15	88	7	3	2	80
2	Amb.36	87	7	3	1	81
3	Amb.50	87	/	12	2	86
4	HZSM5	89	/	2	1	97
5	D50	88	4	6	2	84
6	TFA/Amb.15	65	22	20	6	52
7	TFA/Amb.36	69	23	17	6	54
8	TFA/Amb.50	67	16	13	6	65
9	TFA/HZSM5	70	/	25	7	78
10	TFA/D50	66	8	10	4	78
11	H_2SO_4/Amb15	92	3	17	15	65
12	H_2SO_4/Amb.36	91	3	40	14	67
13	H_2SO_4/Amb.50	89	/	20	16	64
14	H_2SO_4/HZMS5	94	/	19	15	66
15	H_2SO_4/D50	93	/	26	7	67
16[d]	H_2SO_4/Amb.36	50[e]	50	10	10	traces

[a]Selectivity. [b]Oxygenated compounds observed by GC–MS. [c]Calculated by weighing the solid. [d]The substrate is 1-phenylethanol. [e]Styrene is the main product.

It is evident that the di-vinylbenzene sulfonated styrene resins are the ones that give the most interesting results. By comparing Table 1 with Table 2 it can be observed that the use of solid acid catalysts tends to disadvantage styrene polymerization but not to suppress oligomer formation. This may be related to the formation of an intermediate ionic couple near the surface of the acidic resin, which may be attacked by a nucleophile (water or olefin) and under such conditions high weight polymerization may be disadvantaged due to steric hindrance on the surface of the heterogeneous promoter.

Table 2 entry 6-16 shows the results of styrene hydration in mixed catalysis using both solid and liquid acid as the promoter. Although polystyrene remains the main product, the use of both acidic promoters, TFA at Amberlyst 15 and 36 significantly improves the selectivity towards 1-phenylethanol formation but the main product is still the polymer, which is not the case in the mixed solid acid/H_2SO_4 system, which leads to increased selectivity towards dimer formation.

In addition to the polymerization (cation and radical) that occurs parallel to the hydration reaction, a further problem is the reversibility of the reaction that in the presence of acids can lead to the formation of olefin. Indeed, the reaction of 1-phenylethanol with TFA (entry 16) in an aqueous medium in the presence of Amberlyst 36 as a solid acid catalyst gives a product distribution like that obtained from styrene as a substrate, with traces of polystyrene.

It is noteworthy the different composition of the polystyrene obtained in the presence of TFA because ^{1}H and ^{19}F NMR shows the presence of fluorinated ester terminal group (see more details in experimental section), the study of the polystyrene obtained in the presence of TFA.

2.3.2.2. Cyclohexene Hydration

The hydration of cyclohexene appears to be easier than that of styrene, however, careful selection of the catalytic system is required.

In this case, olefin does not polymerize as readily as styrene, and the main products are cyclohexanol and cyclohexyl trifluoroacetate (in the presence of TFA), but, in the case of homogeneous promoters, the amounts of condensation products produced are not negligible.

Table 3 Cyclohexene hydration promoted by liquid acids. Run conditions: T 393K, P autogenous pressure of the system, cyclohexene 2.62 mmol, water 2 mL, acid 1 mmol, time of reaction 4 h.

entry	acid promoter	Conversion (%)	Cyclohexanol Sel.(%)	Addition product (%)[a]	Condensation product (%)[b]
1	TFA	12	48	36	8
2	H_2SO_4	12	92	/	8
3	CH_3COOH	2	/	1	1
4	TsOH	8	31	7	4

[a]Selectivity cyclohexyl trifluoroacetate. [b]Calculated by difference.

The liquid/liquid systems appear to be more effective in multiphase batch hydrations of cyclohexene than the liquid/solid systems although Amberlyst 15 and 36 show similarities to the liquid systems.

Table 4 Cyclohexene hydration catalyzed by solid acids. Run conditions: T 393K, P autogenous pressure of the system, cyclohexene 2.62 mmol, water 2 mL, catalyst 40 mg, time of reaction 4 h.

| entry	Catalyst	Conversion (%)[a]	Cyclohexanol Sel. (%)
1	Amb.15	7	99
2	Amb.36	8	99
3	Amb.50	1	99
4	HZSM5	1	99
5	D50	3	99

[a]There are traces of condensation products.

The reaction carried out in the presence of TFA shows the formation of cyclohexyl trifluoroacetate with 36% selectivity (see tab.3 entry 1). This product is of interest because it could be converted to cyclohexanol via hydrolysis (see scheme 1). This was confirmed by reacting it in the presence of H_2SO_4/Amb36 as catalyst (entry 11 tab. 5).

Table 5 Cyclohexene hydration promoted by liquid acids and catalyzed by solid acids. Run conditions: T 393K, P autogenous pressure of the system, cyclohexene 2.62 mmol, water 2 mL, acid 1 mmol, catalyst 40 mg, time of reaction 4 h.

Entry	Catalyst system	Conversion (%)[a]	Cyclohexanol Sel. (%)	Addition products Sel. (%)
1	TFA/Amb15	12	69	30
2	TFA/Amb.36	12	68	31
3	TFA/Amb.50	11	68	31
4	TFA/HZSM5	7	65	35
5	TFA/D50	10	66	33
6	H_2SO_4/Amb.15	13	100	/
7	H_2SO_4/Amb.36	12	100	/
8	H_2SO_4/Amb.50	12	100	/
9	H_2SO_4/HZSM5	12	100	/
10	H_2SO_4/D50	12	100	/
11[b]	H_2SO_4/Amb36	60[c]	55	/

[a]About 1–3% are traces of condensation products. [b]Cyclohexyl trifluoroacetate as the substrate. [c] Cyclohexene is formed in 42% of selectivity
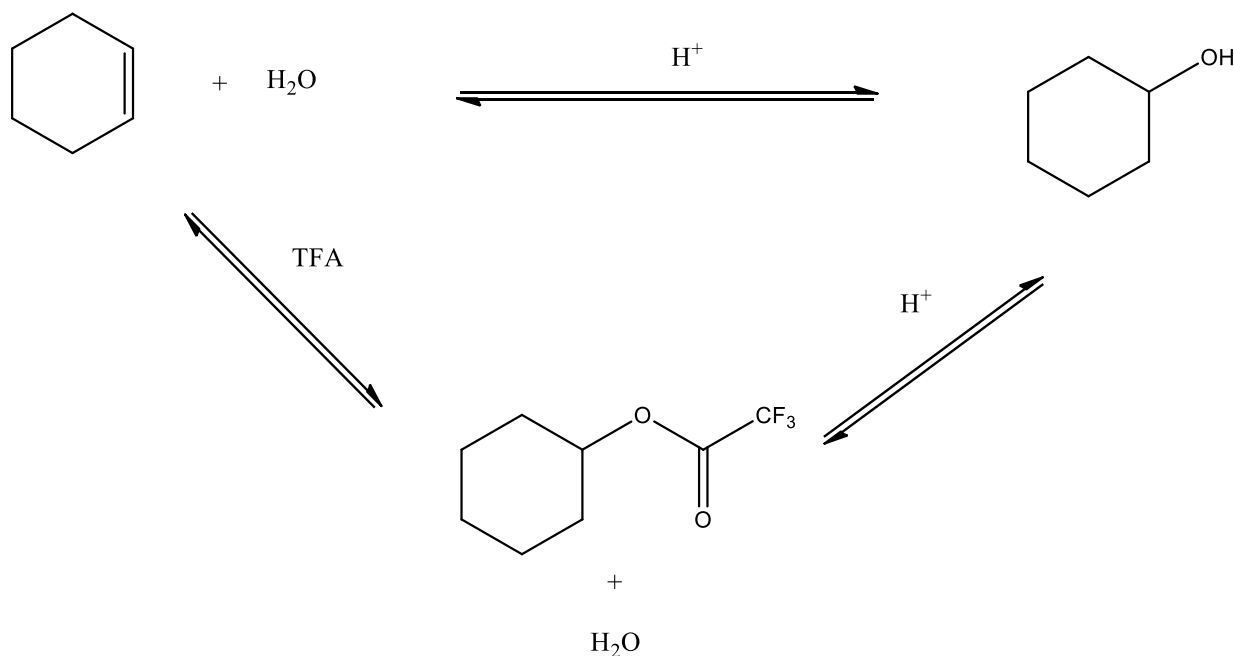
Scheme 1. Cyclohexene hydration paths.

In agreement with the results obtained in homogeneous phase (see tab. 1) also the studies conducted with sulfuric acid and solid promoters lead to the best results in terms of cyclohexanol yield (tab 5 entries 6-10).

2.3.2.3. Hydration of n-hexene

The hydration of n-hexene only occurs at very low conversion, lower than that obtained with cyclohexene, this system seems to be useless for practical application especially with TFA as a liquid acid system. It is likely that the low conversion of this olefin is due to two behaviors of the system: (i) the low solubility of olefin in the aqueous phase; (ii) the low protonation of olefin in dilute acid. As expected, the main product of the reaction is 2-hexanol similarly, of that already obtained in concentrated sulfuric acid [20]. However, Table 6 shows some results suggesting that the best acid system for this reaction is sulfuric acid other acid systems give negligible conversion. The mixed system seems not to be effective and only a negligible increase in conversion is observed with TFA as a promoter. In sulfuric acid, the presence of the solid catalyst does not increase the conversion suggesting that it is not effective compared to pure sulfuric acid.

Table 6 n-Hexene hydration promoted by liquid acids and catalyzed by solid acids. Run conditions: T 393 K, P autogenous pressure of the system, n-hexene 2.62 mmol, water 2 mL, acid 1 mmol, catalyst 40 mg, time of reaction 4 h.

Entry	Catalytic system	Conversion (%)	2-hexanol sel. (%)[a]
1	TFA	2	99
2	H_2SO_4	8	95
3	Amb15	<1	100
4	Amb36	<1	100
5	TFA/Amb15	3	99
6	TFA/amb36	3	99
7	H_2SO_4/Amb15	8	95
8	H_2SO_4/amb36	8	95

[a]Traces of isomers.

2.3.2.4. Cyclohexene hydration: reaction rates, profiles and equilibria

It is well known that in cyclohexene hydration it is quite difficult to achieve high yields due to its reversibility. Indeed, about 10-20% of the total yield can be achieved under conventional hydration conditions in a Batch type reactor [28,43-44].
Reactive distillation is necessary to achieve a high yield in cyclohexanol [28-31]. The use of a sulfonated resin in combination with TFA as an acidic promoter seems to be the most promising system to obtain a high yield of cyclohexanol, considering the problem of reversibility of the reaction.
A typical cyclohexene hydration reaction profile catalyzed by sulfonated resins (Amberlyst 36) and promoted by aqueous TFA is shown in Fig. 1.
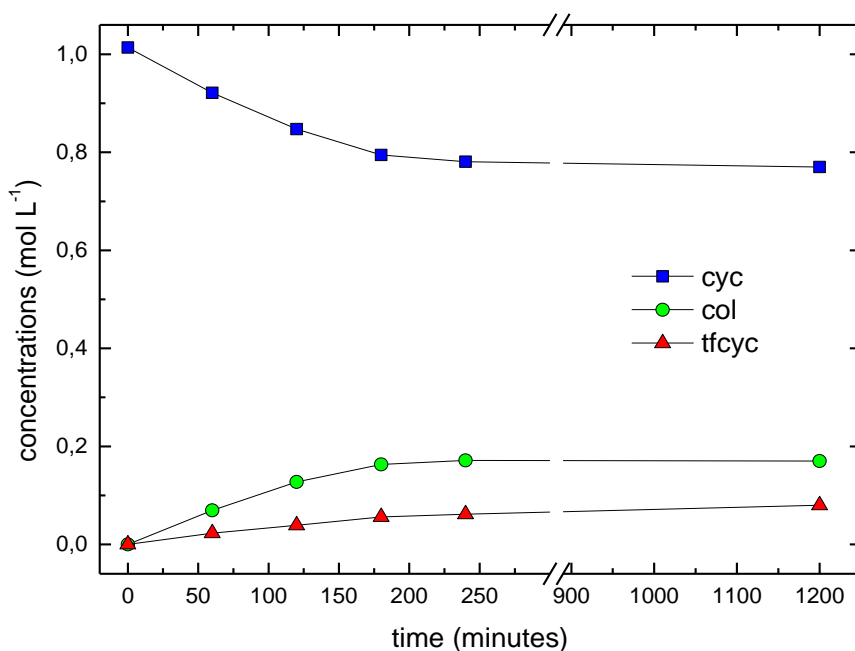
Fig. 1. Reaction profile. Run conditions: Run conditions: T 403 K, P autogenous pressure of the system, cyclohexene 1.14 $mol\,L^{-1}$, water 2 mL, TFA 1.32 $mol\,L^{-1}$, Amberlyst 36 40mg.

The reaction takes place in two phases one aqueous and one organic and, as it clearly appears in Fig. 1, the reaction does not go to completion but reaches a value determined by the multiphase equilibria of the reaction environment. This system is affected by several equilibria, such as liquid/liquid equilibria (of all species), acid dissociation, olefin protonation, hydration, addition equilibrium (Scheme 2).
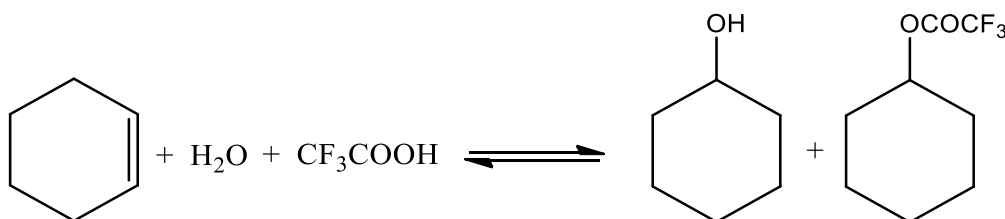
Scheme 2 Overall multiphase equilibrium

To attempt a determination of some reaction parameter, interphase equilibria have been neglected assuming that these equilibria give only a proportional constant that can be incorporated into the overall constant.

Furthermore, it was assumed that the activities of all non-ionic species can be considered as concentrations referring to the volume of both phases. This approximation might hold because the activity of the uncharged molecule is generally proportional to the concentration of the species itself and to that of the charged species, following Setchenow's equation [45,46]. Under these limits, Eq. (1) can describe the general equilibrium. All solution equilibria are calculated from GC analysis of solutions obtained from the extracted sample with CH_2Cl_2,

except for TFA for which literature dissociation degrees are used and employing activity coefficient values calculated for ionic species [47,48].

$$K_{sn}(w) = \frac{[CyTf][Ol]}{[Cy]\,[TFA]}$$ Eq. (1)

It is clear from Fig. 2A, however, that this oversimplified hypothesis does not hold, because there is a clear dependence of this pseudoequilibrium constant (Ksn) obtained from Eq. (1) on the total TFA concentration. This effect could be caused by the salting out effect, which decreases the concentration of cyclohexene in the aqueous phase, thus affecting the equilibrium as a function of the amount of charged species. As a matter of fact, in Eq. (2) the activity of hydrogen ions is considered to compensate for the increase of charged species in solution whose effect causes a reduction in the solubility of cyclohexene. The correction introduced in Eq. (2) allows to obtain a Ks as constant in the concentration range of TFA studied in the present work and at 3 different temperatures as can be observed in Fig. 2B.

A	B
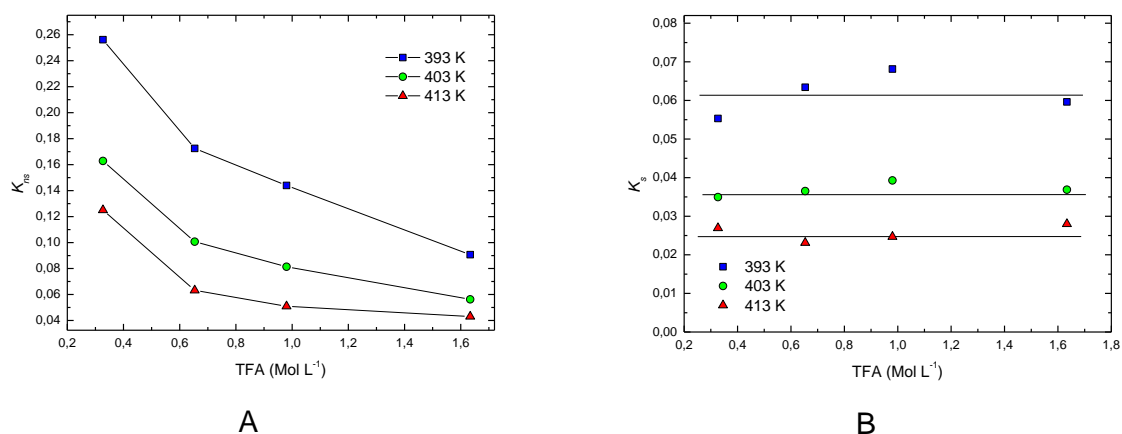
Fig. 2 Overall equilibrium constant obtained by varying temperature and TFA concentrations.

$$K_{S}(w) = \frac{[CyTf][Ol]a_{H+}}{[Cy]\,[TFA]}$$ Equation 2

A linear Van't Hoff plot (Figs. 3 and 4) is obtained by averaging the Ks obtained at different concentrations of TFA and a general exothermic effect with a value of $\Delta H° = -57$ kJ mol^{-1}, and $\Delta S°=175$ J K^{-1} mol^{-1}. The values of agree with thermodynamic data from individual reactions carried out under very ideal conditions, thus suggesting good reliability of the proposed parameter [50,51].
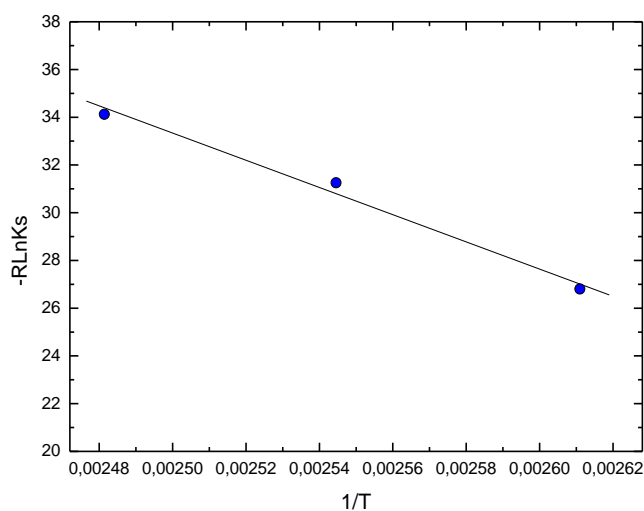
Fig. 3 Van't Hoff plot. Equilibrium constant variations with temperature: $\Delta H^\circ = -56 kJ\, mol^{-1}$ and $\Delta S^\circ = 175\, J\, K^{-1}\, mol^{-1}$.

3.4.1. Influence of the amount of the aqueous phase on the initial reaction rate

Initial reaction rate is a complex parameter because is a combination of the various process occurring in the reaction, however, it gives a reliable value on the overall behavior of the reaction. The presence of two immiscible liquid phase clearly indicates the presence of mass transfer between the two phases, these processes are seldom determining the overall reaction rate. The amount of aqueous phase seems to influence faintly the initial reaction rate also at two different acid concentrations.

This suggests the two phases are mixed homogenously at different substrate aqueous phase ratio.
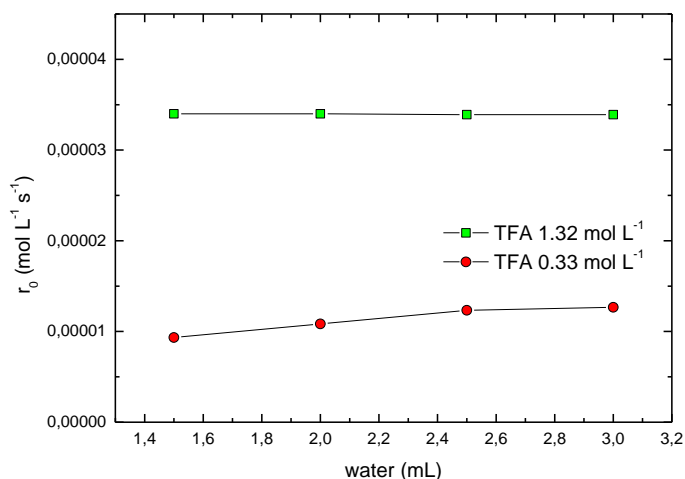
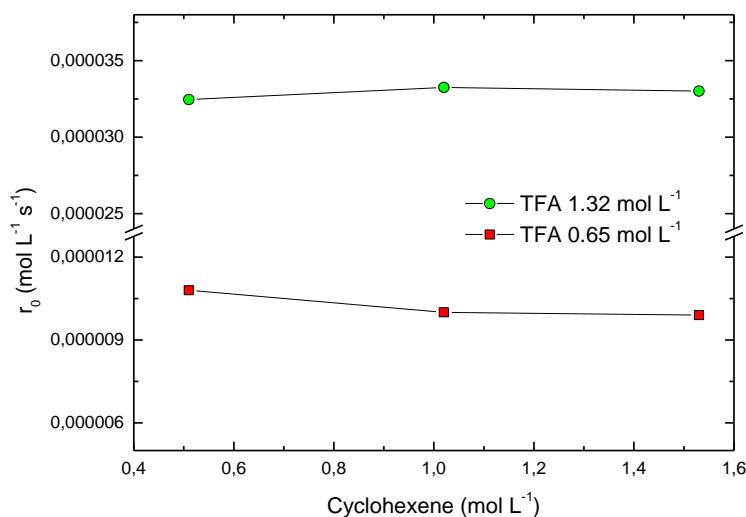Fig. 4. Influence of the amount of the aqueous phase on the initial reaction rate. Run conditions: Run conditions: T 393 K, P autogenous pressure of the system, cyclohexene $1.14\, mol\, L^{-1}$, water 2 mL, Amberlyst 36 40mg.

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2.3.2.5 Influence of cyclohexene amount on the initial reaction rate

The variation of the amount of cyclohexene does not influence the initial reaction rate, the biphasic conditions allow a constant concentration in the aqueous solution of the substrate. This is evidence that the reactions occur in the aqueous phase for this reason the amount of cyclohexene faintly influence the rate of reaction, being the concentration of substrate almost constant in the aqueous phase at low conversions. The constancy of the initial rate of reaction observed in Fig. 5 for two different concentrations of TFA confirms the homogeneity of the emulsion induced by the agitation visually observed at room temperature for the same reaction system.

Fig. 5. Influence of cyclohexene amount on initial reaction rate. Run conditions: Run conditions: T 393 K, P autogenous pressure of the system cyclohexene 1.14 mol L^{-1}, water 2 mL, Amberlyst 36 40mg

2.3.2.6. Influence of TFA concentration on the initial reaction rate

Fig. 6 shows the influence of the TFA concentration on the initial reaction rate, when TFA concentration is 0 the reaction proceeds by the acid catalysis of the sulfonated resins, achieving a conversion of 8% after 4 h of reaction and with an initial rate of reaction of 6 10−6 mol L^{-1} s^{-1}. The increase of the rate appears to initially low but after 0.6 mol·L^{-1} s^{-1} the increasing is stiff with a neat slowing down after 1.5 mol·L^{-1}s^{-1}. This trend looks like a titration suggesting the formation of a TFA-cyclohexene adduct, a further indication of the formation an active adduct TFA-cyclohexene, as the key intermediate is the fact that the flex of the curve coincides with the concentration of the olefin.

Anyway, such evidence allows only a mere hypothesis, because of the complexity of the system. More thermodynamics and mechanistic research are necessary for the determination of the reaction steps.
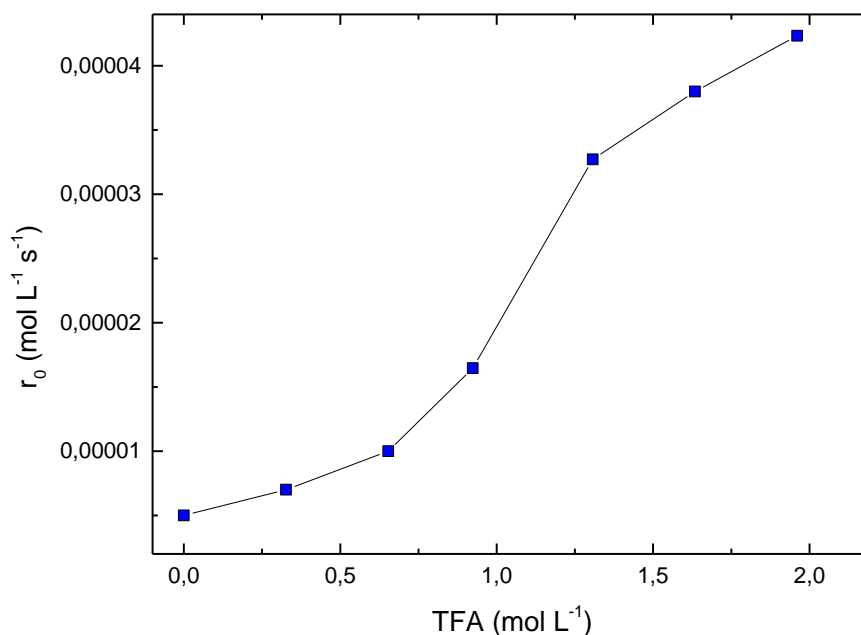
Fig. 6. Influence of the TFA amount on the initial reaction rate. Run conditions: Run conditions: T 393 K, P autogenous pressure of the system, cyclohexene 1.14 mol L^{-1}, water 2 mL, Amberlyst 36 40mg.

2.3.2.7. Influence of the sulfonated resin amount (Amberlyst 36) on the initial reaction rate

Fig. 7 shows the trend obtained between the initial reaction rate and the sulfonated resin amount. It is clear that in both cases with and without TFA the initial reaction rate increases linearly, what is interesting is the fact that the slope of the two straight line are quite similar suggesting that the increase of the initial rate is due to the same phenomenon.

It is likely that the solid catalyst, at the initial stage of the reaction, promotes hydration of the olefin as and it is not influenced by the presence of TFA, similarly TFA addition to the cyclohexene is not promoted by the resins. The slope of the TFA promoted reaction is only 0.54 10^{-7} higher than that of the unprompted one. The intercept of the reactions without TFA is very close to 0 which imply the necessity of the catalyst to achieve the reaction. On the contrary, reactions carried out in the presence of 1.32 mol·L^{-1} of TFA show an intercept close to the initial rate of the reaction carried out without catalyst (filled point at 0 sulfonated resins amount). The green filled circle represent the experimental data at 0 resin concentration, in agreement with the intercept of the straight line of the fitting.
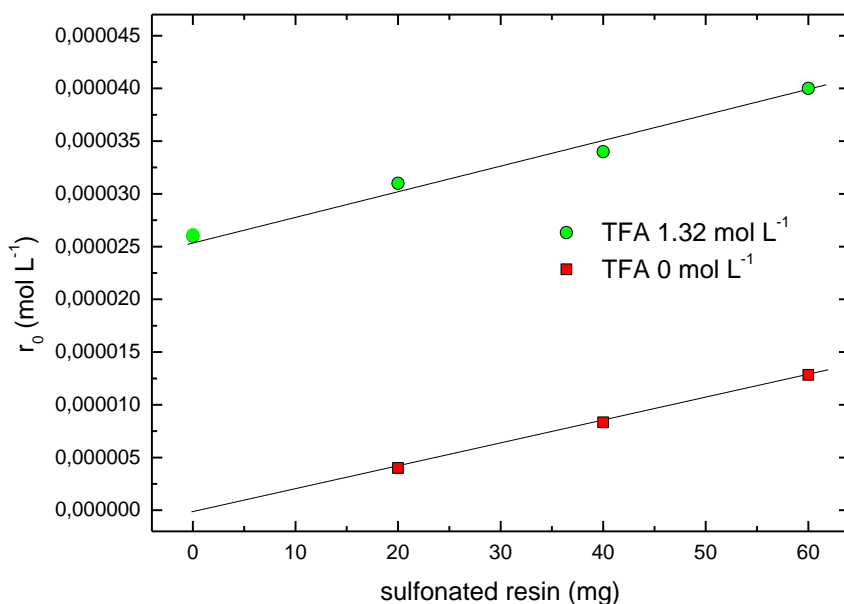
Fig. 7. Influence of the catalyst amount on the initial reaction rate. Run conditions: Run conditions: T 393 K, P autogenous pressure of the system, cyclohexene 1.14 mol L^{-1}, water 2 mL. TFA=0 slope = 2.21 10^{-7}, intercept = -4.4 10^{-7}; TFA = 1.32 mol L^{-1} Slope = 2.45 10^{-7}, Intercept = 2.59 10^{-5}

2.3.2.8. Influence of temperature on the initial reaction rate

The influence of temperature on initial reaction rates are reported in Figs. 8 and 9. The initial trends of the reactions are almost linear with time, but the overall kinetics is not of first order as can be observed in Fig. 1 for the complete reaction, as a matter of fact, the multiphase system allow a constant composition especially at low conversion, showing a zero order like reaction path. In addition, as observed in Figs. 2 and 3 the variation of the ration of the two liquid phases does not alter initial reaction rate. Starting from this evidence, we calculate an overall temperature factor by the Arrhenius plot of Fig. 9. The values of ΔEft=84 kJ mol^{-1} has been calculated with a pre-exponential factor of ΔSft=151 J mol^{-1} K^{-1}. The value of the temperature factor is quite high suggesting no limitation of the diffusion on the reaction rate and agrees with those of similar reactions [51] In addition, such a value suggests that the increase the temperature favors the attainment of the equilibrium, but reactions are exothermic, then the equilibrium is shifted to the left as the temperature increase. These parameters are the starting point for the realization of a reactive distillation process to achieve high conversion to cyclohexanol by using TFA as an easily recoverable low-toxic organic acid [51,52].
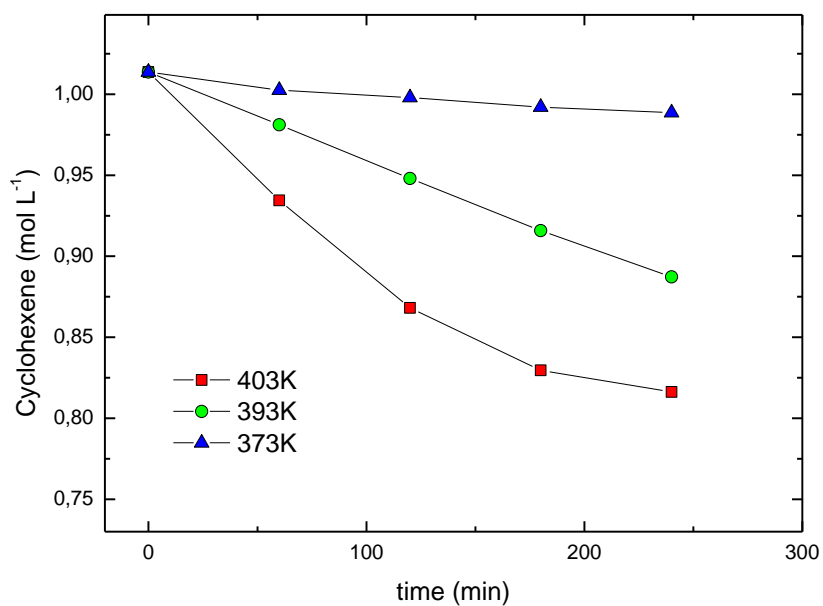
Fig. 8 Influence of Temperature on the initial reaction rate. Run conditions: Run conditions: T 373-403 K, P autogenous pressure of the system, cyclohexene 1.14 mol L^{-1}, water 2 mL, TFA 1.32 mol L^{-1}, Amberlyst 36 40mg
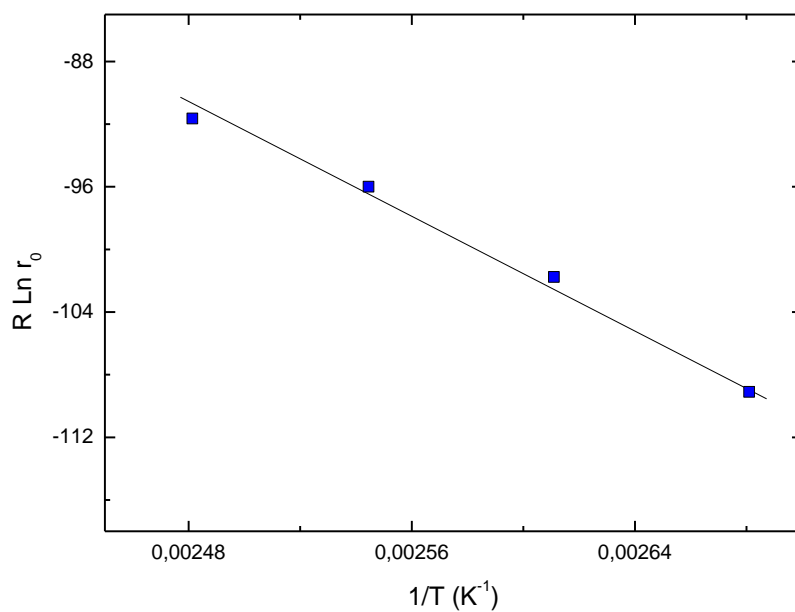

Fig. 9. Arrhenius Plot. Run conditions: Run conditions: T 373-403 K, P autogenous pressure of the system, cyclohexene 1.14 mol L^{-1}, water 2 mL, TFA 1.32 mol L^{-1}, Amberlyst 36 40mg. ΔE_{ft}=84 kJ mol^{-1}, ΔS_{ft} =151 J mol^{-1} K^{-1}

2.3.2.9. Catalyst recycling

The experimental observations above described suggest that the presence of the TFA is main factor that influence the yield to cyclohexanol, however the presence of the acid resin favors the attainment of the equilibrium. This may help in the development of a process based on this reaction. The increase of the reaction rate due to the presence of the resin could be considered as not determining for the practical development of a process. In fact, the increases of the reaction rate, in the presence of 40 mg of catalyst is only 30% (see Fig. 7) with respect of the reaction rate in the absence of the solid acid. However, the absence of an evident deactivation after 4 recycles it suggests that could be practically employed in a process. In addition, because of its ability in the reaction of hydrolysis it could be used in a second stage of cyclohexyl trifluoroacetyl ester saponification to give acid and alcohol (Fig. 10).

As regard TFA recovery, the acid can be easily separated from the reaction environment since it is in the aqueous phase, however, the reuse of the acid phase depends on the hydrolysis step of the cyclohexyl trifluoroacetate, whose study is beyond the aim of the present work. Besides, it is noteworthy that the recovery of the TFA has been studied in the Beckmann rearrangement of oximes, in which there were no needs of neutralization but a simple distillation [52]. In this case, separation is even simpler, since the acidic phase can be reused directly as a liquid aqueous phase.
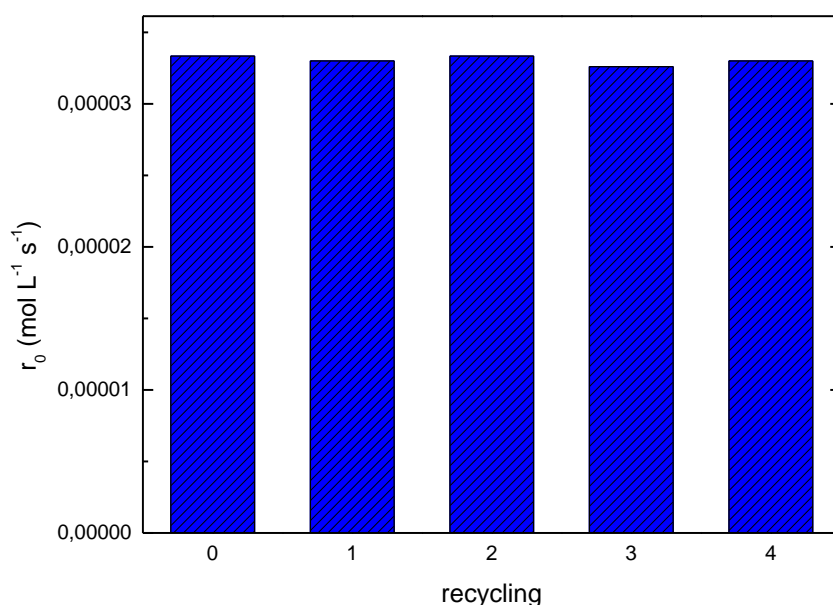

Fig. 10 Catalyst recycling. Run conditions: T 393 K, P autogenous pressure of the system, cyclohexene 1.14 mol L^{-1}, water 2 mL, TFA 1.32 mol L^{-1}, Amberlyst 36 40mg

2.3.3. Conclusions

Here, the potential of TFA as an alternative to the use of sulfuric acid in promoting the hydration of olefins in alcohols is shown. The reactions occurring to reach the equilibrium are acid catalyzed: TFA acts as catalyst, but a further increase of the rate of the processes are achieved by using TFA/sulfonic resins. The thermodynamic parameters of the overall equilibrium are calculated, and it shows a strictly dependence from TFA dissociation suggesting a firm relationship between equilibria and the ionic species in solution. The solid catalyst Amberlyst 36, which is those largely employed during kinetics and equilibrium experiments, shows at 393 K a negligible loss in activity after 4 recycling.

It should be noted that sulfuric acid leads to better results than using TFA. However, the use of sulfuric acid in industry is often considered a problem due to corrosion and re-concentration problems of the used acid, while TFA could simplify the recycling operations. The TFA/sulfonated resin system could be a promising way for an industrial process, also because of its potential in the use of a distillation process[30,35].

2.3.4. Experimental

Materials and instruments

All solvents and products were employed as received without further purification, or by following the usual purification procedures for spectrophotometric analysis.

All the analysis were carried out by GC and GC-MS (Agilent 7890 A, equipped with HP-5 30 m long I.D. 250 µm, film 0.25 µm, coupled to a Agilent 5975 C mass spectrometer or to a flame ionization detector). Some reactions are analyzed also by HPLC (Perkin Elmer LC 250 pump coupled to a diode array detector 235C, equipped with a Merck licrosphere 100 C18 column with water acetonitrile mixtures as eluent) to verify if present in reaction mixture temperature sensitive intermediates or products.

^{1}H NMR, ^{13}C, and ^{19}F spectra were recorded at 400MHz, 100MHz, 376MHz, repectively, using CDCl$_3$ as a solvent on a Brucker Avance II nuclear magnetic resonance spectrometer.
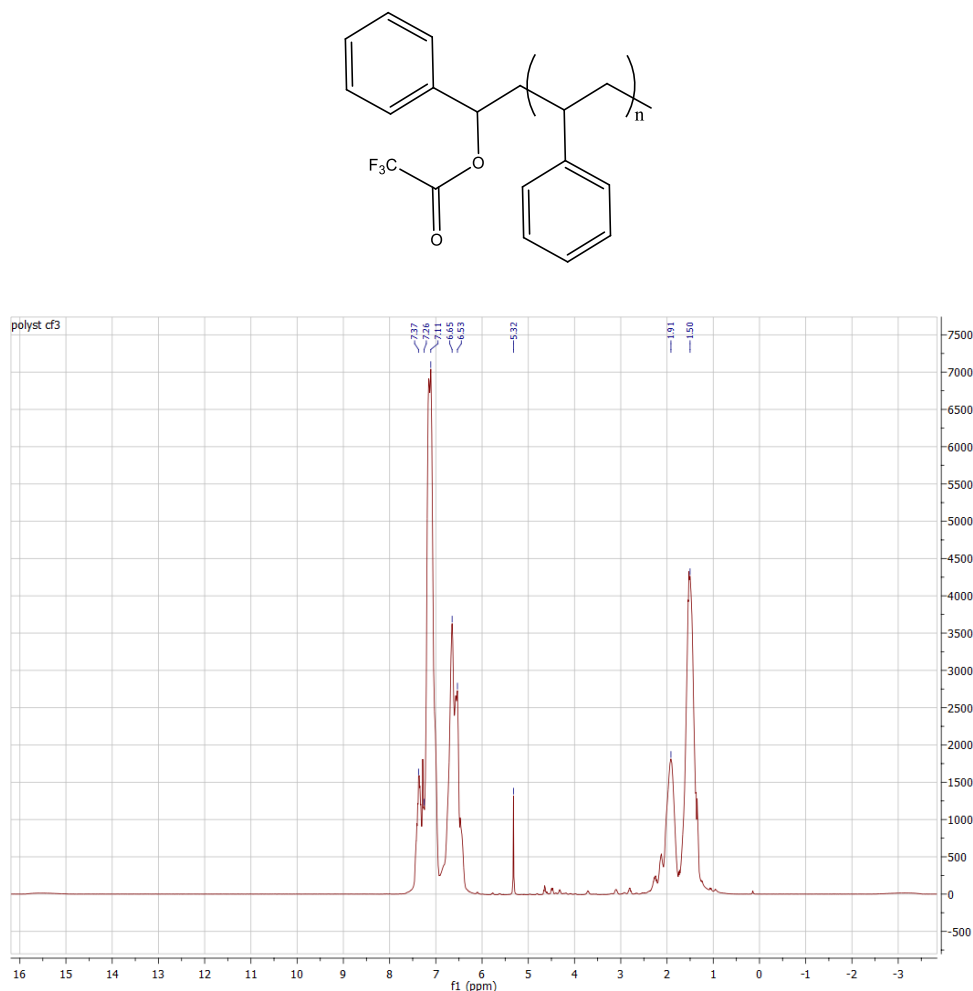
Fig. 11 ^{1}H NMR of the polystyrene in CDCl$_3$. assigned chemical shift: 7.37 - .6.53 ppm aromatics ^{1}H; 5.32 ppm; ^{1}H on C bond to OC=OCF$_3$, 1.91 - 1.50 ppm: chain [1]H.
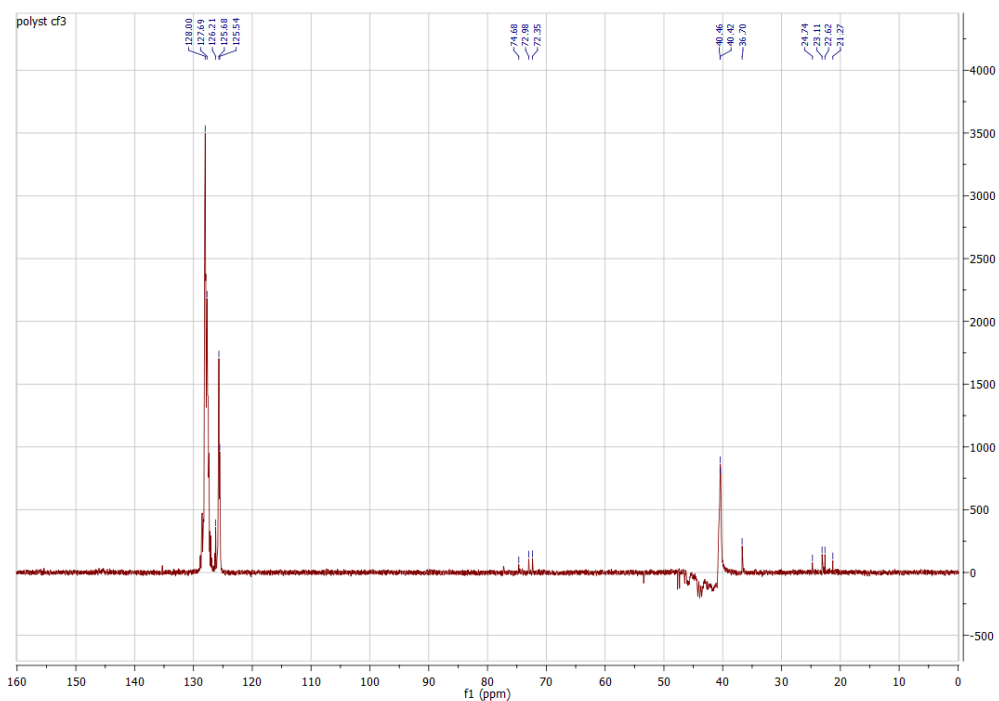
Fig. 12. ^{13}C NMR of the polystyrene. Assigned chemical shift: 128 - 125.54 ppm aromatic, ^{13}C 74.68 - 72.35 ppm ester, ^{13}C 40.46 - 36.70 ppm chain ^{13}C 24.74 - 21.27 ppm Terminal ^{13}C.
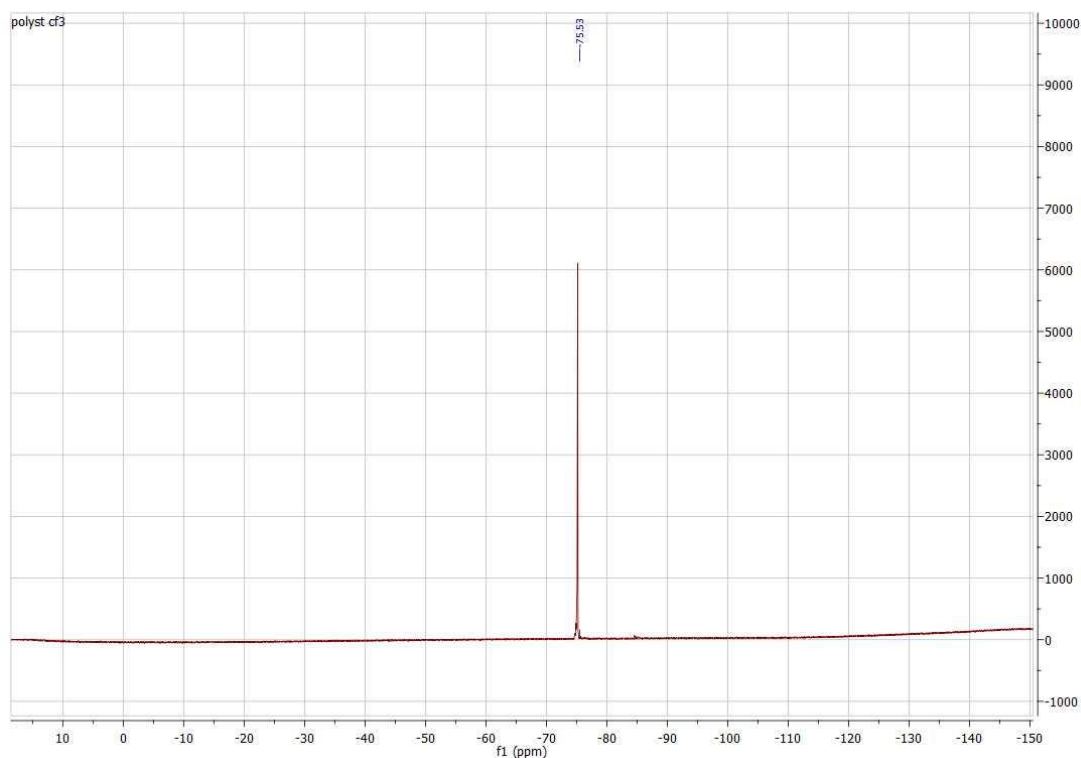

Fig. 13 ^{19}F NMR of the terminal groups. Assigned chemical shift: -75.53 ppm CF_3 ^{19}F

All solids employed as catalyst were commercial products and used after desiccation for at least 20h at 383K in a ventilated oven.

Reaction set-up

All reactions were carried out in an isotherm multi-reactor system equipped with eight aisi 316 autoclave of 8 mL of inner volume. In each autoclave reactants and catalyst are loaded into a glass insert (a modified test tube) closed with a pierced polytetrafluoroethylene plug in order to avoid liquid dispersion outside the insert. The electric heating of an aluminum block ensures that the autoclave is maintained at constant temperature within 0.5 K (see Fig. 1), the control were achieved by PID regulator (CAL 9500P). Each autoclave could be purged with nitrogen, the maximal temperature and operative pressure are 523 K and 30 bar, respectively. The mixing of the biphasic system was achieved with a magnetic bar rotating at 15 Hz driven by a magnetic stirrer. The homogeneity of the emulsion was visually tested, by observing phase separation at a rate of rotation below 10 Hz.

Reactions methodology

In a typical, experiment a magnetic bar, 0.26-2.6 mmol of TFA, 2 mL of water, 2.6 mmol of substrate and 40mg of solid catalyst (if used) are added into the glass insert. The autoclave, after the loading of the stoppered vial, which fits almost exactly the autoclave volume, is closed, outgassed and filled with nitrogen. The aluminum block is now heated at the reaction temperature (383-403K), when the system heater is stabilized, all autoclaves are inserted in its seat. After 5 minutes without agitation, in order to allow temperature equilibration, agitation was turn on and the reaction starts. After the definite time the selected autoclave (or autoclaves) was cooled in a water bath and opened. The test tube was removed and the mixture diluted with 6.5 g of CH_2Cl_2, then 40 mg of tetradecane, as internal standard, was added to the slurry and stirred for 2 minutes. Finally, solid catalyst was filtered and the organic phase separated, from the mixtures, and dried with anhydrous Na_2SO_4.

1-Phenylethanol, cyclohexanol and hexanols synthesis

The reactions are carried out in multiphase systems being styrene, cyclohexene and n-hexene not soluble in water, in additions, there could be the presence of a heterogeneous solid catalyst. In a typical reaction 2.62 mmol of substrate were placed into the reactor together with 1-3 mL of water, 0.87 mmol of promoter and 40 mg of a solid catalyst (if present). Tab. 7 shows the list of all catalytic systems.

Tab. 7 List of substrates and of the catalytic system employed

substrate	Promoter	Solid catalyst
Styrene	H_2SO_4	Amberlyst 15
Cyclohexene	CF_3COOH	Amberlyst 36
n-hexene	CH_3COOH	Amberlite IRC 50
		Dowex D50

All possible combinations of substrate, promoter and heterogeneous catalysts were tested to verify what were those, which gave the best results. As a matter of fact, the typical reaction

conditions are: 4h of reaction, 393K, pressure are autogenous pressure of water, TFA and substrate, about 3 bar.

Analysis

GC and GC-MS analysis were carried by using GC or a GC-MS instruments with the following conditions: temperature program, 5 minutes isotherm at 333K, 20 K min^{-1} to 523 K isotherm at such temperature for 5 minutes; nitrogen flow 1 mL min^{-1}, split ratio 10/1. Quantification of the products are carried out if possible by using calibration with standard (styrene and 1-phenylethanol), for dimers selectivities are calculated by using the same response factor of styrene and oxygenated isomers (mainly dimers of the 1-phenylethanol) are used the same response factor of the alcohol.

2.3.5 References

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Chapter 3:
Carbonylation of Aryl Iodide

In this Chapter the study aiming to outline the best conditions for optimizing the productivity of the [PdCl$_2$(Xantphos)] based catalytic system is reported. In addition to the reaction conditions, the influence of a series of additives were studied to avoid the decomposition of the catalytically active species. A new homogeneous catalytic system based on [PdCl$_2$(Xantphos)]/ferrocene as co-catalyst (1:100 ratio) is delineated, which allows to obtain a very interesting productivity for an industrial application (TOF about 300,000 h^{-1}) for the methoxycarbonylation of iodobenzene.

In addition, a preliminary study for the amino carbonylation of iodobenzene is presented.

3.1 The methoxycarbonylation of iodobenzene to methyl benzoate efficiently catalysed by the [PdCl$_2$(Xantphos)]-Fc/Fc$^+$ system

3.1.1 Introduction

A viable alternative to carboxylic acids derivatives syntheses is the palladium-catalyzed carbonylation of haloarenes. This area of research has attracted considerable interest, because this reaction exhibits high compatibility with a wide variety of functional groups.

From the point of view of the productivity of the reaction, catalyzed in most cases by homogeneous palladium complexes, they proceed well for bromides and aryl iodides. The possibility of performing such reactions on non-activated aryl chlorides, given their low cost and easy availability, remains an open challenge.

The catalytic cycle most widely accepted by academia involves (scheme1) :

(1) The oxidative addition of the aryl halide to a Pd(0) species to form a Pd(II) intermediate.

(2) Coordination of carbon monoxide and migratory insertion of carbonyl to form a Pd(II)-acyl species

(3) Nucleophilic attack at the acyl complex resulting in the final product and regeneration of the Pd(0) species by reductive elimination.

[Pd(II)]

[Pd(0)]

Base·HI

Base

Ar-I

I
Pd(II)
H

I
[Pd(II)]
Ar

Ar(CO)OR

ROH

Pd(II)

I

Ar

O

CO
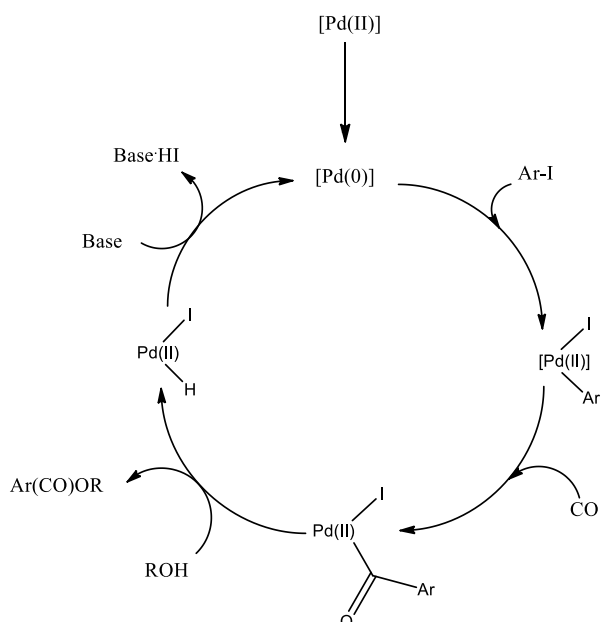
Scheme 1 Proposed mechanism for alkoxycarbonylation of aryl halides

In addition, this reaction must be conducted in the presence of a stoichiometric base (or slight excess) to the aryl halide, to eliminate the HX released from the reaction and shift the equilibrium towards the obtainment of products. Although many studies have been carried out, there are still doubts about the catalytic step in which the base intervenes.

One of the problems related to the use of aryl chlorides for this reaction, seems to be presented by the difficulty of obtaining the intermediate complex Pd(II) aryl, due to the high energy required to break the C-Cl bond during the oxidative addition to Pd(0).

Because of the wide range of products that can be obtained from this reaction, numerous advances have been made in increasing the productivity of the catalytic system, going on to define the best reaction conditions and new palladium-based catalytic systems.

The efforts made to improve the productivity were mainly focused on the study of the ligands of the homogeneous Pd-based catalyst. The best ligands result to be the phosphinic ones, both monodentate like PPh_3, PCy_3, Di(1-adamantyl)-n-butylphosphine etc, and diphosphines like dppp, dppb, dppf, DPEphos, etc.

However, the industrial application appears to be limited to some fine chemistry syntheses. The main problems are related to the catalyst cost/productivity ratio. Moreover, the reaction environment for carbonylation reactions turns out to be very reducing and this can lead to the formation of agglomerates of palladium atoms (Pd-Black), non-active species of the catalyst. As a matter of fact, it is sufficient to compare the productivity of Pd-based catalysts for a simple C-C coupling reaction (e.g. Suzuki) where the TurnOver Number (TON) is between 100,000 and 1,000,000, with the TON of 100-10,000 of the carbonylation reactions of haloarenes [1].

In homogeneous catalysis, the problem of deactivation of the catalytic species has been a known problem for a long time and to overcome this problem, several strategies have been devised that vary depending on the type of reaction performed, which can however be summarized by identifying the best reaction conditions, the best ligand or the use of co-catalysts or additives. Concerning haloarenes carbonylation reactions, only a few examples

are reported in the literature, mainly focused on the use of iron or copper salts [2] that aim to reoxidize the metallic Palladium (Pd-Black) particles to form soluble Pd(II) species able to enter the catalytic cycle again.

Here we present the optimization of the catalytic system based on [PdCl$_2$(Xantphos)] paying particular attention to the effect of some additives on the productivity and the possibility of limiting catalyst deactivation

3.1.2 Results and discussion

Methoxycarbonylation of iodobenzene was chosen as the sample reaction. This is because, by replicating some mild reaction conditions that can be found in the literature (24h reaction time, temperature 70°C , P$_{CO}$ 5 atm)[3], the yield of the reaction is quantitative. Although iodobenzene is relatively more expensive than the corresponding bromine and chlorobenzene, the reaction could be of industrial interest because of the high productivity of the catalyst, which can be used in very small quantities. In fact, in many works focused on the carbonylation of non-activated bromine and chlorobenzene, the catalyst turns out to be used even more than 10% with respect to the substrate, and this nullifies the economic advantage of using less expensive substrates, with an employment in large quantities of the homogeneous catalyst, difficult to recover.
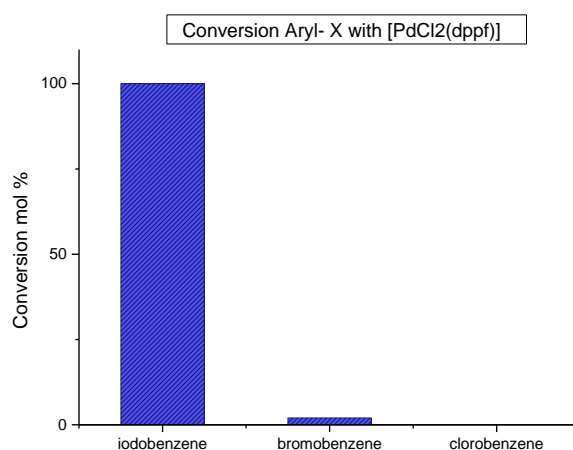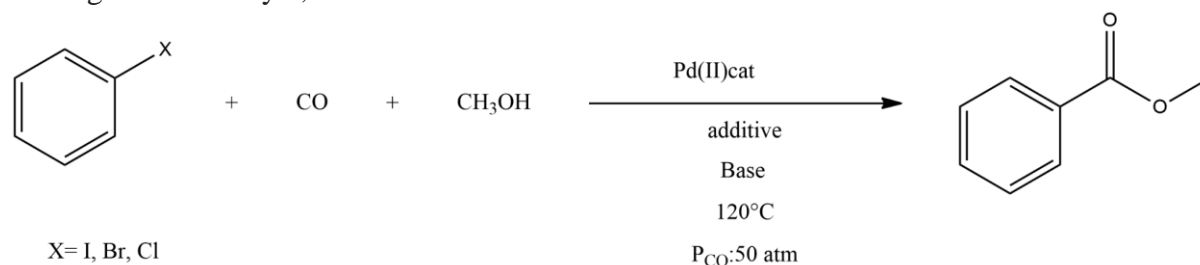

Figure 1 Conversion of Aryl-X with [PdCl2(Xantphos)]. Run Condition: halobenzene= 4,46 mmol, Et3N 1,2 eq., cat 1,4·10^{-3} mmol Solvent: MeOH: 4 mL, t=24 h, T =120°C, P$_{CO}$=50 atm

3.1.2.1 Counterion Influence.

In homogeneous catalysis, the type of counterion of the active metal in the catalyst can significantly influence the productivity of the reaction[4-6]. Therefore, employing a Pd(II) complex with diphenylphopshino ferrocene (DPPF) ligand, the influence of this parameter on this reaction was studied. As can be seen from Fig.2 the nature of the counterion does not show significant changes on the productivity of the reaction. Although triflate leads to better results, it was chosen to operate with chloride as the counterion in order to better study the influence of the reaction parameters on the productivity of the catalytic system.
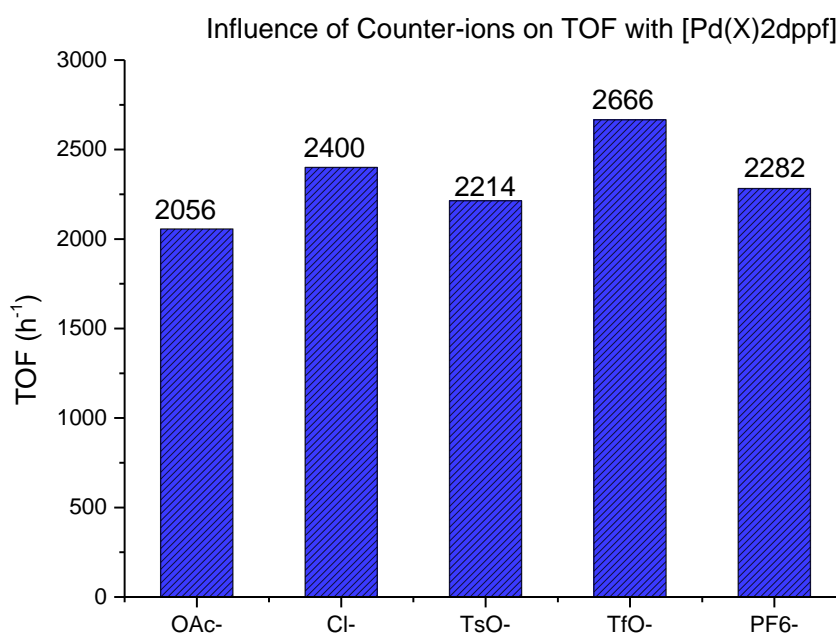
Fig.2 Influence of counter-anions. Run Condition: iodobenzene 4,46 mmol, Et$_3$N 1,2 eq., cat 1,4*10-3 mmol Solvent: MeOH: 4 mL, t=1h, T =120°C, P$_{CO}$=50 bar

3.1.2.2 Influence of Ligand and Pd/L Ratio.

An important parameter for homogeneous catalysis is directly related to the type of ligands used.
In the literature there are many studies focused on the ligands used for this type of reaction, especially on monophosphines, which have been studied from the point of view of steric (Tolman's angle) and inductive effects. In fact, it is reported that for the alkoxycarbonylation of activated chlorobenzenes it is often necessary to use highly basic monophosphines, such as P(Et)$_3$ and PCy$_3$[7], which however have the problem of being very sensitive to oxygen and degrade very easily. Recently, the possibility of using diphosphinic chelating agents has been studied, especially from the family of ferrocenic phosphines (such as dppf). Several new phosphines have been synthesized, observing the influence of substituents from a steric-inductive point of view.

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The use of bidentate phosphine ligands in carbonylation reactions is attracting much interest, as they are attributed with a greater ability to prevent catalyst poisoning by multi-coordination of CO at the metal center, which could lead to the formation of Pd-metal [8-12].

Fig.3 shows the productivities obtained by using a wide range of diphosphinic ligands. As can be seen, there is an increase in productivity as a function of increasing the ligand bite angle [13]. In particular, the best result was obtained with Xantphos. In fact with a substrate/catalyst ratio of 3200/1 and 6400/1 a total conversion was obtained after 1 hour of reaction.

Xantphos, a ligand developed by van Leeuwen for hydroformylation reactions, has characteristics that make it particularly interesting for application in catalytic reactions. Indeed, its large bite angle (110°) and its high degree of flexibility in the coordination at the metal center (97-133°) are characteristics that allow it to obtain a dynamic coordination that is very important for both stability and productivity of the catalytic system. Comparing the results obtained with DPEphos and dppf, which have bite angles very close to Xantphos (uncoordinated binder bite angles 108 and 106), the results obtained are slightly inferior due to the greater stiffness of the ligand, which can affect the coordination phases of the reagents at the metal center.[3].
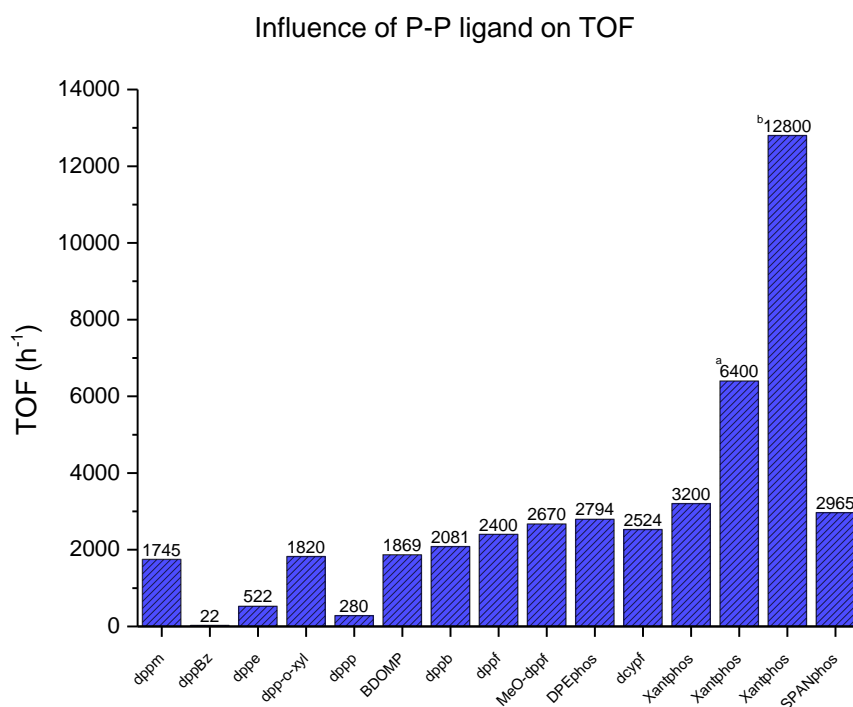

Influence of P-P ligand on TOF

Fig.3 Influence of Diphosphine lingand. Run Condition: iodobenzene 4,46 mmol, Et$_3$N 1,2 eq., cat [PdCl$_2$(P-P)]= $1,4*10^{-3}$ mmol, [a]cat $7*10^{-4}$, [b]cat: $3.2*10^{-4}$ mmol, Solvent: MeOH: 4 mL, t=1h, T =120°C, P$_{CO}$=50 atm

In addition to the type of ligand, the influence of the [PdCl$_2$(Xantphos)]/Xantphos ratio was studied. As it is possible to observe from fig.4 starting from the preformed complex the best results are obtained. Increasing the amount of free ligand in the reaction environment a drastic decrease in productivity is observed, probably this is due to the formation of

palladium tetra coordinated complexes less active for catalysis, and/or due to a competition in the coordination of the reagents with the metal center.
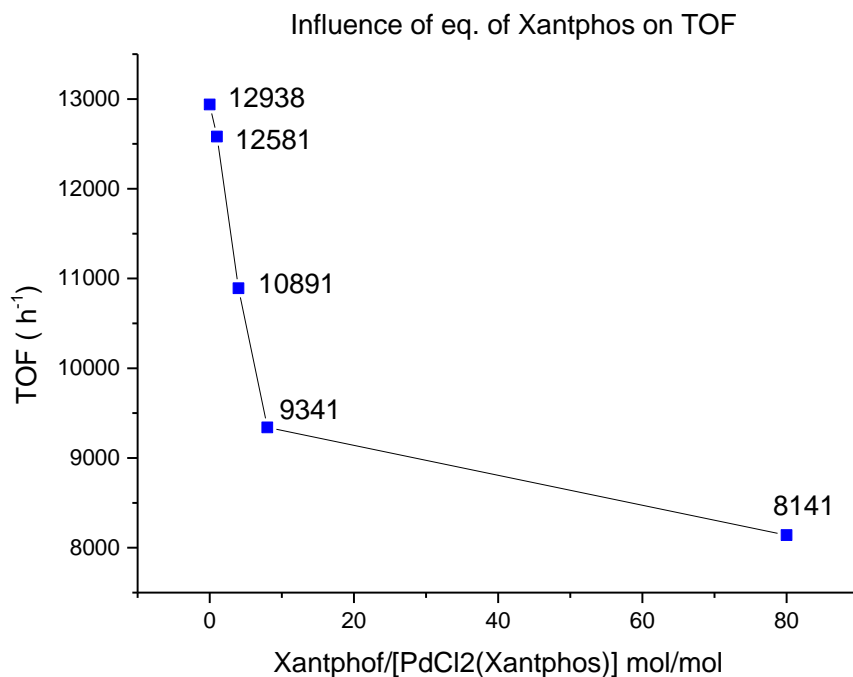

Influence of eq. of Xantphos on TOF

Fig 4 Influence of equivalent of free Xantphos. Run Condition: iodobenzene 4,46 mmol, Et$_3$N 1,2 eq., cat= [PdCl$_2$(Xantphos)]= cat: 3.2*10^{-4} mmol, Solvent: MeOH: 4 mL, t=1h, T=120°C, P$_{CO}$=50 atm

3.1.2.3 Influence of Substrate/Catalyst Ratio.

From fig. 5, it is observed that with a substrate/catalyst ratio of 3200/1 and 6400/1, a total conversion is obtained at 1 hour. Even under conditions where the substrate/catalyst ratio is 270500/1 a final conversion of over 60% is obtained and this shows that the homogeneous [PdCl$_2$(Xantphos)] catalyst turns out to be particularly active even at very low concentrations (it reaches TOFs above even 1 million). For the influence of the reaction parameters, it was chosen to operate the reaction with the ratio 270500/1 and run the reaction for 30 minutes, to avoid that the decrease in concentration of the reagent could become limiting for the reaction rate. Under these conditions it is possible to operate a systematic study on the other variables such as Temperature, CO pressure, the influence of additives etc., without small errors on the conversion can bring big errors on the determination of the number of catalytic cycles of the Pd based catalyst.
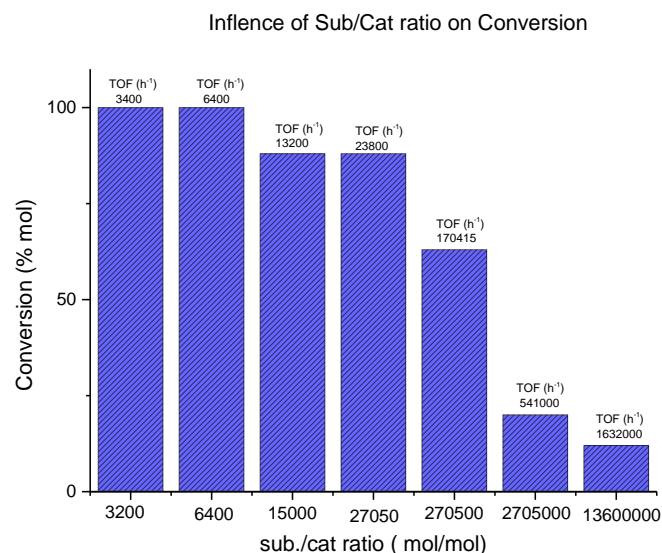
Inference of Sub/Cat ratio on Conversion

Fig 5 Influence Substrate/Catalyst Ratio. Run Condition: iodobenzene 4,46 mmol, Et$_3$N 1,2 eq., cat= [PdCl$_2$(Xantphos)], Solvent: MeOH: 4 mL, t=1h, T =120°C, P$_{CO}$=50 atm

3.1.2.4 Influence of the nature of alcohol

One of the parameters studied in the alkoxycarbonylation reaction is the influence of the alcohol used as both solvent and reactant.

As can be seen in fig.6 the TOF decreases as the pKa of the alcohol and the length of the carbon chain increase. These results appear to agree with the reactivity of alcohols (nucleophilic attack) towards the Pd-acyl species, commonly accepted as an intermediate in the catalytic cycle

Influence of Alcohol on TOF
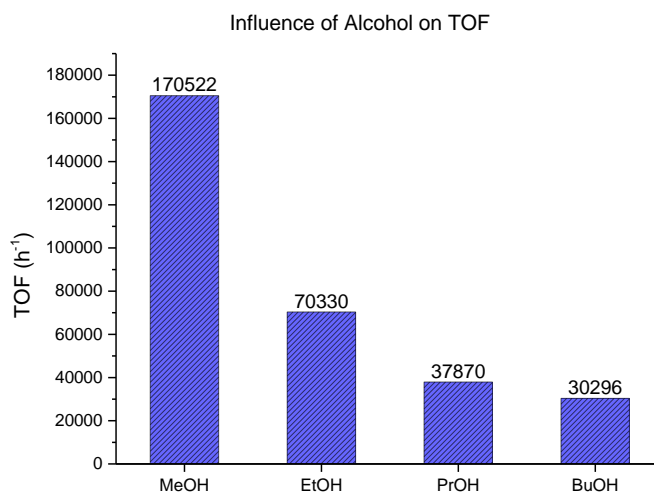
Fig 6. Influence of Alcohols. Run Condition: iodobenzene 4,46 mmol, Et$_3$N 1,2 eq., cat=cat:1,6*10^{-5} mmol [PdCl$_2$(Xantphos)], Solvent: Alcohols: 4 mL, t=1h, T =120°C, P$_{CO}$=50 atm

3.1.2.5 Influence of reaction time on TON and TOF

Theoretically for an ideal catalytic system, the TON/time trend should increase linearly, while the TOF/time trend should remain constant. Instead, as can be seen from fig. 7, the trend tends to plateau. This can be mainly due to two factors. Firstly, it is possible that as the yield of the reaction increases, the kinetics are limited more and more by the decreasing concentration of iodobenzene, in fact under the conditions under consideration, where the catalyst is very dilute, the reaction takes 8 hours to complete. Second, it is possible that the reaction conditions, such as T and P_{CO}, are too high, resulting in slow decomposition of the catalyst. It is not possible to exclude the formation of nanoparticle Palladium, which is found to be less active than the Pd(0) species.

To exclude any problems related to the decrease of iodobenzene concentration, the successive tests were performed at half hour.
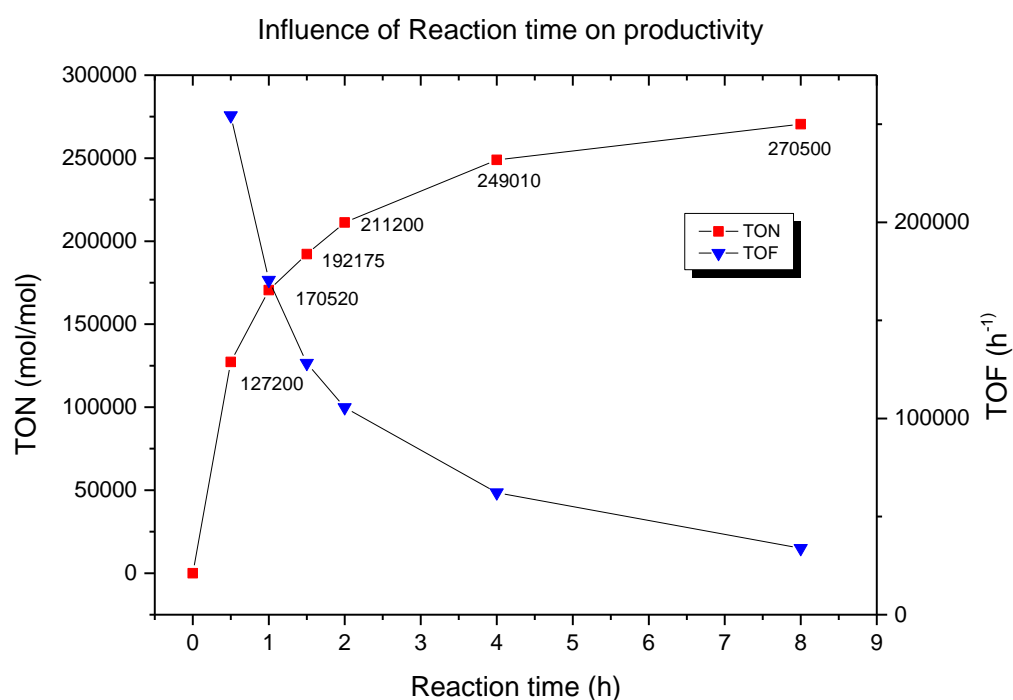

Fig 7. Influence of Alcohols. Run Condition: iodobenzene 4,46 mmol, Et_3N 1,2 eq., cat=cat:1,6*10^{-5} mmol [PdCl$_2$(Xantphos)], Solvent: Alcohols: 4 mL, T =120°C, P_{CO}=50 bar

3.1.2.6 Influence of temperature on productivity

As it is possible to observe from fig 8 for the homogeneous catalyst [PdCl$_2$(Xantphos)] the increase of the reaction temperature leads to an increase of the productivity, up to reach the maximum at 120°C, with a TOF of more than 250000 h^{-1}. At higher temperatures a drastic decrease in productivity is observed probably due to the thermal decomposition of the catalyst, indeed at 130°C, at the end of the reaction the presence of traces of metallic

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palladium was observed. Using the Arrhenius Plot, it was possible to determine the activation energy which is 19.989 Kcal/mol
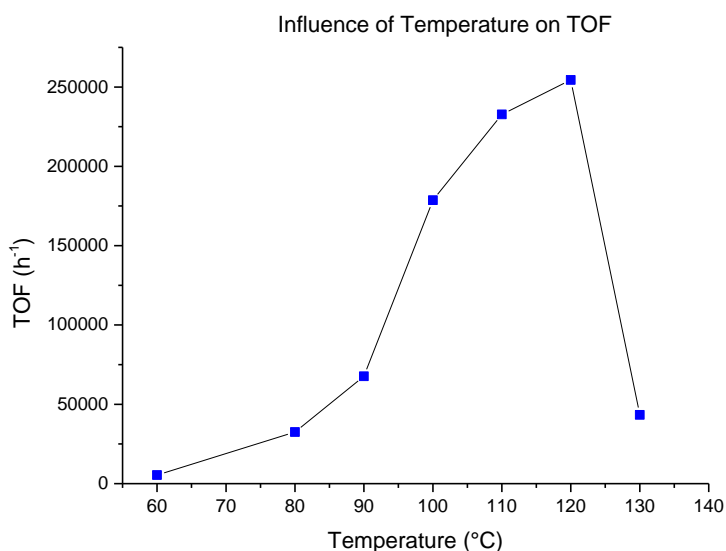

fig 8. Influence of Temperature. Run Condition: iodobenzene 4,46 mmol, Et$_3$N 1,2 eq., cat=cat:1,6*10^{-5} mmol [PdCl$_2$(Xantphos)], Solvent: MeOH: 4 mL, t=0,5h, P$_{CO}$=50 bar

3.1.2.7 Influence of carbon monoxide pressure.

As can be seen from Fig 9 there is a very important increase in productivity when going from 1 atmosphere to 10 atmospheres of CO, going from a TOF of 27000 h^{-1} up to a TOF of about 250000 h^{-1}. With an increase in pressure there is no visible increase in methyl benzoate yield. This indicates that the rate determining step is the oxidative addition of aryl halide to Pd(0) and not the formation of the Pd-acyl species by CO insertion. In addition, high pressures, the formation of double carbonylation products is not observed.[14-15]

In addition, the transformation of the Pd(II) species to Pd(0) occurs easily in this reaction environment, which is particularly reducing. It is possible that increasing the concentration of CO, in addition to promoting the formation of the active Pd(0) species, promotes the kinetics of the reaction due to the high concentration of dissolved CO in the reaction solvent, which remains constant over time.

In some cases, especially when the conversion reached high values (from 60-70% and up), traces of Pd-metal were observed. It is possible that as soon as the aryl halide concentration begins to be below 30%, the carbon monoxide insertion kinetics leading to the formation of "polycarbonyl" species, which are particularly unstable and lead to the formation of palladium metal agglomerates, is favored.
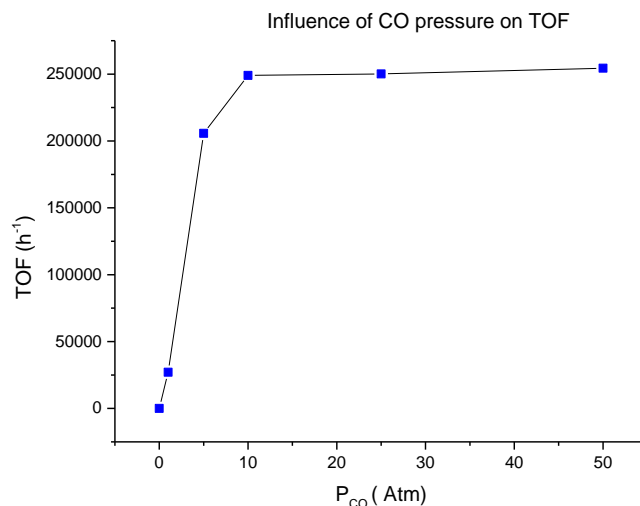
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Fig.9 Influence of CO Pressure. Run Condition: iodobenzene 4,46 mmol, Et₃N 1,2 eq., cat=cat:1,6*10⁻⁵ mmol [PdCl₂(Xantphos)], Solvent: MeOH: 4 mL, t=0,5h, T =120°C

3.1.2.8 Influence of Bases

For this type of carbonylation, the most widely accepted catalytic cycle involves the use of a base whose purpose is to remove the HX and allow the reaction to continue.

As can be seen from Fig.10 it is possible to carry out the reaction with both inorganic and organic bases.

In the reaction medium both the inorganic bases and the iodides formed during the reaction are not very soluble in methanol and this could shift the equilibrium towards the formation of the products. Moreover, it is possible to suppose that strong bases can react with alcohol to form the corresponding alkoxide, favoring the attack on Pd-Acyl species. However, they show less activity than organic bases, probably because strong bases can form Pd-OH species which are less stable in the reaction environment, in fact with bases such as NaOH and KOH, at the end of the reaction has been observed the presence of metallic palladium.

Organic bases and their corresponding salts are much more soluble in the reaction environment, but not all of them lead to high productivity. As can be seen in the case of pyridine, the coordinating bases lead to a drastic decrease in conversion probably because they compete in the coordination of the metal center with the other reactants, or because they lead to the formation of homogeneous Pd species that are not active for catalysis.

Non-nucleophilic organic bases, such as trialkylamines, show the best activities. But as shown in Fig 10., a negative trend in productivity can be observed as the number of carbons on the alkyl chain increases. Although the most widely accepted catalytic cycle involves a reductive elimination of HX from a Pd(II) species in order to originate again the active Pd(0) species, it is still not clear how the base is involved in this step. It is possible that as the steric size of the amine increases, there is less interaction between it and the coordination sphere of the Pd(II) species and thus the reductive elimination is less favored.
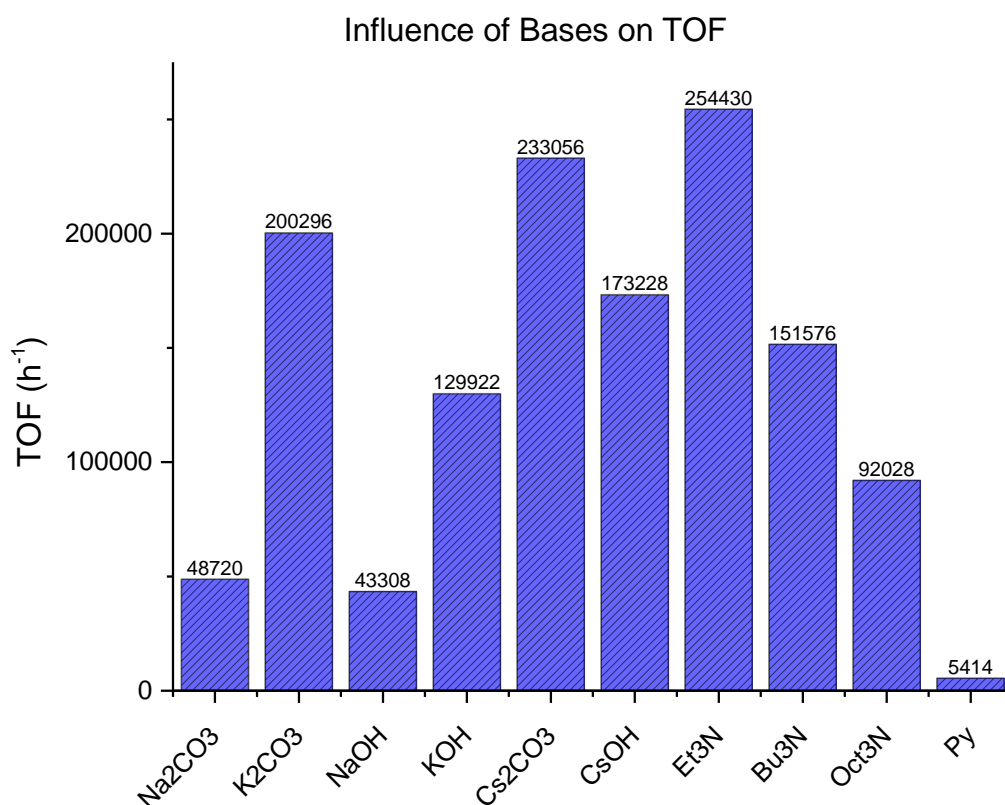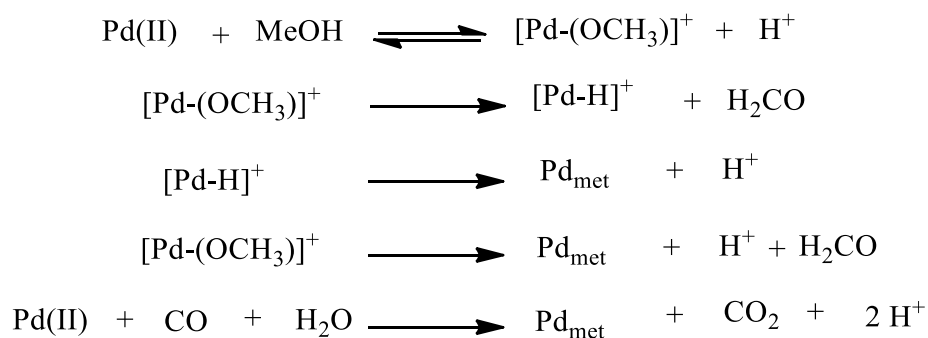
143

Influence of Bases on TOF

3.1.2.9 Effect of promoters/co-catalyst

One of the main problems with reactions catalyzed by homogeneous palladium complexes is the decomposition of the active species resulting in the formation of Pd-Black metallic clusters.

$$Pd(II) \; + \; MeOH \; \rightleftharpoons \; [Pd\text{-}(OCH_3)]^+ \; + \; H^+$$

$$[Pd\text{-}(OCH_3)]^+ \; \longrightarrow \; [Pd\text{-}H]^+ \; + \; H_2CO$$

$$[Pd\text{-}H]^+ \; \longrightarrow \; Pd_{met} \; + \; H^+$$

$$[Pd\text{-}(OCH_3)]^+ \; \longrightarrow \; Pd_{met} \; + \; H^+ + H_2CO$$

$$Pd(II) \; + \; CO \; + \; H_2O \; \longrightarrow \; Pd_{met} \; + \; CO_2 \; + \; 2\,H^+$$

Scheme 2 Decomposition patterns

The patterns which leads to the decomposition of the catalytic species change depending on the type of reaction. For alkoxycarbonylation reactions, decomposition and agglomeration to metallic palladium can occur primarily due to the instability of the palladium hydride species that can form during the reaction (Scheme 2).

Although in the carbonylation reactions of aryl halides the active species, commonly accepted by the reaction mechanism is Pd(0), the macro-particles of metallic Pd turn out to be enormously less reactive than the homogeneous species[16-18].

Strategies to avoid the decomposition of the homogeneous catalyst are numerous and mainly aimed at improving the stability of the catalytic species of Pd(0), which can be done by identifying the optimal reaction conditions (temperature and P_{CO}) or by optimizing the amount and type of ligands.

Another approach to optimize the catalyst activity is to prevent the metallic palladium particles from agglomerating to large macroparticles. In this way the Pd(0) nanoparticles could be brought back to soluble Pd(II) species which are able to re-enter the catalytic cycle.
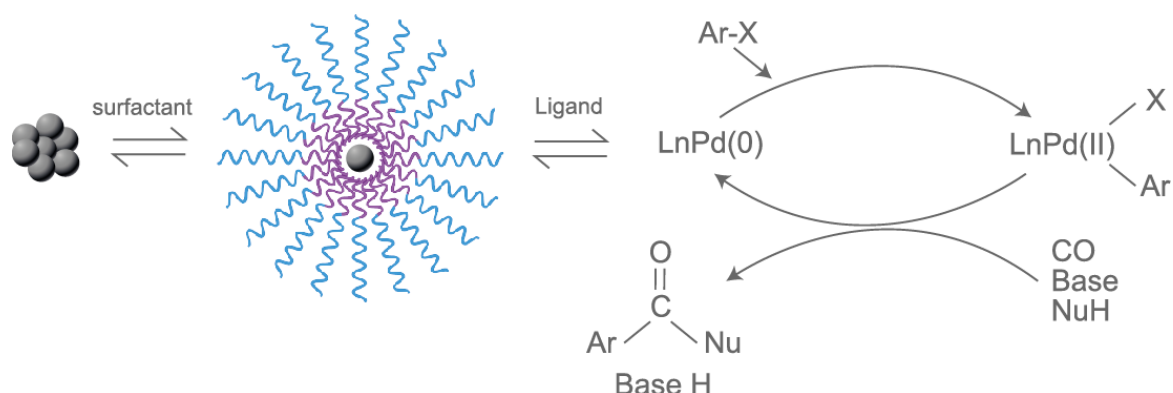
To optimize system productivity, the effects of different types of additives were studied. These additives have been divided for convenience into "Surfactants", "Reducers" and "Oxidizers".

3.1.2.10 Influence of Surfactant

As is well known, the reduction of transition metals in the presence of surfactants leads to the formation of metal nanoparticles, the size of which can be modulated according to the type of surfactant used[20-23].

These nanoparticles are stabilized and do not agglomerate into large metallic particles.

It is also known that Pd-nanoparticles can be used as precursors for the catalytically active species, which in the reaction considered is Pd(0) [24-25].

For this reason, as can be seen from fig.11, the effect of 3 surfactants has been studied, one cationic (TBAI), one non-ionic (SPAN-60) and one anionic (SDS).
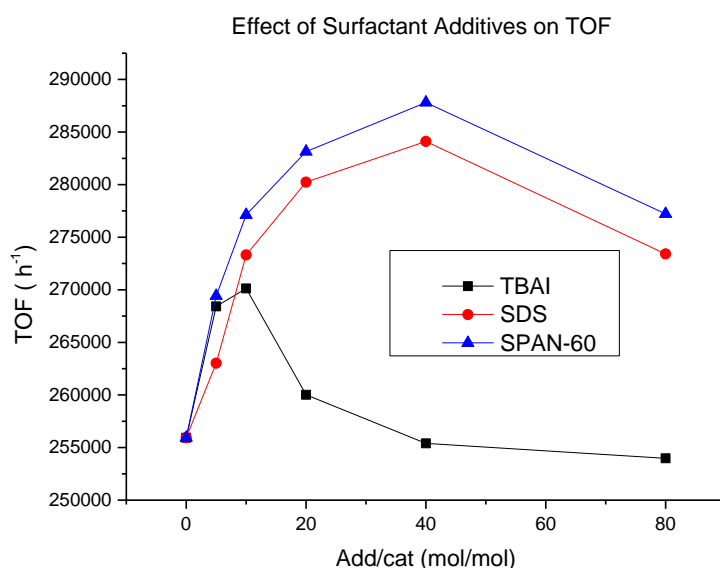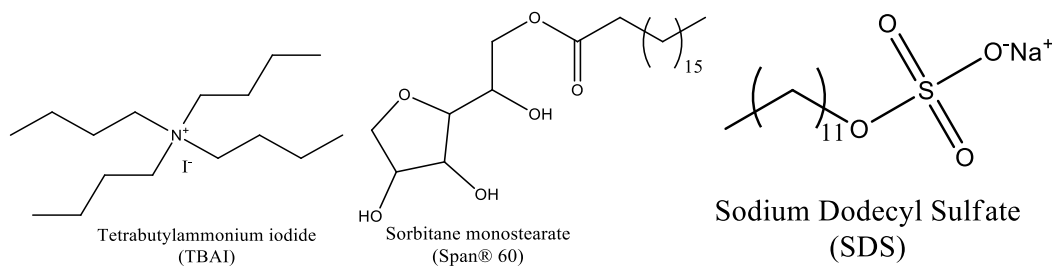

Tetrabutylammonium iodide (TBAI)   Sorbitane monostearate (Span® 60)   Sodium Dodecyl Sulfate (SDS)

Fig 11. Influence of Surfactants. Run Condition: iodobenzene 4,46 mmol, Et$_3$N 1,2 eq., cat=cat:1,6*10^{-5} mmol [PdCl$_2$(Xantphos)], Solvent: MeOH: 4 mL, t=0,5h,T=120°C, P$_{CO}$=50 bar

As can be observed, for SPAN-60 and SDS, a growth in productivity is observed as the amount of surfactant increases, up to a maximum at an Add/Pd ratio of 40. At higher amounts of surfactant, a slight decrease in productivity is observed, probably due to a better stabilization of the nanoparticles, which therefore enter the catalytic cycle with greater difficulty.

Interesting is the case of TBAI. It is plausible that an increase in the amount of TBAI leads to the formation of stable complexes of (II), as was recently demonstrated by T. Strassner, who, for the Mizoroki-Heck reaction in the presence of tetralkylhalogenides, has observed the formation of monomeric and dimeric species of stable Pd(II) [26].

3.1.2.11 Influence of Selective Oxidant on productivity

Another strategy to limit the negative effect on productivity due to Pd-metal formation could be to solubilize it through the formation of palladium(II) complexes by the use of oxidants. This also introduces the issue that it could interfere with the concentration of the active Pd(0)

species. The choice of the appropriate oxidant is not easy, as this could inhibit the reduction of Pd(II) species to active Pd(0) species. The proposed study on the effect of various oxidants, could be useful to determine the concentration and type of oxidants to be used to selectively reoxidize the Pd-metal (and not the active species of Pd (0)), and that once transformed into soluble Pd(II) species can be reduced to a Pd(0) species due to the reducing reaction environment.
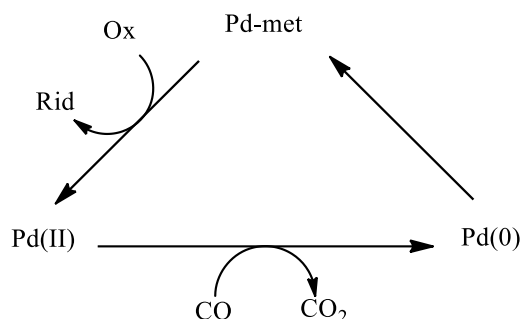
Scheme 3 Possible pattern for limiting Pd-Metal using selective oxidants

It is reported in the literature that the use of some organic oxidants, such as benzoquinone, or inorganic oxidants such as Fe(III) salts can regenerate Pd(II), an active species for oxidative carbonylation reactions. In this case, we chose to see if it was possible to obtain soluble Pd(II) species from Pd-met, from which catalytically active Pd(0) species could be originated again. However, in alkoxycarbonylation of iodobenzene, as can be seen from the graph, an increasing the concentration of oxidant additives leads to a decrease in the productivity of the system. Although the reduction of Pd(II) to Pd(0) in carbonylation reactions occurs rather easily, the presence of these oxidants could shift the equilibrium towards the formation of Pd(II) complexes, thus removing the catalytically active species from the reaction.
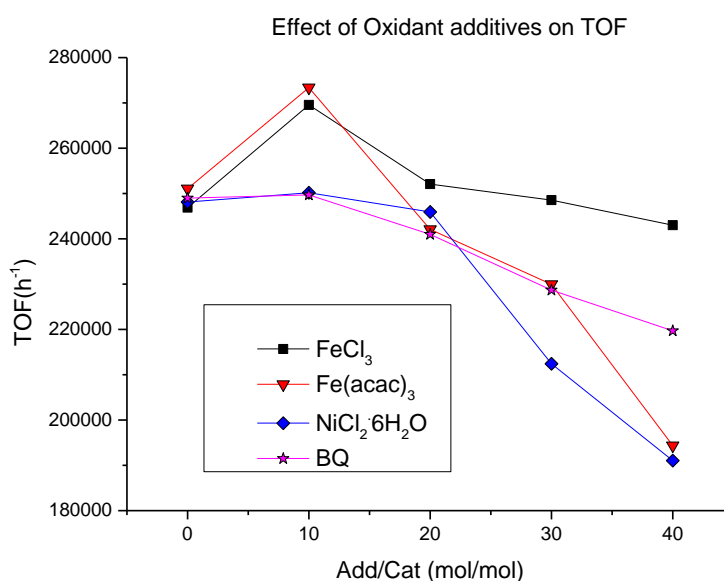

Fig 12. Influence of Oxidant additives. Run Condition: iodobenzene 4,46 mmol, Et_3N 1,2 eq., cat=cat:1,6*10^{-5} mmol [$PdCl_2$(Xantphos)], Solvent: MeOH: 4 mL, t=0,5h, T=120°C, P_{CO}=50 bar

3.1.2.12 Influence of Reducing additives on productivity

As can reported in fig.13 the effect of some reducing agents on the productivity of catalyst has been studied. With ascorbic acid there is an increase in TOF up to a maximum of about 290000 h^{-1} at an Add/Pd ratio of 30/1. As the amount of ascorbic acid increases, a dramatic decrease in productivity is observed.

It is known that ascorbic acid can be used as a sacrificial reductant for the synthesis of Pd(0) complexes, active for the catalysis. But in a similar way, it can be employed for the production of Pd-Met nanoparticles, which are less active than homogeneous species.

Oxalic acid exhibits a similar trend, with a maximum at an add/Pd ratio of 30. In this case, as the amount of additive increases, a less pronounced decrease is observed than the trend for ascorbic acid. As it is known oxalic acid (or oxalate formed in situ by reaction with Et$_3$N), can be used as a mild reducing agent [27], but at the same time it can be used as a chelating agent for several transition metals [28]. It is plausible that zero palladium complexes form with these reducing agents, which are stable but inactive for this catalysis. In addition, under the reaction conditions, the studied reductants may be involved in the stabilization of some intermediate Pd(II) species formed by the oxidative addition of iodobenzene to Pd(0) species.
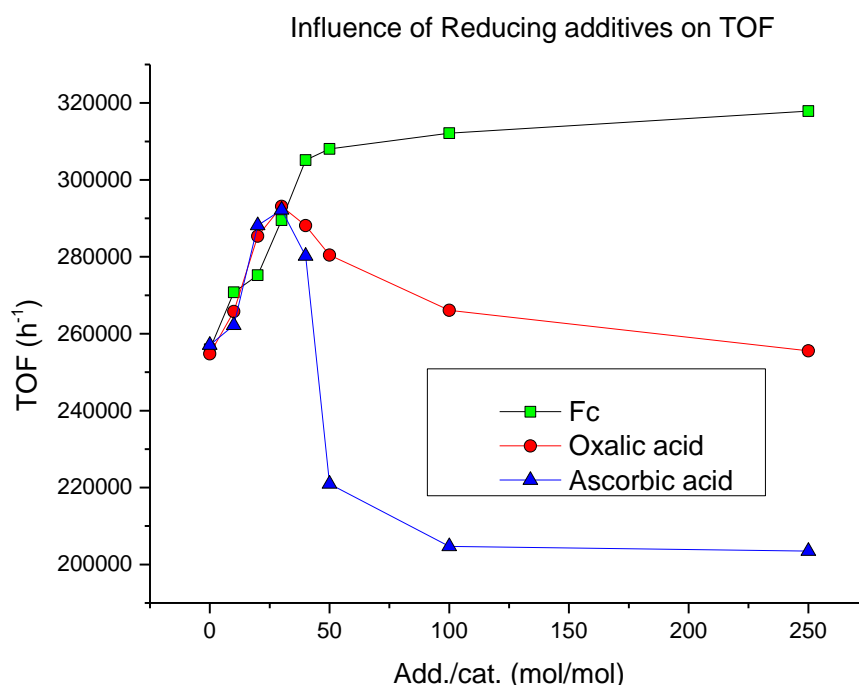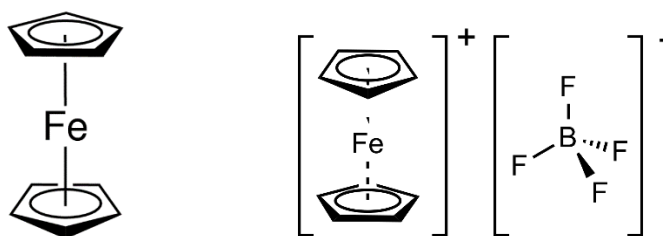

Fig 13 Influence of Oxidant additives. Run Condition: iodobenzene 4,46 mmol, Et$_3$N 1,2 eq., cat=cat:1,6*10^{-5} mmol [PdCl$_2$(Xantphos)], Solvent: MeOH: 4 mL, t=0,5h, T=120°C, P$_{CO}$=50 bar

Interesting is the trend of ferrocene (Fc), which tends to a plateu with a TOF value above 310000 h^{-1} (fig.13). The reversibility of the redox couple Fc/Fc$^+$ has been known for a long time and is commonly used in electrochemistry as a standard [29]. The robustness of this redox pair finds application in the study of numerous electron transfer processes.

Recently, ferrocenium (Fc$^+$), has been employed as an oxidant for the regeneration of the Pd(II) species for the Heck reaction[30].

In the alkoxycarbonylation of iodobenzene, it is probable that Fc is involved in the generation of the catalytically active Pd(0) species, resulting in the formation of Fc$^+$.

The Fc$^+$, in these redox equilibria can lead to the reoxidation of Pdmet formed by decomposition of the homogeneous catalyst.
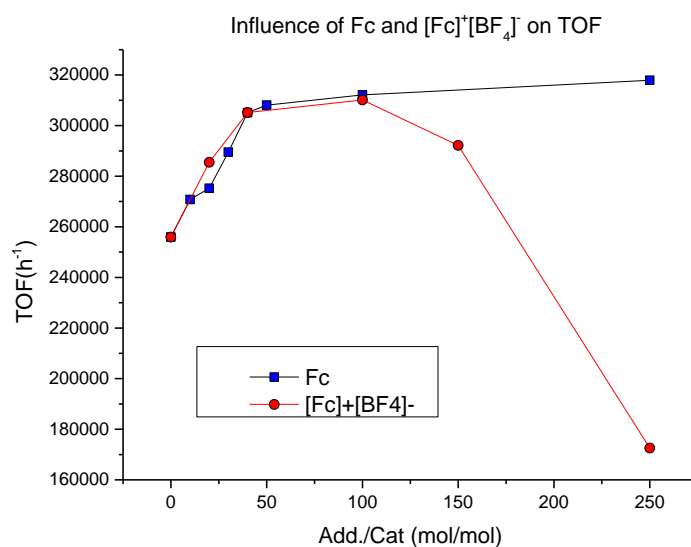

Fig 14 Influence of Oxidant additives. Run Condition: iodobenzene 4,46 mmol, Et$_3$N 1,2 eq., cat=cat:1,6*10^{-5} mmol [PdCl$_2$(Xantphos)], Solvent: MeOH: 4 mL, t=0,5h, T=120°C, P$_{CO}$=50 bar

This hypothesis is supported by Fig 14 in which a similar trend in productivity is observed as the Fc$^+$ tetrafluoroborate/Pd ratio increases, up to a maximum value of 100 eq.

At higher concentrations a decrease is observed due to the shift of the Pd(0)→Pd(II) equilibrium towards the inactive species for this catalysis.

It is therefore possible to hypothesize a reaction mechanism (reported in Scheme 4) in which the Fc/Fc$^+$ redox couple is involved in both catalyst regeneration and generation of the active species.
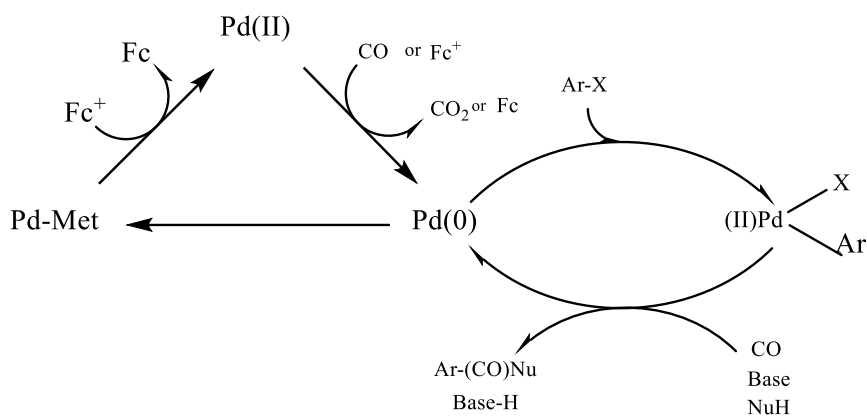
Scheme 4. Proposed mechanism for the alkoxycarbonylation reaction of iodo-arenes, catalyzed by palladium complexes, in the presence of the Ferrocene/Ferrocenium pair

3.1.3 Conclusions

The catalytic system consisted by [PdCl$_2$(Xantphos)] turns out to be particularly active for the methoxycarbonylation of iodobenzene even at low concentrations.

The optimization of the catalytic system, aimed at determining the best reaction conditions to avoid the decomposition of the homogeneous complex, allowed to obtain TOFs higher than 300'000 h^{-1}. In particular, it was shown that the redox couple Fc/Fc$^+$ increases the performance of the catalyst. The experimental evidence allows to hypothesize a mechanism in which the redox couple allows both to generate the active species of Pd (0) and to avoid the agglomeration of large particles of metallic Pd, oxidizing it to soluble species of Pd (II), which can again enter the catalytic cycle.

3.2 Preliminary studies on aminocarbonylation of iodobenzene

3.2.1. Introduction

The aminocarbonylation reaction of iodobenzene has limitations related to the operating conditions. The main problem that may limit the productivity of the catalyst is related to the pressure under which the reaction is performed. In fact, for this reaction it is widely reported in the literature that as the pressure increases the selectivity tends to split into the product of mono and double carbonylation.

Amide formation is favored at low pressure values, but from the catalytic point of view these operating conditions can lower the reaction kinetics.

Furthermore, due to the basic nature of the nucleophile used, there is a problem related to competition in neutralizing the acid halide released during the catalytic cycle. It is plausible to speculate that the amine used may compete with the base, thereby lowering the concentration of a reactant, limiting the productivity of the catalytic system.

Also in this case, from a catalyst point of view, the main cause of deactivation is related to the formation of large particulate agglomerates of metallic Pd. Based on the results obtained for the alkoxycarbonylation reaction, preliminary results are presented on the influence of some additives used with the aim of limiting catalyst deactivation.

3.2.2 Results and discussion

The aminocarbonylation of iodobenzene has been studied by using the decylamine as nucleophile.

The reaction needs a catalyst and the addition of a base, usually NEt_3, to move the equilibrium neutralizing the hydrogen iodide which form during the reaction.
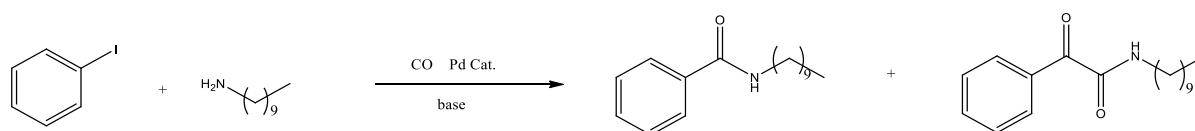
Scheme 1 reaction test for amino-carbonylation of iodobenzene.

In literature usually NEt_3 is proposed as it is considered non-interfering with the coordination of the ligands to the Pd metal center. However, the primary amine used as nucleophile (1-decylamine) has similar basicity of the NEt_3, therefore it could be also reacts with HI.

With the aim of highlighting this aspect, we have evaluated how different ratios of decylamine and NEt_3 can influence the catalytic activity of the complex $[Pd(OAc)_2(PPh_3)_2]$ and the Table 1 confirms as expected that both the decylamine and NEt_3 can react with HI efficiently.

Tab.1: Influence of 1-decylamine/Et3N ratio on TOF.

decilam./Et$_3$N (mol/mol)	Conv. (%)	TOF (h^{-1})
1:1	71	158
1:0	47	97
2:0	74	171

Run condition: [Pd(OAc)$_2$(PPh$_3$)$_2$] ($2*10^{-5}$ mol), iodobenzene (0,004 mol), solvent: Toluene= 4mL total volume, T = 120°C, P CO = 5 bar, t = 1h

Regarding the catalyst, it is widely reported that the Pd-based catalyst containing PPh$_3$ are active in such reaction [31-33].

Therefore, we preliminary studied the reactivity of the Pd(II)-PPh$_3$ catalyst system and the influence of some reaction parameters on the TOF and on the selectivity.

3.2.2.1 Influence of the nature of ionic ligands on the catalytic activity

At first, we tested the complexes in Table 2 to investigate the influence of the coordinating ability of the ionic ligands. We have been found that all the catalysts were active in such reaction (reaction 1) leading to a 100% selectivity to N-decylbenzamide. The values of TOF obtained are very similar to each other, suggesting that the coordinating ability of ionic ligands is not decisive in the rate determining step.

Table 2: data relating to the use of different types of counter-ion.

precatalyst	TOF (h^{-1})
[Pd(OAc)$_2$(PPh$_3$)$_2$]	158
[PdCl$_2$(PPh$_3$)$_2$]	143
[PdBr$_2$(PPh$_3$)$_2$]	135
[PdSO$_4$(PPh$_3$)$_2$]	148
[Pd(TsO)$_2$(PPh$_3$)$_2$]	153

Run conditions: [Pd(X)$_2$PPh$_3$] (6.7 * 10-6mol), Iodobenzene (0.004 mol), 1-decylamine (1eq.), Et$_3$N (1eq.), solvent: Toluene 4mL total volume, T = 120 °C, P CO = 5 bar, t = 1h; [iodob./cat.≈600].

3.2..2.2 Influence of free PPh$_3$ on the catalytic activity

We observed that Pd metal was formed at the end of each reaction, therefore in order to avoid it we added an excess of free PPh_3 and we studied its influence on the TOF. The results are showed in Table 3.

Tab.3: influence of PPh_3/cat ratio on TOF.

PPh_3/cat. (mol/mol)	TOF (h^{-1})
0	158
1	269
10	348
30	415
50	481
70	306

Run condition: [Pd(OAc)$_2$PPh$_3$] (6.7 * 10-6mol), Iodobenzene (0.004 mol), 1-decylamine (1 eq.), Et$_3$N (1 eq.), solvent: Toluene 4 mL total volume, T = 120 °C, P CO = 5 bar, t = 1h; [iodob./cat.≈600].

As widely reported in literature the addition of an excess of free PPh_3 effectively avoid the formation of Pd metal, favoring the formation of active Pd(0) species in solution. However a large excess of ligand could move the equilibrium towards the formation of Pd(0) species too stable respect the needs of the catalysis (for instance $[Pd(CO)_n(PPh_3)_{4-n}]$, with n =1-4) or, under a different point of view, the such free ligands could compete for the coordination to the metal with the reagents. As a consequence of these equilibria among the active-less active-inactive species which occur in solution, the TOF increases in a first time and then and passes through a maximum of 481 h^{-1} at molar ratio PPh_3/Pd = 50/1.

3.2.2.3 Influence of the nature of the amine and of the base on the catalytic acitity

As such double nature (base and nuclephile) of the amine used in the aminocarbonylation can influence the TOF, we tested different aliphatic amines in addition to 1-decylamine. The Table 4 shows the TOF and the selectivity obtained with different ammine.

Table 4: data relating to the use of different types of amines.

Amine	pKa	Sel. % amide	Sel. % α-ketoamide	TOF (h^{-1})
t-BuNH$_2$	10.68	78	22	106
cyclohexylamine	10.67	53	47	424
n-BuNH$_2$	10.78	100	/	630
1-decylamine	10.64	100	/	481

Run condition: [Pd(Cl)$_2$PPh$_3$] (6.7 * 10-6mol), Iodobenzene (0.004 mol), amine (1 eq.) Et$_3$N (1 eq.), solvent: Toluene 4 mL total volume, T = 120 °C, P CO = 5 bar, t = 1h; [iodob./cat.≈600].

The amine tested have very similar basicity but different nucleophilicity as the latter is strongly influenced also by the steric hindrance.

According to this, the Table 5 shows that the TOF vary widely. The t-BuNH$_2$, for instance, is sterically hindered in comparison to n-BuNH$_2$ and the TOF obtained was $106 \, h^{-1}$ and $630 \, h^{-1}$ respectively. Furthermore, the nucleophilicity of the amines also influences the selectivity which depends on the rate of nucleophilic attack to the acyl group bound to the Pd center. According to this, the selectivity was 100% with the less hindered n-BuNH$_2$ and 1-decylamine whereas with the more hindered cyclohexylamine (53% of amide, 47% of α-ketoamide) and t-BuNH$_2$ (78% of amide, 22% of α-ketoamide) the selectivity is lower being favored also the double carbonylation.

In all these experiments NEt$_3$ was added as base to neutralize the HI. Studying the reactivity of n-BuNH$_2$, we tested the influence of different bases as substitute of the NEt$_3$.

Table 5: data relating to the use of different types of bases.

Bases	pKa	Conversion (%)		Selectivity (%)		TOF (h^{-1})
		iodobenzene	n-BuNH$_2$	amide	byproducts	
DBU	13.5	56	66	77	23	621
K$_2$CO$_3$	10.33	20	19	84	16	237
Bu$_3$N	10.89	36	38	80	20	407
PhONa·3H$_2$O	10	35	41	100	0	322
Et$_3$N	10.8	57	80	78	22	630

Reaction conditions: [PdCl$_2$(PPh$_3$)2] ($3.7 * 10-6$ mol), PPh3 (50eq), iodobenzene (0.004 mol), n-BuNH2 (1eq.), Base (1eq.), Toluene solvent 4mL volume total, T = 120 °C, P $_{CO}$ = 5 bar, t = 1h; [iodob./cat.≈1100].

In Table 5 are showed the results. In order to select the bases with the best performances we analyse both the consumption of iodobenzene and the n-BuNH$_2$.

In Figure 1 it is possible to observe how the higher values in TOF correspond to the use of NEt$_3$ (630 mol / mol Pd) and DBU (621 mol / mol Pd).
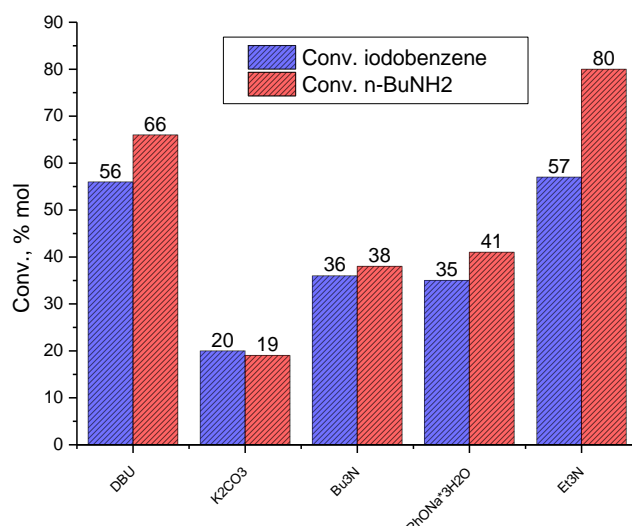
Fig.1 Conversion of iodobenzene and n-BuNH₂ with different Bases

It is possible to point out that the addition of NEt_3 and DBU leads to higher catalytic activity (TOF) but in such cases the consumption of the amine (reagent) is greater than that of iodobenzene, indicating a competitive reaction with HI.

3.2.2.4 Influence of the ligand on the catalytic activity of the complex

With the aim to increase the catalytic activity and avoid the formation of inactive Pd metal, it has been studied the influence of some N-N and P-P chelating ligands on the TOF and on the selectivity.

Chelating phosphine ligands

The Table 6 shows the influence on TOF of different P-P chelating ligands as function of with the respective P-Pd-P bite angle.

Table 6. Influence on TOF of different chelating ligands with the corresponding bite angle.

ligand	Bite Angles[27] (°)	Conv. iodob. (%)	TOF (h^{-1})
dppBe	81,9	21	115
dppp	91,6	29	173
dppf	98,7	50	389
xantphos	104,6	67	486
PPh_3	-	34	158

Reaction conditions: [Pd (OAc)₂ / L] (6.7 * 10-6mol), iodobenzene (0.004 mol), 1-decylamine (1eq.), Et₃N (1eq.), Toluene solvent 4mL total volume, T = 120 °C, P $_{CO}$ = 5 bar, t = 1h; [iodob./cat.≈ 600].

The TOF values increase proportionally to the bite angle P-Pd-P reaching the best TOF = 486 h^{-1} with xantphos that has the highest bite angle. According to the literature the diphosphine plays an important role in favoring the species of Pd(II) and/or Pd(0), important for the catalytic cycle. In all these cases the possible deactivation due to formation of palladium metal is avoided without adding an excess of phosphine but at the same time some ligands probably form too stable species which would however low the rate of reaction. For this ragion, even if Pd metal deactivation does not occur, some of such ligands lead to lower TOF than PPh_3 whereas Xanphos leads to the best results (TOF = 486 h^{-1}).

Influence of N-N ligands on the catalytic activity of the Pd-complexes

Table 7 shows that the N-N chelating ligand in the Pd(II) complexes used as precursor strongly lower the catalytic activity, even if the selectivity towards amide was 100% in all the experiments.

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As Pd metal is not found at the end of reaction, such ligands are able to avoid reduction followed by decomposition, but the higher stability of the intermediates formed during the cycle slow down the final rate of the cycle.

Table 7. Influence on TOF of different diazotate ligands

Ligand	Conv. iodob. (%)	TOF (h^{-1})
phen	12	70
bipy	15	99
neocuproine	6	39
BPM	12	74
biQ	10	58
PPh$_3$	34	158

Run conditions: [Pd (OAc)$_2$ / L] (6.7 * 10-6mol), iodobenzene (0.004 mol), 1-decylamine (1eq.), Et$_3$N (1eq.), Toluene solvent 4mL total volume, T = 120 °C, P$_{CO}$ = 5 bar, t = 1h; [iodob./cat.≈ 600].

3.2.3.5 Effect of temperature and pressure on the TOF

The catalytic activity as function of the temperature has been measured for the different ammine and catalysts. In all these cases the TOF passes through a maximum value in the range of temperature 110-130 °C. At temperatures higher than 130°C decomposition of the Pd-complexes occurs with consequent decreases of the TOF. The selectivity does not depend by the temperature.

The influence of pressure has been tested in the range 1-60 atm of CO. The TOF linearly increases with the pressure even if the selectivity to amide decreases. According to this, the Table 8 shows that the double carbonylation is favoured by increasing the pressure.

Table 8: Influence of P$_{CO}$ on TOF and Selectivity.

P (atm)	TOF (h^{-1})	Selectivity (%)	
		Amide	α-keto-am.
5	389	100	0
20	442	90	10
50	550	76	24

Run conditions: [Pd(OAc)$_2$(dppf)] (6.7 * 10-6mol), iodobenzene (0.004 mol), 1-decylamine (1eq.), Et$_3$N (1eq.), Toluene solvent 4mL total volume, T = 120 °C, t = 1h; [iodob./cat.≈ 600].

3.2.3.6 Influence of Additivies on productivity

Based on the results obtained for methoxycarbonylation of iodobenzene, screenings were performed with some additives.

Due to the basic and nucleophilic nature of the amine, the additives used in methoxycarbonylation lead to a considerable decrease in the productivity of the reaction. It is possible that the metal salts used as additives may react with the amine, forming complex species that limit the availability of the reagent in the reaction environment. Also the pair Fc/Fc+ showed the same trend, in this case, as reported in the literature it is possible to assume that the pair ferrocene/ferrocenium can go to oxidize the amine reagent, resulting in a decrease in productivity[34].

As can be seen from Table 9 the only additive that brought a modest improvement in productivity is the non-ionic surfactant SPAN-60

Table 9, influence of SPAN-60/Cat ratio on TOF

SPAN-60/cat	TOF (h^{-1})
0	486
1	490
10	515
30	575
50	598
70	600

Run conditions: [Pd(OAc)$_2$(xantphos)] (6.7 * 10-6mol), iodobenzene (0.004 mol), 1-decylamine (1eq.), DBU (1eq.), Toluene solvent 4mL total volume, T = 120 °C, t = 1h; [iodob./cat.≈600].

3.2.4 Conclusions

From this screening of operational variables, it is clear that, even for amino carbonylation, the best catalytic system is that consisting of the [Pd(OAc)$_2$Xantphos] precatalyst. Numerous variables can affect the productivity and selectivity of the reaction. Pressure predominantly affects selectivity due to the possible formation of double carbonylation products.

The difference in pKa of the amines and bases used is an important parameter to take into account to avoid that productivity of the reaction is affected by competition in the neutralization of HI produced in the catalytic cycle.

Also in this case the formation of metallic palladium appears to be the main cause of deactivation of the catalyst, the chelating diphosphinic allows to limit this phenomenon, assisted by the presence of non-ionic surfactant SPAN-60, which could allow to avoid the nucleation of macroparticles of metallic Pd, facilitating the reintegration of Pd (0) species in the catalytic cycle.

3.3 Experimental Section

Reagents

Iodobenzene, bromobenzene, chlorobenzene, palladium(ii) chloride, palladium(ii) acetate, bis(triphenylphosphine)palladium(ii) dichloride, 1,1-bis(diphenylphosphino)methane (dppm), 1, 2-bis(diphenylphosphino)ethane(dppe), 1,3-bis(diphenylphosphino)propane(dppp), 1,4-bis(diphenylphosphino)butane(dppb), 1,2-bis(diphenylphosphino)benzene(dppBz), 1,1'-bis(diphenylphosphino)ferrocene(dppf), (1,1′-bis(paramethoxyphenylphosphino)ferrocene(MeO-dppf), (oxydi-2,1-phenylene)bis(diphenylphosphine)(DPEphos), 1,1′-bis(di-cyclohexylphosphino)ferrocene(dcypf), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), (4,4,4′,4′,6,6′-hexamethyl-3,3′,4,4′-tetrahydro-2,2′-spirobi[[1]benzopyran]-8,8′-diyl)bis(diphenylphosphane)(SPANphos), 2,2′-biquinoline (BQ), 2,2′-bipyrimidine (BPM), 2,9-dimetil-1,10-fenantrolina(neocuproine), 2,2′-bipyridine(bipy), 1,10-phenanthroline(phen) sodium iodide, sodium carbonate, sodium hydroxide, potassium carbonate, potassium hydroxide, cesium carbonate, cesium hydroxide, tributylamine, triethylamine, trioctylamine, pyridine, 1-decylamine, cyclohexylamine, 1,5-diazabiciclo(5.4.0)undec-7-ene (DBU), sodium phenoxide trihydrate, iron(iii) chloride, iron(iii) acetylacetonate, ferrocene (FC) nickel (ii) chloride hexahydrate, tetrabutylammonium iodide(TBAI), (2R)-2-[(2R,3R,4S)-3,4-dihydroxyoxolan-2-yl]-2-hydroxyethyl octadecanoate(SPAN-60), sodium dodecyl sulfate(SDS), p-benzoquinone (BQ), oxalic acid, ascorbic acid, were all Aldrich products and employed without any purification and all solvent are ACS reagent supplied by Aldrich. Carbon monoxide was supplied by SIAD Company Italy ('research grade', purity >99.9%). 1,3-Bis(di(orthomethoxyphenyl)phosphino)propane (BDOMP) was given to us courtesy by Hyosung. Ferrocenium tetrafluoroborate was synthesized by oxidation of FC with anhydrous $FeCl_3$, with subsequent addition of HBF_4 (48%),in a mixture of H_2O/acetone (20:80 v/v) to obtain a dark blue solid with yields between 50-70% . The solid, once dry, was characterized with FT-IR

Equipments and characterization

The catalyst precursors were weighted on a Sartorious Micro balance (precision 0.001 mg). Gas-chromatographic (GC) analysis was performed on a Hewlett Packard Model 7890, Series II chromatograph fitted with a HP5, 30 m $\times$ 0.35 mm $\times$ 0.53 μm column (detector: FID; carrier gas: N_2, 0.2 mL/min; oven: 318 K (3 min) to 523 K at 15 K/min).GC/MS analyses were performed on a MS Agilent apparatus 5975C Model, interfaced with an Agilent chromatograph 7890 A Model equipped with a HP5 column (30 m $\times$ 0.25 mm $\times$ 0.25 μm, oven: 318 K (3 min) to 523 K at 15 °C/min).Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Magna 750 instrument in KBr powder.

Catalyst Synthesis

All complex was prepared as reported in literature with slight variations. The synthesis of PdCl$_2$(Xantphos) is shown as an example: 0.3 mmol of PdCl$_2$ is placed in a mixture of 5 mL diethyl ether and 2 mL acetonitrile and left stirring until the palladium salt is completely dissolved. Then 0.31 mmol of Xantphos dissolved in diethyl ether was added dropwise. After 1 h of reaction, the resulting solid was filtered with the minimum amount of cold ether and left to dry overnight (yields 60-90%). All complexes were characterized by FT-IR and NMR.

Catalytic reactions

The catalysis was carried out in a stainless-steel batch reactor. In a typical experiment, Pd-based catalyst, together with iodobenzene and Base (typically NEt$_3$), were added the nucleophile (for alkoxycarbonylation MeOH as solvent, for aminocarbonylation Toluene as solvent).

The reactor was carefully flushed with CO at room temperature with stirring and then pressurized with 0.5 MPa of CO and heated up to 393 K in ca. 10 min without stirring. The pressure was adjusted to the desired value and, while stirring, maintained constant throughout the experiment (1–4 h) by continuously supplying the carbon monoxide from a reservoir.

At the end of each experiment the reactor was quickly cooled and carefully depressurized. The reaction products were detected and quantified by the GC and GC-MS analysis.

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Chapter 4:
# Carbonylation reaction with CO Surrogate

4.1 Introduction

Despite the numerous reactions involving CO, its use requires special safety regulations, both for transport and storage. In addition, CO, being a colorless and odorless toxic gas, requires special equipment for its use at high pressure [1-4].

Chemists, to circumvent these challenges are spending much effort to find safer and easier to handle "CO surrogates" [5] The main effort is aimed at identifying molecules, which under appropriate reaction conditions, release CO in situ, directly into the reaction environment [6-10] Thanks to this amount of work by organic and industrial chemists, there are now numerous examples of molecules that can be conveniently used as CO surrogates in transition metal-catalyzed carbonylation reactions, such as chloroform, metal carbonyls, N-formyl saccharin, CO2, and formic acid/salt. But as is evident, these alternatives are limited to a laboratory scale only [11].

Chloroform as CO Surrogate:

Chloroform, an inexpensive and readily available chemical, is known to hydrolyze in a strongly alkaline environment to generate CO [12-13]. However, $CHCl_3$ is not free from problems related to carbonylation reactions, in fact, it can give rise to side reactions (such as cycloadditions) related to the formation of dichlorocarbene [14-16]. But despite this, already from the beginning of the 90's, it is possible to find examples of applications of $CHCl_3$ as CO generator for carbonylation reactions. Alper reports the first example of the use of $CHCl_3$, employing a strongly alkaline reaction environment (a 60% KOH aqueous solution), and by using [$PdCl_2(PPh_3)_2$] as catalyst performs carboxylation reactions of halobenzenes, obtaining the corresponding carboxylic acids in yields exceeding 90% [17]. The problem with this synthesis, however, is related to the use of high catalyst concentrations, which make this protocol unsustainable from an industrial point of view.

X= I, Br
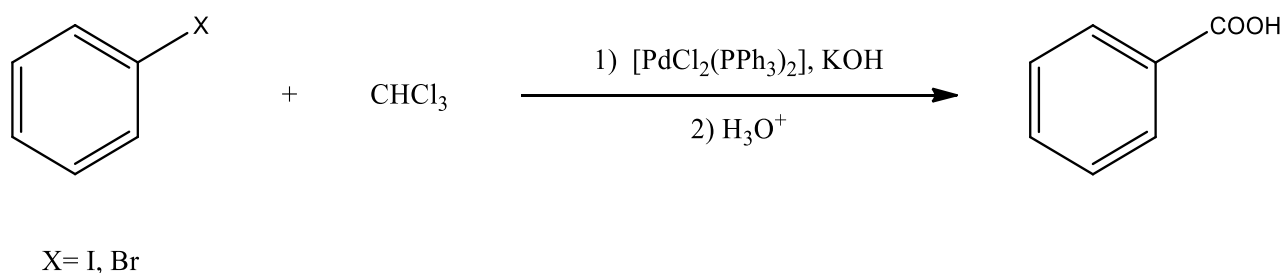
Scheme 1. Pd-catalyzed carbonylation using $CHCl_3$ as CO-generator.

A few years later, in 2016, Hu reports the possibility of employing a similar system for Sonogashira carbonyl coupling between iodobenzene and phenylacetylene, employing Pd-based catalysts and a CO generation system consisting of $CsOH \cdot H_2O$ and $CHCl_3$ in toluene. The reaction environment shows better compatibility with the functional groups of the substrates used as reactants, but again high amounts of metal catalyst and long reaction times are required to achieve appreciable conversions[18].

In a similar approach, in the same year, Sharma proposed the use of $CHCl_3$ as a CO generator to perform of Suzuki carbonylation coupling reaction of aryl halides with arylboronic acids for the synthesis of aromatic ketones.
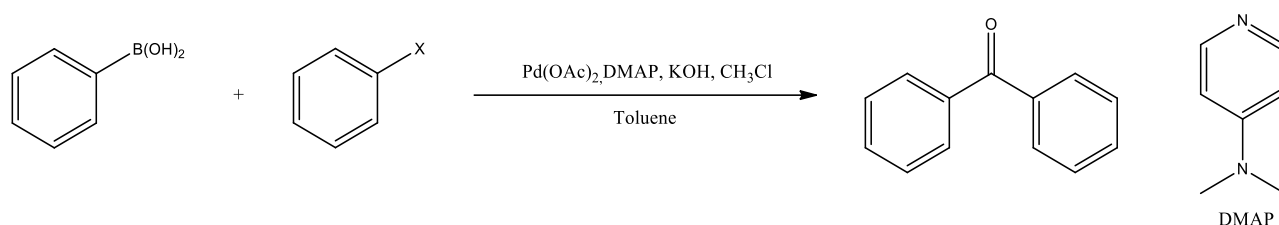
Scheme 5. Suzuki carbonylation coupling using $CHCl_3$ as CO generator

In this case, the CO generation system consists of $CHCl_3$ and KOH in toluene as solvent, and the complex formed in situ between $Pd(OAc)_2$ and DMAP as ligand, with yields above 80% after 12 h of reaction [19]

Metal carbonyl as a co surrogate

An additional source of CO is represented by the carbonyl metals Mx(CO)x (M = transition metal, x= number of CO molecules).

For some of these complexes, CO can be released due to thermal decomposition, such as in the Mond process of Ni purification in which it thermally decomposes Ni(CO)4. The use of these molecules as CO generators, although in some examples has led to satisfactory results in terms of yield, is not sustainable. Although for the small-scale user, CO is not directly handled, the synthesis of these metal carbonyls necessarily requires the use of gaseous CO. The most used metal carbonyls as a CO surrogate include molybdenum carbonyl, cobalt carbonyl, iron carbonyl, etc.

In 2012, Lee reports the use of $Mo(CO)_6$ for the synthesis of benzoylacetonitriles by carbonylation catalyzed complexes of $[PdCl_2(PPh_3)_2]$, aryl iodides, and trimethylsilylacetonitrile (Scheme 20).
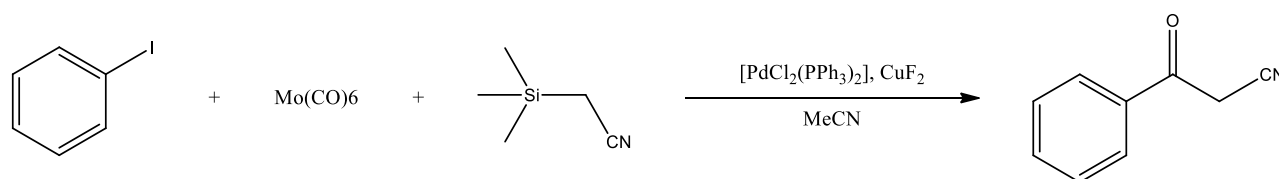
Scheme 6 Synthesis on Benzoylacetonitriles using $Mo(CO)_6$ as CO-generator[20].

While, in 2013 Wu reports carbonyl cyclization of isocyanates and 2-haloanilines for the synthesis of various 2-aminobenzoxazinones, employing $Mo(CO)_6$, $Pd(OAc)_2$ as the precursor of the catalytic species, and K_3PO_4 as the base , achieving yields between 40-90%[21]

An example of using $Co_2(CO)_8$ as a CO generator is presented by the work of Elango in 2013, in which he reproduces palladium-catalyzed carbonylation of aryl halides, employing [$Pd(OAc)_2$Xantphos] as a catalyst with a microwave system to heat the reaction environment and to generate CO from the carbonyl metal, achieving high yields in short reaction times[22]. Similar approaches have also been employed with [$Fe(CO)_5$] as a CO surrogate for reductive carbonylation reactions of various aryl halides to the corresponding aldehydes[23].

N-formylsaccharin as a co surrogate

Another CO generator successfully employed for carbonylation reactions is N-formylsaccharine, an easily handled crystalline compound (Fig. 2).
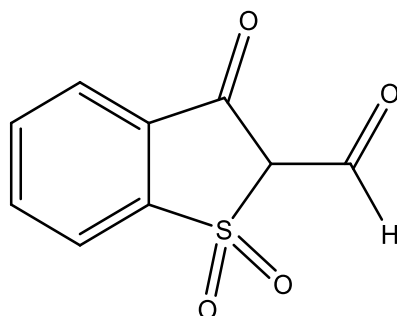
Fig. 2. Structure of N-formylsaccharin

The first example of use in this application area is reported by Manabe in 2013, through a reductive carbonylation reaction of aryl bromides[24] and later also employed for the synthesis of acyl fluorides by carbonylation of aryl halides[25]
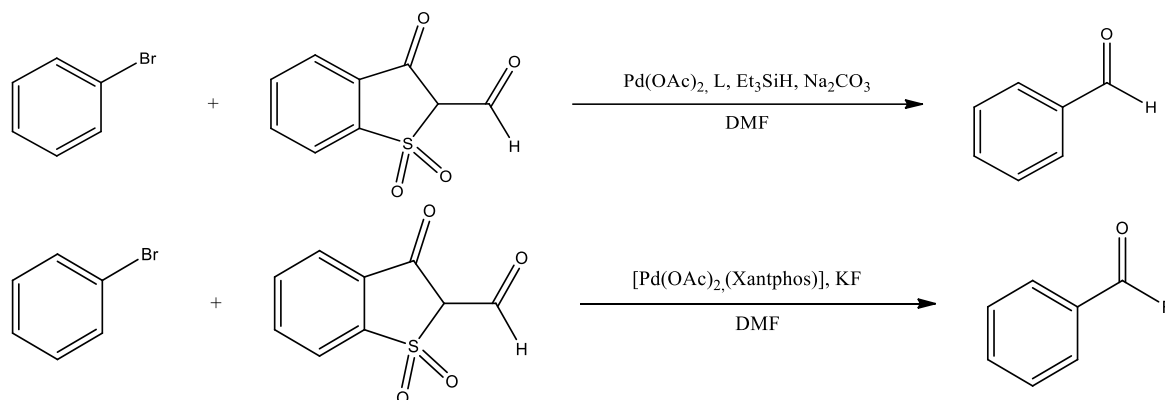
One of the problems is that the synthesis of N-Formylsaccharin involves the reaction of saccharin and the mixed anhydride of formic and acetic acid. Such anhydride as will be seen later, can be considered a CO generator.

This problem was circumvented by Gehrtz, who presented the synthesis of N-formylsaccharin by CO_2 reduction[26].

CO₂ as a co surrogate

CO$_2$ as a co surrogate

Among all possible CO surrogates, the most interesting one is undoubtedly CO_2 which is abundant, non-toxic and cheap[27].

In literature there are many works on the study of new catalytic systems to obtain a series of products of industrial interest from CO_2, unfortunately the activities of these systems are not satisfactory for applications on an industrial scale. [28]

The main problem related to CO_2 is its extreme thermodynamic stability and its difficult activation [29-30].

Despite this, there are examples of using CO_2 and reducing compounds (such as H_2, $NaBH_4$, hydrosilanes etc.) in hydroformylation reactions of aryl halides, with Pd and Rh based catalysts, but often these reactions require long reaction times and high temperatures to activate CO_2[31]

Formic Acid and salt as a co surrogate

The best candidate to be the surrogate for CO is formic acid (HCOOH) and its salts. Although it is now obtained by carbonylation of methanol and subsequent hydrolysis of methylformate, it can be obtained by catalytic reduction of CO_2 using Pd, Rh, and Ru catalysts [33], but it can also be recovered from the waste of biorefinery processing[34]. Thus, it is possible to consider HCOOH as a virtuous example for CO_2 circular economy [35-36]
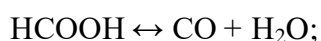
In addition to this, formic acid turns out to be very interesting, because depending on the catalytic system employed, it can be considered both a CO generator due to dehydration reactions and an H_2 generator thanks to decarboxylation reactions.

Dehydrogenation:

$$HCOOH \leftrightarrow H_2 + CO_2;$$
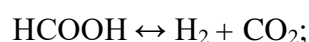
($\Delta G° = -32.9$ kJ·mol⁻¹, $\Delta H° = 31.2$ kJ·mol⁻¹, and $\Delta S° = 216$ J-mol⁻¹·K⁻¹)

Dehydration:

$$HCOOH \leftrightarrow CO + H_2O;$$

($\Delta G° = -12.4$ kJ·mol⁻¹, $\Delta H° = 29.2$ kJ·mol-1, and $\Delta S° = 139$ J·mol⁻¹·K⁻¹)

Formic acid thermally decomposes at high temperatures to release a molecule of H_2O and CO. This reaction can be catalyzed by strong inorganic acids such as H_2SO_4 (Morgan's Reaction[37]), this strategy is commonly used in the laboratory, on a small scale to obtain high purity CO, but this reaction is incompatible with the common transition-metal catalysed carbonylation reaction.

Another possibility for obtaining CO from HCOOH is to have it react with acetic anhydride, resulting in the formation of mixed formic-acetic anhydride.

$$HCOOH + Ac_2O \longrightarrow \text{(mixed anhydride)} + CH_3COOH$$
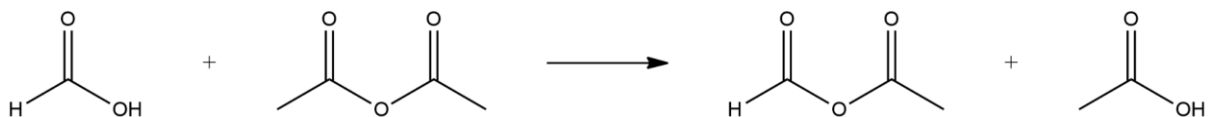
This molecule is unstable, and already at relatively basic temperatures (T 45-50°C) leads to the release of an acetic acid molecule and CO.

$$\text{(mixed anhydride)} \xrightarrow{\text{thermal decomposition}} CO + CH_3COOH$$
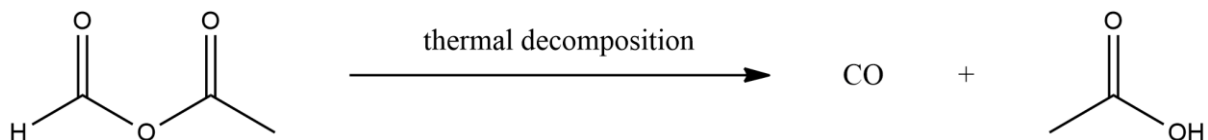
Even formates can be used as a source of CO, in fact Cacchi in 2003 reports the use of lithium formate and acetic anhydride as a carbon monoxide generator for hydroxycarbonylation reactions of aryl halides, through the use of a Pd-based complex[38].

$$Ar\text{-}X + HCOOLi \xrightarrow[\text{LiCl, DMF}]{\text{Pd Cat. Ac}_2\text{O}} Ar\text{-}COOH$$
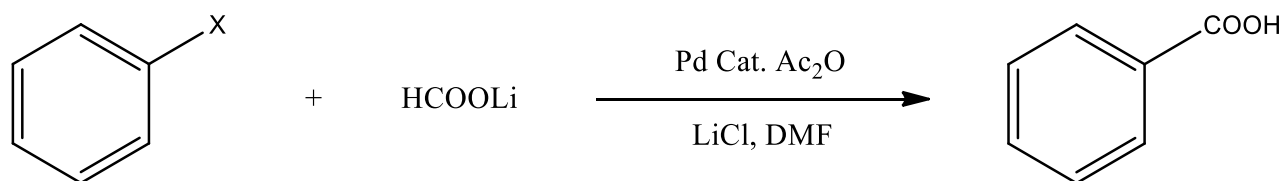
X= I, Br, OTf

Besides acetic anhydride, some alternative activators for the formic acid dehydration reaction can be found in the literature. As reported by F.Wu , using dicyclohexycarbodimide (DCC) as an activator performed a Suzuki carbonylative coupling reaction between iodobenzenes and phenylacetylenes. Indeed DCC react with formic acid leading to the generation of CO and dicyclohexylurea[39].

But the use of these activators implies the onset of some not negligible problems, such as the need to use higher quantities of homogeneous catalysts than those used in typical carbonylations due to possible inhibition or decomposition of the active catalytic species. Moreover, these activators can give side-reaction with some reagents or reaction products, making purification operations more difficult

Skrydstrup, in 2013, proposed the generation of CO from potassium formate, without the use of activators[40]. The generated CO was then used for Pd-catalyzed hydroxycarbonylation of aryl iodides, employing a Pd(II)-salt and the ligand 1,1′-Bis(di-tert-butylphosphino)ferrocene (dtbpf) pre-catalyst, but the reaction requires very long time to have appreciable yields.

In this chapter, a study of the use of heterogeneous acid catalysts (Amberlyst 36) for the generation of CO from formic acid is presented. With a specifically designed multi-chamber reactor, it was possible to avoid the problem of incompatibility between strongly acidic environments and some types of carbonylation, where a basic co-catalyst is required (e.g.,

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haloarene carbonylations), and avoid the possible side-reaction between formic acid and substrate (e.g. addition on olefins[41]).

In addition, the first example of synthesis of CO/ethene copolymers obtained by palladium-catalyzed carbonylation with CO generated by a formic acid/acetic anhydride system is presented.

For this reason, the possibility of employing Formic Acid/Acetic Anhydride as a carbon monoxide generator system to perform CO/ethene polymerization catalyzed by homogeneous palladium complexes has been explored. In this way, the problem represented using dehydration activators, is transformed into an advantage due to the simultaneous generation of CO and formation of a suitable solvent mixture to perform the polymerization.
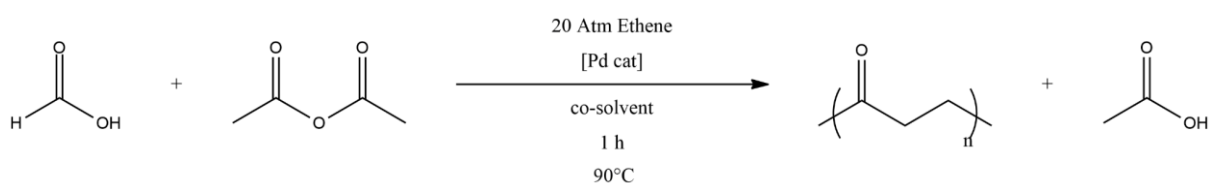
For this carbonylative polymerization obtained for the first time using formic acid as a CO surrogate, the influence of some reaction parameters has been studied, paying particular attention to the effect of co-solvents on the productivity and the distribution of molecular weights of the polymers thus synthesized.

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4.2 Selective dehydration of formic acid to CO and water efficiently catalysed by the sulfonated poly(styrene-divinylbenzene)

4.2.1 Introduction

Methanoic acid or formic acid (FA) HCOOH, is a biodegradable, non-flammable and non-toxic colorless liquid with a pungent odor. The market for formic acid is estimated to be about 600 ktons in 2020 and is mainly used in the animal feed industry (as a preservative), leather tanning, textile industry, rubber and chemical industry as a synthetic intermediate. It is completely miscible with water and many polar solvents but only partially miscible with hydrocarbons. Currently, the main industrial synthesis involves the hydrolysis of methyl formate, which is produced by carbonylation of methanol. The possibility of synthesizing formic acid (or its salts) by reduction of CO_2 with H_2, using transition metal catalysts, has appeared to this production. Formic acid can also be recovered as a processing waste from the biorefinery, which through the processes of transformation of biomass leads to the formation of large quantities of waste FA (see synthesis of levulinic acid).

In recent years, research is increasingly oriented towards environmentally sustainable chemistry. FA has turned out to be a molecule of great interest for the development of new eco-sustainable technologies.

It is considered as a sustainable and safe hydrogen reservoir (hydrogen content 4.4% wt), also because of its liquid form at room temperature, which makes it easier to handle than other alternatives (such as H_2 gas, NH_3, diesel and gasoline etc).

Formic acid can be considered as a source of both H_2 and CO: This allows chemists to plan a parallel synthesis pathway to the current syngas-based chemical value chain.

It is well-known that formic acid decomposition can take place by dehydration (decarbonylation) and dehydrogenation (decarboxylation).

The gas mixture generated by the dehydrogenation of formic acid can be used directly as a feed gas for an H_2/air fuel cell with the advantage that the CO_2 generated by the formic acid can be hydrogenated again to structure a carbon-free emission process. [1] For this reason in literature it is possible to find a huge amount of publications aimed at studying catalytic or electrocatalytic systems to make the most of the dehydrogenation reaction of formic acid[2-4]. In addition to applications in the energy sector, formic acid is also interesting in the field of synthetic chemistry. The possibility of being able to use formic acid in hydrogen transfer reactions at mild reaction conditions is particularly interesting because of a reduction in the cost of specific instrumentation required to work at high pressures. Also in this area of research, the academic world has put a lot of effort in order to outline processes related to the circular economy of CO_2 [5-8].

For example, it is noteworthy the hydrogenation of levulinic acid with formic acid for the synthesis of γ-valerolactone GVL, using heterogeneous catalysts based on Ru [9].

The dehydration also has interesting application developments for chemical synthesis. That formic acid decomposes in the presence of sulfuric acid with the liberation of carbon monoxide was first reported by Doebereiner. [10] This reaction has been studied by many since the early 1900s, particularly by Morgan, so much so that the sulfuric acid-catalyzed formic acid dehydration reaction is also known as Morgan's Reaction[11-14].

This reaction is commonly used to synthesize high purity carbon monoxide, both at laboratory and industrial scale (Kock carbonylations). The decomposition of formic acid in the liquid phase has been studied extensively in the case of strong inorganic acids, such as sulfuric acid[15], phosphoric acid and perchloric acid [16]. These studies revealed a likely reaction mechanism in which protonation of formic acid is an essential decomposition reaction step:


(a)

(b)

(c)
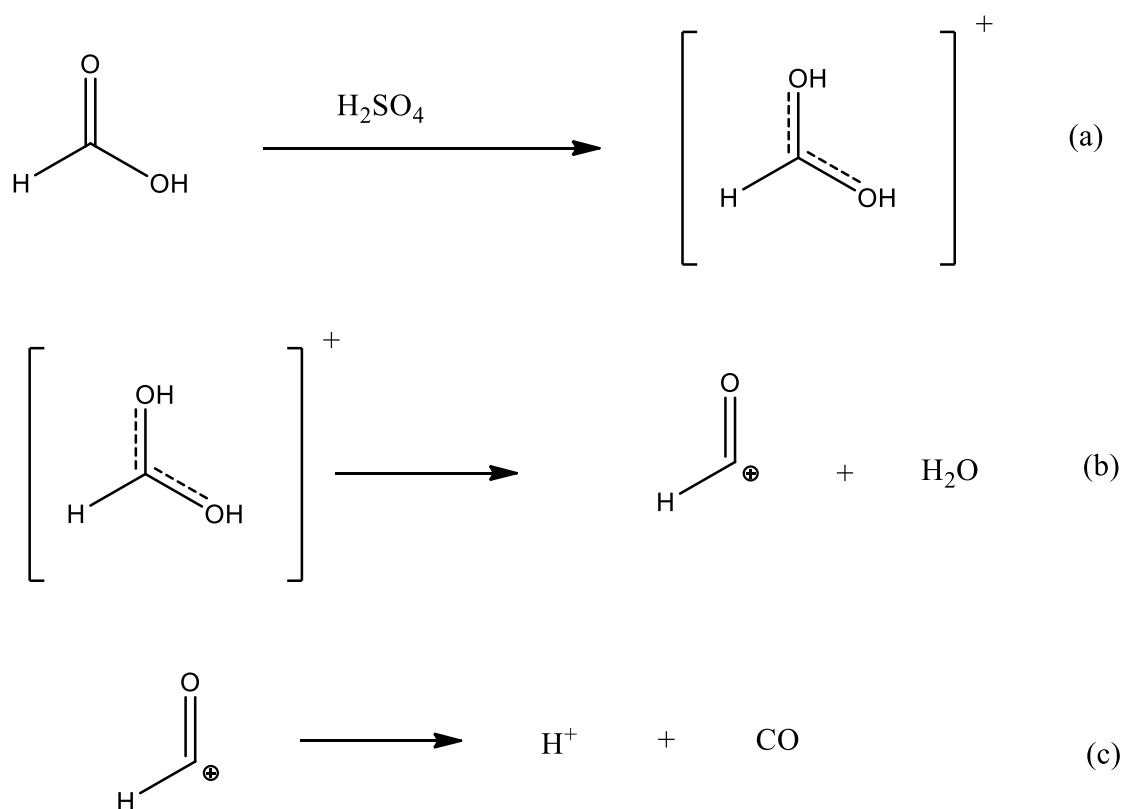
To obtain more detailed information on the determining step of the reaction, some studies on the decomposition of isotopically enriched formic acid were performed. These observations show that the limiting step in this reaction is related to the breakdown of the carbon-oxygen bond, and not to the breakdown of the carbon-hydrogen bond. This means that reaction (b) is the slowest reaction.

The mechanism is in accordance with those of esters and ethers, in which is formed a protonized compound which undergoes decomposition.

In addition to liquid-phase formic acid dehydration, vapor-phase dehydration has also been intensively studied to eliminate the use of sulfuric or phosphoric acid and offers an easily controllable method for carbon monoxide production. Relatively to this aspect it is possible to find many works related to the study of heterogeneous catalytic systems, which however require very drastic operating temperatures (150-350 °C). Typically, the catalysts used for the gas phase decomposition reaction are metal oxides, such as TiO_2, SiO_2, Al_2O_3, Fe_2O_3 etc.

The mechanism proposed for gas-phase dehydration on heterogeneous catalysts appears to be like that reported for liquid-phase dehydration, considering the possibility that on the catalyst surface OH groups with acidic properties are present.

From a mechanistic point of view, it is possible to find several works focused on the determination of the reaction path, but noteworthy is the work of Dalmai [17] who reports the importance of OH groups for the dehydration of formic acid on the silica surface, thus allowing a generic dehydration mechanism to be postulated:
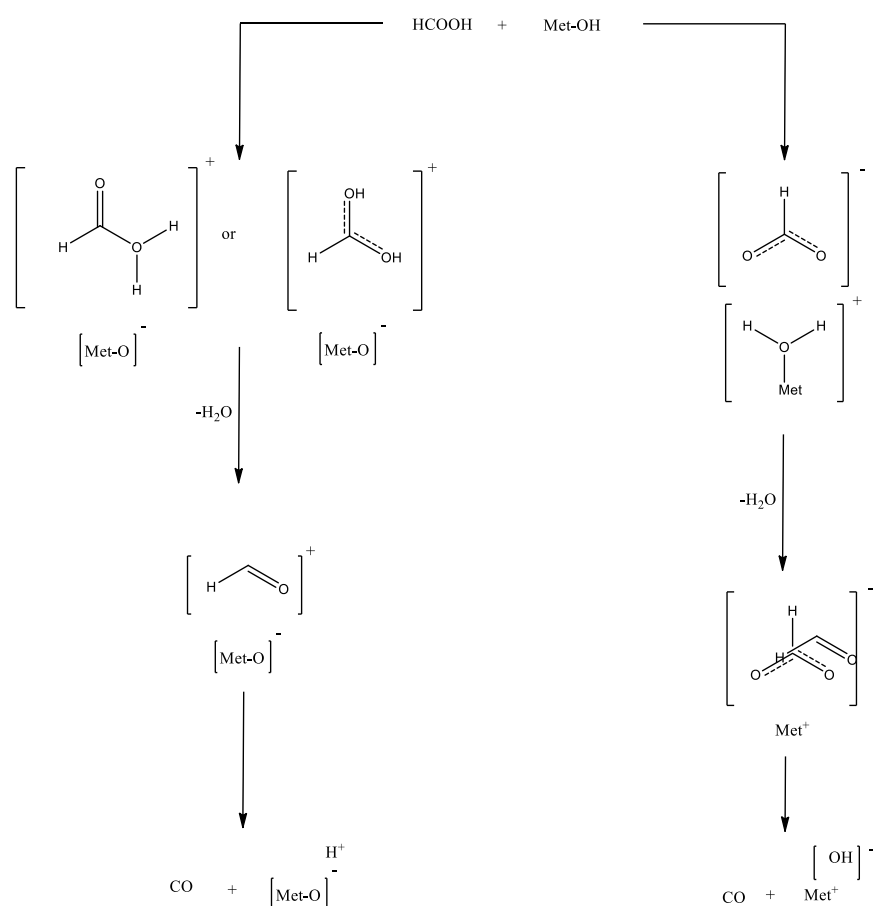
There seem to exist two mechanisms for the dehydration: one proceeding via proton transfer from the surface to the formic acid on surfaces with acidic OH groups, the other via formation of a formate ion on surfaces of a neutral or basic character.

Currently, these two synthesis routes are useful for CO production from a renewable source, but they turn out to be incompatible with most transition metal-catalyzed carbonylation

reactions. To solve this problem, two elegant solutions have been proposed for the use of CO produced ex-situ for carbonylation reactions catalyzed by Palladium complexes.

For example, Skrydstrup in 2013 has proposed a glass reactor, with a special dual-chamber configuration (figure 1) [18]
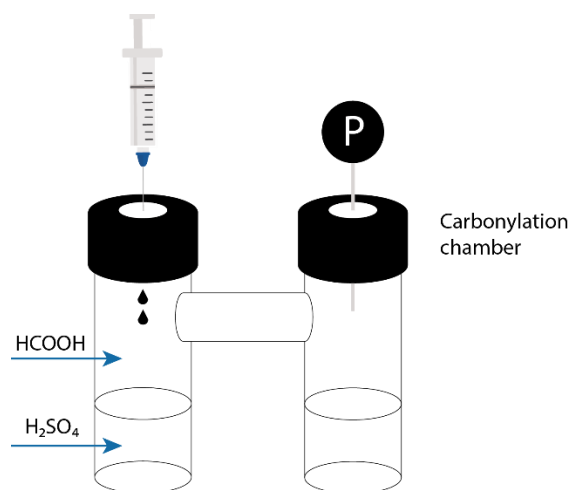

Fig. 1 . Glass dual-chamber reactor

This system allows for H_2SO_4-catalyzed dehydration of formic acid and allow to perform carbonylation in the adjacent chamber using homogeneous palladium catalysts.

Pale, in 2015, proposed a similar configuration for the decomposition of formic acid at 150℃ (figure 2), employing a zeolitic catalyst[19].
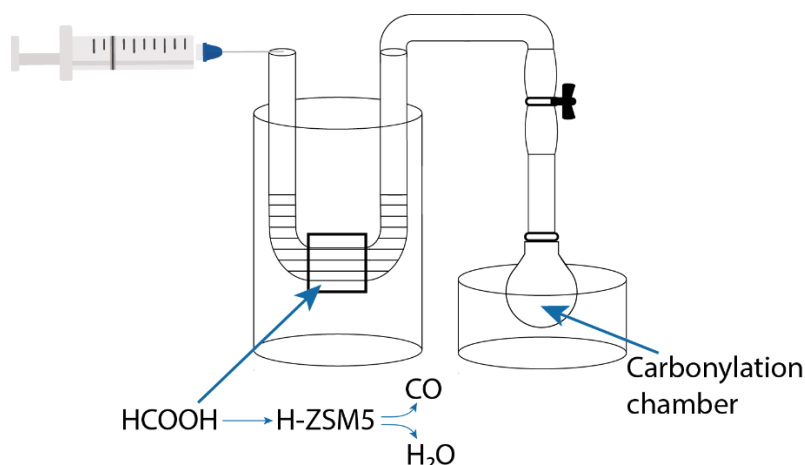
Fig. 2. Reactor for carbonylation with CO generated ex-situ with heterogeneous catalyst

The problem with these systems is that such a setup allows it to work only at low CO pressures, with associated problems related to reaction rates.

Starting from these assumptions, the effects of organic acids commonly used for palladium-catalyzed carbonylation reactions on the generation of CO from formic acid have been

studied. In addition to this, the possibility of employing heterogeneous acid catalysts (acid resins) under reaction conditions compatible with a decomposition of formic acid in the liquid phase was investigated. In particular, the kinetic of CO release of the homogeneous HCOOH/p-toluenesulfonic acid and the heterogeneous HCOOH/Amberlist systems have been studied and compared.

After studying the influence of these parameters on the generation of CO, a particular multi-chamber reactor has been designed that allows to use the carbon monoxide generated Ex-situ in carbonylation reactions even at high pressure. This system allows to circumvent the problem related to the incompatibility of acid and reaction environments required for some carbonylation reactions.

4.2.2 Results and discussion

4.2.2.1 Calibration of the volume of the batch reactor and quantitative determination of CO

In the absence of a known volume batch reactor, a volume calibration had to be performed using the gas equation:

$$V\Delta P = zRT\,\Delta n$$

Due to the non-ideal nature of carbon monoxide, it is necessary to consider the compressibility factor (Z) to correct for the deviation from the ideal gas law. The compressibility factor for a real gas is a parameter that varies with gas composition, pressure, and temperature. Given the importance of this correction factor, especially at industrial level, in literature it is possible to find many studies regarding its semi-empirical determination or through mathematical models [20-22].

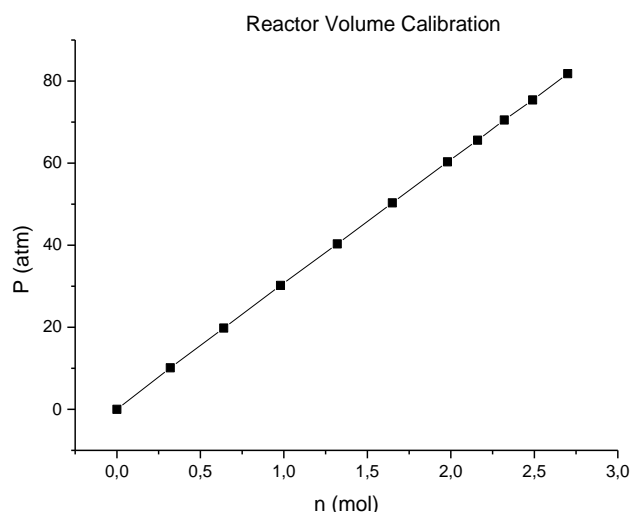The reactor volume was calibrated at pressure and temperature conditions that allow Z=1 to be used.

Fig.3 calibration curve of volume reactor

Temperature was held constant at 295.98 K, the CO pressure monitoring was performed by using a WIKA S-10 pressure transmitter connected with a digital device for acquisition and elaboration of the data using an electronic transducer ($\pm$ 0.01 atm), and the moles of CO introduced into the reactor were weighed using a Mettler Toledo balance. From the P measured as a result of the moles of CO introduced into the reactor (n, measured as the weight of CO) the volume (V) was easily calculated. A series of calibration points were collected, each after 15 minutes of equilibration, over a pressure range of 5 to 80 atm, leading to a V value of 27.87 mL.

In the study of the effect of catalysts and other parameters, the time-pressure plot obtained allowed the molar amount of CO evolved from formic acid in the gas phase to be determined using the real gas law. The compressibility factor (z) of carbon monoxide at different temperatures and pressures was extrapolated from data reported in the literature [23-24].

4.2.2.2 Homogeneous Bronsted acids catalysing the dehydration of formic acid

The Bronsted acids listed in figure 4 have been used for a preliminary screening in the dehydration of formic acid (Morgan reaction).
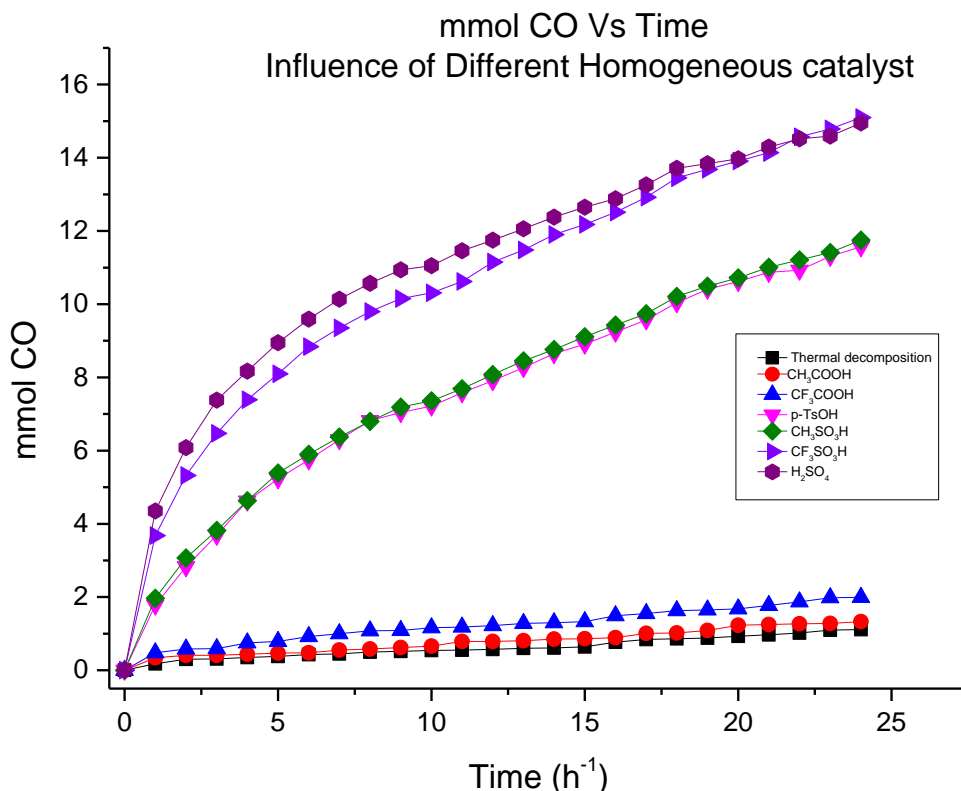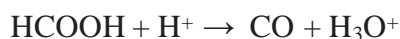
$$HCOOH + H^+ \rightarrow CO + H_3O^+$$

Fig.4 mmol CO vs time with different Bronsted acid. 1 mmol of acid, HCOOH= 5 mL, t=24 h, T= 90°C.

As expected, by increasing the pKa also increases the amount of CO produced and, at 90°C, the methansulfonic acid appears as the most active leading to the best result of 0.62-0.63 mmol/h of CO (measured in the gas phase). Moreover, Table 1 shows the CO formed because of the thermal decomposition of formic acid.

entry	PKa	Acid	mmolCO/h
1	4,76	CH_3COOH	0.052
2	3,745	$HCOOH$	0.046
3	0,52	CF_3COOH	0.081
4	-1,9	CH_3SO_3H	0.485
5	-2	H_2SO_4	0.623
6	-2,8	p-TsOH	0.571
7	-14,7	CF_3SO_3H	0.629

Table 1 reaction rate with different Bronsted acid. 1 mmol of acid, HCOOH= 5 mL, T= 90°C

4.2.2.3. Influence of the p-toluenesulfonic acid concentration

As p-TsOH (p-toluenesulfonic acid) is a strong acid widely used as promoter in several metal catalysed reactions [25] and is the functional group of some Amberlyst type resins, in the present paper we focused on it to generate CO from HCOOH.
After 24 h (under the reaction conditions of Table 1) the p-TsOH can leads to 11.57 mmol of CO which can be increased up to 13.70 mmol, by using the corresponding anidride.
Such value is slightly lower than of those obtained by using H_2SO_4 (14.95 mmol) and can be increased by increasing the temperature and the acid concentration.
The Figures 5 and 6 show the influence on the amount of CO generated from formic acid of the temperature and of the acid concentration, respectively.
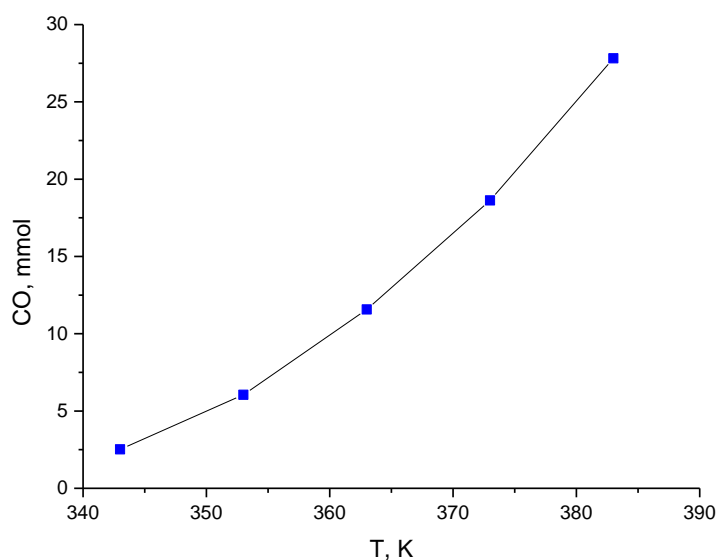

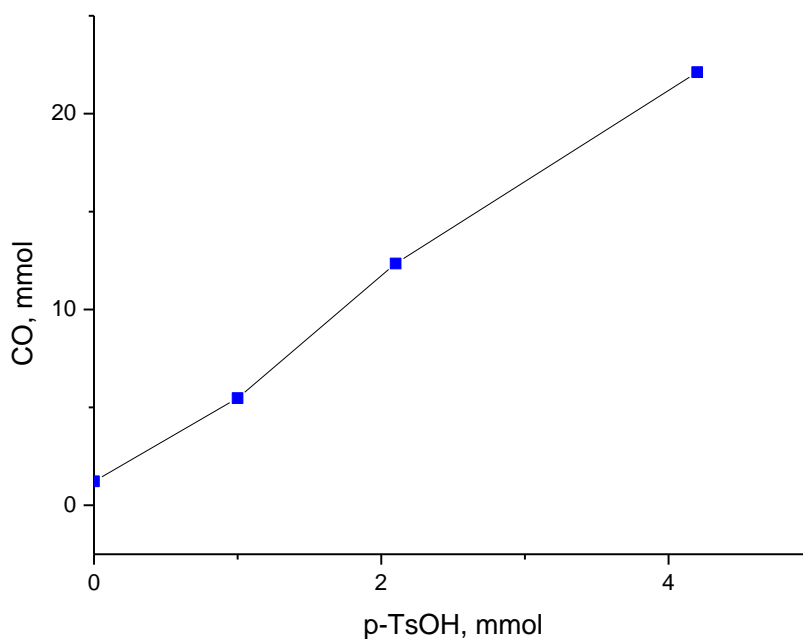Fig.5 mmol CO vs temperature. 1 mmol of p-TsOH, HCOOH= 5 mL, t=24 h.

Fig. 6 mmol CO vs mmol p-TsOH, 5 mL of formic acid, t=6,5 h, T= 363 K.

4.2.2.4 Heterogeneous Bronsted acids catalysing the dehydration of formic acid

Since vigorous stirring was ensured by a magnetic stirrer, which could mechanically alter the polymer structure and consequently influence the catalytic activity and the possibility to reuse the resin, we decided to compare the results obtained with the three different set-up.
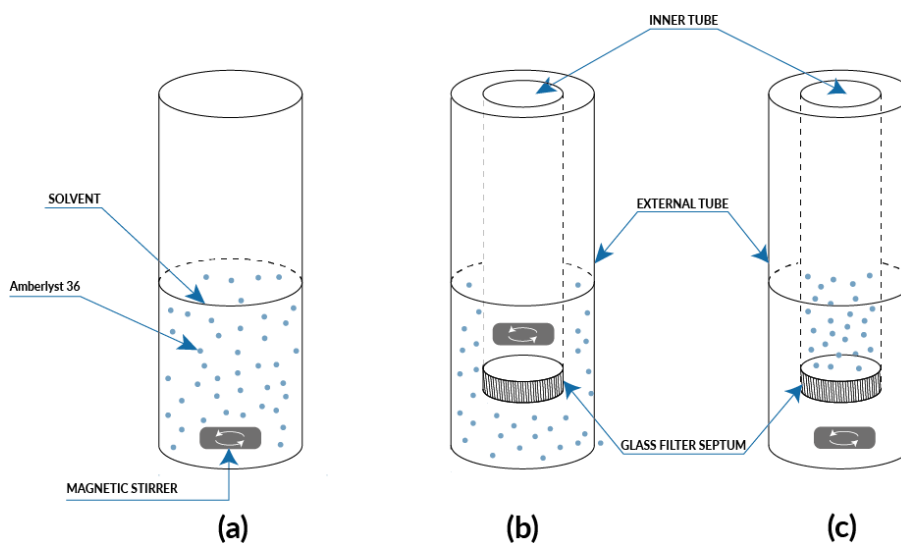

Fig.7 different design of reactor for heterogeneous catalyst

In the set-up usually used in the homogeneous systems (Figure 7, a), the stir bar and the polymer suspension were in the same glass vessel and at the end of reaction the macro-

structure of the polymer was undoubtedly damaged (pulverized). Therefore, in order to minimize it, we designed two new reactor set-up (Figure 7, b and c). In the reactor set-up b) the vessel was formed by two coaxial glass tubes where the magnetic stir bar was positioned on the inner tube (closed in the bottom by a porous septum) while the Amberlyst was dispersed in the liquid between the two tubes. Vice versa, in the reactor set up c) the Amberlyst was in the inner tube while the magnetic stirrer was positioned outside.

The figure 8 shows the mmol of CO evolved in the gas phase after 24 h. The set-up b and c lead to the best results with the possibility to easily reuse the Amberlyst.
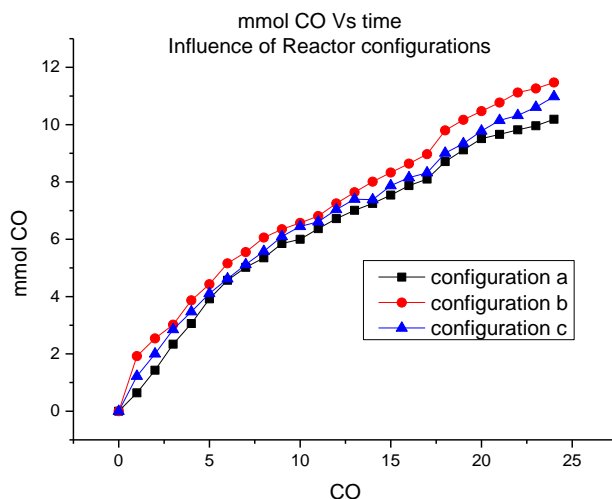

Fig.8 mmol CO vs Time with different reactor configuraton, 5 mL HCOOH, t=24 h, T=363 K.

The sulfonated poly(styrene-divinylbenzene) polymers, commercialized as Amberlyst 36 and 15 resins, have been used as heterogeneous Bronsted acid as catalyst for the dehydration of formic acid.
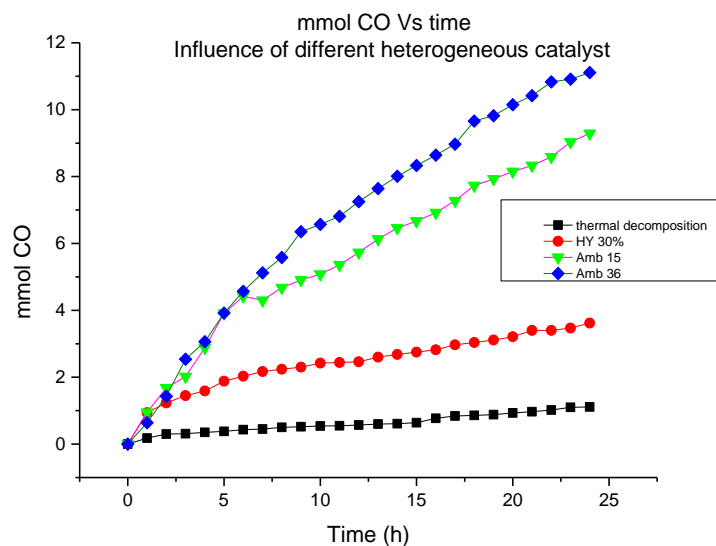

Fig.9 mmol CO vs Time with different Heterogeneous catalyst, 5 mL HCOOH, cat. 1 meq H$^+$, t=24 h, T=363 K

The Table 2 show that the heterogeneous system formed by Amberlist 36 (solid) and HCOOH (liquid) leads to the same amount of CO evolution (ca. 11.11 mmol of CO in 24 hours) than the homogeneous ones (11.57 mmol of CO, with p-TsOH and HCOOH), under the same experimental conditions, while a Highly dealuminated zeolite (HY30) shows a much lower activity than acid resins

acid	mmol CO in 24h
p-TsOH	11.57
Amberlist 36	11,11
Amberlist 15	9,29
HY30	3.94

Table 2 mmol of CO in 24h with different heterogeneous catalyst, compared with p-TsOH

According to such results, it is possible to carry out the Morgan reaction by using a heterogeneous catalyst with the advantage of being able to recover it easily, compared to the homogeneous system. By increasing the amount of Amberlyst 36, it is possible to further increase the rate of CO evolution reaching for instance 26.97 mol of CO in 24h at 110 °C.

4.2.2.5 Recycling test

As can be seen from fig 10, using the particular set-up of the reactor (set-up b fig 7) the resin can be recycled at least 5 times without obvious loss of catalytic activity.
To verify the necessity of a regeneration step of the resin, some tests have been performed, in which the resin has been subjected to an acid wash (HCl 10%), compared to the recovered resin simply washed with water, no difference is noted in the amount of CO generated in subsequent recycling.
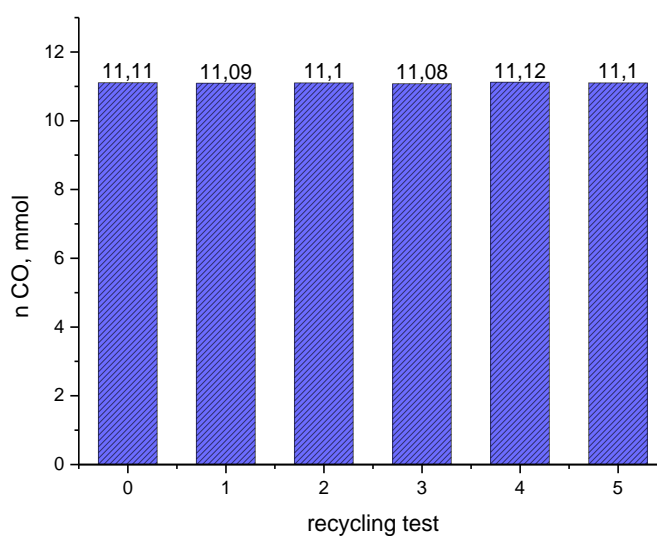

Fig. 10 recycling test. 5 mL formic acid, Amb 36 = 1 meq, t=24h, T= 363 K.

4.2.3 Conclusions

In summary, the Amb. 36 heterogeneous catalyst allows generating CO with a productivity like that obtained with homogeneous catalysts such as p-TsOH. The reaction conditions allow dehydration to be carried out in the liquid phase, making it possible to work at temperatures that are not excessively high, compatible with possible carbonylation reactions catalyzed by transition metal complexes.

4.3 Carbonylation using formic acid as CO generator

Based on the study on the generation of CO from formic acid with organic acids it has been assumed the possibility to exploit this reaction to perform carbonylation reactions.

To perform carbonylation reactions, even at high pressures, it was necessary to design a new multi-chamber reactor, specifically designed to be able to use the CO generated ex-situ, even at high pressure values.

As can be seen from Figure 1, the new reactor was obtained by a modification of a batch reactor.
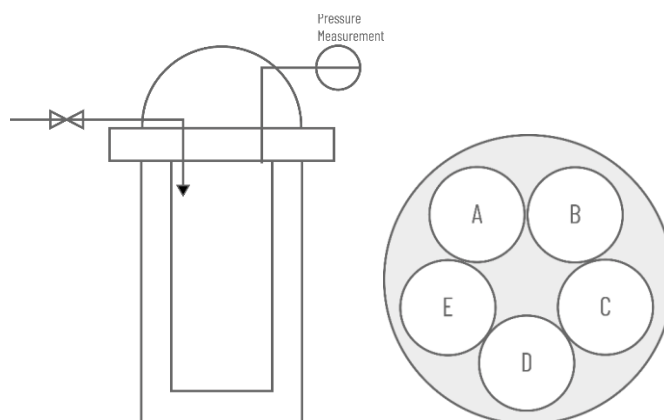

Fig 1 Schematic representation of the multi-chamber batch reactor

The dehydration of formic acid is performed in chamber A, while palladium-catalyzed carbonylation reactions are performed in chambers B-E.

This type of configuration can be used to screen the different catalytic systems (chambers B-E), studying reactions in which pressure and temperature are kept constant. To avoid contamination of the various chambers or entrainment of formic acid, each chamber is equipped with a glass reactor that contains the reagents and a suitably shaped cap that favors the condensation of any vapors. As for the CO generation reactions, a pressure of 10 bar of an inert gas (in this case N_2) was used to avoid evaporation of the formic acid (see experimental part)

This type of set-up prevents formic acid from giving rise to side reactions. For example, the possible addition of formic acid to olefins or acid-base reaction.

Furthermore, as seen in Chapter 3 for carbonylation reactions of iodoarenes, the catalytic system requires a base to remove the HI. It is natural that in that case the base, reacting with the formic acid could block the catalytic cycle.

In addition, depending on the amount of acid used for the dehydration reaction, this system can also be used for carbonylation reactions that require low pressures to ensure the selectivity of the reaction (See amino-carbonylation of iodobenzene).

4.3.1 Carbonylation of olefins Using HCOOH As CO generator

This reactive system has been successfully applied for olefin carbonylation reactions.
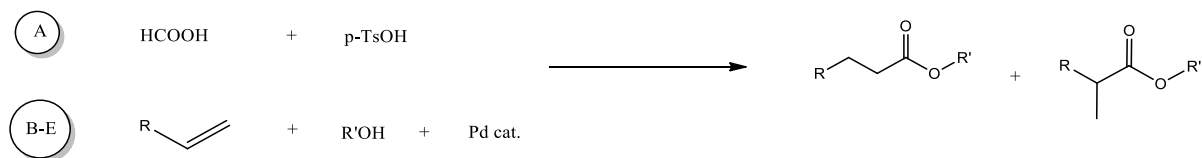
For this type of reaction, p-TsOH was chosen to be used to generate CO from formic acid.

In this case, by modulating the amount of acid catalyst, it was possible to operate at pressures above 40 atm to ensure good kinetics of the reaction.

The results obtained for the carbonylation reaction of olefins using formic acid as a CO generator, shown in the tables 1 and 2, are in line with the literature(See Chapter 2.1)

Tab 1. Influence of 1-Olefin on methoxycarbonylation using HCOOH as CO generator

Chambers	olefins	TON	Sel. % (L/B)
B	1-hexene	870	70/30
C	1-Octene	820	69/31
D	1-Decene	830	70/30
E	cyclohexene	750	/

Run conditions: A: HCOOH 5 mL, p-TsOH: 5.5 mmol; B-E: 1-olefin: 2,0 mmol; cat: $Pd(OAc)_2(PPh_3)_2$: $2,0*10^{-3}$ mmol; PPh3/Pd: 12/1; p-TsOH/Pd: 8/1. T: 363 K, t: 24 h, Solv: MeOH 5 mL;

Tab. 2 Influence of ROH on alcoxycarbonylation of 1-Hexene using HCOOH as CO generator

Chambers	olefins	TON	Sel. % (L/B)
B	MeOH	870	70/30
C	EtOH	810	70/30
D	PrOH	750	68/32
E	BuOH	680	67/33

Run conditions: A: HCOOH 5 mL, p-TsOH: 5.5 mmol B-E: 1-Hexene: 2,0 mmol; cat: $Pd(OAc)_2(PPh_3)_2$: $2,0*10^{-3}$ mmol; p-TsOH/Pd: 8/1. T: 363 K, t: 3 h, Solv: ROH 5 mL;

4.3.2 Carbonylation Aryl halides Using HCOOH As CO generator

Based on the results obtained in the carbonylation reactions of iodobenzene catalyzed by [PdCl$_2$(Xantphos)], studied in chapter 3, reactions were performed to verify the possibility of using formic acid as a CO generator for this reaction as well.
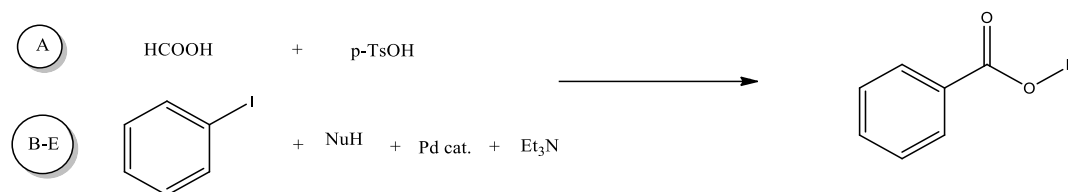
In alkoxycarbonylation, the pressure does not affect the selectivity of the reaction, since even at high pressures, the formation of the double carbonylation product (Ketoester) is not observed, for this reason p-TsOH was used to generate CO at other pressures (>40 atm) rapidly.

Table.3 Alkoxycarbonylation aryl halides with CO generated by HCOOH

Chambers	Iodoaryl	Conversion
B	iodobenzene	100
C	4-iodotoluene	100
D	2-iodotoluene	87
E	1,4-diiodobenzen	100[a]

Run conditions: A: HCOOH 5 mL, p-TsOH: 5.5 mmol; B-E: iodoaryl: 2,0 mmol; cat: [PdCl$_2$(Xantphos)] : 2,0*10^{-3} mmol; Et$_3$N 1 eq. T: 363 K, t: 3 h, Solv: MeOH 5 mL; [a]related to dimethylterephthalate

For amino-carbonylation reactions, where pressure can affect selectivity, a modest amount of Amb36. was chosen to generate CO at pressures not exceeding 5 atm. The conversion of the reaction after 5 hours results to be total, and the selectivity results to be predominant towards the formation of monocarbonylation products. (table 4).

Table 4. Aminocarbonylation aryl halides with CO generated by HCOOH

Chambers	Iodoaryl	Sel. (am/Ketam)
B	iodobenzene	100/0
C	4-iodotoluene	98/2
D	2-iodotoluene	100
E	4-iodophenol	88/12

Run conditions: A: HCOOH 5 mL, Amb36=1 meq H$^+$; B-E: iodoaryl: 2,0 mmol; cat: [PdCl$_2$(Xantphos)] : 2,0*10^{-3} mmol; 1-decylamine 1 eq, Et$_3$N 1 eq. T: 363 K, t: 3 h, Solv: Toluene total volume 5 mL.

4.3.3 Conclusions

In conclusion, the possibility of performing CO generation from organic acidic HCOOH has been verified, and it has also been successfully performed in the presence of acidic resins. This system has been conveniently used to perform carbonylation reactions on olefins with CO generated, at high pressures (P> 40 atm).

With the particular design of the proposed new reactor, could be conveniently used to perform carbonylation reactions with CO generated from HCOOH, working at high pressures (P> 40 atm) or low CO pressures depending on the amount of acid catalyst for Morgan Reaction. In this way it's possible to control the selectivity of the reactions. With this system, possible parasitic reactions between formic acid and other reactants can be avoided (like formation of formate esters)

4.4 Formic Acid as *in situ* CO generator for the synthesis of perfectly alternating polyketones CO-Ethene

It is reported that the mixtures formic acid/ and acetic acid/water can be used as a sustainable solvent for the synthesis of polyketones (PKs), which are obtained by catalytic copolymerisation of CO and ethylene. [26-27] To the best of our knowledge there are no examples of polymerisation by carbonylation of olefins and carbon monoxide obtained *in situ* from CO surrogate.

For this reason, the possibility of using HCOOH/Ac$_2$O as CO generator to perform CO/ethene polymerisation catalyzed by homogeneous palladium complexes was explored. In this way, the problem posed using dehydration activators is transformed into an advantage due to the simultaneous generation of CO and the formation of a suitable solvent mixture to perform the polymerization (Scheme 1).
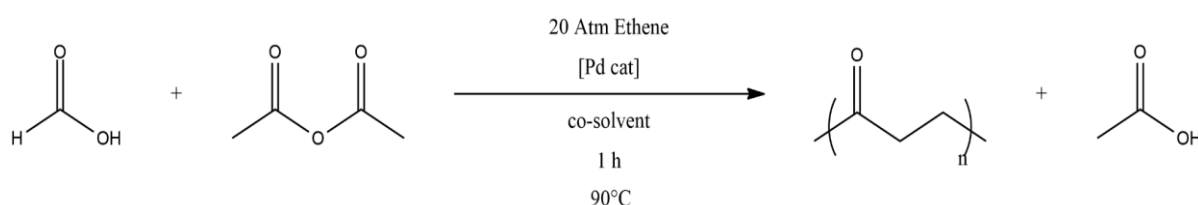
Scheme 1 Synthesis Polyketone CO- Ethene using Formic Acid as CO generator

For this carbonylative polymerization, obtained for the first time using HCOOH as a CO surrogate, the influence of certain reaction parameters was studied, paying attention to the effect of the co-solvents on molecular weight distribution of the polymers thus synthesized. In particular, with [Pd(OAc)$_2$(dppp)] as a catalyst, formic acid, acetic anhydride and co-solvents with a high dielectric constant (such as DMSO and ethylene glycol diacetate, $\varepsilon = 46$), it is possible to obtain polymers with a molecular weight of over 80'000, with a productivity over 1800 gpol/(gPd* h).

4.4.1 Results and discussion

4.4.1.1 Polymer Characterization

Based on previous work, to study certain reaction parameters, it was decided to carry out the polymerisation of ethene and CO generated in situ by HCOOH and Ac_2O using 1,4-dioxane as a solvent [26].

The properties of polyketones, such as solubility and melting point, can vary greatly depending on the alternation of the two monomers in the chain. With FT-IR characterisation (FIG 4), it is possible to observe the absorptions at typical values for polyketones CO/ethene. In particular, the value at 1690 cm^{-1} for the stretching of the carbonyl group is typical of perfectly alternating polyketones.
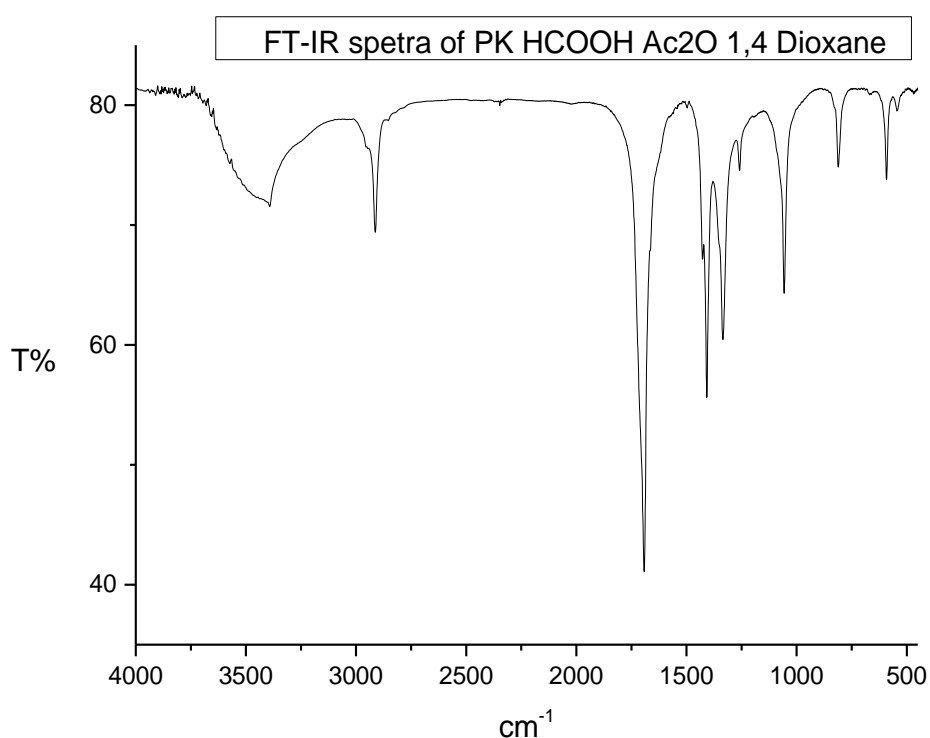

FIG 1: FT-IR spectra of Polyketones obtained from HCOOH/Ac_2O as CO generator in KBr

The melting point of the polymers obtained are 528-529 K. The tabulated value for perfectly alternating CO-Ethene polyketones is in the range of 528-531 K (which varies according to the crystallinity of the polymers, α and β form).
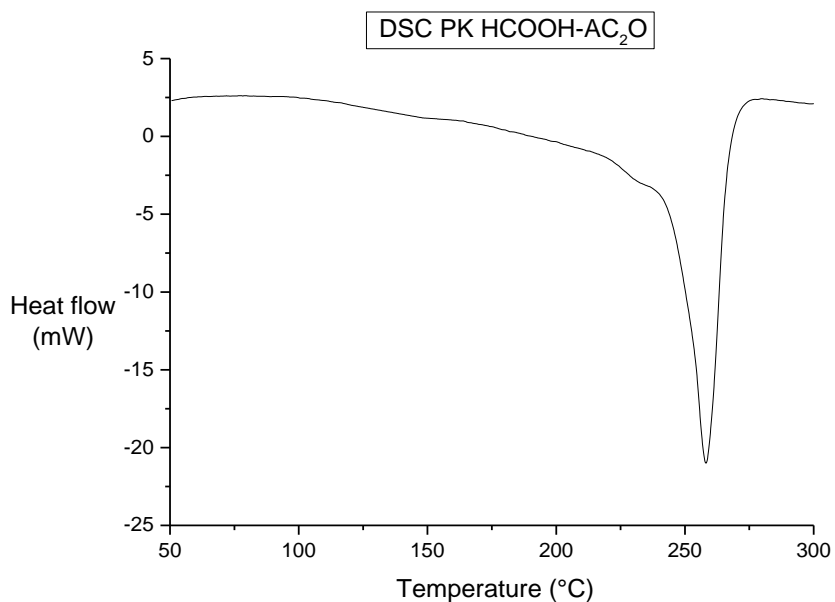
Fig 2 DSC analysis of PK HCOOH/Ac2O/1,4 Dioxane

This is further evidence that the resulting polymers are perfectly alternated, in fact it is reported that for PKs CO/ethene with a low CO content in the polymer chain, the melting point decreases dramatically (e.g., PK30, with only 30% CO melts at temperatures of 403 K). [28-29]

NMR analysis showed that the end-groups of the polyketones obtained are exclusively ketonic. (Fig 3-4 and Tab1)
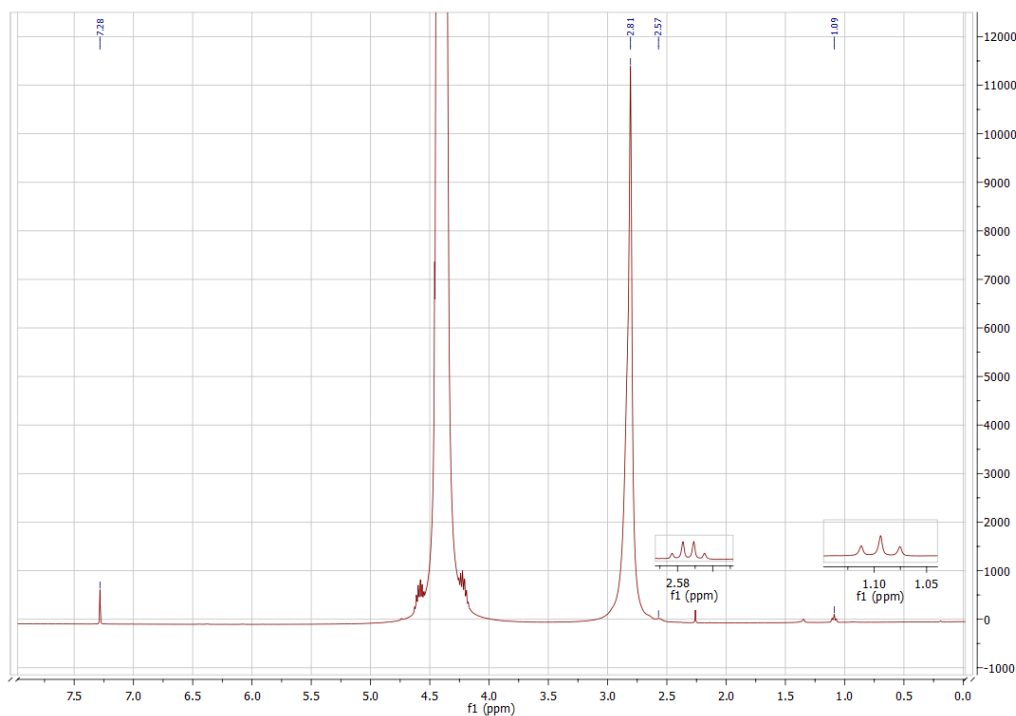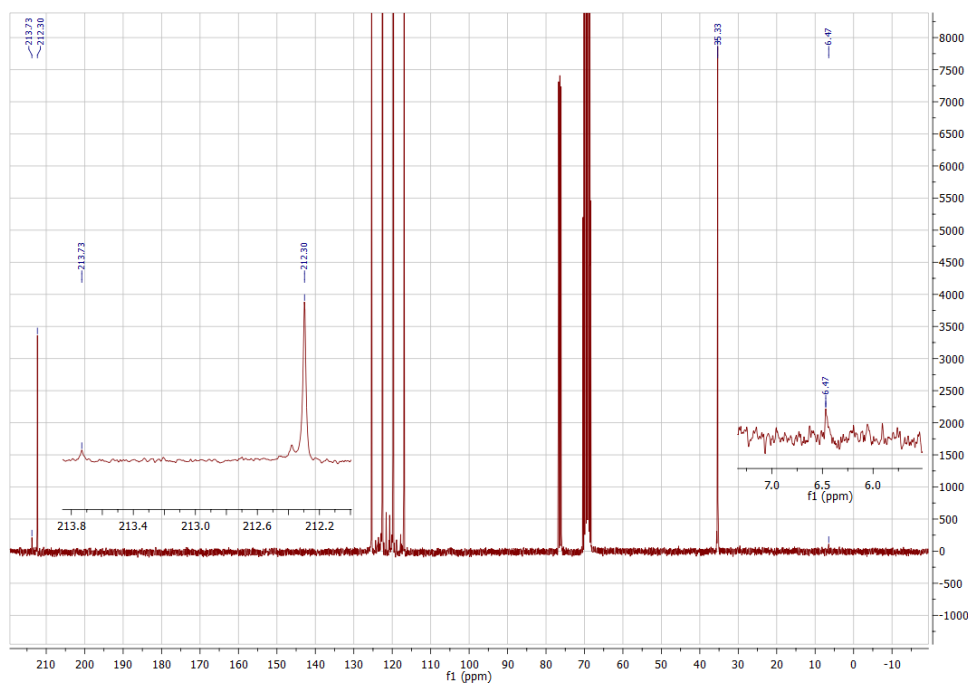
Fig 3 and 4. ^{1}H-NMR and ^{13}C-NMR of PK obtained with HCOOH/Ac$_2$O/1,4 Dioxane

Table 1 : Signals ^{1}H-NMR and ^{13}C-NMR for CO ethene polymers usign HCOOH. as CO generator

	^{1}H-NMR		^{13}C-NMR	
-C(O)C*H*$_2$C*H*$_2$-	2,80	-C(O)*C*H$_2$*C*H$_2$-	35,30	
-C(O)CH$_2$-C*H*$_3$	1,09	-C(O)CH$_2$-*C*H$_3$	6,47	
-C(O)C*H*$_2$-CH$_3$	2,56	-*C*(O)CH$_2$CH$_2$-	212,30	
		-*C*(O)CH$_2$-CH$_3$	213,73	

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4.4.1.2 On catalytic System

As can be seen from Fig.5, small quantities of CO are generated by thermal decomposition, even in the absence of dehydration activators. The same reaction carried out in the presence of 1 mmol Ac_2O leads to a considerable increase in the amount of CO produced (from 0,9 to 2,2 MPa). With the use of $[Pd(OAc)_2(dppp)]$, no increase in the mmol of CO produced can be observed, and the non-negligible presence of CO_2 in gaseous mixture has been observed.
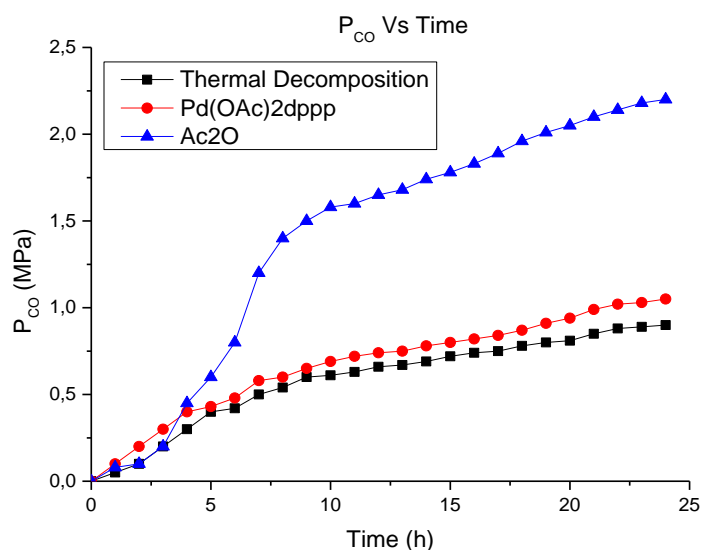

Figure 5 Generation of CO from formic acid in presence of 1 mmol Ac_2O, 1,6 E-06 mol of $[Pd(OAc)_2(dppp)]$ or by thermal decomposition, 5mL of HCOOH, 363 K, 24h

As is well known, for the copolymerisation reaction of olefins and CO, the nature of the anion of the catalyst and the type of solvent can influence the productivity of the reaction. Initially, of the anion of the $[Pd(X)_2(dppp)]$ complex was screened for polyketone synthesis, using $HCOOH/Ac_2O$ to generate CO *in situ* and 1,4-dioxane as co-solvent.

As can be seen from Fig. 6, productivity is not particularly affected by the presence of weakly coordinating strong acid anions. Instead, chloride leads to a drastic decrease, as is typical for the classical polymerization performed with CO/Ethene in MeOH. Given the similarity of the productivities and the high concentration of HCOOH in the reaction environment, the anions of the palladium (II) complexes are easily replaced by $HCOO^-$ ions, which is evidently more difficult in the case of the $[PdCl_2(dppp)]$ complex.
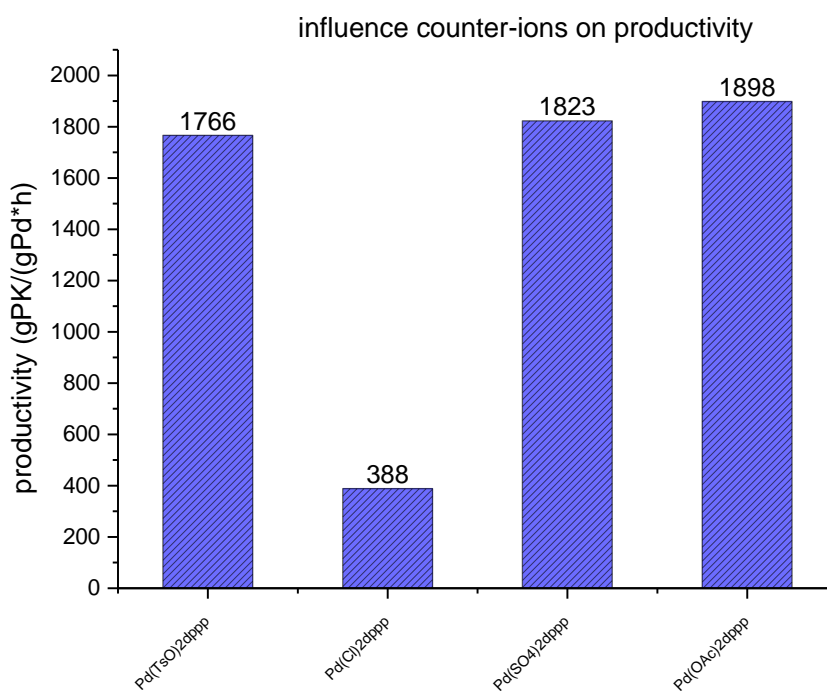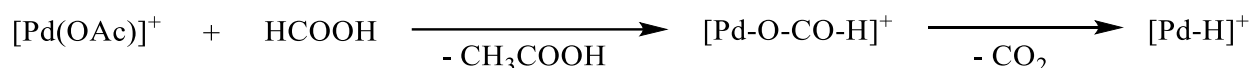
Figure 6: influence of catalyst counter-anion on productivity: HCOOH: 2 mL, Ac$_2$O: 2 mL, 1,4 Dioxane 2 mL, cat: Pd(X)$_2$(dppp)]1,6 E-06 mol, T:363 K, Time:1 h

Typically, for the synthesis of polyketones, the catalytic system requires the use of an acidic as co-catalyst to avoid the deactivation of the catalyst due to the formation of Pd-black. The presence of acid is required to regenerate the inactive Pd(0) species to form the palladium hydride species Pd(II)-H (scheme 1)

$$Pd(0) \; + \; H^+ \; \rightleftharpoons \; [Pd(II)\text{-}H]^+$$

Scheme 1 Formation of Palladium hydride

In the system studied, given the difference in acidity between formic acid and acetic acid, it is plausible that the palladium hydride species [Pd-H]$^+$ is generated from HCOOH [24,26] (scheme 2):

$$[Pd(OAc)]^+ \; + \; HCOOH \; \xrightarrow[-\;CH_3COOH]{} \; [Pd\text{-}O\text{-}CO\text{-}H]^+ \; \xrightarrow[-\;CO_2]{} \; [Pd\text{-}H]^+$$

Scheme 2 formation of Palladium Hydride by formic acid

In the catalytic synthesis of polyketones, the distribution of molecular weights and productivity are dependent on the type of catalyst and solvent composition. For example, polymerisation carried out in HCOOH/H$_2$O and CH$_3$COOH/H$_2$O, with [PdCl$_2$(dppp)], makes

it possible to obtain polyketones with average molecular weights of around 30,000 and 50,000, respectively [26,27]

Solvent mixtures in which polymerizations are performed is complicated and tends to change over time, due to the generation of CO from HCOOH. To study the effect of such a mixture on the productivity of the reaction, the dielectric constant (ε) of the co-solvent was considered.

As can be seen from table 2, the productivity does not change particularly in function of the different solvents mixtures, whereas it is possible to observe a considerable increase in the average molecular weight of the polymers obtained with increasing ε of the co-solvent fig7 . It is possible that the co-solvent may stabilize cationic Pd(II) species by favouring the growth of the polymer chain to the disadvantage of the kinetics of the termination step.

Table 2 Influence of dielectric constant of co-solvent on productivity of catalyst

Co-solvent	dielettric costant ε (F/m)	productivity $g_{Pk}/(g_{Pd}*h)$
1,4 dioxane	2,25	1900
DMC	3,2	1820
THF	7,58	1990
EtNO$_2$	19,7	1520
PhCN	26	1255
MeNO$_2$	35,87	1400
GVL	36,47	1730
Ethylen glycol diacetate	46	1870
DMSO	46,7	1910

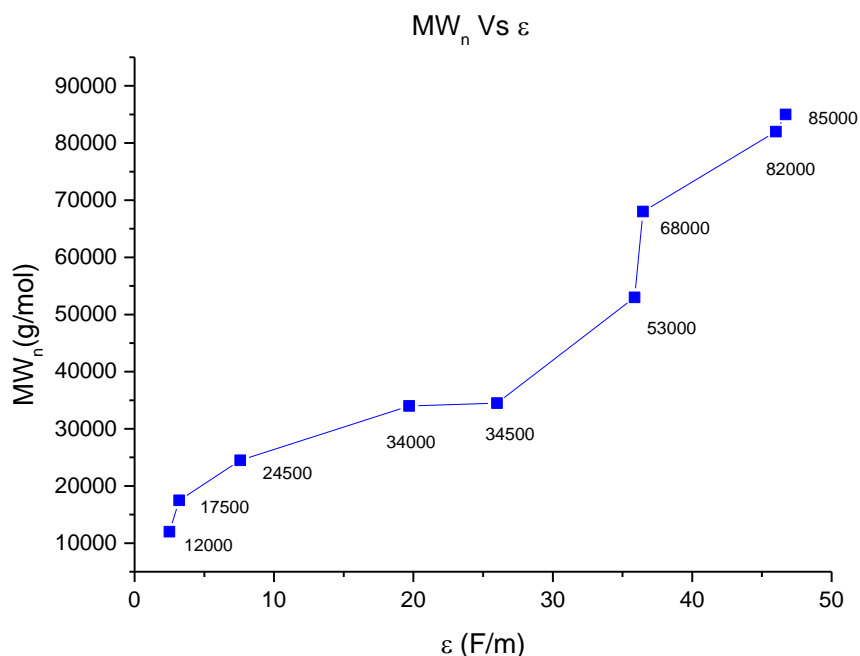Run condition: HCOOH 2 mL, Ac$_2$O: 2 mL, co-solvent: 2 mL, cat: [Pd(OAc)$_2$(dppp)] 1,6 E-06 mol, T: 363 K, Time:1 h

Figure 7: influence co-solvent on MW_n: HCOOH 2 mL, Ac_2O: 2 mL, co-solvent: 2 mL, cat: [Pd(OAc)$_2$(dppp)]1,6 E-06 mol, T: 363 K, Time:1 h

4.4.1.3 on catalytic mechanism

From this, it is possible to propose the main patterns relating to the growth of the polymer chain and the termination phase, and to propose a plausible reaction mechanism.

The presence of exclusively ketone terminal groups makes it possible to assume that the initial polymerisation species is a Pd-H$^+$ species. Although the patterns of termination may be manifold, the presence of Ac_2O in the reaction environment means that it is possible to exclude the possibility of termination by H_2O, but only by HCOOH (or CH_3COOH), and this is confirmed by the absence in the NMR analysis of olefinic signals due to possible termination by b-hydride elimination (Scheme.3)
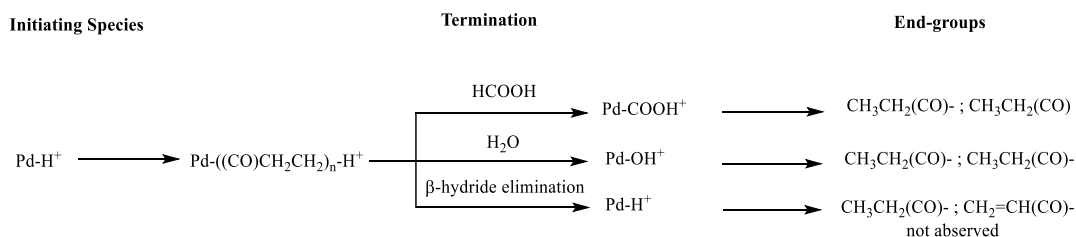
Scheme 3 possible termination path

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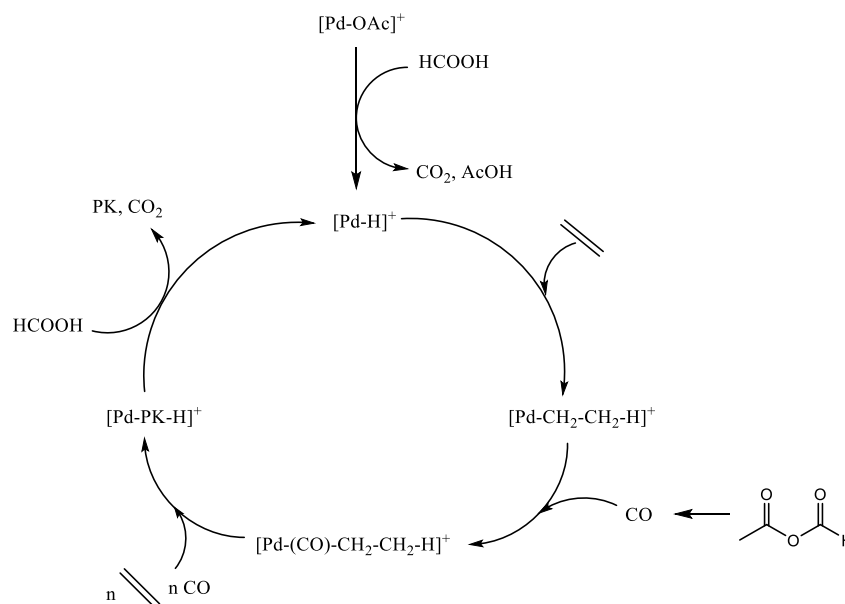It is therefore possible to propose a reaction mechanism (fig. 8):

Fig. 8 proposed reaction mechanism for synthesis of PK obtained with HCOOH/Ac$_2$O/co-solv

4.4.2 Conclusions

In conclusion, we herein report an alternative synthesis of polyketones, a class of high-performance thermoplastic polymers, employing formic acid as *in situ* CO generator.

In particular, the system consisting of HCOOH/Ac$_2$O and [Pd(OAc)$_2$dppp] allows the generation of both CO and a solvent mixture that enables perfectly alternating copolymerization, without the need to employ additional acidic co-catalysts.

In addition, the system is flexible and it is possible to vary the distribution of molecular weights by changing the type of solvent mixture used, in particular with co-solvents with $\varepsilon=$ 46 it is possible to obtain polymers with a numerical average molecular weight higher than 80'000 g/mol with a productivity higher than 1800 gPk/(gPd*h). Moreover, from the characterization of the polymers, it was possible to propose a catalytic reaction mechanism that allows to obtain exclusively ketone terminal groups.

4.5 Experimental section

Dehydration reactions

The reactions have been carried out in a batch reactor of 27.87 mL provided with a magnetic stirrer. In a typical experiment 5 ml of HCOOH and Amberlyst 36 was introduced on reactor and carefully flushed with N_2 at room temperature with stirring and then pressurized with 1 MPa of N_2 and heated up to 373 K in *ca.* 10 min under vigorous stirring. the CO pressure monitoring was performed by using a WIKA S-10 pressure transmitter connected with a digital device for acquisition and elaboration of the data using an electronic transducer (± 0.01 atm)

Carbonylation reaction using HCOOH as CO generator

5 mL of HCOOH and the acid catalyst (5.5 mmol of p-TsOH for the alkoxycarbonylation reactions and 200 mg of Amb 36 for the aminocarbonylation reactions) are introduced into chamber A of the multi-chamber reactor.In chambers B-E, the Pd-based catalyst, nucleophile (plus optional base) and solvent are introduced. The reactor undergoes 3 cycles of vacuum washing. Subsequently, 1MPa of N_2 is introduced to prevent evaporation of formic acid. Once the reaction temperature is reached, the system is left to react for 3-5h.
Once the reactor is vented, the reaction products are analyzed by GC and GC-MS.

Formic acid/Acetic anhydride and ethene copolymerization

Copolymerisation is carried out in an *ca.* 30 mL autoclave using magnetic stirring. In order to avoid contamination by metallic species of the internal surface of the autoclave, solvent and catalyst were contained in ca. 20 mL Pyrex bottle placed inside the autoclave. In a typical experiment, 1.00 mg of [Pd(OAc)$_2$(dppp)] ($1,6*10^{-6}$mol), 2 mL of 1,4 dioxane, 2 mL of formic acid and 2 mL of acetic anhydride were placed in the reactor, then was washed by pressurising with *ca.* 0.01 MPa of ethene, at room temperature and then depressured to atmospheric pressure (this cycle was repeated three times , with magnetical stirring). The autoclave was heated to 363 K and when the CO pressure arrived to the desired value (typically 2 MPa) was charged 2 MPa atm of ethene, while stirring, maintained constant throughout the experiment. After 1 hour, at the end of the experiment the autoclave was quickly cooled and carefully vented off. The product was filtered, washed with water twice times and twice whit acetone, and then dried under vacuum overnight.The polymer was weighted and the productivity was calculated as gPK/(gPd h).

Characterization

The gas phase products (CO, CO_2 and H_2) were analyzed by GC using a 18 ft × 1/8 SS Silica Gel, 60/80 packed column.

All polymers were analyzed by FT-IR and NMR spectroscopies. FT-IR spectra were recorded on a Nicolet Magna 750 instrument in KBr powder.

All the NMR spectra were recorded on a Bruker Ascendet ™ 400 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in 1,1,1,3, 3,3-hexafluoroisopropanol/$CDCl_3$ (10/1) using the Inverse [1]H-Gated Decoupling Technique.

The thermogravimetric analysis were recorded with DSC-TGA Linseis PT1000 under N_2, with a temperature ramp of 303 K to 773 K with 283 K/min.

4.6 References

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General Conclusions

From an industrial point of view, the development of new processes, aimed at reducing the environmental problems of production cycles, is extremely important. Although it is possible to find a wide literature about these aspects, it is not always possible to apply industrially all the solutions proposed by the academic and industrial world. Often, one of the main problems is that of matching the aspect of environmental sustainability with the economics of the new synthetic ways proposed.

In this perspective, the work of this thesis has focused on studying new catalytic processes, able to represent a more sustainable alternative from an environmental and economic point of view compared to current industrial processes based on carbonylation reactions.

Although it is not easy to summarize all the aspects covered in this work, discussed separately at the end of each chapter, but some of the results obtained for carbonylation reactions aimed at the synthesis of esters, amides, isocyanates, ureas and polymers, with the new catalytic systems based on Palladium, are encouraging for a possible industrial scale-up.

In addition, the results obtained with the study carried out on formic acid as a generator of *green* CO, may represent the starting point for future studies, and be able to include the reactions of carboxylation in the concept of circular economy of CO_2.

List of pubblications

Publications

-Manente, F., Pietrobon, L., Ronchin, L., Vavasori, A. (2021). *Trifluoroacetic Acid Hydroxylamine System as Organocatalyst Reagent in a One-Pot Salt Free Process for the Synthesis of Caprolactam and Amides of Industrial Interest*. Catal. Letters, 1-7.

-Bortoluzzi, M., Castro, J., Gobbo, A., Ferraro, V., Pietrobon, L., Antoniutti, S. (2020*). Tetrahedral photoluminescent manganese (II) halide complexes with 1, 3-dimethyl-2-phenyl-1, 3-diazaphospholidine-2-oxide as a ligand.* New J Chem, 44(2), 571-579.

-Bortoluzzi, M., Castro, J., Gobbo, A., Ferraro, V., Pietrobon, L. (2020). *Light harvesting indolyl-substituted phosphoramide ligand for the enhancement of Mn (II) luminescence*. Dalton Trans, 49(22), 7525-7534.

-Pietrobon, L., Ronchin, L., Sadraoui, C., Pontello, R., Tosetto, C., Vavasori, A. (2020). *Pd/C Catalyzed selective hydrogenation of nitrobenzene to cyclohexanone oxime in the presence of $NH_2OH \cdot HCl$: Influence of the operative variables and insights on the reaction mechanism.* Appl. Catal A-Gen, 598, 117570.

-Vavasori, A., Bravo, S., Pasinato, F., Kudaibergenov, N., Pietrobon, L., Ronchin, L. (2020). *Supported palladium metal as heterogeneous catalyst precursor for the methoxycarbonylation of cyclohexene*. Mol. Catal., 484, 110742.

-Bianchini, E., Pietrobon, L., Ronchin, L., Tortato, C., Vavasori, A. (2019). *Trifluoroacetic acid promoted hydration of styrene catalyzed by sulfonic resins: Comparison of the reactivity of styrene, n-hexene and cyclohexene*. Appl. Catal. A-Gen, 570, 130-138.

Publications In progress

-Pietrobon, L., Vavasori, A., Fardin, A., Ronchin, L. *Selective dehydration of formic acid to CO and water efficiently catalysed by the sulfonated poly(styrene-divinylbenzene)* (Submitted to the editor)

-Pietrobon, L., Vavasori, A., Ronchin, L. *Selective generation of CO from formic acid efficiently used in the Pd(II)-catalyzed copolymerization with ethylene to Poly(1-oxo-trimethylene)* (submitted to the editor)

-Pietrobon, L., Vavasori, A., Ronchin, L., *The methoxycarbonylation of iodobenzene to methyl benzoate efficiently catalysed by the [PdCl$_2$(Xantphos)] complex* (submitted to the editor)

-Pietrobon, L., Vavasori, A., Ronchin, L., (2021)The [PdCl$_2$(dppf)]/FeCl$_3$/O$_2$ system efficiently catalyzes the oxidative carbonylation of aniline to phenylisocianate (submitted to the editor)

Congress Communications

-Pietrobon, L., Vavasori, A. *"Synthesis of Acrylates From CO$_2$ and Ethylene"* in: Joint Doctoral Program in Chemistry 2nd Winter School, 14-15 February 2019

-Pietrobon, L., Vavasori, A., Ronchin, L., *New Palladium-Based Catalytic System for the Sustainable Synthesis of Esters*, Book of Abstract part 2 of XXVII Congresso Nazionale della Società Chimica Italiana SCI2021- LA CHIMICA GUIDA LO SVILUPPO SOSTENIBILE, 14-23 September 2021

-Pietrobon, L., Vavasori, A., Ronchin, L., *Sustainable Generation of CO from Formic Acid for Carbonylation of Alkenes* Book of Abstract part 2 of XXVII Congresso Nazionale della Società Chimica Italiana SCI2021- LA CHIMICA GUIDA LO SVILUPPO SOSTENIBILE, 14-23 September 2021

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