NORBORNENE FUNCTIONALIZATION THROUGH ASYMMETRIC PD- AND RH-CATALYZED CARBONYLATION PROCESSES

Carolina Blanco Jiménez

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Departament de Química Física i Inorgànica

Norbornene functionalization through asymmetric Pd- and Rh-catalyzed carbonylation processes

Memoria presentada por

Carolina Blanco Jiménez

Tarragona, Julio 2010

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Prof. Dra. Carmen Claver Cabrero, Catedràtica del Departamento de Química Física i Inorgànica de la Facultat de Química de la Universitat Rovira i Virgili, y la Prof. Dra. Aurora Ruiz Manrique, Catedrática del Departamento de Química Física i Inorgànica de la Facultat de Química de la Universitat Rovira i Virgili,

HACEN CONSTAR:

Que la memoria que lleva por título: "**Norbornene functionalization through asymmetric Pd- and Rh-catalyzed carbonylation processes**", que presenta Carolina Blanco Jiménez para obtener el grado de Doctor en Química, ha sido realizada bajo nuestra dirección en el Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili.

Tarragona, Julio 2010

Prof. Dra. Carmen Claver Prof. Dra. Aurora Ruiz

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Quiero agradecer al Prof. Sergio Castillón, por sus invaluables contribuciones a lo largo del desarrollo de esta tesis.

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agradecer a Jessica y Elizabeth por su alegría y por estar pendientes del desarrollo de esta tesis durante estos últimos meses. Evidentemente, no pueden faltar las dos personas que me han estado acompañando a lo largo de este camino, Angélica y Verónica. Chicas…..no tengo palabras para expresar el sinnúmero de sentimientos que se me vienen en este momento, ya que aparte de ser mis compañeras de laboratorio, se han convertido en mis amigas. Gracias a las dos, por los ánimos que me han infundido durante todo este tiempo, por su colaboración y por estar pendientes de todo. Hemos pasado momentos inolvidables no sólo a nivel profesional sino también a nivel personal, y éstas son memorias que llevaré conmigo para siempre. Gracias por soportar las tardes interminables en que me daba por cantar o por bailar, y gracias por la confianza que han depositado en mí. A las dos me resta decirles que muchos ánimos con la tesis…..cada vez queda poco y espero que podamos celebrar juntas este gran logro.

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Quiero dedicar mi mayor agradecimiento a las personas que más quiero, mis padres, Martha y Ever, por todo el esfuerzo que han hecho por mí, por sus innumerables consejos y por su apoyo incondicional en todo momento. A mi hermano Sebastián, por su apoyo y buena energía. A Diana, Johana, Lorena, Jenny, Amanda, Rossy por los ánimos que me han infundido durante estos años. Esta tesis es dedicada de todo corazón a ustedes.

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Structure of the thesis

This thesis is divided into five chapters:

Chapter 1. Introduction and Scope

This chapter first present the importance of the carbonylation reactions. The alkoxycarbonylation, copolymerization and hydroformylation reactions are reviewed in details. For each reaction, general aspects, mechanism, antecedents and main achievements are discussed. The state-of-the-art and current requirements justify the objectives of this thesis, proposed at the end of this chapter.

Chapter 2. Palladium-catalyzed carbonylation of norbornene

This chapter describes the use of monodentate and bidentate phosphine ligands in the palladium-catalyzed methoxycarbonylation of norbornene. Screening of ligands and optimization of the reactions conditions is developed in order to control the chemoselectivity of the reaction to the ester formation.

Chapter 3. Mechanistic aspects of the Pd-catalyzed methoxycarbonylation of norbornene.

This chapter deals with mechanistic aspects of the methoxycarbonylation of norbornene. HP-NMR studies are performed under similar conditions to those used in the catalytic reactions. The studies on the monophosphine system are focussing on the activation of the palladium precursor in the absence of acid.

Chapter 4. Asymmetric Rh-catalyzed hydroformylation of norbornene

This chapter reports on the application of diphosphite ligands derived from carbohydrates in the rhodium-catalyzed hydroformylation of norbornene. The effect of structural modifications of the backbone and the phosphite moiety are discussed.

Chapter 5. Concluding remarks. This chapter summarizes the main conclusions of the work presented in this thesis.

List of symbols and abbreviations

ABDPP = 1,6-anhydro-2,4-bis(diphenylphosphino)pyranose

acac = acetylacetonate

BFFPA = (S)-1-[(R)-1',2-bis(diphenylphospnio)-ferrocenyl]ethyldimethylamine

Bipy= 2,2-bipyridine

BPPM = (2S-4S)-1-(tert-butoxycarbonyl)-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine

C = Conversion

COD = 1,5-cyclooctadiene

Cy = cyclohexyl

D = deuterium

dba = dibenzylideneacetone

DBP-DIOP = (2,3-*O*-isopropylidene-2,3-dihydroxy-1-4-bis(5H-dibenzophospholyl)butane)

d^{t}bpx = bis(di-*tert*-butylphosphino)-ortho-xylene

d^{t}bpp = 1,3-bis(di-*tert*-butylphosphino)propane

dd = doublet of doublet

ddd = doublet of doublet of doublet

DDPPI = 1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-1-iditol

dppe = 1,2-ethanediylbis(diphenylphosphine)

dppp = 1,3-propanediylbis(diphenylphosphine)

dppb = 1,4-butanediylbis(diphenylphosphine)

ee = enantiomeric excess

GC = Gas Chromatography

GC-MS = Gas Chromatography Mass Spectrometry

HP-NMR = High-pressure Nuclear Magnetic resonance spectrometry

Hz = Hertz

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J = Coupling constant

L-L = Bidentate Ligand

NBN = norbornene

NMDPP = *neo*-menthyldiphenylphosphine

NMR = Nuclear Magnetic resonance spectrometry

OAc = acetate anion

OTf = Trifluoromethanesulfonate anion

OTs = *p*-toluensulfonate anion

p = para

Ph-BPE = (-)-1,2-bis((2R,5R)-2,5-diphenylphospholano)ethane

PhCN = benzonitrile

P-D = phosphorus-deuterium coupling

phen = 1,10-phenanthroline

ppm = part per million

p-TsOH = *p*-toluensulfonic acid

RT = room temperature

s = singlet

t = tert

T = temperature

Tangphos = (1S,1S',2R,2R')-1,1'-di-*tert*-butyl-(2,2')-diphospholane

^{t}Bu = *tert*-butyl

TFA = Trifluoroacetic acid

TfOH = Trifluoromethanesulfonic acid

THF = Tetrahydrofuran

TMS = Tetramethylsilane

TOF = Turnover frequency

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Chapter 1

Introduction and Scope

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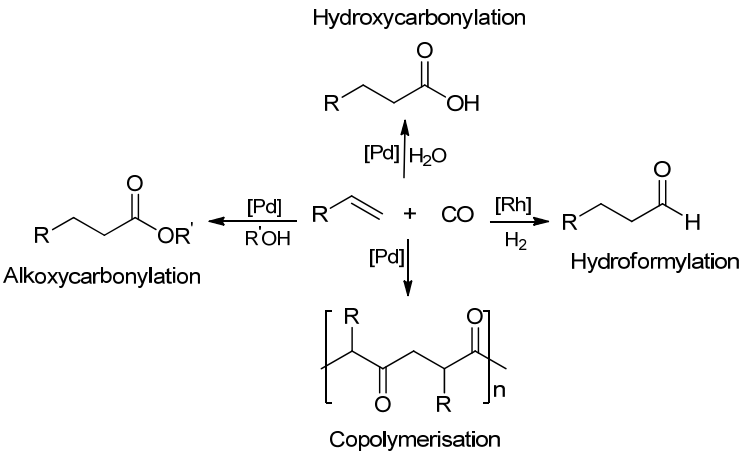
The transition metal-catalyzed carbonylation of alkenes is a reaction involved in several important processes to obtain fine chemicals and intermediates for organic synthesis (Scheme 1.1).[1,2] In these processes acids, esters or aldehydes can be formed from simple alkenes in the presence of carbon monoxide and a nucleophile, typically water, alcohol or hydrogen. When the nucleophile is water o alcohol, the process is called hydroxycarbonylation or alkoxycarbonylation, respectively.[2,3] Alkoxycarbonylation is also sometimes referred as hydroesterification. When the nucleophile is hydrogen the process is called hydroformylation since in this case, a proton and a formyl group are added (Scheme 1.1). The most studied processes are currently the Rh-catalyzed hydroformylation of alkenes[1a,d,4] and the Pd-catalyzed hydroxy- or alkoxycarbonylation of alkenes.[1b,5,6]



Scheme 1.1. General scheme for carbonylation of olefins.

Hydroformylation has been applied in the synthesis of intermediates and in fine chemicals in particular in vitamins flavours and fragrances.[7] Due to the versatile chemistry of the aldehydes obtained through the hydroformylation

reaction, further conversions into alcohols, amines, carboxylic acid derivatives, and other products are available. For this reason, hydroformylation appears as a clean and economical method of obtaining functionalized organic molecules and constructing complex structures.[7,8] The asymmetric version of this reaction is one of the most important synthetic strategies for the preparation of optically chiral aldehydes, which are versatile intermediates for the synthesis of many biologically active compounds.[9]

Both palladium-catalyzed hydroxy- and alkoxycarbonylation of alkenes, have also been widely studied.[3,5,10] However, less successful work has been reported on these reactions than on hydroformylation due to the difficulty of obtaining simultaneously both high regio- and enantioselectivities.[9,11]

The palladium-catalyzed copolymerization and terpolymerization, where the use of chiral Pd catalysts allows the control of the stereoselectivity is also of high interest.[12] Because this work focused in norbornene carbonylation, in this chapter an overview of the Pd-alkoxycarbonylation, Pd-copolymerization, Rh-hydroformylation reactions and their mechanisms will be presented.

1.1 Asymmetric palladium-catalyzed alkoxycarbonylation of olefins

The asymmetric synthesis of carboxylic acids and their related esters is performed from olefins, carbon monoxide, and water or alcohols (represented as R^2OH in Scheme 1.2) in the presence of a chiral palladium catalyst. From this reaction the linear and the branched products can be obtained. The regioselectivity of one isomer is thus a key point in this reaction. However, high regioselectivity to the branched product is essential for monosubstituted alkenes when enantioselectivity is required.[1c] For α-alkenes the interest is to obtain the linear product due to their application as detergents and surfactants.[13]

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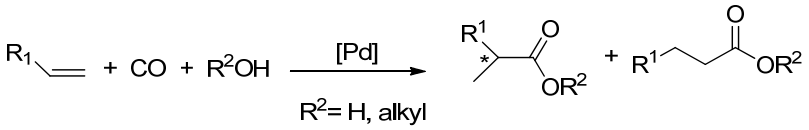
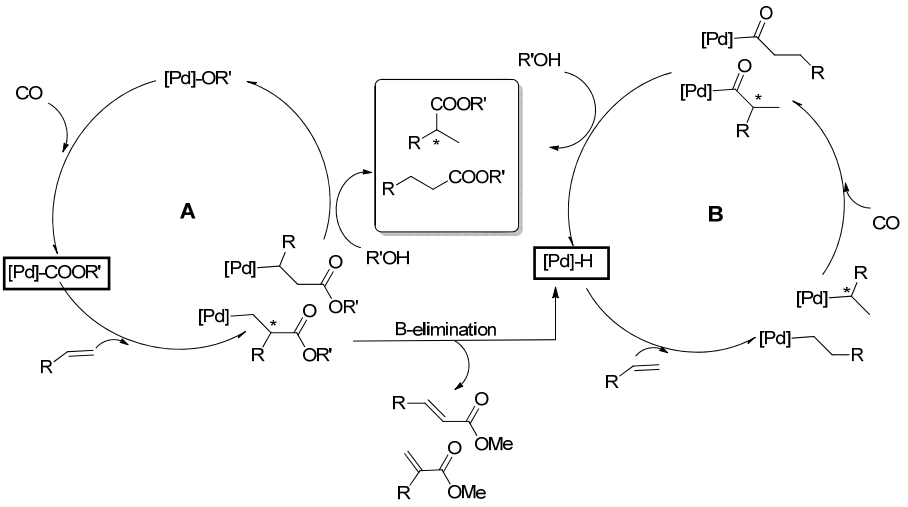


Scheme 1.2 General scheme for alkoxy- and hydroxycarbonylation of olefins.

Different palladium catalysts bearing chiral mono and bidentate ligands in the presence of acids have been developed.[14] For this process, most of the studies have reported the use of vinylarenes due to the interest in the preparation of non-steroidal drugs.[15] The asymmetric alkoxycarbonylation of vinyl acetate has also been reported by several groups.[16] In the last years however, the use of new substrates such as norbornene was also reported, due to the potential industrial applications in the cosmetic industry.[17]

1.1.1 Mechanism for the palladium-catalyzed alkoxycarbonylation of olefins

For the alkoxycarbonylation reaction, two mechanisms have been suggested.[3,18] The catalytic cycle can either start from an alkoxycarbonyl-palladium species (cycle **A**) or and hydrido-palladium complex (Cycle **B**) (Scheme 1.3). In the alkoxycarbonyl cycle, the alkene is inserted into the Pd-carbon bond of the alkoxycarbonyl-palladium complex, followed by alcoholysis to yield an alkoxy-palladium complex and the ester. Coordination and migratory insertion of CO then regenerate the initial alkoxycarbonyl-palladium complex. In the hydride cycle (cycle **B**), the first step is the coordination and insertion of the alkene into the Pd-H bond to form an alkyl complex, followed by coordination and migratory insertion of CO to produce a Pd-acyl species. Alcoholysis of the Pd-acyl regenerates the Pd-H complex and yield the ester. The production of the Pd-H species from complexes formed in Cycle **A** was also demonstrated to occur through the β-elimination of an unsaturated ester after alkene insertion.



Scheme 1.3 Proposed mechanisms for the Pd-alkoxycarbonylation of olefins.

In chapter 3, details about the mechanism and the elementary steps for the alkoxycarbonylation reaction will be discussed.

1.1.2 Asymmetric palladium-catalyzed alkoxycarbonylation of styrene and derivatives

The asymmetric alkoxycarbonylation of vinylarenes catalyzed by palladium complexes bearing chiral phosphine ligands has attracted much attention over the last decades.[1d,2,5] The reaction products are important intermediates in the synthesis of pharmaceuticals such as 2-arylpropionic acids, the most important class of non-steroidal anti-inflammatory drugs, particularly ibuprofen and naproxen.[15]

Catalysts containing bidentate diphosphine ligands have been frequently used for this reaction, but generally afford low regioselectivity to the branched product.[10] In 1997, a $PdCl_2$-$CuCl_2$-chiral diphosphine **1** (DDPPI) system (Figure 1.1) was reported to achieve 98% *ee* and 99% regioselectivity to the

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branched ester for the methoxycarbonylation of styrene.[19] This result, however, has not been reproduced.[5] In the same year, 86% *ee* was achieved by Inoue and co-workers together with a regioselectivity of 44% to the branched ester using $Pd(OAc)_2$ in the presence of a chiral diphosphine (S,R)-BPPFA **2** (Figure 1.1) and *p*-TsOH under mild conditions.[17b] Chan and co-workers reported the use of ferrocenyl phosphine containing oxazoline moieties in the same reaction and achieved 64% *ee* using the bidentate phosphine **3** (Figure 1.1) with $PdCl_2$ and *p*-TsOH. [20] Although this enantiomeric excess was relatively high, it should be noted that only 40% regioselectivity was obtained. More recently, Claver and co-workers reported the use of the families of ferrocenyl diphosphine from *Solvias* in the same reaction.[21] High enantioselectivities (up to 86% using ligand **4**) were achieved but the regioselectivities to ester were in all cases very low (*ca* 15%).

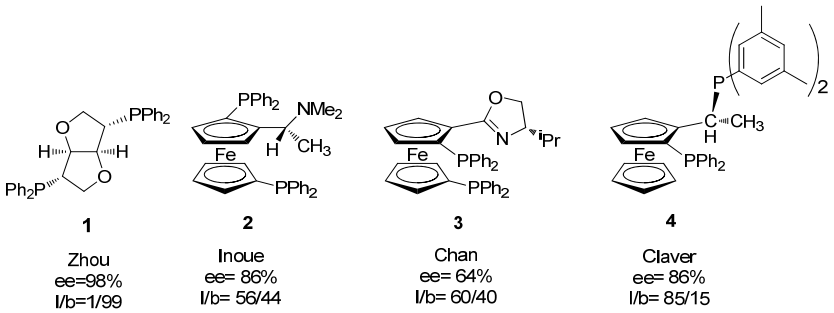

Figure 1.1 Bidentate ligands used in the methoxycarbonylation of styrene.

In the case of monodentate ligands, monophosphines have provided high regioselectivity to the branched ester, although the enantioselectivity is usually low. Cometti and Chiusoli reported that the use of the catalytic system $Pd(dba)_2$/NMDPP **5** (Figure 1.2)/CF_3COOH under mild conditions provided 52% *ee* and 95% regioselectivity to the branched ester.[22] In 1997, Nozaki and co-workers reported on the application of palladium complexes with binaphthol-derived phosphines **6** (Figure 1.2) in the methoxycarbonylation of

2-vinyl-6-methoxynaphthalene. [23] Using a catalytic system formed by $PdCl_2$ and 2 equivalents of **6** under mild conditions, 53% of *ee* were achieved for the branched ester. In 2005, systems containing phosphetane ligand **7** (Figure 1.2) were reported to yield high regioselectivity to the branched ester and *ee*'s up to 29% in the methoxycarbonylation of styrene.[24]

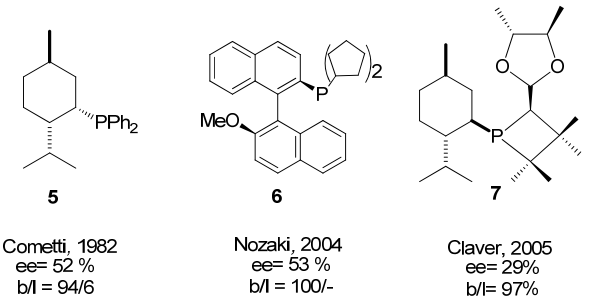

Figure 1.2 Monodentate phosphine ligands used in the methoxycarbonylation of vinylarenes.

1.1.3 Asymmetric palladium-catalyzed alkoxycarbonylation of norbornene

The palladium-catalyzed alkoxycarbonylation of [2.2.1] bicyclic olefins, such as norbornene (Scheme 1.4), presents an increasing interest for both academic and industrial research.[17]. This process however has been scarcely studied, although some reports appeared in the last years.[17]

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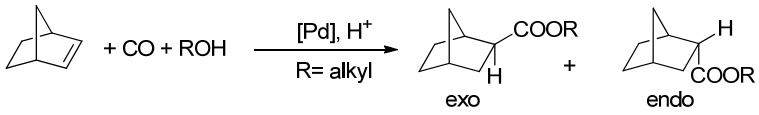
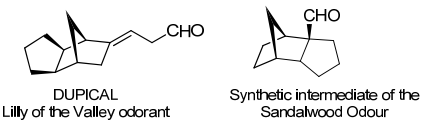


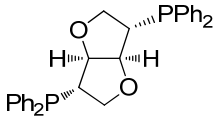
Scheme 1.4 Palladium-catalyzed alkoxycarbonylation of norbornene.

The functionalization of norbornene is important for the production of valuable compounds with potential applications in perfumery industry, such as Dupical® and Sandalwood odour (Scheme 1.5).[25] The alkoxycarbonylation of norbornene affords the formation of three carbon chiral centres upon one C-C bond formation. Due to its structure, there is no regio-selectivity issue, but instead *endo*/*exo* selectivities and enantioselectivities are significant. Furthermore, the versatile functional groups located opposite to the C=C bond, may lead to interesting building blocks.



Scheme 1.5 Functionalization of norbornene.

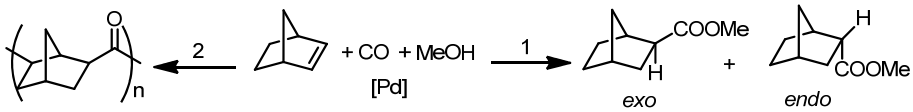
To the best of our knowledge, only a few studies had appeared on the palladium-catalyzed alkoxycarbonylation of norbornene. In 1996, Wang *et al.* were the first to report the asymmetric alkoxycarbonylation of norbornene by using $Pd(OAc)_2$/**1**/*p*-TsOH (**1**, Figure 1.3) as catalytic system obtaining 72% of chemoselectivity in ester and 92% *ee* (*exo* product) under 50 atm of CO at 120°C.[17c,d]. However, these results have not been reproduced under the given conditions, and the ether was obtained as the major product. In Wang's study the ether was obtained as by-product.



1

Figure 1.3 Chiral diphosphine DDPPI used by Wang and co-workers.

In 1997, Inoue *et al.* carried out the alkoxycarbonylation of different olefins using as catalyst the cationic palladium complexes $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ under 5 atm of CO at 100°C for 20 hours.[17b] For norbornene as substrate, the best chemoselectivity into ester obtained in this work was 74%. Both examples showed that chemoselectivity to ester is a difficult issue in the case of palladium catalyzed alkoxycarbonylation of norbornene. The control of selectivity is an important issue in this reaction, since different products such as esters and polyketones can be obtained. Polyketones are produced under alkoxycarbonylation conditions by alternating insertion of carbon monoxide and olefins (Scheme 1.6).[26]



Scheme 1.6 Alkoxycarbonylation (**1**) and copolymerization (**2**) of norbornene.

1.2 Palladium-catalyzed copolymerization of CO/olefins

1.2.1 Mechanism

The first mechanistic considerations were reported by Drent on the basis of end-group analysis of the copolymer.[27] The mechanism proposed in Scheme

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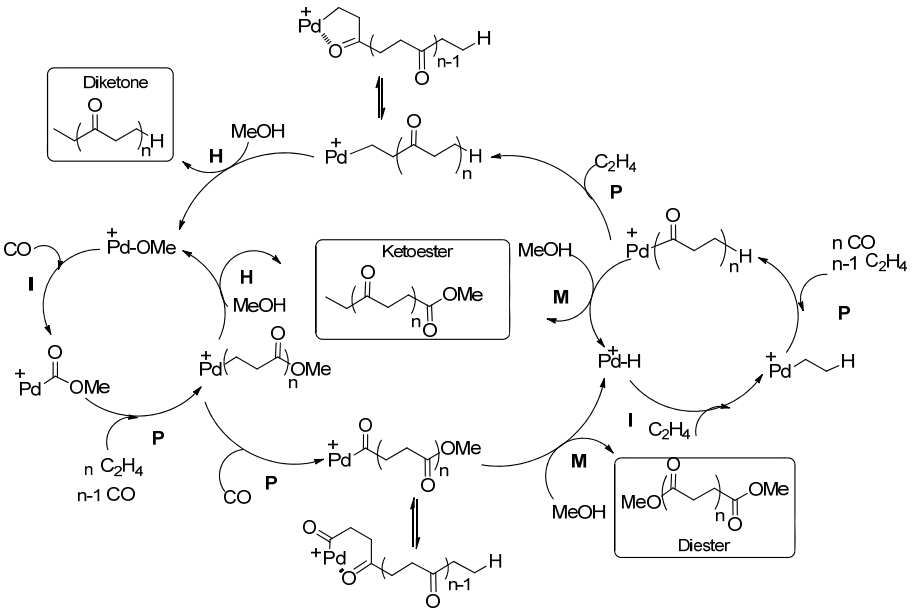
1.7 comprises two independent catalytic cycles (**A** and **B**), which can start from a palladium carbomethoxy species (cycle **A**) or a palladium hydride (cycle **B**). The cycle **A** starts from the insertion of CO into a Pd-methoxy bond to give a palladium carbomethoxy complex Pd-C(O)OMe. Multiple alternating alkene and CO insertions (**P**) and the subsequence termination step by methanolysis (**M**) or protonolysis (**H**) generate copolymers containing keto-ester or diester end groups. The cycle **B** starts with the insertion of alkene into a palladium hydride bond (**I**) and affords a palladium alkyl complex. The CO insertion into the Pd-alkyl bond is reversible and generates a Pd-acyl complex. The insertion of alkene into a Pd-acyl is rapid and irreversible, thus the propagation can take place by alternating insertions of CO and alkene (**P**). The CO insertion of alkene into a Pd-acyl bond is thermodynamically disfavoured. Successive insertions of alkene are limited due to the fact that the CO insertion into a palladium alkyl is reversible and faster than the alkene insertion.



Scheme 1.7 Proposed catalytic cycles for the copolymerization of CO/olefin. (ethene is used as a model alkene).

When copolymerization reaction is carried out in methanol, two possible chain transfer reactions (or termination steps) can produce copolymers with either keto-ester or diketone end groups, by methanolysis (**M**) of the Pd-acyl bond or protonolysis (**H**) of the Pd-alkyl bond, respectively (see chapter 3, section 3.1). However, when no chain transfer reagent, such as methanol, is present in the catalytic system, the common chain transfer is the β-hydrogen elimination.[28] The palladium complex containing an alkene group can suffer β-hydrogen elimination, releasing the polymer with unsaturated end group and generating a Pd-H complex (Scheme 1.8). The Pd-H complex will start a new chain with and alkyl end group.

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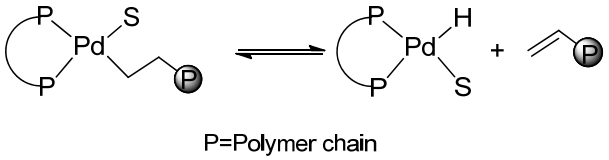


Scheme 1.8 β-hydrogen elimination as chain transfer mechanism.

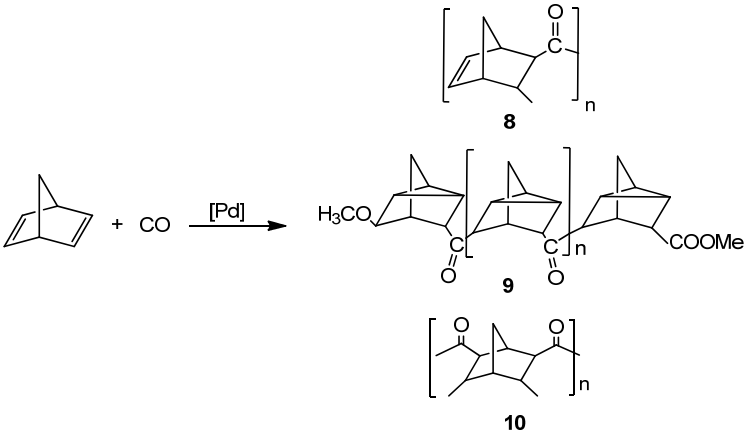
As it was shown for the mechanism of the alkoxycarbonylation reaction (section 1.1.1), the same steps of the catalytic cycle are presented in both processes being the only difference the multiple alternating insertion of olefin and carbon monoxide in case of copolymerization reactions. Thus, the active species Pd-H or Pd-COOMe for the copolymerization process can be generated as it is shown in Chapter 3 (section 3.1).

1.2.2 Palladium-catalyzed copolymerization of CO/norbornene and derivates

Copolymerization of carbon monoxide with norbornene and its derivates has been more studied than the palladium-catalyzed alkoxycarbonylation reaction.[12,29] Copolymerization of strained olefins, such as norbornene, is interesting because the resulting copolymers and cooligomers have unique structural feature and chemical properties.[30] On the other hand, strained olefins have revealed themselves as useful substrates to study the mechanism of insertion of the olefin into metal-acyl bond during the chain growth process (see below).[31]

The palladium catalyzed copolymerization of CO and strained olefins such as norbornene and norbornadiene dates back to the late 1960s when $PdCl_2$ was found to be an active catalyst for this reaction.[32] In 1965, Tsuji *et al.* reported the first copolymerization of carbon monoxide and norbornadiene in the presence of benzene and palladium dichloride as catalytic precursor. The

copolymer **8** (Scheme 1.9) was obtained as a white powder under 98 atm of CO at 50°C during 18 hours.[32a] Five years later, Graziani *et al.* reported the same reaction using methanol as solvent in the presence of palladium dichloride as catalytic precursor under 1 atm of CO at 25°C.[32b] Under these conditions, copolymer **9** (molecular weight=1850 $gmol^{-1}$, n=15) (Scheme 1.9) was identified by NMR spectroscopy.



Scheme 1.9 Palladium-catalyzed copolymerization of norbornadiene.

Later, Sen *et al.* described the synthesis of norbornadiene copolymers of relatively high molecular weight (3380 $gmol^{-1}$) (**8**, **10**, Scheme 1.9) and of norbornene cooligomer (350 $gmol^{-1}$) (**11**, Scheme 1.10) by catalysis with the phosphine-modified Pd complex $[Pd(CH_3CN)(PPh_3)_3](BF_4)_2$.[33] A similar Pd(II) catalyst containing two PPh_3 ligands, namely $[Pd(CH_3CN)_2(PPh_3)_2](BF_4)_2$, has been employed by Inoue *et al.* for the copolymerization of CO-norbornene. [34] Unlike the precursor with three phosphines, 2:2 cooligomers with enol-lactone structure and 3:3 cooligomers with ketal-lactone structure were obtained (**12, 13** Scheme 1.10). The ability of Pd(II) stabilized by triphenylphosphine to catalyze the copolymerization of CO and strained olefins has been exploited by Liaw for the synthesis of 1,3-

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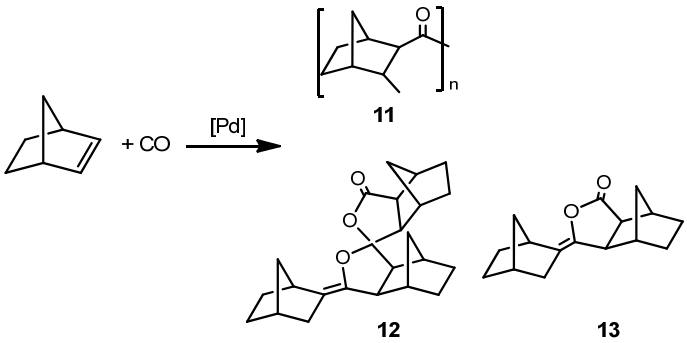
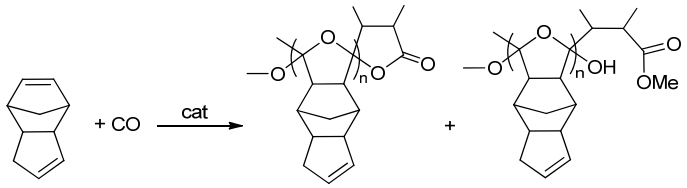
dicyclopentadiene-CO copolymers with 1,2- and 1,4-ketone ring structures. The catalytic system were prepared in situ from $[Pd(CH_3CN)_4](BF_4)_2$ and variable amounts of PPh_3.[35] Drent *et al.* were the first to use palladium (II) chelating dinitrogen ligands such a bipy to prepare active Pd(II) catalyst for the alternating copolymerization of CO and strained olefin.[36]



Scheme 1.10 Palladium-catalyzed copolymerization of norbornene.

The reactions with 1,3-dicyclopentadiene were carried out in methanol in the presence of 1,4-benzoquinone as organic oxidant and yielded a polyketone product with a spiroketal backbone structure[36] (Scheme 1.11).



Scheme 1.11 Polyspiroketal products by alternating copolymerization of CO and strained olefins.

The chelating P-N ligand *o*-(diphenylphosphino)-N-*p*-fluorobenzaldimine has been reported to form catalyst of the formula $[Pd(P\text{-}N)(CH_3)(CH_3CN)]BF_4$ which yield high molecular weight CO-norbornene copolymers (M_w= 2.5 Kg

mol^{-1}) in aprotic solvents.[37] Recently, *Li et al.* reported the use of $PdCl_2$/phen/$M(CF_3SO_3)_n$ (where M=La, Y, Yb, Zn and Cu) as catalytic system for the copolymerization of norbornene with CO to prepare polyketone.[38] It was found that 1,10-phenanthroline (phen) and $Cu(CF_3SO_3)_2$ exhibit the highest activity. Copolymer of molecular weight 1090 gmol^{-1} was obtained when the reaction was carried out in methanol at 90°C and 30 atm of CO. According to the different end groups, three termination modes (see section 1.2.1) were identified (**14**, **15**, and **16**) in the norbornene/CO copolymers as it is shown in Figure 1.4.

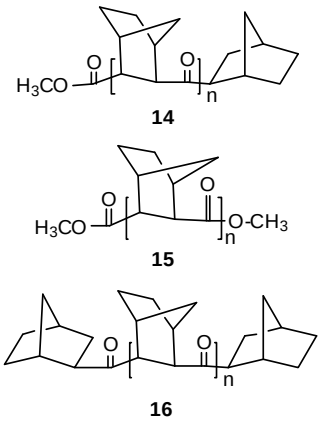


Figure 1.4 Copolymer CO-norbornene obtained by Li *et al.*

As previously mentioned, many models studies aimed at elucidating the elementary steps of CO/olefin copolymerizations catalyzed by metal systems have successfully been carried out with the use of strained olefins in aprotic media. The products resulting from the insertion olefins such as norbornene and norbornadiene do not contain β-hydrogens accessible to the metal center.[31] This makes the inserted product quite stable.

Elsevier et al, have studied the sequential insertions of CO and norbornene, norbornadiene and dicyclopentadiene into Pd-alkyl and Pd-acyl bonds

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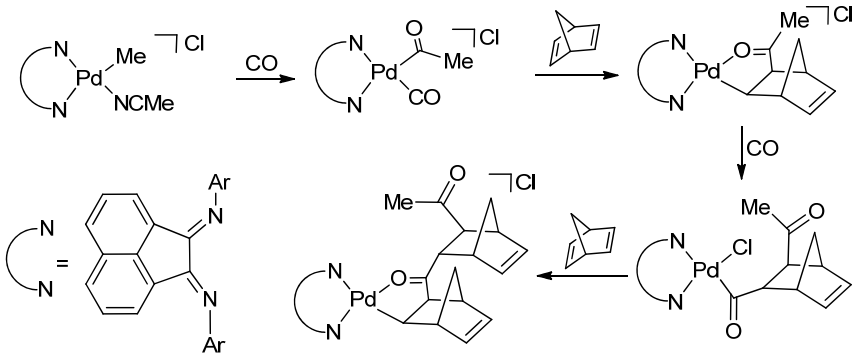
supported by the rigid backbone dinitrogen ligands such as Ar-BIAN (Scheme 1.12).[39]

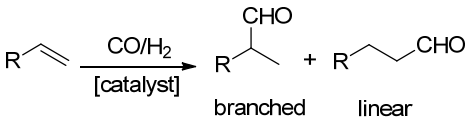


Scheme 1.12 Sequential insertion of norbornadiene into Pd-alkyl and Pd-acyl bonds.

The Pd complexes isolated after olefin insertion were found to have a similar structure arising from *cis* addition of PdC(O)R to the *exo* face of the olefin. Further studies of the insertion of CO and various norbornenes into Pd-alkyl and Pd-acyl bonds, respectively, have been reported by Boersma, van Koten *et al* for Pd(II) complexes stabilized by bipy.[40] These authors confirmed that the *cis*, *exo* insertion of the olefin is both stereo- and chemoselective and showed the first example of reversible olefin insertion in a isolated Pd(II) complex as well as the first isolated CO/olefin cooligomer connected to a Pd(II) center.

1.3 Rhodium-catalyzed hydroformylation of olefins

Hydroformylation –also called oxo-process- is the reaction of an alkene with synthesis gas (CO/H_2) to form aldehydes in the presence of a catalyst (Scheme 1.13). This reaction was discovered by Otto Roelen in 1938 during his research on cobalt-catalyzed Fischer-Tropsch reactions.[41] In the case of substituted substrates, both the branched and the linear aldehyde can be formed.



Scheme 1.13 Metal-catalyzed hydroformylation of olefins.

Nowadays, hydroformylation is one of the most important homogeneously catalyzed reactions in industry; more than 8 million tons of hydroformylation-product are produced per year.[8] The most important processes in industry are the rhodium-catalyzed hydroformylation of propene and 1-butene and the cobalt-catalyzed hydroformylation of iso-octenes.[8] Although most of the aldehydes are converted into alcohols and used as detergent or plasticizer alcohols, aldehydes are interesting products for fine chemistry, for example for fragrances and vitamins.[7,8] Moreover, the aldehyde functionality is a very versatile group, which can be converted to acids or amines, alcohols, esters (Scheme 1.14).

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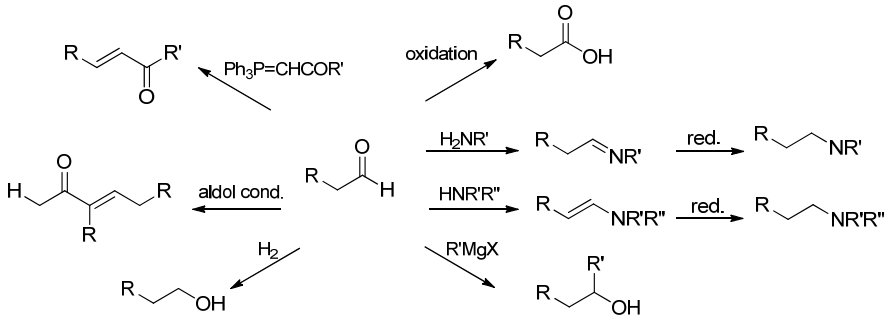


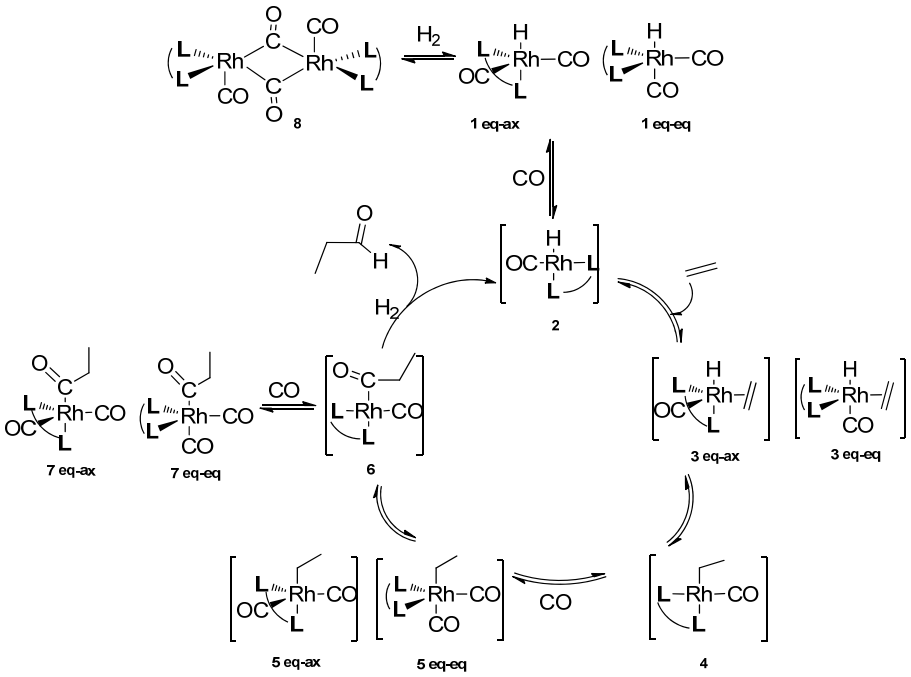
Scheme 1.14 Aldehydes as versatile intermediates in organic synthesis.

1.3.1 Mechanism for the Rh-catalyzed hydroformylation of olefins

The mechanism of the hydroformylation reaction has been widely studied.[1a,42] The rhodium-catalyzed hydroformylation proceeds via the same mechanism, which is also known as the dissociative mechanism as it is shown for ethene in Scheme 1.15.[43] For bidentate ligands (L-L) the common starting complex is [RhH(L-L)$(CO)_2$], complexes **1eq-eq** and **1eq-ax,** containing the ligand coordinated in equatorial positions (denoted eq-eq in the Scheme) or in axial-equatorial positions (complexes denoted **eq-ax**). Dissociation of equatorial CO from complex **1** leads to the square-planar intermediate **2**, which associate with alkene to give complexes **3**, where the ligand can again be coordinated in two isomeric forms **eq-ax** and **eq-eq,** having a hydride in an axial position and alkene coordinated in the equatorial plane.

Complexes **3** undergo migratory insertion of the alkene into the rhodium-hydride leading to the square-planar alkyl complex **4.** This species can undergo β-hydride elimination, thus leading to isomerisation, or can react with CO to form the trigonal bipyramidal (TBP) complexes **5**. Complex **5** undergo the second migratory insertion to form the acyl complex **6,** which can react with CO to give saturated acyl intermediates **7** or with H_2 to give the aldehyde

product and the unsaturated intermediate **2.** The reaction with H_2 involves presumably oxidative addition and reductive elimination.[44] Apart from the hydrogenolysis step, all the elementary steps in the catalytic cycle are reversible.



Scheme 1.15 Mechanism of the Rh-asymmetric hydroformylation in presence of bidentate ligand (L-L).

1.3.2 Asymmetric Rh-catalyzed hydroformylation of monosubstituted alkenes

The hydroformylation of monosubstituted alkenes has been extensively studied due to the interest in the synthesis of linear aldehydes (non-chiral) or the enantioselective synthesis of 2-substituted branched aldehydes using hydroformylation catalysts.[45,46] For example, 2-aryl propionic acids can be

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synthesized enantioselectively starting from vinyl arenes. Similar compounds, such as (S)-Naproxen are important products in the pharmaceutical industry. Nowadays, the application of the Rh-catalyzed asymmetric hydroformylation of several other monosubstituted alkenes was successfully carried out, such as allyl cyanide and vinyl acetate.[1b,45,46] In general 1,3-diphosphite and phosphine-phosphite ligands provided the best results in these processes.[1a]

The initial success in the rhodium-catalyzed asymmetric hydroformylation of vinylarenes came from Union Carbide with the discovery of the diphosphite ligand (2R,4R)-pentane-2,4-diol (Figure 1.5, **17**). Good chemo-, regio- and enantioselectivities (ee up to 90%) have been obtained with this ligand in the Rh-catalyzed the hydroformylation of styrene.[47] The use of 1,3-diphosphite ligands **18** and **19** (Figure 1.5) were successfully applied in the Rh-catalyzed asymmetric hydroformylation of styrene yielding high enantioselectivities (ee up to 93%) and excellent regioselectivity.[48] Recently, related C1-symmetry diphosphite ligands conformationally more flexible than ligands **17** and **18** (Figure 1.5, **20**, **21**, **22**) or incorporating an increase in steric hindrance at the C-6 position (Figure 1.5, **23**, **24**) were probed in the hydroformylation of styrene and vinyl acetate with good- regio and enantioselectivity (up to 81% and 68%, respectively),[49] but these selectivities resulted to be lower than with ligand **17**.
The catalytic system containing ligand **25** (Figure 1.5) afforded very good enantioselectivity in the rhodium-catalyzed hydroformylation of vinyl acetate and allyl cyanide, although low selectivities were obtained in the hydroformylation of styrene.[50]
The development of the (R,S)-BINAPHOS (**26**) and (S,R)-BINAPHOS (**27**) ligands (Figure 1.5) in 1993 by Takaya and Nozaki was a very important discovery in the rhodium-catalyzed asymmetric hydroformylation.[51] Up to 95% ee together with a high regioselectivity towards the branched product was

obtained in the hydroformylation of styrene and a range of others substrates using Rh/BINAPHOS systems.[52]

Diphosphine ligand such as (S)-BINAPINE and Esphos (Figure 1.5, **28**, **29**, respectively), were found to give excellent enantioselectivities in the asymmetric hydroformylation of styrene, allyl cyanide, and vinyl acetate.[53]

The Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes has received much less attention than their monosubstituted counterpart. To the best of our knowledge, only a few examples of asymmetric Rh-catalyzed hydroformylation of 1,2-disubstituted and 1,1-disubstituted alkenes have been reported so far. [54,55]

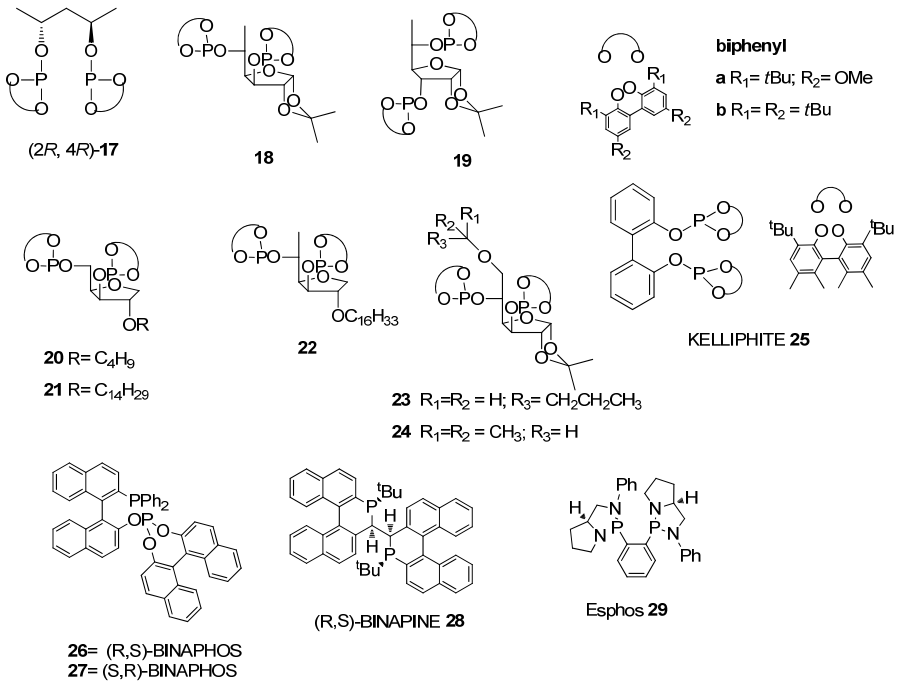

Figure 1.5 Phosphorus ligands used in the asymmetric hydroformylation reaction.

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1.3.3 Asymmetric Rhodium-catalyzed hydroformylation of norbornene

The asymmetric hydroformylation of bicyclic olefins such as norbornene has received a few attention although some reports appeared in the last years.[56-60] The first report on this process appeared in 1986 when Parrinello and co-workers obtained 26% *ee* and 88% of chemoselectivity to the *exo*-aldehyde using $PtCl_2$/DBP-DIOP **30** (Figure 1.6)/$SnCl_2$ as the catalytic system.[56] They later reported the use of the chiral ligand BPPM **31** (Figure 1.6) in the same reaction affording 60% *ee* using $PtCl_2$-$SnCl_2$ system under 186 bar *syn* gas at 30°C for 20 hours.[57] The use of the chiral ligand ABDPP **32** (Figure 1.6), derived from D-glucose was reported by Wang and co-workers in the rhodium-catalyzed hydroformylation of norbornene. Low enantioselectivities (22-25%) were achieved using $[RhCl(COD)]_2$ as precursor under 60 bar *syn* gas 80°C during 24 hours.[58]

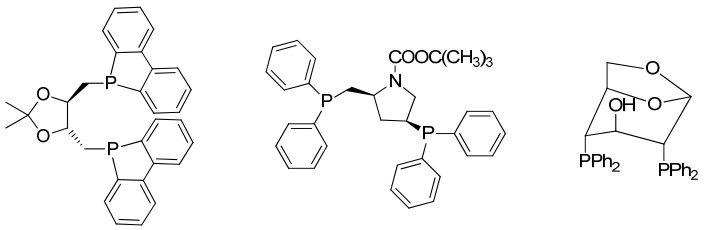

Figure 1.6 Ligands used in asymmetric metal-hydroformylation of norbornene.

In 2005, Bunel and co-workers reported the first highly enantioselective Rh-hydroformylation of norbornene into the *exo* aldehyde with ee's up to 92% using the diphospholane ligands **33** and **34** (Figure 1.7). However, the reaction rates are very low (TOF $8h^{-1}$) for these catalytic systems. Using these ligands, they also reported the hydroformylation of several derivatives of this substrate with similar enantioselectivities (Scheme 1.16).[59]

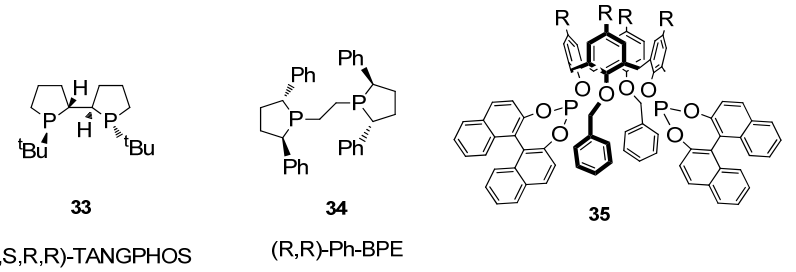

Figure 1.7 Bidentate ligands used in the asymmetric Rh-hydroformylation of norbornene.

More recently, the hemispherical diphosphite ligands **35** (Figure 1.7) with a conical calixarene skeleton was used in the asymmetric Rh-hydroformylation of norbornene, achieving enantioselectivities up to 61% with the *exo*-aldehyde being the major product.[60] Interestingly, when this reaction was carried out in water, mainly the *endo*-aldehyde product was formed, thus contrasting with previous experiments performed in toluene.[61] Under these conditions, the enantioselectivities were moderate (up to 39 %).

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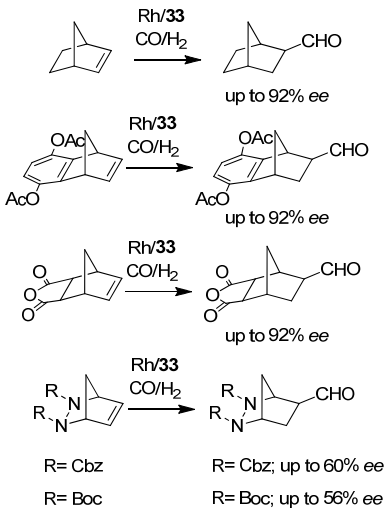

Scheme 1.16 Rh-catalyzed asymmetric hydroformylation of norbornene and derivates using ligand **33**.

1.4 Objectives and Scope

Carbonylation reactions haven been widely investigated in the OMICH (Organometallic and Homogeneous Catalysis) group Department of Physical and Inorganic Chemistry at the University Rovira i Virgili.

Both Pd-catalyzed methoxycarbonylation and Rh-catalyzed hydroformylation reactions have been object of contributions and revisions on this research group. The substrates investigated as benchmark in these processes have been mainly styrene and related vinylarenes. Therefore, the aim of the present thesis is to investigate the carbonylation (both Pd-catalyzed methoxycarbonylation and Rh-catalyzed hydroformylation) of a new challenging substrate scarcely studied: Norbornene. The transformation of this substrate in esters and aldehydes offers potential applications for the production of valuable compounds and intermediates in fine chemistry.

To achieve this goal the following objectives are proposed:

1. To study the catalytic behaviour of Pd complexes bearing monodentate and bidentate phosphine ligands, in order to control the selectivity in the palladium-catalyzed methoxycarbonylation of norbornene.
2. To explore the effect of the reaction conditions, in the palladium methoxycarbonylation of norbornene using catalytic systems modified with mono- and bidentate phosphine ligands.
3. To investigate some mechanistic aspects of the palladium-catalyzed methoxycarbonylation of norbornene using palladium systems NMR methods, including High-Pressure techniques.
4. To apply diphosphite ligands derived from carbohydrates, in the rhodium-catalyzed hydroformylation of norbornene.

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Chapter 2

Pd-Catalyzed Carbonylation of Norbornene

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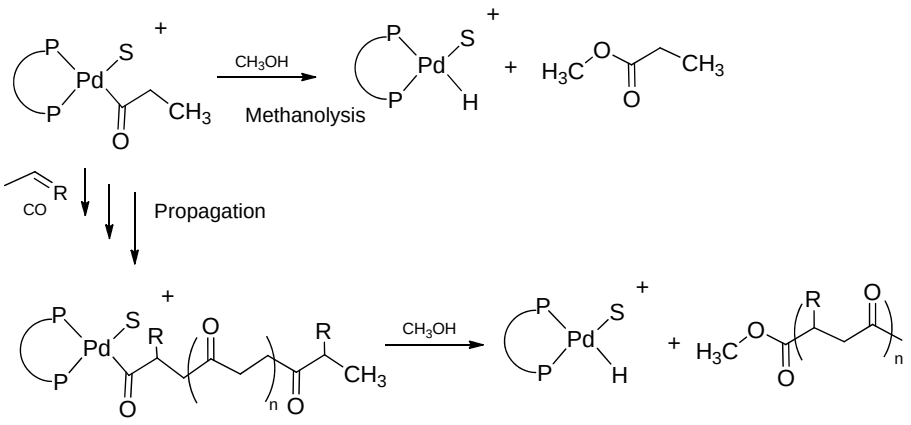
2.1 Effect of catalyst precursors and reaction parameters

2.1.1 Background

The alkoxycarbonylation of olefins belongs to a family of industrially relevant carbonylation reactions that are efficiently catalyzed by homogeneous palladium complexes.[1] Despite the limited number of starting materials, minor changes in the catalytic system and/or the reaction conditions greatly affect the selectivity, leading to the formation of a variety de products spanning from esters, ethers, di-esters, and polyketones.[2] Copolymerization is a competing reaction for alkoxycarbonylation that usually takes place under similar conditions. The mechanistic steps, initiation, insertion and termination, are similar for both reactions.[2a] In copolymerization reaction the termination step can occurs through three different ways: methanolysis, protonolysis and β-hydrogen elimination. The main difference between alkoxycarbonylation and copolymerization mechanism is the number of multiple insertions of CO and olefin in case of copolymers (propagation step). Thus, the control of the chemoselectivity of the reactions for the formation of ester or copolymers depends on the propagation *vs* chain termination steps. In each case, after the first olefin/CO insertion, there are two possibilities: a) termination by methanolysis to form an ester, or b) propagation of the chain by multiple alternating olefin/CO insertions to form cooligomers or copolymers. The Scheme 2.1 shows the two steps on the basis that the first olefin insertion occurs into a palladium hydride.



Scheme 2.1 Methanolysis *vs* Propagation steps.

The chemoselectivity issue has attracted the attention of many scientists for years.[2] Initially, it was concluded that monodentate ligands such as triphenylphosphine favour the methoxycarbonylation of ethene to give methylpropanoate while catalyst modified with cationic palladium bidentate phosphine ligands such as dppe, dppp, and dppb lead to polyketones.[3] For the latter system, it was shown that a variation of chain length between the phosphine groups, results in significant changes in both the rate and the molecular weight of copolymer product.[4] Subsequently, it has been shown that the chemoselectivity of the reaction can be controlled by the appropriate choice of the diphosphine ligand, methoxycarbonylation of ethene being favoured by sterically hindered diphosphines.[5] Actually, the best ligand for methyl propanoate formation is probably d^{t}bpx (1,2bis-(di-tert-butylphosphinomethyl)benzene) which is being used in the Pd methoxycarbonylation of ethene developed by Lucite International.[6] The use of diphosphines such as DIOP, BINAP in presence of palladium precursor, have shown to afford high selectivity in the alternating copolymerization of propene and carbon monoxide. These catalysts have allowed the formation of

copolymers with high molecular weight providing access to a potentially interesting class of new materials.[7] High selectivity to the ester formation in the alkoxycarbonylation of propene has been reported using palladium catalyst bearing monophosphines such as bis(2,4-dimethylphenyl)phenylphosphine and triphenylphosphine.[8] Typically, palladium complexes with bidentate nitrogen ligands (e.g. 2.2'-bipyridine or 1.10-phenanthroline) in presence of noncoordinating anions catalyze efficiently the alternating copolymerization of styrene and carbon monoxide[9] whereas Pd systems with monodentate[10] and bidentate phosphine ligands[11] catalyze the alkoxycarbonylation of styrene. For cyclic alkenes, such as cyclohexene it has been shown that cationic palladium complex bearing triphenylphosphine provided high activity and selectivity to the ester formation.[12]

In the case of bicyclic alkenes, such as norbornene, monodentate phosphine and bidentate nitrogen ligands have been effective in the copolymerization reaction with carbon monoxide.[13] About the alkoxycarbonylation of norbornene, there is not studies enough to conclude about the trend of the ligand to the ester formation.

As mentioned, the choice of the ligand, catalytic system, and the optimization of reaction conditions allow the predominant formation of the ester or polyketone.

For this reason, in this work, our objective has been to study the effect of using both monodentate (**1**) and bidentate phosphine (**2-4**) ligands (Figure 2.1) in the selectivity of the palladium-catalyzed alkoxycarbonylation of norbornene. We have chosen phosphines because these ligands have shown to be efficient in many alkoxycarbonylation reactions.[14]

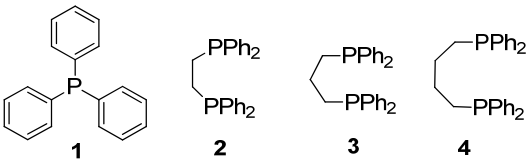


Figure 2.1 Ligands used in this study.

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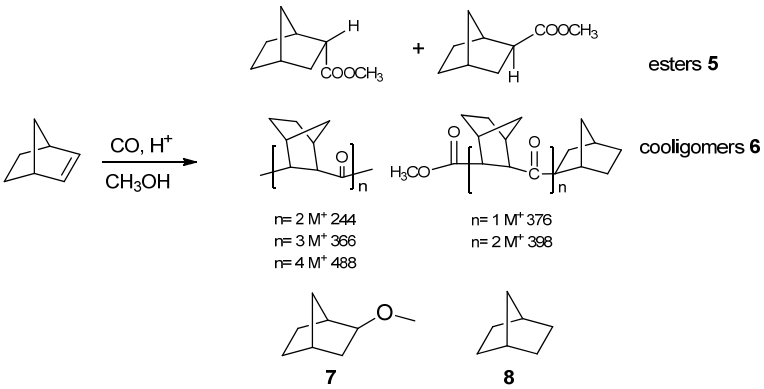
2.1.2 Results and Discussion

Study of the reaction conditions

The screening of the reaction conditions (acid, solvent, alcohol, and palladium precursor) for the palladium-catalyzed methoxycarbonylation of norbornene was performed using triphenylphosphine **1**, which is an available ligand generally used in homogeneous catalysis as model. The catalytic results will be discussed in this section.

Effect of the acid

It has been observed that in the palladium-catalyzed methoxycarbonylation reaction the presence of acid is required in order to favour the formation of Pd-H species.[15] We have studied the effect of the acid with different pKa in this reaction using norbornene as substrate. The catalytic reactions were carried out under 30 bars of CO during a period of 24 hours at 70°C in CH_3OH/THF as a mixture solvent. Similar reaction conditions have been previously used in the Pd-catalyzed methoxycarbonylation of styrene.[11b,16] The results are summarized in Table 2.1 and the products and obtained are shown in Scheme 2.2.



Scheme 2.2 Products observed in the Pd-catalysed methoxycarbonylation of norbornene.

When the reaction was performed in the absence of acid no conversion was obtained (Table 2.1, entry 1). Conversions decrease in the order pTsOH=TFA>$C_2O_4H_2$>HCOOH=CH_3COOH which indicates that the best conversions were obtained with the strongest acids (Table 2.1, entries 2-6).

Table 2.1 Effect of the acid promotor[a]

Entry	Acid	pKa	%C[b]	%5[b]	%6[b]	%7[b]	%9[c]
1	-	-	0	-	-	-	-
2	p-TsOH	-2.7	99	29	20	10	41
3	TFA	-0.5	99	35	32	8	25
4	$C_2O_4H_2$	1.2	97	36	54	-	10
5	HCOOH	3.8	49	10	70	8	8
6	CH_3COOH	4.8	49	9	62	-	29

[a] Reaction Conditions: $Pd(OAc)_2$: 0.021 mmol, PPh_3: 0.042 mmol, acid: 0.210 mmol, NBN: 1.05 mmol, CH_3OH/THF (1:1) 5ml, 24 h, 70°C, 30 bars of CO. [b] The data on conversion and chemoselectivities of **5**, **6**, and **7**, were determined by GC and GC-MS analysis. [c] **9=** unidentified oligomeric by-products.

Concerning chemoselectivity to ester, the best results were obtained with trifluoroacetic acid TFA (35%) and oxalic acid $C_2O_4H_2$ (36%) (Table 2.1, entries 3 and 4). When formic acid (HCOOH) was used, the chemoselectivity was poor and cooligomers were obtained (70%) (Table 2.1, entry 5).

As described in Table 2.1, the reaction was not chemoselective and in all cases, a mixture of esters (**5**), and others by-products such as cooligomers (**6**), were detected (Scheme 2.2). Under acidic conditions 2-methoxybicyclic [2.2.1]heptane **7** (Scheme 2.2) was also observed. Etherification products are formed by the acid-catalyzed Michael addition of CH_3OH to olefins.[17]

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Effect of the palladium precursor

The effect of different palladium precursors such as $Pd(OAc)_2$, $PdCl_2$ and $Pd_2(dba)_3$ was studied in the palladium-catalyzed methoxycarbonylation of norbornene. Taking into account the results shown in the previous experiments (Table 2.1), $C_2O_4H_2$ and TFA, which provided the best chemoselectivity to ester, were used as acid. The catalytic reactions were carried out using ligand **1** under 30 bars of CO during a period of 24 hours at 70°C in a mixture of CH_3OH/THF. The results obtained are summarized in Table 2.2.

Table 2.2 Effect of the palladium precursor[a]

Entry	Precursor	% C[b]	%5[b]	%6[b]	%7[b]	%8[b]	%9[c]	% *exo/endo*
1[d]	$Pd(OAc)_2$	99	35	32	8	-	25	nd
2[e]	$Pd(OAc)_2$	97	36	54	-	-	10	60:40
3[d]	$PdCl_2$	45	25	61	7	-	6	65:35
4[e]	$PdCl_2$	98	31	55	-	8	6	35:65
5[d]	$Pd_2(dba)_3$	67	10	63	-	15	12	75:25
6[e]	$Pd_2(dba)_3$	97	47	38	-	10	5	50:50

[a] Reaction Conditions: Pd: 0.021mmol, PPh_3: 0.042mmol, acid: 0.210 mmol, NBN: 1.05 mmol, CH_3OH/THF (1:1) 5ml, 24 h, 70°C, 30 bars of CO. [b] The data on conversion and chemoselectivities of **5**, **6**, **7**, **8** were determined by GC and GC-MS analysis. [c] **9**= unidentified oligomeric by-products. [d] TFA. [e] $C_2O_4H_2$.

Excellent conversions (up to 98%) were obtained with all palladium precursors in presence of $C_2O_4H_2$ (Table 2.2, entries 2, 4, and 6). Excellent conversion (99%) was obtained with $Pd(OAc)_2$ in presence of TFA (Table 2.2, entry 1) and

moderate (up to 67%) with $PdCl_2$ and $Pd_2(dba)_3$ in presence of TFA (Table 2.2, entries 3, 5).

In terms of chemoselectivity, a mixture of products between ester and cooligomers were obtained. The best chemoselectivity to ester (47%) was obtained in the presence of $Pd_2(dba)_3/PPh_3/C_2O_4H_2$ as a catalytic system (Table 2.2, entry 6). When Pd(II) precursors were used, the chemoselectivities in ester ranged between 25 and 36% (Table 2.2, entries 1-4).

In general, cooligomers were the major products identified under these conditions except for the catalytic systems $Pd(OAc)_2/PPh_3$/TFA and $Pd_2(dba)_3/PPh_3/C_2O_4H_2$ (Table 2.2, entries 1 and 6) in which esters *exo*, *endo* were the major products. However, the highest formation of cooligomers (70%) was still obtained with $Pd(OA)_2/PPh_3$/HCOOH catalytic system (Table 2.1, entry 5).

In terms of stereoselectivity a mixture of *exo*/*endo* isomers was obtained in all cases. The best value to the *exo*-isomer formation was achieved using $Pd_2(dba)_3/PPh_3$/TFA (75:25 *exo*/*endo*). However, the chemoselectivity to ester was only 10% (Table 2.2, entry 5). When $PdCl_2/PPh_3/C_2O_4H_2$ was used as a catalytic system the highest stereoselectivity to the *endo*-isomer (35:65 *exo*/*endo*) was achieved (Table 2.2, entry 4).

In summary, the best palladium precursor to favour the ester formation was $Pd_2(dba)_3$ in presence of $C_2O_4H_2$ and, $Pd_2(dba)_3$ in presence of TFA to favour the copolymerization reaction.

Influence of the methodology used to form the catalyst

The effect of using the isolated system $[PdCl_2(PPh_3)_2]$ or the $PdCl_2/PPh_3$ *in situ* system in the presence of TFA and $C_2O_4H_2$ was investigated in the palladium-catalyzed methoxycarbonylation of norbornene. The catalytic results are listed in Table 2.3.

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In presence of both the isolated $[PdCl_2(PPh_3)_2]$ and the *in situ* $PdCl_2/PPh_3$ system (Table 2.3, entries 1, 2 and 4) practically total conversion was obtained. However, when the *in situ* $PdCl_2/PPh_3$/TFA system was used, the conversion was moderate (Table 2.3, entry 3). The best chemoselectivity to ester (53%) (Table 2.3, entry 1) was obtained when the isolated system $[PdCl_2(PPh_3)_2]$ was probed in presence of TFA. High stereoselectivity was also obtained with this system (75:25 *exo/endo*) (Table 2.3, entry 1). As in the previous cases, co-olygomers have been observed. When $PdCl_2/PPh_3$/TFA was tested as a catalytic system, high selectivity (61%) to the cooligomers formation was achieved (Table 2.3, entry 3).

Table 2.3 Isolated system $[PdCl_2(PPh_3)_2]$ *vs in situ* system $PdCl_2/PPh_3$[a]

Entry	Catalyst	%C[b]	%5[b]	%6[b]	%9[c]	%*exo/endo*
1[d]	$[PdCl_2(PPh_3)_2]$	99	53	47	-	75:25
2[e]	$[PdCl_2(PPh_3)_2]$	99	35	51	14	75:25
3[d]	$PdCl_2/PPh_3$	45	25	61	14	65:35
4[e]	$PdCl_2/PPh_3$	98	31	55	14	35:65

[a] Reaction Conditions: Pd/L: 1/2, acid: 0.210 mmol, NBN: 1.05 mmol, CH_3OH/THF (1:1) 5ml, 24 h, 70°C, 30 bars CO. [b] The data on conversion and chemoselectivities of **5**, **6** were determined by GC and GC-MS analysis. [c] **9** = unidentified oligomeric by-products [d] TFA. [e]$C_2O_4H_2$.

Effect of the alcohol

It has been observed that the alkoxycarbonylation reaction is carried out in a mixture of solvents to perform the catalysis.[11b,16] Typically, THF is used in conjunction with an alcohol responsible of the final step to the formation of ester.[5,18] In this section, using $[PdCl_2(PPh_3)_2]$ and $Pd(OAc)_2/PPh_3$ as palladium

precursors, the effect of different alcohols using THF as co-solvent will be discussed. The catalytic results obtained are listed in Table 2.4.

Table 2.4 Effect of the alcohol (THF is used as co-solvent)[a]

Entry	Catalysts	ROH/THF	%C[b]	%5[b]	%6[b]	%9[c]	%10[b]
1[d]	$[PdCl_2(PPh_3)_2]$	CH_3OH	99	53	47	-	-
2[e]	$[PdCl_2(PPh_3)_2]$	CH_3OH	99	35	51	14	-
3[d]	$[PdCl_2(PPh_3)_2]$	CF_3CH_2OH	100	25	69	6	-
4[e]	$[PdCl_2(PPh_3)_2]$	CF_3CH_2OH	95	19	66	5	10
5[d]	$Pd(OAc)_2/PPh_3$	CH_3OH	99	35	32	25	8
6[e]	$Pd(OAc)_2/PPh_3$	CH_3OH	97	36	54	10	-
7[d]	$Pd(OAc)_2/PPh_3$	CF_3CH_2OH	51	0	48	42	10
8[e]	$Pd(OAc)_2/PPh_3$	CF_3CH_2OH	32	0	20	67	13

[a] Reaction Conditions: Pd/L: 1/2, acid: 0.210 mmol, NBN: 1.05 mmol, alcohol/THF (1:1) 5ml, 24 h, 70°C, 30 bars of CO. [b] The data on conversion and chemoselectivities of **5**, **6**, and **10** were determined by GC and GC-MS analysis. [c] **9**= unidentified oligomeric by-products. [d]TFA. [e] $C_2O_4H_2$.

When CH_3OH was used in the presence of the isolated palladium system $[PdCl_2(PPh_3)_2]$ with TFA and $C_2O_4H_2$ (Table 2.4, entries 1 and 2) excellent conversions were obtained (99%). The best chemoselectivity to ester (53%) was achieved with the palladium system $[PdCl_2(PPh_3)_2]$/TFA (Table 2.4, entry 1). When CF_3CH_2OH was used instead of CH_3OH conversions remained high (95-100%) (Table 2.4, entries 3 and 4). However, the chemoselectivity to ester was found to decrease considerably (Table 2.4, compare entries 1, 2 *vs* entry 3, 4). Moderate selectivity to cooligomers (69%) was obtained using CF_3CH_2OH in presence of $[PdCl_2(PPh_3)_2]$/TFA (Table 2.4, entry 3).

When CH_3OH was used as solvent in the presence of the *in situ* palladium system $Pd(OAc)_2/PPh_3$/TFA or $C_2O_4H_2$ (Table 2.4, entries 5 and 6) high conversions between (97-99%) together with moderate chemoselectivity to ester were achieved (35-36%). When CF_3CH_2OH was used instead of CH_3OH with $Pd(OAc)_2/PPh_3$ systems in presence of TFA and $C_2O_4H_2$, a significant decrease in both conversion and chemoselectivity to ester was observed (Table 2.4, entries 7 and 8).

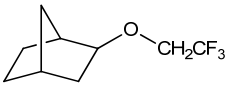

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Figure 2.2 Ether formed during the methoxycarbonylation of norbornene in presence of trifluoroethanol.

In general, both isolated palladium system and the *in situ* system, trifluoroethanol favour the copolymer formation (Table 2.4, entries 3-4 and 7-8), driving to a significant decrease in chemoselectivity to ester. These results are in agreement with previously reported by Milani and co-workers where CF_3CH_2OH was used as a solvent to favour the palladium-copolymerization CO-styrene.[19]

Effect of the ligand: Monodentate *vs* Bidentate phosphine systems

Looking for more selective systems for the Pd methoxycarbonylation of norbornene we decided to study the effect of using bidentate ligands in this reaction. The most obvious difference between monodentate and bidentate ligands is that the latter are always *cis* coordinated, whereas the former can also coordinate in a *trans* fashion.[2a] If bidentate phosphines are used, the starting (or growing) polymer chain and the fourth coordination site are always *cis* to

each other, which is the most favourable position for insertion reactions. If monodentate phosphines are used, both Pd-alkyl and Pd-acyl species prefer a *trans* orientation for steric reasons.[2a] In fact, it has been shown by NMR spectroscopy that $[PdCl_2(Ph_3)_2]$ complex exist preferentially in a *trans* orientation and no detection of *cis*-isomer has been observed.[20]

To study the behaviour of diphosphines as ligands, different neutral palladium dichloride complexes with diphosphines **2**, **3**, and **4** (Figure 2.1) were tested in this reaction. In all cases, diphosphines in presence of $C_2O_4H_2$ provided very poor conversions. In order to increase the solubility of these systems in the medium, cationic palladium complexes containing ligands **2-4** were synthesized by reaction between the neutral palladium dichloride complexes and AgOTs in dichloromethane. The catalytic reactions using these complexes were carried out in the absence of acid because it has been suggested that these complexes can generate palladium hydride species *in situ*.[21] The results are summarized in Table 2.5.

In all cases, excellent conversions were observed (Table 2.5, entries 1-4). These systems clearly favour the formation of cooligomers. The highest chemoselectivity to cooligomer (100%) was obtained using $[Pd(H_2O)(OTs)(dppp)](OTs)$ as catalyst, increasing the pressure from 30 to 50 bars of CO (Table 2.5, compare entries 2 and 4). These cationic systems have been studied previously in reactions of copolymerization CO-olefin.[22] The results suggest that they are highly selective catalysts for the production of polyketone.

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Table 2.5 Palladium cationic systems with diphosphines[a]

Entry	Catalyst	%C[b]	%5[b]	%6[b]	%9[c]
1	[Pd(H_2O)(OTs)(dppe)](OTs)	100	8	65	27
2	[Pd(H_2O)(OTs)(dppp)](OTs)	100	17	61	22
3	[Pd(H_2O)(OTs)(dppb)](OTs)	100	10	65	25
4[d]	[Pd(H_2O)(OTs)(dppp)](OTs)	100	0	100	-

[a] Reaction Conditions: catalyst: 0.021 mmol, NBN: 1.05 mmol, CH_3OH/THF (1:1) 5ml, 24 h, 70°C, 30 bars of CO. [b] The data on conversion and chemoselectivities of **5**, **6** were determined by GC and GC-MS analysis. [c] **9**= unidentified oligomeric by-products. [d] 50 bars of CO.

2.1.3 Conclusions

A systematic study of the palladium-catalyzed methoxycarbonylation of norbornene using monodentate and bidentate phosphine ligands in different reaction conditions has been for the first time undertaken. Monodentate phosphine **1** in presence of different palladium precursors and under acidic conditions gave a mixture of products of methoxycarbonylation and copolymerization of norbornene. The use of trifluoroethanol as alcohol, favoured the copolymer formation. Palladium cationic complexes bearing bidentate ligands **2-4**, provided full conversions and favoured the copolymerization reaction.

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2.1.4 Experimental

General Procedures. All palladium complexes were synthesised using standard Schlenk techniques under a nitrogen atmosphere. Diethyl ether, toluene and THF were distilled over sodium-benzophenone and dichloromethane was distilled over P_2O_5. All solvents were deoxygenated before use. All neutral palladium complexes $[PdCl_2(NCPh)_2]$[23], $[PdCl_2(COD)]$[24], $[PdCl_2(\mathbf{1})_2]$[25], $[PdCl_2(\mathbf{2})]$[26], $[PdCl_2(\mathbf{3})]$,[27] $[PdCl_2(\mathbf{4})]$,[28] and the cationic palladium complexes $[Pd(H_2O)(OTs)(\mathbf{2})]OTs$,[29] $[Pd(H_2O)(OTs)(\mathbf{3})]OTs$,[30] $[Pd(H_2O)(OTs)(\mathbf{4})]OTs$[30] were synthesised according to previously literature methods. $PdCl_2$ was purchased from Johnson Matthey Inc. and used without further purification. All other reagents were used as received from commercial suppliers. Deuterated solvents used for routine NMR measurements were dried over molecular sieves. ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ NMR spectra were recorded on a Varian Mercury 400 spectrometer (400.14, 100.63 and 161.98 MHz respectively). Chemical shifts were referenced to either TMS as an internal standard (^1H, $^{13}C\{^1H\}$ NMR spectra) or 85% H_3PO_4 as an external standard ($^{31}P\{^1H\}$NMR spectra).

Gas chromatography analyses were performed using a Hewlett-Packard 5890 series II chromatograph with flame ionization detector and Ultra-2 (5% diphenylsilicone-95% dimethylsilicone 25m X 0.2 mm Ø) capillary column.

General Procedure for Methoxycarbonylation Experiments

High pressure experiments were carried out in a Berghof autoclave, and the reaction mixtures were magnetically stirred and electrically heated. In a typical experiment, a solution of the palladium precursor (0.021 mmol), TFA (0.210 mmol) and norbornene (1.05 mmol) in 5 ml of THF/CH_3OH mixture (1:1) were introduced into the evacuated autoclave. Carbon monoxide was introduced and the system was then heated. When thermal equilibrium was

reached, stirring was initiated. After reaction, the autoclave was cooled to room temperature and depressurised. The product was filtered in a short column of celite and solvent was removed under vacuum. Conversions, chemo- and stereoselectivities were determined by GC, GC-MS and NMR analysis.

Characterization of the products

In all cases, the conversion of the substrate was determined by gas chromatography. The chemoselectivity in ester was determined by GC-MS. The ester was also identified by comparison with a standard patron. The chemoselectivity in cooligomer was determined by GC-MS. Cooligomers were identified by GC-MS and were compared with published data on the literature In all cases, it was found molecular ion peaks with m/z = 244, 276, 366, 398, 488, which coincided with CO-norbornene cooligomers published,[31] whose structures are shown in Scheme 2.2 (see, cooligomers **6**).

Determination of stereoselectivity *exo/endo*

The stereochemistry of the methoxycarbonylation products *exo* and *endo* were easily assigned by NMR mono- and bidimensional. Examining the coupling pattern of H^a in **11** and **12** it was possible to distinguish these *exo* and *endo* stereoisomers (Figure 2.3). According with a study of the stereochemistry of the *exo* and *endo* hydrophenylation products of norbornadiene,[32] it has been observed that as the dihedral angle between H^a and H^b in the *exo* isomer **11** is close to 90°, the coupling constant between H^a and H^b is close to ~0 Hz. Thus H^a of the *exo* isomer **11** is dd as it only couples to H^c and H^d but not with H^b. On the other hand, the corresponding dihedral angle between H^a and H^b in the *endo* isomer **12** is approximately 42° and would give a coupling constant of ~5 Hz. Thus, H^a of the *endo* isomer **12** would be expected to have a ddd pattern as

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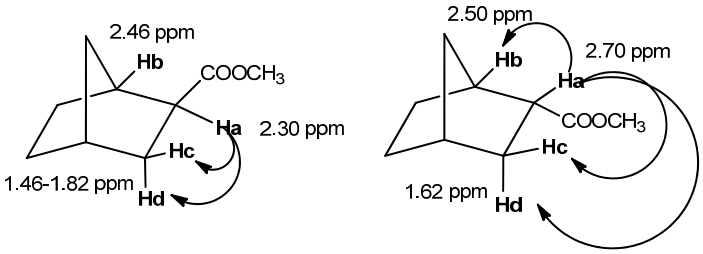
it couples to H^c, H^d, as well as H^b. Taking into account this we were able to assign the *exo* and *endo* isomers by NMR.



***exo* 11** ***endo* 12**

Figure 2.3 Isomers e*xo/endo*.

The ratio of *exo/endo* products was measured by ^1H NMR, GC and compared with a mixture of esters *exo/endo* which is commercially available.

2.2 Chemo and stereoselective palladium-catalyzed methoxycarbonylation of norbornene

2.2.1 Background

As it has been described above, the nature of the phosphorous ligands can modify the chemoselectivity of the Pd catalyzed carbonylation of olefins. Steric and electronic properties of a ligand can drastically influence the selectivity of the alkoxycarbonylation reaction. Palladium complexes bearing the *cis*-chelating bidentate ligands $Bu^t_2PCH_2C_6H_4CH_2PBu^t_2$ (dtbpx)[6a,b] $Bu^t_2P(CH_2)_3PBu^t_2$ (d^tbpp),[33] have provided very high rates and selectivity to the esters formation. It has been suggested that the selectivity arises because of steric properties of the ligands. In particular bulky ligands inhibit the chain growth process and promote termination step. The fact that the ligand become unidentate during some steps of the catalytic cycle, has also been proposed.[34] Recent computational studies also concluded that sterically bulky diphosphine ligands strongly favour ester formation over polymerization.[35] Extensive screening of monodentate and bidentate ligands has shown[14,36] that trialkylphosphine ligands such as $P(^tBu_3)$ are more effective than aryl monodentate, e.g. PPh_3, in the methoxycarbonylation of olefins with $[Pd(OAc)_2(PPh_3)_2]/PPh_3$ catalysts. Similarly, alkyl diphosphine ligands containing bulky end groups are preferred, affording ester product with high selectivity.[10]

The aim of this work is to study the control of chemo- and stereoselectivity in the methoxycarbonylation of norbornene (Scheme 2.3) catalyzed by palladium complexes bearing the bidentate (**1-5**) and the monodentate phosphine (**6-7**) ligands (Figure 2.4). These ligands have been chosen because of the efficiency of donor and bulky ligands as for instance **1** (d^tbpx) as well as bulky monophosphines in the production of ester products. The synthesis of a series

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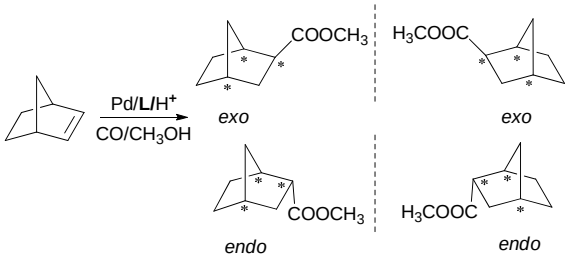
of Pd complexes, their characterization and their application as catalysts in this reaction are described.



Scheme 2.3 Pd-catalyzed methoxycarbonylation of norbornene.

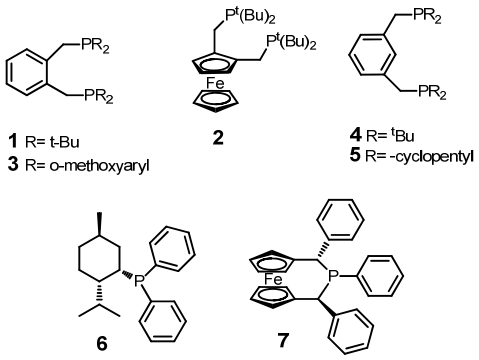
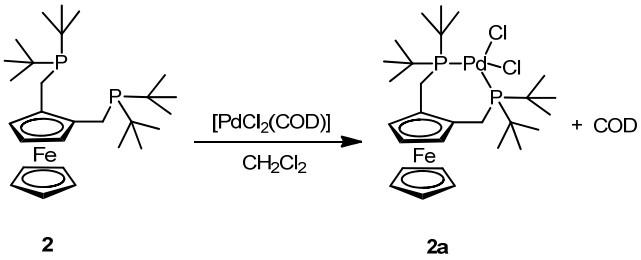


Figure 2.4 Monodentate and bidentate phosphine ligands used in this study.

2.2.2 Results and discussion

Synthesis of dichloro palladium (II) complexes [$PdCl_2$(2)] (2a) and [$PdCl_2(6)_2$] (6a)

The neutral palladium (II) dichloride complex **2a** was obtained by reaction of [$PdCl_2$(COD)] with 1.1 equivalent of the bidentate ligand **2** in dichloromethane at room temperature (Scheme 2.4). The complex **2a** was obtained as an orange powder that was recrystallized in CH_2Cl_2/ether to be isolated as red crystals. Single crystals suitable for X-ray diffraction were obtained fort this mixture of solvents. The product was also characterized by multinuclear NMR spectroscopy and elemental analysis. The $^{31}P\{^1H\}$ NMR spectrum of **2a** showed a singlet signal at 44 ppm.



2 **2a**

Scheme 2.4 Synthesis of complex **2a**.

The molecular structure of **2a** is shown in Figure 2.5. Selected bond lengths and angles are listed in Table 2.6 and 2.7.

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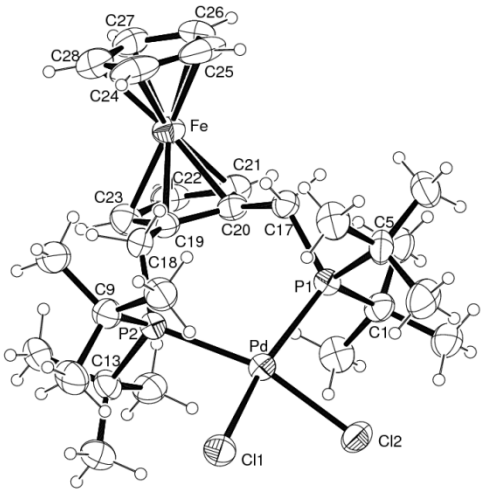

Figure 2.5 ORTEP drawing (30% probability ellipsoids) with atom labeling scheme of the complex **2a**. Solvent molecules and hydrogen atoms are omitted for clarity.

The crystal structure shows a distorted square planar coordination geometry containing one molecule of ether. The angle for Cl(1)-Pd-Cl(2) was found to be 84.12(6)°. The bite angle (P(2)-Pd-P(1)) of the diphosphine **2** when coordinated at palladium center was 103.95(6)°. The Pd-Cl(1) and Pd-Cl(2) bond lengths were measured to be 2.3481(17)Å and 2.3529(17), respectively. The Pd-P bond lengths were 2.3331(17) and 2.3206(16) for Pd-P(1) and Pd-P(2), respectively. These values are very similar to those previously reported for the related Pd(II) dichloride complexes with phosphines.[16]

Table 2.6 Experimental X-ray diffraction parameters and crystal data for 2a

Empirical Formula	$C_{28}H_{48}Cl_2FeP_2Pd.\ C_4H_8O$
M	751.86
Crystal system	Monoclinic
Space group	P 21/n
a/Å	11.558(3)
b/Å	14.646(3)
c/Å	20.721(4)
β/°	94.29(3)
Unit cell volume/Å^3	3497.8(13)
D_{calcd}/g cm^{-3}	1.428
Z	4
μ(Mo Kα)/mm^{-1}	1.196
F(000)	1568
T/K	293(2)
λ/Å	0.71073
Absorption correction	refdelf
Refinement method	Full-matrix least squares on F^2
Data/parameter	6012/352
Final R indices	$[I>2\sigma(I)]$ R_1= 0.0510, wR_2= 0.1159
R indices (all data)	R_1= 0.1008, wR_2= 0.1359
Goodness-of-fit on F^2	0.894
Absolute structure parameter	0.000
Largest diff peak and hole (e/Å^3)	1.0385/-0.4219

Table 2.7 Selected bond length (Å) and angles (°) for 2a

Pd-P(1)	2.3331(17)
Pd-P(2)	2.3206(16)
Pd-Cl(1)	2.3481(17)
Pd-Cl(2)	2.3529(17)
P(2)-Pd-P(1)	103.95(6)
P(2)-Pd-Cl(2)	162.48(6)
P(1)-Pd-Cl(2)	88.24(6)
P(2)-Pd-Cl(1)	87.08(6)
P(1)-Pd-Cl(1)	163.23(6)
Cl(2)-Pd-Cl(1)	84.12(6)

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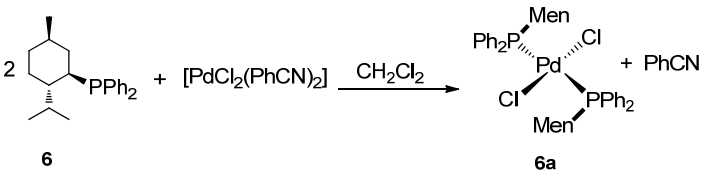
The neutral palladium complex *trans*-[$PdCl_2$(**6**)$_2$] **6a** was obtained by reaction of [$PdCl_2(PhCN)_2$] with 2 equivalents of the monodentate ligand **6** in dichloromethane at room temperature (Scheme 2.5). The complex was isolated by precipitation with diethyl ether, as a pale-yellow solid and characterized by multinuclear NMR spectroscopy and elemental analysis. The $^{31}P\{^1H\}$ NMR spectrum of **6a** showed a singlet signal at 22.7 ppm attributed to the *trans* configuration. Structural studies have confirmed that phosphorus ligands with high steric hindrance prefer a *trans* geometry.[20]



6 **6a**

Scheme 2.5 Synthesis of complex **6a.**

Catalytic reactions

Palladium catalyzed methoxycarbonylation of norbornene using diphosphine 1 as ligand.

Effect of the acid and catalytic precursor.

The diphosphine ligand **1** (Figure 2.4) has shown to provide exceptional activity, selectivity and stability to Pd catalysts in the methoxycarbonylation of terminal and internal alkenes,[37] styrene,[38] vinyl acetate[39] and ethene,[6b] exhibiting extremely high selectivity towards the ester products. For this reason diphosphine **1** was chosen here as a model ligand in the palladium-methoxycarbonylation of norbornene.

As indicated above, the presence of acid is often required to facilitate the formation of Pd-H species.[15b] However, to increase the scope of ligands and substrates as well as to avoid the corrosion of the reaction vessel, it is important

to minimize the amount of acid. We therefore explored the effect of the acid and catalytic precursors on the methoxycarbonylation of norbornene using ligand **1** and the results are summarised in Table 2.8

Table 2.8 Effect of the acid and catalytic precursor using ligand **1**[a]

Entry	Catalytic Precursor	Acid	C(%)[b,c]	S(%)[b,c]	%(*exo*/*endo*)
1[d]	$PdCl_2$/**1**	-	86	22	nd
2	$PdCl_2$/**1**	*p*-TsOH	99	75	100/-
3	$PdCl_2$/**1**	$MeSO_3H$	99	39	nd
4	$PdCl_2$/**1**	CF_3SO_3H	99	54	100/-
5	$PdCl_2$/**1**	$C_2H_2O_4$	99	61	100/-
6[e]	$PdCl_2$/**1**	Poly-SO_3H	75	75	100/-
7	$PdCl_2$/**1**	TFA	91	100	100/-
8	[$PdCl_2$(**1**)]	TFA	99	100	100/-
9	[$Pd_2(dba)_3$]/**1**	TFA	77	94	100/-

[a] Reaction conditions: Pd (0.021 mmol), acid (0.210 mmol), norbornene (1.05 mmol), MeOH/THF 5 ml (1:1), 30 bars of CO, 70°C, 24 h. [b] All conversions and chemoselectivities were determined by GC and GC-MS. [c] C= conversion; S= selectivity in ester. [d] Without acid. [e] Poly-SO_3H=sulfonic acid grafted polyolefin SMOPEX®101. nd= not determined.

The catalytic reactions were performed using $PdCl_2$/**1** as a catalytic system under 30 bars of CO at 70°C for 24 hours. First, we performed an experiment in the absence of acid and although 86% of conversion was obtained, the chemoselectivity was very low (22%) (Table 2.8, entry 1). The use of the acids *p*-TsOH, $MeSO_3H$, CF_3SO_3H, $C_2H_2O_4$ (Table 2.8, entries 2-5) and the sulfonic acid grafted polymer SMOPEX®101 (Table 2.8, entry 6) provided conversions

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ranging between 75 and 99% and selectivity to ester between 39 and 75%. In all cases, the presence of cooligomers as reaction by-products was observed. However, when TFA was used (Table 2.8, entry 7) the only reaction product was the desired ester in 91% conversion. Furthermore, under these conditions, total selectivity to the *exo* product was achieved. Using the isolated palladium complex [$PdCl_2$(**1**)] (Table 2.8, entry 8), the conversion increased to 99%, and the chemoselectivity (100%) and the stereoselectivity (100% *exo*) remained excellent. Concerning the palladium precursors, the use of [$Pd_2(dba)_3$] as Pd(0) source in the presence of ligand **1** provided a conversion of 77% and the chemoselectivity remained high at 94% (Table 2.8, entry 9). Surprisingly however, when [$Pd(OAc)_2$] was used under the same conditions, no conversion was observed.

In summary, excellent results in terms of conversion, chemoselectivity and *exo*selectivity were obtained using [$PdCl_2$(**1**)] as catalyst precursor in the presence of trifluoroacetic acid.

Palladium catalyzed methoxycarbonylation of norbornene using bidentate phosphine ligands 1-5

Once the desired chemoselectivity was obtained using ligand **1,** ligands (**2-5**) (Figure 2.4) were investigated in order to compare the influence of both moieties, the backbone and the P substituent. A series of bulky diphosphines based on a ferrocenyl backbone (**2**) and a xylene backbone (**3**, **4**, **5**), was tested in the palladium-catalyzed methoxycarbonylation of norbornene (Figure 2.4). The results are summarized in Table 2.9.

The reaction temperature has often a significant effect on the activity and selectivity of catalytic systems and as such, the systems described were tested at room temperature and 70°C for *in situ* catalysts.

Table 2.9 Methoxycarbonylation of norbornene using bidentate phosphine ligands (**1-5**)[a]

Entry	Precursor	T	C(%)[b,c]	S(%)[b,c]	%(*exo*/*endo*)
1	$PdCl_2$/ **1**	RT	19	100	100/-
2	$PdCl_2$/ **1**	70	91	100	100/-
3	$PdCl_2$/ **2**	70	75	100	100/-
4	$PdCl_2$/ **3**	70	14	89	100/-
5	$PdCl_2$/ **4**	70	<5	<5	-
6	$PdCl_2$/ **5**	70	<5	<5	-

[a]Reaction conditions: Pd (0.021 mmol), L/Pd: 2, TFA (0.210 mmol), norbornene (1.05 mmol), MeOH/THF(1:1), 30 bars of CO, 24 h. [b]All conversions and chemoselectivities were determined by GC and GC-MS. [c]C=conversion; S=selectivity to ester.

When the *in situ* $PdCl_2$/**1** system which contains the ligand based on a *ortho*-xylene backbone and the ^{t}Bu groups was tested at room temperature, very low conversion (19%) was obtained, although excellent chemo- (100%) and stereoselectivity (100%) were achieved (Table 2.9, entry 1). However, when the reaction temperature was increased to 70°C, an important increase in conversion was observed (91%) while the chemo- and stereoselectivity were not affected (Table 2.9, entry 2). When the *in situ* system using the ligand based on a ferrocenyl backbone (**2**) and the ^{t}Bu groups at the phosphorus atom was used at room temperature, no catalytic activity was obtained. However, when the reaction temperature was augmented to 70°C a significant increase in conversion (75%), chemoselectivity to ester (100%) and *exo*selectivity (100%) were observed (Table 2.9, entry 3). Comparing ligand **1** with ligand **2** under the same conditions, the best results in terms of conversion were obtained with ligand **1** which contains the *ortho*-xylene backbone and ^{t}Bu groups at the phosphorus atom. In both cases, excellent chemoselectivities and

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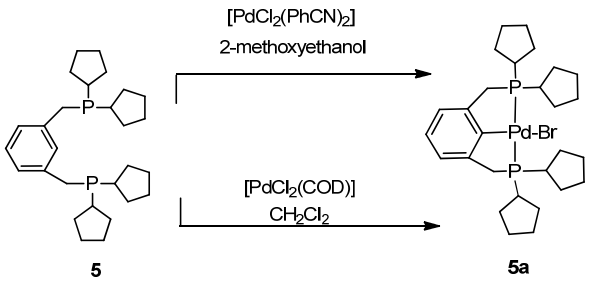
stereoselectivities were achieved (Table 2.9, compare entry 2 *vs* entry 3). When the *ortho*-xylene backbone is retained but the ^{t}Bu groups are replaced by *ortho*-methoxyaryl groups (**3**) the activity was drastically reduced at 70°C, although the chemoselectivity remained high and the stereoselectivity excellent (Table 2.9, entry 4). As in the previous case, no activity was observed with this system at room temperature.

The effect of the nature of the ligand (bite angle and coordination mode) in the Pd-catalyzed methoxycarbonylation reaction can be compared using the catalytic systems with *ortho*- and *meta*-xylene backbone and identical P-substituents (Table 2.9, entries 2 *vs* 5). In the case of a larger bite angle, ligand **4**, the activity and the chemoselectivity were very poor, <5% (Table 2.9, entry 5). An identical behaviour was observed for catalytic system with ligand **5** which contains identical *meta*-xylene backbone and cyclopentyl P-substituents (Table 2.9, entry 6). In summary, the best results in terms of chemo- and *exo*selectivity are obtained with ligands **1** and **2** which both contain ^{t}Bu groups and form a 7-membered chelating ring with the palladium atom. Highly electron donating and bulky diphosphine ligands are required for the successful Pd-catalysed methoxycarbonylation of norbornene.

Related to ligands **4** and **5**, it was found in the literature that structurally similar ligands form very stable tridentate palladium pincer complexes.[40,41] Analogous complexes could be responsible here for catalyst deactivation.

According with these observations, in order to corroborate the formation of these complexes, the synthesis of Pd (II) pincer complex with ligand **5** was performed following two different methodologies The pincer complex (**5a**) was obtained by reaction of $[PdCl_2(COD)]$ in presence of CH_2Cl_2 or $[PdCl_2(PhCN)_2]$ in presence of 2-methoxyethanol (Scheme 2.6). In both cases, the X-ray crystal structure analysis was obtained and revealed as we expected,

the formation of Pd(II) pincer complex. The crystals were obtained by recrystalization from CH_2Cl_2/pentane and characterized by multinuclear NMR spectroscopy and elemental analysis. The $^{31}P\{^1H\}$ NMR spectrum of complex **5a** showed a singlet signal at 52 ppm.



Scheme 2.6 Synthesis of pincer complex **5a**.

For our surprise, the molecular structure of complex **5a** showed the coordination of a bromide ion to the palladium center instead of a chloride. In order to know about the origin of the presence of the bromide, we decided to check all the reagents, mainly the starting material which is commercially available and we found in the literature that this kind of diphosphines are usually synthesised starting from a dibromo compound.[42] In order to confirm this hypothesis we performed an electrospray mass experiment in a positive and negative mode of acquisition using a 6210 Time of Flight LC/MS Agilent spectrometer. The results have shown, in the positive-ion mode a peak at m/z 443 corresponding to the monoprotonated diphosphine $[M\text{-}H]^+$. In the negative ionization mode was observed a peak with m/z 80 corresponding to a bromide ion. Therefore, we can confirm that the free ligand (molecular formula $C_{28}H_{44}P_2$) was contaminated with HBr.

The molecular structure of **5a** is shown in Figure 2.6. Selected bond lengths and angles are listed in Table 2.10 and 2.11. The coordination sphere around

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the palladium atom was found to correspond to a slightly distorted square-planar geometry, with angles of 166.84(4)° and 178.00(12)° for P(1)-Pd-P(2) and C12-Pd-Br, respectively. The Pd-Br bond distance of 2.034 Å and Pd-P bond length of 2.282 Å are comparable with those observed in the analogous $[PdBr(C_6H_3\text{-}2,6\text{-}CH_2PCy_2)_2]$[40a] and $[PdBr(C_6H_3\text{-}2,6\text{-}CH_2PPh_2)_2]$.[41] Two chelated five membered rings are present in the complex. These rings are quite strained due to constrain imposed by the atoms forming the two adjacent five-membered chelated rings. Part of this strain is released by formation of unequal P(1)-Pd-Br (95.74°) and P(2)-Pd-Br (97.06°). These values are similar to those reported for similar palladium (II) pincer complexes.[40,41]

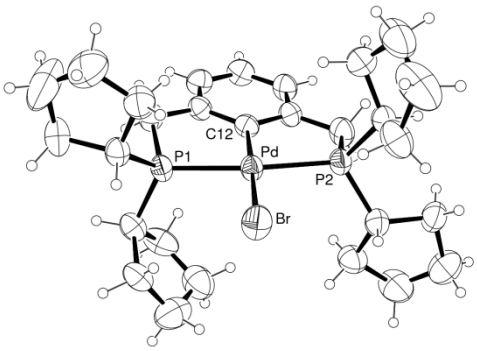

Figure 2.6 ORTEP drawing (30% probability ellipsoids) with atom labeling scheme of the complex **5a**. Carbon and hydrogen atoms are omitted for clarity.

Table 2.10 Experimental X-ray diffraction parameters and crystal data for 5a

Empirical Formula	$C_{28}H_{43}BrP_2Pd$
M	627.87
Crystal system	Orthorhombic
Space group	P_{bca}
a/Å	15.151(3)
b/Å	17.180(4)
c/Å	21.361(4)
β/°	90.00
Unit cell volume/Å^3	5560(2)
D_{calcd}/g cm^{-3}	1.500
Z	8
μ(Mo Kα)/mm^{-1}	2.234
F(000)	2576
T/K	293(2)
λ/Å	0.71073
Absorption correction	refdelf
Refinement method	Full-matrix least squares on F^2
Data/parameter	5864/289
Final R indices	[I>2σ(I)] R_1= 0.0395, wR_2= 0.0959
R indices (all data)	R_1= 0.852, wR_2= 0.1079
Goodness-of-fit on F^2	0.860
Absolute structure parameter	0.000
Largest diff peak and hole (e/Å^3)	0.6400/-0.4271

Table 2.11 Selected bond length (Å) and angles (°) for 5a

Pd-P(1)	2.2828(12)
Pd-P(2)	2.2823(12)
Pd-C(12)	2.034(4)
Pd-Br	2.5152(7)
P(1)-Pd-P(2)	166.84(4)
P(1)-Pd-C(12)	83.33(12)
P(2)-Pd-C(12)	83.97(13)
C(12)-Pd-Br	178.00(12)
P(1)-Pd-Br	95.74(3)
P(2)-Pd-Br	97.06(3)

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Effect of the reaction temperature on the Pd-catalyzed methoxycarbonylation of norbornene using isolated catalyst bearing bidentate ligands (1-3 and 5)

Due to the promising results in terms of conversion, chemo and stereoselectivity previously obtained with the diphosphine ligands at 70°C, the effect of the reaction temperature was studied using preformed catalysts bearing the bidentate ligands **1**, **2**, **3** and **5**. The results are summarized in Table 2.12.

Table 2.12 Effect of the reaction temperature using isolated catalyst bearing bidentate ligands (**1-3** and **5**)[a]

Entry	Precursor	T(°C)	C(%)[b,c]	S(%)[b,c]	%(*exo*/*endo*)
1	[$PdCl_2$(**1**)]	RT	42	100	100/-
2	[$PdCl_2$(**1**)]	70	99	100	100/-
3	[$PdCl_2$(**2**)]	RT	99	100	100/-
4	[$PdCl_2$(**2**)]	70	99	100	100/-
5	[$PdCl_2$(**3**)]	RT	0	0	-
6	[$PdCl_2$(**3**)]	70	56	69	100/-
7	[PdBr(**5**)]	RT	<5	<5	-
8	[PdBr(**5**)]	70	<5	<5	-

[a]Reaction conditions: Pd (0.021 mmol), TFA (0.210 mmol), norbornene (1.05 mmol), MeOH/THF(1:1), 30 bars of CO, 24 h. [b]All conversions and chemoselectivities were determined by GC and GC-MS. [c]C=conversion; S=selectivity to ester.

When the isolated palladium system [$PdCl_2$(**1**)] was tested at room temperature the conversion was of 42% together with excellent both chemoselectivity (100%) and stereoselectivity (100%) (Table 2.12, entry 1). However, when the

reaction temperature was increased to 70°C, as shown before, the conversion was found to improve to 99%, while chemoselectivity and stereoselectivity were unaltered (Table 2.12, entry 2). Using the isolated palladium complex [$PdCl_2$(**2**)] not temperature effect was observed and total conversion, chemoselectivity to the ester product and stereoselectivity were achieved at both RT and 70°C (Table 2.12, entries 3 and 4). However, the reaction temperature affected drastically the results when the isolated palladium system [$PdCl_2$(**3**)] was tested. When the reaction was carried out at room temperature no catalytic activity was observed (Table 2.12, entry 5). However, at 70°C, the conversion was enhanced up to 56% with moderate chemoselectivity 69% and excellent stereoselectivity (100%) (Table 2.12, entry 6). When complex **5a** previously synthesized, was tested in the catalytic reaction no activity was observed at both RT and 70°C. This lack of activity can be attributed to the formation of the previously described pincer Pd complex.

Because the best results in terms of conversion, chemo- and stereoselectivity were obtained with complex [$PdCl_2$(**2**)] (**2a**) at RT in presence of 50 equiv. of norbornene, we study the effect of the substrate concentration in the palladium-catalyzed methoxycarbonylation of norbornene. The results are listed in Table 2.13.

Table 2.13 Effect of norbornene concentration using complex **2a** in the Pd-catalyzed methoxycarbonylation reaction[a]

Entry	Precursor	NBN (equiv)	C (%)[b,c]	S(%)[b,c]	%(*exo*/*endo*)
1	[$PdCl_2$(**2**)]	50	99	100	100/-
2	[$PdCl_2$(**2**)]	100	99	100	100/-
3	[$PdCl_2$(**2**)]	200	23	100	100/-
4	[$PdCl_2$(**2**)]	500	<5	nd	nd

[a]Reaction conditions: Pd (0.021 mmol), TFA (0.210 mmol), MeOH/THF 5ml (1:1), 30 bars of CO, RT. [b]All conversions and chemoselectivities were determined by GC and GC-MS. [c]C=conversion; S=selectivity to ester.

When the catalytic reaction was carried out in presence of 50 equiv. norbornene, excellent conversion (99%), chemo- (100%) and stereoselectivity (100% *exo*) was obtained (Table 2.13, entry 1). When the ratio Pd/NBN was increased from 50 to 100 equiv. the results in terms of conversion, chemo and stereoselectivity were unaltered (Table 2.13, entry 2). However, when the ratio Pd/NBN was increased from 100 to 200, the conversion drastically decreased (23%), although both chemo- and stereoselectivity remained excellent (Table 2.13, entry 3). It was concluded that no effect on the chemoselectivity to the ester formation was observed when the norbornene concentration was studied. When the ratio Pd/NBN was 500, practically no catalytic activity (<5%) (Table 2.13, entry 4).

Palladium catalyzed methoxycarbonylation of norbornene using monodentate phosphine ligands 6-7

Catalytic precursors containing monodentate phosphines and phosphetanes have been recently reported to be active in the Pd catalysed methoxycarbonylation of styrene,[10c,16] but only a few successful examples of monophosphine ligands have achieved significant activity, regioselectivity and enantioselectivity.[10a,10b] To the best of our knowledge, the Pd-catalysed methoxycarbonylation of norbornene has scarcely been studied with monodentate phosphine ligands.[21] Here, we use two different monodentate phosphine ligands (Figure 2.4, ligands **6**, and **7**). The results are summarised in Table 2.14.

Table 2.14 Methoxycarbonylation of norbornene using monodentate phosphine ligands **6** and **7**[a]

Entry	Catalyst	Acid	T(°C)	C(%)[b,c]	S(%)[b,c]	%(*exo*)(ee)
1	$PdCl_2$/**6**	NO	RT	100	100	100(3)
2	$PdCl_2$/**6**	NO	70	98	100	100(9)
3	[$PdCl_2$(**6**)$_2$]	NO	RT	100	100	100(10)
4	[$PdCl_2$(**6**)$_2$]	NO	70	100	100	100(10)
5	[$PdCl_2$(**6**)$_2$]	YES	RT	89	90	100(11)
6	$PdCl_2$/**7**	NO	70	53	25	-
7	$PdCl_2$/**7**	YES	70	99	90	100(40)
8	[$PdCl_2$(PhCN)$_2$]/**7**	YES	RT	14	100	100(46)

[a]Reaction conditions: Pd (0.021 mmol), L/Pd: 2, TFA (0.210 mmol), norbornene (1.05 mmol), MeOH/THF (1:1), 30 bars of CO, 24h. [b]All conversions and chemoselectivities were determined by GC and GC-MS. [c]C=conversion; S=selectivity to ester.

When $PdCl_2$/(S)-NMDPP (**6**) was used as catalytic system at room temperature without any added acid, 100% of conversion was observed together with an excellent chemo- (100%) and *exo*selectivity (100%) (Table 2.14, entry 1). However, the enantiomeric excess achieved was very poor. The fact that $PdCl_2$/**6** provided an active Pd-catalyst in the absence of added acid fits the observations reported by Nozaki and co-workers in the palladium-catalysed methoxycarbonylation of styrene.[43] A slight decrease in conversion (98%) was observed when the reaction was performed at 70°C (Table 2.14, entry 2) however, both chemo- and *exo*selectivity remained unaltered. When the isolated [$PdCl_2$(**6**)$_2$] (**6a**) system was probed as catalytic precursor, both room temperature and 70ºC reactions yielded excellent conversion (100%) (Table 2.14, entries 3 and 4) together with an excellent chemo- (100%) and

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*exo*selectivity (100%). When the reaction was carried out under acidic conditions at room temperature, a slight decrease in both conversion and chemoselectivity was observed compared with the reaction performed without acid under the same conditions (Table 2.14 entries 3 *vs* 5).

The (S,S)-ferrocenylphosphine **7**, which is a new chiral phosphine[44] that has never been used previously in organometallic catalysis, was probed in this reaction. The experiments were performed using the catalytic system $PdCl_2$/**7**. The absence of acid drastically affected both the conversion and the selectivity (Table 2.14, entry 6). However, very good conversion, chemoselectivity and *exo*selectivity were obtained using the monophosphine **7** under mild acidic conditions (Table 2.14, entry 7). The enantiomeric excess was moderate (40%). When $[PdCl_2(PhCN)_2]$ was used as palladium precursor instead of $PdCl_2$ the enantioselectivity was increased to 46% at room temperature (Table 2.14, entry 8). However, the conversion significantly decreased both chemo- and stereoselectivity remained excellent (Table 2.14, entry 8).

The effect of the palladium precursor was studied with ligand **6**. The results are listed in Table 2.15. As mentioned above, when $PdCl_2$/**6** was used as catalytic system, excellent conversion, chemo- and *exo*selectivity were obtained in the absence of acid (Table 2.15, entry 1). However, when $[Pd_2(dba)_3]$ (Table 2.15, entry 2) and $[Pd(OAc)_2]$ (Table 2.15, entry 4) were tested in the presence of ligand **6** without acid no conversion was observed. These results suggest that palladium dichloride plays a crucial role in the activity and selectivity of the reaction. To corroborate this observation, we carried out the catalytic reaction using $[Pd_2(dba)_3]$/**6** system in the presence of HCl (1 equiv.). Moderate conversion (65%) together with an excellent chemo- and *exo*selectivity (100%) were achieved (Table 2.15, entry 3). Similarly, a drastic increase in conversion (100%) together with an excellent chemo- and *exo*selectivity (100%) were also

obtained when $Pd(OAc)_2$/**6**/HCl (1equiv.) (Table 2.15, entry 5) was used as a catalytic system. Insights about these results will be rationalizated in Chapter 3 section 3.2.1.

Table 2.15 Effect of palladium precursor usign complex **6a** in the palladium-catalyzed methoxycarbonylation of norbornene.

Entry	Catalyst	HCl (1 equiv)	C(%)[b,c]	S(%)[b,c]	%(*exo*)(ee)
1	$[PdCl_2)]$/**6**	NO	98	100	100(10)
2	$[Pd_2(dba)_3]$/**6**	NO	0	0	0
3	$[Pd_2(dba)_3]$/**6**	YES	65	100	100(7)
4	$Pd(OAc)_2$/**6**	NO	0	0	0
5	$Pd(OAc)_2$/**6**	YES	100	100	100(9)

[a]Reaction conditions: Pd (0.021 mmol), L/Pd: 2, MeOH/THF (1:1), 30 bars of CO, 70°C, 24h. [b]All conversions and chemoselectivities were determined by GC and GC-MS. [c]C=conversion; S=selectivity to ester.

Taking into account the excellent results in terms of conversion and selectivity obtained with $[PdCl_2(\mathbf{6})_2]$ (**6a**) as catalyst, the effect of norbornene concentration was investigated. The results are summarized in Table 2.16.

Excellent conversion (100%), chemo- (100%) and *exo*selectivity (100%) was observed in presence of 50 and 100 equiv. of norbornene (Table 2.16, entries 1 and 2). However, when the ratio Pd/NBN was increased to 200 a slight decrease in chemoselectivity (71%), although both conversion (100%) and *exo*selecitivity remained excellent (100%). Cooligomers were detected as by-products reaction (Table 2.16, entry 3). When the ratio Pd/NBN was increase from 200 to 500 a significant decrease in both conversion (42%) and chemoselectivity (49%) was obtained. However, the *exo*selectivity was

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still excellent (Table 2.16, entry 4). When the Pd/NBN ratio was 1000, both conversion (23%) and chemoselectivity (26%) were significant affected. As previously mentioned, cooligomers were detected.

Table 2.16 Effect of norbornene concentration using complex **6a** in the palladium-catalyzed methoxycarbonylation of norbornene

Entry	Catalyst	NBN (equiv)	C(%)[b,c]	S(%)[b,c]	%(*exo*)(ee)
1	$[PdCl_2(\mathbf{6})_2]$	50	100	100	100(10)
2	$[PdCl_2(\mathbf{6})_2]$	100	100	100	100(6)
3	$[PdCl_2(\mathbf{6})_2]$	200	100	71	100(7)
4	$[PdCl_2(\mathbf{6})_2]$	500	42	40	100(8)
5	$[PdCl_2(\mathbf{6})_2]$	1000	23	26	100(11)

[a]Reaction conditions: Pd (0.021 mmol), L/Pd: 2, MeOH/THF (1:1), 30 bars of CO, RT, 24h. [b]All conversions and chemoselectivities were determined by GC and GC-MS. [c]C=conversion; S=selectivity to ester.

2.2.3 Conclusions

The results described here show that, by controlling the reaction conditions and using the adequate ligands, norbornene can be chemo- and stereoselectively functionalized. Subtle modifications of the palladium phosphine catalyst lead to significant results in activity and selectivity.

- The palladium system containing bulky and basic diphosphine **1** and **2** in the presence of TFA provides excellent conversions, chemo- and stereoselectivities.
- Ligands **4** and **5** which coordinate forming pincer complexes (as it has been shown in the Pd complex with ligand **5**) do not show catalytic activity.
- The palladium system bearing monophosphine **6** is active in the absence of acid and 100% of conversion, chemo- and stereoselectivity are obtained.
- The promising results in terms of *ees* obtained using the ligands **6** and **7** show a new route for the transformation of norbornene into useful intermediates for organic synthesis.
- Concerning the palladium precursors, the study carried out with ligand **6** demonstrated that the $PdCl_2$ is the best precursor.
- Finally, for system **6a**, the concentration of norbornene affect both conversion and chemoselectivity, providing control of the formation of esters or cooligomers for low or high concentrations, respectively.

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2.2.4 Experimental

General Procedures. All palladium complexes were synthesised using standard Schlenk techniques under a nitrogen atmosphere. Diethyl ether, toluene and THF were distilled over sodium-benzophenone and dichloromethane was distilled over P_2O_5. All solvents were deoxygenated before use. The ligand **3**[45] and the palladium complexes $[PdCl_2(NCPh)_2]$,[23] $[PdCl_2(COD)]$,[24] $[PdCl_2(\mathbf{1})]$(**1a**),[15b] $[PdCl_2(\mathbf{3})]$[45] (**3a**), were prepared according to literature methods. The ligands **2** and **7** were supplied gently by Dr. Graham Eastham from Lucite International and Dr. Angela Marinetti from the Institut de Chimie des Substances Naturelles *C.N.R.S*, respectively. $PdCl_2$ was purchased from Johnson Matthey Inc. and used without further purification. All other reagents were used as received from commercial suppliers. Deuterated solvents used for routine NMR measurements were dried over molecular sieves. ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ NMR spectra were recorded on a Varian Mercury 400 spectrometer (400.14, 100.63 and 161.98 MHz respectively). Chemical shifts were referenced to either TMS as an internal standard (^1H, $^{13}C\{^1H\}$ NMR spectra) or 85% H_3PO_4 as an external standard ($^{31}P\{^1H\}$NMR spectra). Gas chromatography analyses were performed using a Hewlett-Packard 5890 series II chromatograph with flame ionization detector and Ultra-2 (5% diphenylsilicone, 95% dimethylsilicone) (25m X 0.2 mm Ø) capillary column. Enantiomeric excesses were determined by GC analysis (Chiraldex-GTA capillar column 30m X 0.25mm X 0.12μm film thickness).

Syntheses of Pd complexes

Synthesis of [$PdCl_2$(2)] (2a)

A solution of ligand **2** (269.70 mg, 0.54 mmol) in dichloromethane (10 ml) was added to a solution of [$PdCl_2$(COD)] (146.00 mg, 0.51 mmol) in dichloromethane (5 ml). The resulting red solution was stirred for 1h and concentrated under reduced pressure. Addition of diethyl ether led to the precipitation of an orange solid, which was filtered off, washed with diethyl ether, and dried under vacuum. The orange solid was recrystallized from CH_2Cl_2/pentane to obtain red complex **2a** as red crystals.

Complex 2a: Yield: 300.5 mg (82%). ^{1}H NMR (CD_2Cl_2, 400.14 MHz, ppm): δ 1.48 (d, 18H, J_{HP}= 13.6 Hz, t-Bu), 1.51 (d, 18H, J_{HP}= 13.6 Hz, t-Bu), 3.16 (dd, 2H, J_{HH}=4.8 Hz, J_{HP}=14.4 Hz, RCH_2P), 3.44 (m, 2H, RCH_2P), 4.10 (s, 5H, Cp-ring), 4.18 (m, 3H, C_5H_3 ring), 4.50 (d, 1H, J_{HH}=4.0 Hz, C_5H_3-ring). ^{13}C{^{1}H} NMR (CD_2Cl_2, 100.63 MHZ, ppm): δ 25.0 (m, CH_2), 30.0 (m, CH_3), 30.8 (m, CH_3), 31.8 (s, tert-C), 32.3 (s, tert-C), 66.3 (s, CH), 70.7 (s, Cp), 71.5 (s, Cp subst), 82.3 (s, C quat.). ^{31}P{^{1}H} NMR (CD_2Cl_2, 161.98 MHZ, ppm): δ 44.0 (s). Anal. Calc. for $C_{28}H_{48}FeP_2PdCl_2$ (679,79 g/mol): Calc.: C, 49.42; H, 7.06 Found: C, 48.31 H, 7.00.

Synthesis of [$PdCl_2$(6)$_2$] (6a)

A solution of ligand **6** (173.48 mg, 0.53 mmol) in dichloromethane (5ml) was added to a solution of [$PdCl_2(PhCN)_2$] (100.00 mg, 0.26 mmol) in dichloromethane (3 ml) at room temperature. The resulting yellow solution was stirred for 1 h and concentrated under vacuum. Addition of diethyl ether yielded the precipitation of a pale-yellow solid, which was filtered and washed with diethyl ether before being dried under vacuum.

Complex 6a: Yield: 166.3 mg (75%). ^{1}H NMR (CD_2Cl_2, 400.14 MHz, ppm): δ 0.65 (d, J_{HH}= 6.8 Hz, CH_3), 1.02 (d, J_{HH}= 6.0 Hz, CH_3), 1.06 (d, J_{HH}= 7.2 Hz, CH_3), 1.15 (m, CH_2), 1.45 (m, CH_2), 1.55 (m, CH_2), 1.63 (m, CH_2), 1.69 (m,

CH_2), 1.85 (s br. CH), 2.55 (m, CH), 2.61 (m, CH), 3.70 (m, P-CH), 7.31-7.44 (m, Ar), 7.62-7.69 (m, Ar). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 100.63 MHZ, ppm): δ 18.76 (s, CH_3), 21.32 (brs, CH_2), 21.43 (s, CH_3), 25.17 (s, CH_3), 28.6 (t, J_{PC}= 8.0 Hz, CH), 29.73 (brs, CH_2), 31.66 (t, J_{PC}= 6.8 Hz, CH), 32.8 (m, CH), 32.9 (s, CH_2), 33.08 (s, CH_2), 40.37 (s, CH), 127.6 (t, J_{PC}=10.1 Hz, Ar), 128.6 (t, J_{PC}=8.5 Hz, Ar), 130,09 (s, Ar), 130,66 (s, Ar), 133.41 (t, J_{PC}=10.4 Hz, Ar), 137.03 (t, J_{PC}=11.1 Hz, Ar). $^{31}P\{^1H\}$ NMR (CD_2Cl_2, 161.98 MHZ, ppm): δ 22.7 (s). Anal. Calc. for $C_{44}H_{58}P_2PdCl_2$ (826.20g/mol): Calc.: C, 63.96; H, 7.08. Found: C, 62.53; H, 6.92.

Synthesis of [PdBr(5)] (5a)

The synthesis of complex **5a** was carried out following two different procedures:

a) According to the general procedure previously described for the synthesis of complex **2a**. The product was isolated as a white solid. Yield: 51.6 mg, 42%.

b) A solid sample of $[PdCl_2(PhCN)_2]$ (141.47 mg, 0.37 mmol) was added to a solution of the ligand **5** (217.51 mg, 0.49 mmol) in 2-methoxyethanol (10 ml). The yellow solution was refluxed for 30 min, then allowed to cool, and the solvent was removed to leave a yellow powder. Extraction with hot ethanol and cooling and reducing the volume of ethanol solution gave a white solid. The solid was recrystallized from CH_2Cl_2/pentane mixture to obtain complex **5a** as colourless crystals.

Complex 5a: Yield: 185.3 mg (60%). ^1H NMR (CD_2Cl_2, 400.14 MHz, ppm): δ 1.58 (m, 8H, -CH_2-), 1.72 (m, 8H,-CH_2-), 1,85 (m, 8H, P-CH_2), 2,06 (m, 8H, P-CH_2), 2.47 (m, 4H, P-CH), 3.23 (t, J=11.6 Hz, 4H, P-CH_2Ar), 6.90-7.30 (m, 3H, Ar). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 100.63 MHZ, ppm): δ 26.20 (m, CH_2), 26.54 (m, CH_2), 28.90 (s, CH_2), 29.34, (s, CH_2), 35.50 (t, $J_{(C-P)}$= 9.0 H_z, P-CH_2Ar), 35.58

(d, $J_{(C-P)}$=3.0 Hz, P-CH), 122.41, 122.51, 122.62, 124.91, 150,41, 161,02. $^{31}P\{^{1}H\}$ NMR (CD_2Cl_2, 161.98 MHZ, ppm): δ 52.1 (s). Anal. Calc. for $C_{28}H_{43}P_2PdBr$ (627.91 g/mol): Calc.: C, 53.56; H, 6.90. Found: C, 54.16; H, 6.72.

X-ray data collection and Structure Determination of [$PdCl_2$(2)] (2a) and [PdBr(5)] (5a)

Data collection for crystal structure of [$PdCl_2$(**2**)] (**2a**) and [PdBr(**5**)] (**5a**) was carried out at 293(2) K on an Enraf Nonius CAD4 single crystal diffractometer (Mo-Kα radiation, λ= 0.71073 Å). Cell refinement, indexing and scaling of all the data set were performed using programs Denzo and Scalepack.[46] The structure was solved by direct methods and subsequent Fourier analyses[47] and refined by the full-matrix least-squares method based on F^2 with all observed reflections.[47] All the calculations were performed using the WinGXSystem, Ver 1.70.01.[48]

MS analysis

The MS spectrum was obtained by direct injection on an 6210 LC/TOF mass spectrometer (Agilent Technologies, Palo Alto, U.S.A.), equipped with an electrospray ionisation source. MS source parameters were set with gas temperature of 250ºC, drying gas flow of 5 l/min, nebulizer gas pressure of 12 psi, and a capillary voltage of 3500 V. Data acquisition was realised both in negative and positive centroid acquisition mode, with an skimmer voltatge of 65V, a fragmentor voltage of 150V, and an acquisition range from 50 to 1500 m/z, at a rate of 1.02 spectra/sec. The instrument was calibrated in positive and negative ion modes using a tuning mixture, and an internal reference standard was used to calibrate the exact mass during the analysis (both from Agilent Technologies, Palo Alto, and U.S.A.). The average of scans obtained

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were, in positive mode, the protonated ion (m/z 443.3010), and, in negative mode, the bromide ion with a m/z of 78.9200 and 80.9178.

Catalysis

High-pressure experiments were carried out in a Berghof autoclave, and the reaction mixtures were magnetically stirred and electrically heated. In a typical experiment, a solution of the palladium precursor (0.021 mmol), TFA (0.210 mmol) and norbornene (1.05 mmol) in 5 ml of THF/CH_3OH mixture (1:1) were introduced into the evacuated autoclave. Carbon monoxide was introduced and the system was then heated. When thermal equilibrium was reached, stirring was initiated. After reaction, the autoclave was cooled to room temperature and depressurized. The product was filtered in a short column of celite and solvent was removed under vacuum. Conversions, chemo- and stereoselectivities were determined by GC, GC-MS and NMR analysis.

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Chapter 3

Mechanistic Aspects of the Pd-Catalyzed Methoxycarbonylation of Norbornene

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3.1 Background

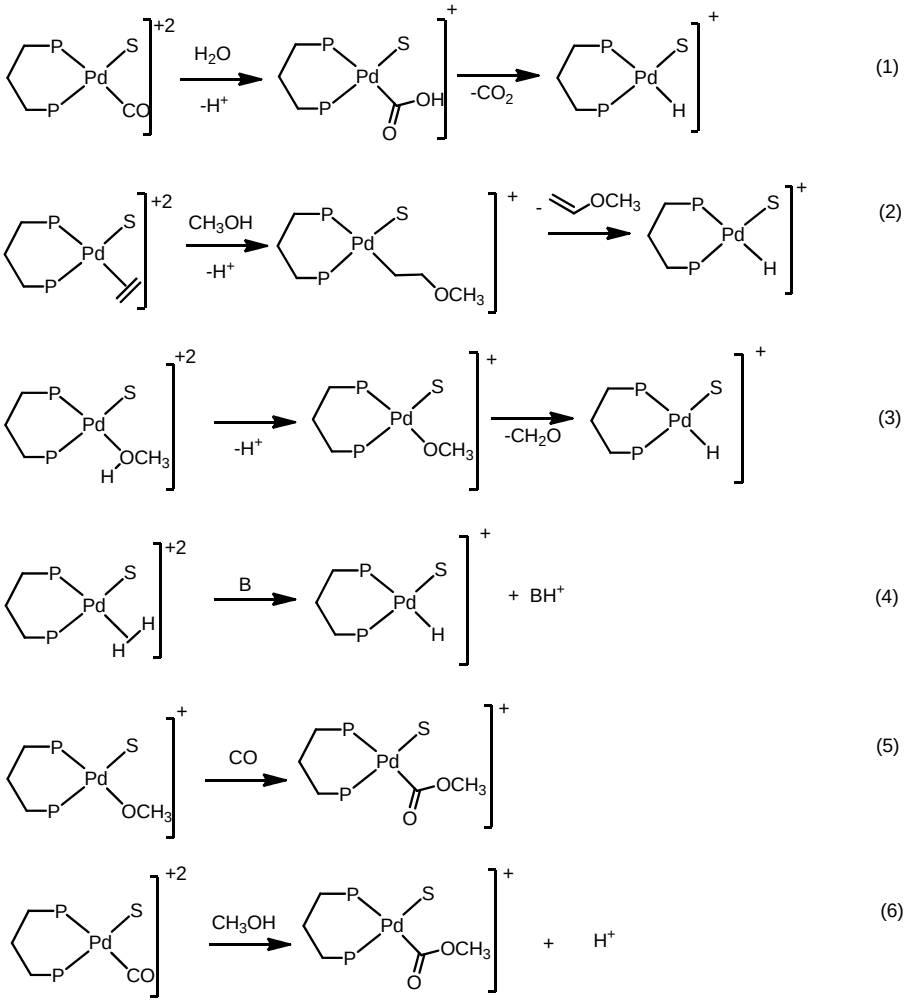
One of the key steps in the design of new catalytic systems is the understanding of the mechanisms operating in the catalytic reactions. NMR and IR spectroscopy are the most common tools to identify the resting states of the reactions in the study of the mechanism.[1] Theoretical calculations have also been used to determine transition states of low energy.[2] The important advances achieved using these techniques in the study of the intermediates for processes such as Rh-catalyzed hydroformylation are well-known.[3] However, the detection of the intermediates in Pd-carbonylation reactions has proven to be more difficult.[4]

In this section, an overview of some mechanistic aspects reported concerning the alkoxycarbonylation of alkenes using mono-and bidentate ligands will be described.

As shown in Chapter 1 (section 1.1.1), both palladium hydride and palladium carbomethoxy complexes are initiators in the alkoxycarbonylation reaction.[5] The palladium hydride can be generated by different ways, starting from palladium (0) or palladium (II) species.[4,6] The equation 1 (Scheme 3.1) show the formation of the hydride species by the water gas shift reaction, involving the nucleophilic attack of water to a palladium carbonyl. The Wacker type process (equation 2, Scheme 3.1),[7,8,9] leads to the hydride by insertion of an alkene in palladium-alkoxy bond, followed by the β-elimination of hydrogen.[10] The equation 3 (Scheme 3.1) shows the formation of Pd-H starting from a palladium-methoxy complex, in which formaldehyde is generated under reaction conditions. In some studies, hydrogen is used in order to favour the heterolytic formation of hydride in the presence of a divalent palladium-salt and a base (equation 4, Scheme 3.1).[11]

The formation of alkoxycarbonyl species can occur by CO insertion into a palladium-methoxy bond (equation 5, Scheme 3.1).[12,13] The Pd(II)-OMe

complex is formed by nucleophilic attack of methanol to palladium(II) precursor. The alkoxycarbonyl species can also formed by direct nucleophilic attack of methanol over the CO coordinated to Pd centre (equation 6, Scheme 3.1).[12,13]



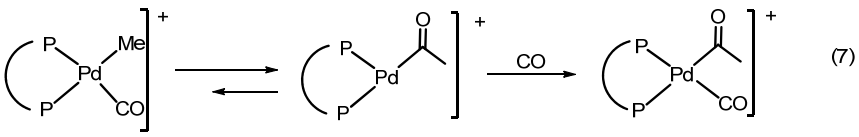
Scheme 3.1 Palladium hydride and carbomethoxy formation ways.

Experimental evidences of the hydride mechanism have been reported for systems modified with monodentate and bidentate ligands.[14,15,16] Neutral palladium complexes of the type [$PdHCl(PPh_3)_2$] can be synthesized by oxidative addition of strong acids, as HCl to Pd (0) complexes such as [$Pd(CO)(PPh_3)_3$] or [$Pd(PPh_3)_4$].[17] Related hydride complexes have been synthesized using others monophosphines such as PCy_3,[16] PBu_3.[18] The cationic hydride complexes of palladium can be prepared by several methods, for example by replacing an anion ligand in neutral palladium hydride with a neutral ligand,[19] or by the protonation of zero-valent palladium complexes.[20] There have been reports of the formation of cationic palladium hydrides containing a coordinated solvent molecule such as H_2O or CH_3CN.[21,22] Evidence of the formation of Pd(II) hydride of the type [$PdH(O_3SC_6H_4$-*p*-$Me)(PPh_3)_2$] from [$Pd(PPh_3)_2(C_2H_4)$] complex have been reported by Elsevier *et al.* [23] This palladium hydride complex is a key intermediate in the catalytic cycle for methoxycarbonylation of styrene. Iggo *et al.* [24] described the preparation of *trans*-[$PdH(Br)(PPh_3)_2$] by pressurizing palladium (II) complex [$PdBr_2(PPh_3)_2$] with H_2. These hydride complexes have been characterized by NMR and IR spectroscopy.

The presence of acid is often required in the alkoxycarbonylation reaction to promote catalytic activity via the formation of Pd-hydride species.[25] However, there is an interesting exception, in which high yields and excellent selectivities were achieved in the methoxycarbonylation of styrene using NMDPP and dicyclohexylphosphine in the absence of acid.[26] To the best our knowledge this behavior has not been investigated.

The nature of intermediate species present during the catalytic cycle has attracted the attention of many researchers. Firstly, if the initiator is a palladium-hydrido complex, the intermediate species formed will be a Pd-alkyl; whereas, if the catalytic cycle starts with carbomethoxy-palladium complex the intermediate complex formed will be a Pd-alkylcarbomethoxy species. In

copolymerization reactions, the formation of diesters suggests the insertion of alkenes in palladium carbomethoxy species.[6a] [Pd(alkyl)(ethene)] insertions are virtually excluded, because the CO insertion into the Pd-alkyl bond is 10^5 faster than ethene insertion, which avoids the double ethene insertion.[27] High pressure NMR studies with model compounds in aprotic solvents have provided interesting information on the energy barriers associated with the migratory insertion of CO and ethene occurring during the propagation step. It has been proved that the migratory insertion of CO in $[Pd(R)(CO)(P\text{-}P)]^+$ complexes (R=Me, Et) is reversible, following first order kinetics and it is therefore dependent of the CO concentration in solution (Scheme 3.2, equation 7).[28]

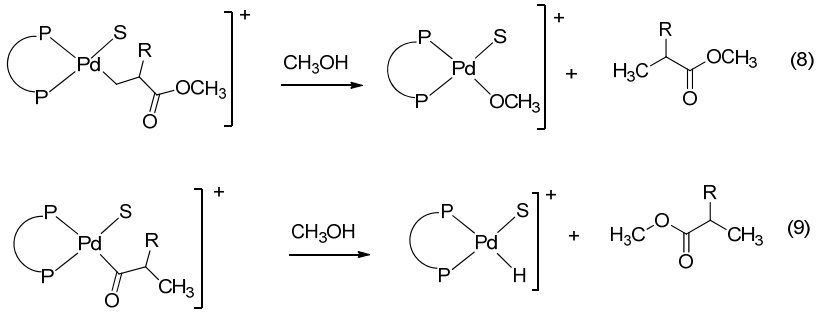


(7)

Scheme 3.2 Migratory insertion of CO into a Pd methyl bond.

In the methoxycarbonylation reaction two different ways to produce the ester have been proposed according to the mechanisms described: by methanolysis over the Pd-acyl complex to produce the palladium-hydride and the ester (equation 8, Scheme 3.3), or by protonolysis over a Pd-alkylcarbomethoxy complex to form the ester and the Pd-methoxy, the precursor of Pd-carbomethoxy complex (equation 9, Scheme 3.3). The methanolysis reaction has been recently studied by van Leeuwen,[16,29] Iggo,[30] Bianchini[31] and MacGregor,[32] focusing on the alcoholysis of palladium-acyl species. The *intra*-molecular attack of *cis*-coordinated methanol (equation 10, Scheme 3.4)[16,29,30] and the *inter*-molecular attack of methanol at the acyl carbon (equation 11, Scheme 3.4), have been proposed.[31,33] McGregor and coworkers investigated

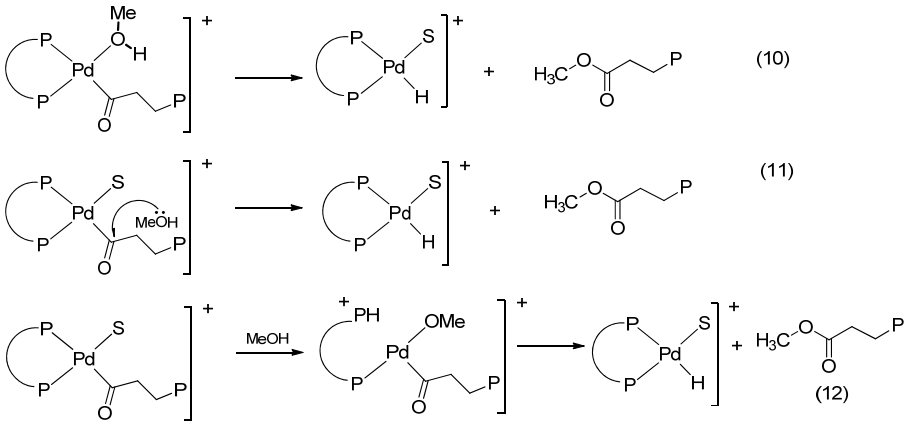
the *intra-* or *inter*-molecular methanolysis of Pd-acyl bonds and concluded that the *inter*-molecular attack may be important in this process and that the energetic barriers are strongly dependant on the metal coordination environment. They calculated the activation energies for *inter*-molecular attack of MeOH on $[Pd\{C(O)Et\}(P\text{-}P)(L)]^+$ species where L= CO, MeCN, or MeOH and reported that methanolysis occurs when L=CO or MeOH, but not when L=MeCN, which is in agreement with experimental data.[31] They also studied the behavior of the monophosphine systems *cis* and *trans*-$[Pd\{C(O)Et\}(PPh_3)_2(MeOH)]^+$ and reported that the transition state is somewhat higher for the *cis* species than for the *trans* complex. Furthermore, they predicted that the loss of a PH_3 ligand to form an acyl unsaturated species would greatly facilitate the methanolysis step.



Scheme 3.3 Proposed pathways for the formation of the ester product.

A third proposal for the methanolysis suggests a decoordination of an arm of the diphosphine followed by the protonation of the free phosphine moiety to generate a methoxy group on the palladium centre (equation 12, Scheme 3.4).[32,34] The elimination of the ester and transfer of the proton form the protonated phosphine to palladium and recoordination of the phosphine

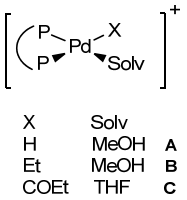
moiety complete the methanolysis. In some cases, the methanolysis has been proposed to be the rate determining step.[33,35]



Scheme 3.4 Different mechanistic ways for termination step in carbonylation reactions.

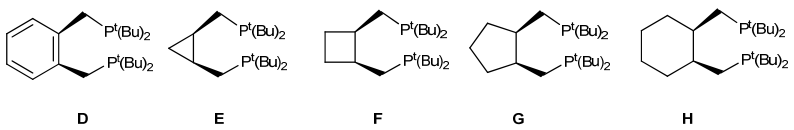
Mechanistic studies into the palladium-catalyzed alkoxycarbonylation reaction using bidentate ligands have also been performed. Zacchini *et al*, reported an investigation which provided spectroscopic evidences for all intermediates in the hydride catalytic cycle for the methoxycarbonylation of ethene.[36] They observed that [PdH(L-L)(MeOH)X)] (**A**) complexes (where L-L=1,2-bis-$(CH_2PBu^t_2)_2C_6H_4$ and X= BF_4^-, $CF_3SO_3^-$) were formed by reaction of [Pd(L-L)(dba)] with methanol and HBF_4 or CF_3SO_3H in the presence of oxygen or benzoquinone.[14] The hydride complex $[PdH(L\text{-}L)(MeOH)]^+$ was shown to reacts with ethene at room temperature forming the alkyl palladium complex $[Pd(L\text{-}L)Et(MeOH)]^+$ (**B**). The ethyl complex was stable in THF at low temperature. On adding 1 equiv of CO to $[Pd(L\text{-}L)Et(THF)]^+$, [Pd(L-

L)COEt(THF)]$^+$ (**C**) was immediately formed. All these intermediates were identified by multinuclear NMR spectroscopy and ^{13}C labeling[37] (Scheme 3.5).



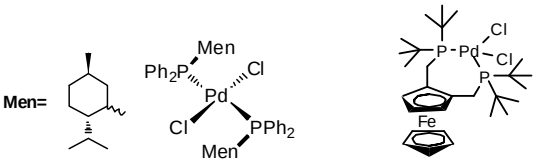
Scheme 3.5 Intermediates characterized by Zacchini *et al.* in the Pd-catalyzed methoxycarbonylation of ethene.

Recently, Iggo and co-workers reported a HP-NMR study of the methoxycarbonylation of ethene catalyzed by palladium complexes bearing bidentate ligands.[38] They observed that palladium complex [Pd(O_2CCF_3)(L-L)]$^+$ (where L-L=1,2-bis-($CH_2PBu^t_2$)$_2C_6H_4$) (**D**) was converted under catalytic conditions to the hydride complex [Pd(H)(MeOH)(L-L)]$^+$ on heating in a methanolic solution. In agreement with Zacchini's report, the formation of an ethyl complex in the absence of CO was observed by in situ NMR studies. The protonation of the diphosphines **E-H** (Scheme 3.6) by reaction with methanesulfonic acid and the role of the corresponding protonated phosphines in catalysis were studied.



Scheme 3.6 Phosphine ligands studied in the palladium asymmetric methoxycarbonylation of ethene.

In chapter 2 (section 2.2), we described the catalytic performances of the complex the [$PdCl_2$(**6**)$_2$] (**6a**) and [$PdCl_2$(**2**)] (**2a**) (Scheme 3.7) in the methoxycarbonylation of norbornene. The use of both palladium systems provided good activity and selectivity in this process. In this chapter, our NMR investigations on these catalytic systems using HP NMR techniques are described.



6a **2a**

Scheme 3.7 Complexes used in the NMR studies.

3.2 Results and discussion

3.2.1 Study of the monophosphine system [$PdCl_2$(**6**)$_2$] (**6a**) under methoxycarbonylation conditions

As mentioned in chapter 2 (section 2.2), when [$PdCl_2$(**6**)$_2$] (**6a**) was used as the catalyst precursor in the Pd-catalyzed methoxycarbonylation of norbornene, total chemoselectivity to the ester formation (100%) and *exo*-selectivity (100%) were achieved in the absence of acid, in contrast with most of the catalytic systems used in the methoxycarbonylation reaction of alkenes.[39] In this chapter, NMR investigations on the formation of catalytically active species for [$PdCl_2$(**6**)$_2$] (**6a**) under catalytic conditions are described.

In order to obtain information about the behaviour of this catalytic system, the reactivity of complex **6a** towards all reagents present during catalysis was first investigated using HP NMR techniques. Later, the reactivity of this complex towards methanol, CO, and norbornene was studied separately and in a stepwise fashion. The results obtained are described in the following sections.

a) Reaction of complex 6a in the presence of norbornene and carbon monoxide (30 atm) in CD_3OD/THF

First, we studied the reaction of complex **6a** in the presence of norbornene (10 equiv.) and carbon monoxide (30 atm) in CD_3OD/THF.

A 10-mm HP NMR sapphire tube was therefore charged with a solution of complex [$PdCl_2$(**6**)$_2$] **6a** in a mixture of CD_3OD/THF (ratio 1:1 in volume). A first $^{31}P\{^1H\}$ NMR spectrum was acquired at room temperature before pressurizing with CO. In this spectrum, a signal with singlet multiplicity at δ=22.7 ppm corresponding to the starting material [$PdCl_2$(**6**)$_2$] **6a** was readily detected (Figure 3.1, a).

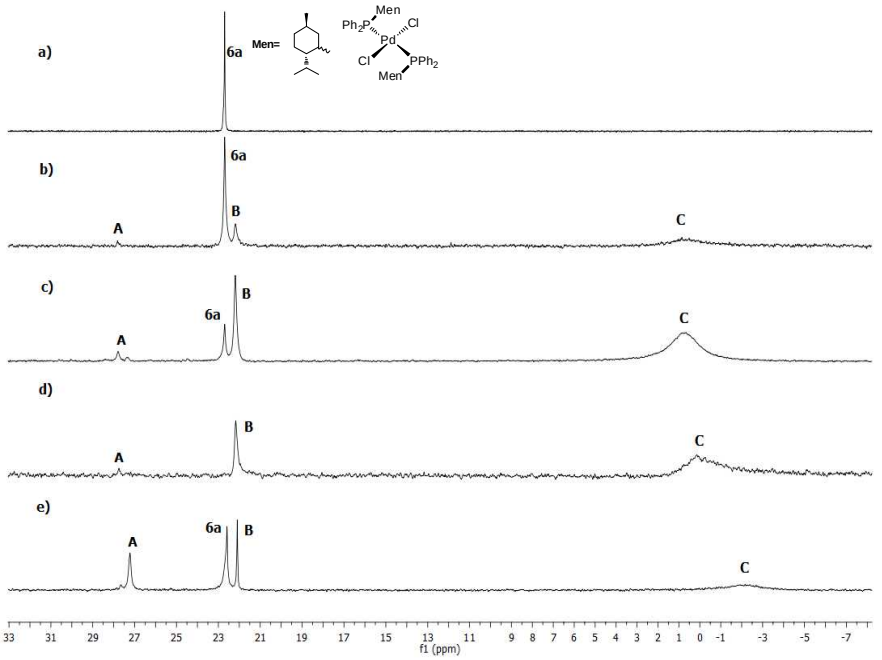


Figure 3.1 Sequence of $^{31}P\{^{1}H\}$ NMR spectra at RT. a) **6a** in CD_3OD/THF b) **6a** + 10 equiv. NBN + 30 atm CO in CD_3OD/THF after 5 hours shaking c) **6a** + 10 equiv. NBN + 30 atm CO in CD_3OD/THF after 4 days d) **6a** + 10 equiv. NBN + 30 atm CO in CD_3OD/THF after one week e) **6a** + 10 equiv. NBN in CD_3OD/THF after releasing CO pressure.

Norbornene (10 equiv.) was then added and the tube was charged with 30 atm of CO. No significant changes in the $^{31}P\{^{1}H\}$ spectrum was observed during the first 4 hours under these conditions. However, after shaking the NMR tube during 5 hours outside of the spectrometer, new signals were observed at δ= 27.3 (**A**, s), 22.1 (**B**, s) and 0.79 ppm (**C,** br s) (Figure 3.1, b). The presence of signals for **6a** at 22.7 ppm and a small amount of phosphine oxide at 36.1 ppm (not shown in Figure 3.1) was also detected. At longer reaction times under these conditions, the same signals were detected (Figure 3.1, c). The decrease in

intensity of the signal corresponding to the starting material **6a** and the increase of signals at δ=22.1 (**B**, s) and 0.79 (**C**, br s) ppm was significant. After one week, the signal for **6a** was no longer observed and only signals for **A**, **B** and **C** were detected (Figure 3.1, d). When the CO pressure was released and a new $^{31}P\{^{1}H\}$ NMR spectrum was acquired at room temperature, the signal corresponding to **6a** was again detected (Figure 3.1, e), indicating the occurrence of a reversible process involving CO.

When the experiment was repeated using ^{13}CO, in the corresponding $^{13}C\{^{1}H\}$ NMR spectrum at room temperature two signals were detected at δ= 177 and 185 ppm. These signals were readily assigned to the ester product and free CO, respectively. The detection of the former signal indicated that the methoxycarbonylation reaction was taking place.

In order to investigate the effect of temperature, a new sample of complex **6a** was prepared in CD_3OD/THF (Figure 3.2, a) and norbornene (10 equiv) was added, the solution was then transferred into a 10-mm high-pressure (HP) NMR tube and charged with 30 atm of CO and the temperature raised to 353 K. In the corresponding $^{31}P\{^{1}H\}$ NMR spectrum, only four signals were observed: that of the phosphine oxide at δ=36.1 (s, not shown in the Figure 3.2), that of **6a** and signals **A** and **C** at δ=27.3(s), and -0.9 (br s, shifted from 0.79 to -0.9) ppm, respectively (Figure 3.2, b). After warming this sample overnight at 353 K, the same four signals were observed. The decrease in intensity of the signal for **6a** and the increase in intensity of signal **C** was significant (Figure 3.2, c). At longer reaction times at 353 K, the $^{31}P\{^{1}H\}$ NMR spectrum only showed three signals, the phosphine oxide, and signals **A** and **C** (Figure 3.2, d). In these experiments, the absence of the previously detected signal **B** was evident and suggested that the corresponding species was either not formed or reacted very rapidly at this temperature.

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CARBONYLATION PROCESSES
Carolina Blanco Jiménez
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In the carbonyl region of the corresponding $^{13}C\{^1H\}$ NMR spectrum, only the two signals corresponding to the ester product (δ=177 ppm) and free CO (δ= 185 ppm) were observed.

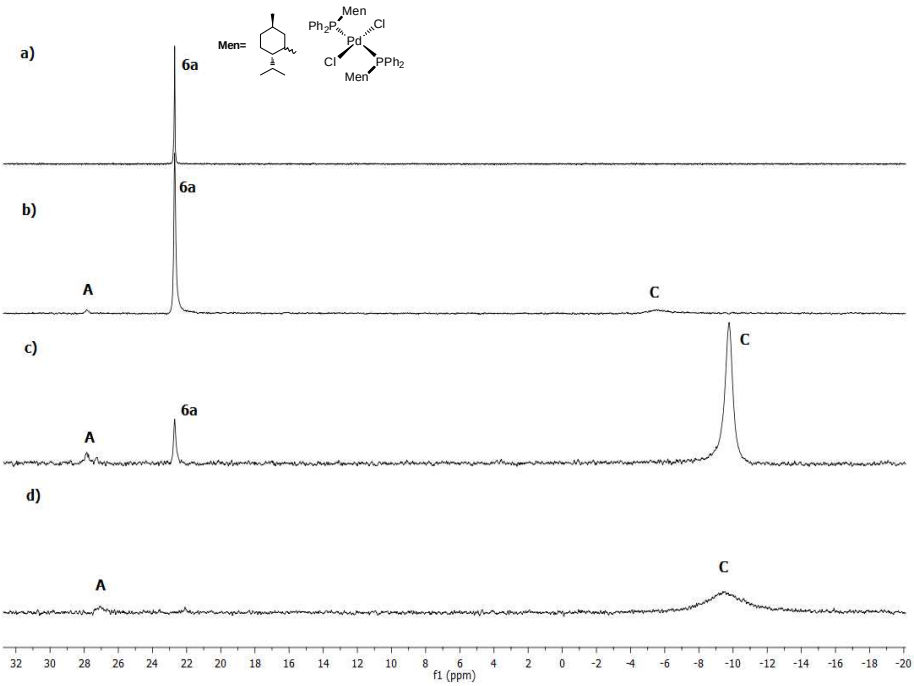


Figure 3.2 Sequence of $^{31}P\{^1H\}$ NMR spectra at variable temperature. a) **6a** in CD_3OD/THF at RT b) **6a** + 10 equiv. NBN + 30 atm CO in CD_3OD/THF at 353 K initial c) **6a** + 10 equiv. NBN + 30 atm CO in CD_3OD/THF overnight at 353 K d) **6a** + 10 equiv. NBN + 30 atm CO in CD_3OD/THF after 2 days at 353 K.

To conclude, we observed the presence of the three new signals **A**, **B** and **C** when the reaction of complex **6a** in the presence of norbornene and carbon monoxide in CD_3OD/THF was studied. The presence of phosphine oxide was

also detected. The detection of the signal corresponding to the methoxycarbonylation ester product indicated that the catalytic reaction had taken place. However, no signals corresponding to Pd-CO coordinated complexes could be observed by $^{13}C\{^{1}H\}$ NMR spectroscopy.

In order to get more information about the identity of the signals **A**, **B** and **C**, the reactivity of this complex towards methanol, norbornene and carbon monoxide was investigated separately, and the results are described in the next sections.

b) Complex 6a in CD_3OD/THF

In order to investigate the stability of the complex **6a** in the solvent mixture used during catalysis, a CD_3OD/THF solution of the complex **6a** was charged into a 5-mm NMR tube fitted with a Young's tap. The singlet signal at 22.7 ppm corresponding to the starting material **6a** was readily detected in the $^{31}P\{^{1}H\}$ NMR spectra acquired at room temperature (Figure 3.3, a). When a new $^{31}P\{^{1}H\}$ NMR spectrum was acquired at 343 K, the previously detected singlet signal **A** at δ=27.3 ppm was observed as a minor product, together with those of phosphine oxide and the starting material **6a**. The decrease in intensity of the signal corresponding to the starting material **6a** was significant (Figure 3.3, b). At longer reaction times, the increase of signals assigned to the phosphine oxide and signal **A** was significant at this point (Figure 3.3, c). At this stage, the NMR tube was taken out from the spectrometer and a large amount of palladium black was observed in the tube, indicating the decomposition of palladium species under these conditions. Such a reduction reaction was previously reported under similar conditions.[40] The reduction of Pd(II) species to Pd(0) in presence of an excess of monodentate and bidentate phosphines in presence of alcohols was described by several groups. For example, triphenylphosphine was shown to enable the reduction of Pd(II) metal centre

to Pd(0) in presence of alcohols, being itself oxidized to triphenylphosphine oxide during this process. [40]

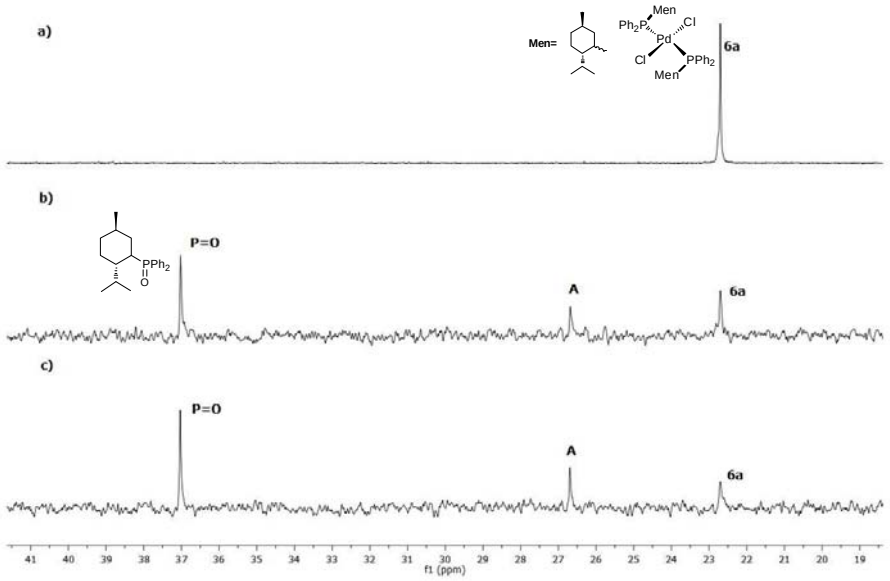


Figure 3.3 Sequence of $^{31}P\{^{1}H\}$ NMR spectra of complex **6a** in CD_3OD/THF a) Initial at RT b) After a few minutes at 343 K c) After 4 hours at 343 K.

c) Reaction of complex 6a in the presence of norbornene in CD_3OD/THF-d_8

In view of the results described in the previous section, the experiment was repeated in the presence of norbornene. One of the aim of this experiment was to investigate whether Pd species such as a Pd-H or Pd-OMe species were formed during the reduction of Pd(II) to Pd(0) in methanolic solution.

However, when the experiment was carried out and monitored by multinuclear NMR spectroscopy, no new signals were detected. Interestingly, although signals for the phosphine oxide and **A** were again detected, the presence of bulk

palladium metal was not observed, even when the solution was warmed up to 353 K for several hours. The ^{1}H signals corresponding to norbornene remained unchanged throughout the experiment, indicating that no reaction involving this species had taken place. It was therefore concluded that the reduction of Pd(II) to Pd(0) was somewhat inhibited by the presence of norbornene and that no reactive Pd species towards this substrate were formed during the reaction.

d) Reaction of complex 6a in the presence of carbon monoxide (30 atm) in CD_3OD/THF

In this section, the reactivity of complex **6a** in CD_3OD/THF towards carbon monoxide was investigated.

A solution of the precursor **6a** in a mixture of CD_3OD/THF (ratio 1:1 in volume) was prepared and placed into a 10-mm high pressure (HP) NMR tube (Figure 3.4, a). After pressurizing the tube with 30 atm of CO, a $^{31}P\{^{1}H\}$ NMR spectrum was acquired at room temperature being the only signal detected which correspond to the complex **6a** at δ= 22.7 ppm. The reaction was then monitored by ^{31}P NMR and after 4 hours at room temperature, a new singlet signal at δ= 22.1, previously assigned as **B**, was detected together with the resonance corresponding to the phosphine oxide (Figure 3.4, b). At longer reaction times, the intensity of the signal at δ= 22.7 ppm corresponding to the starting material **6a** decreases, while the signal **B** at δ= 22.1 ppm was observed to increase significantly (Figure 3.4, c). The signal **C** was also detected as a broad singlet resonance at δ= 0.9 ppm and corresponded to the major phosphine containing product. The ratio of intensity of the ^{31}P signals **6a**/**B**/**C** was measured at this point to be 1/4/15. After four days at room temperature, the signal corresponding to the starting complex **6a** was not observed and only three signals were detected: the broad singlet resonance at δ=0.9 ppm (**C**), the signal **B** at δ= 22.1 ppm, and the phosphine oxide at δ= 36.1 ppm (Figure 3.4, d). When the experiment was repeated using CO enriched with ^{13}CO in the

carbonyl region of the corresponding $^{13}C\{^1H\}$ NMR spectra recorded at room temperature and at 203 K, only one resonance attributed to free CO was detected at δ= 185 ppm.

From this experiment we can conclude that species corresponding to signals **B** and **C** were formed under CO although they do not contain a Pd-carbonyl group coordinated.

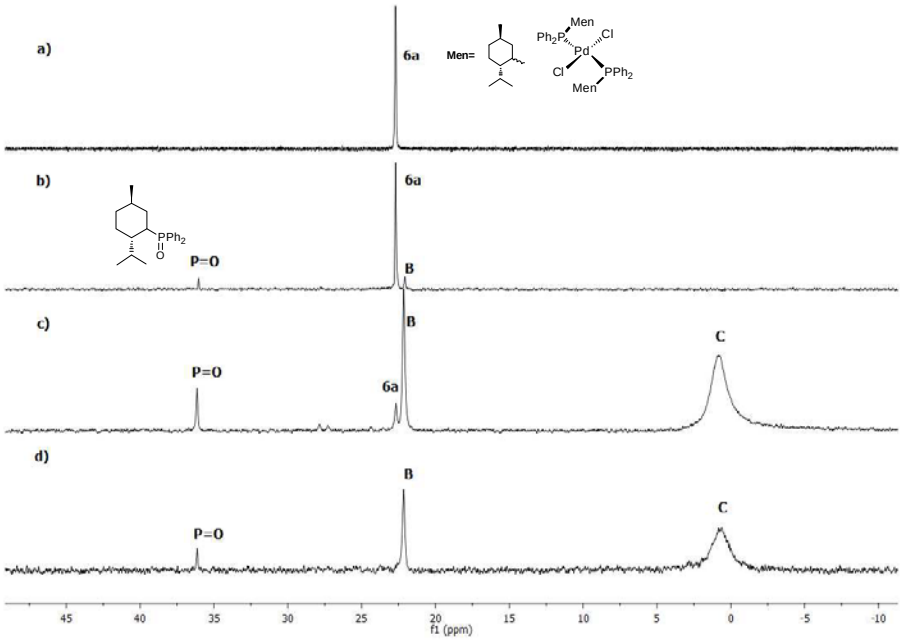


Figure 3.4 Sequence of $^{31}P\{^1H\}$ NMR spectra at RT. a) **6a** in CD_3OD/THF b) **6a** + 30 atm CO in CD_3OD/THF after 4 hours shaking c) **6a** + 30 atm CO in CD_3OD/THF after 2 days d) **6a** + 30 atm CO in CD_3OD/THF after 4 days.

When the experiment was repeated to 343 K, the signal **B** was not detected in the corresponding $^{31}P\{^1H\}$ NMR spectra. After 45 minutes at this temperature, only three signals were observed: the signal corresponding to **6a**, that of

phosphine oxide at 36.1, and the signal **C** detected as a broad singlet at δ= 0.42 ppm (Figure 3.5, b). When the sample was heated at 343 K for two hours, only two signals were present, the phosphine oxide at δ= 36.1 and the broad singlet **C** at -2.40 ppm (Figure 3.5, c). The presence of Pd black was significant at this stage, again indicating the decomposition of palladium species.

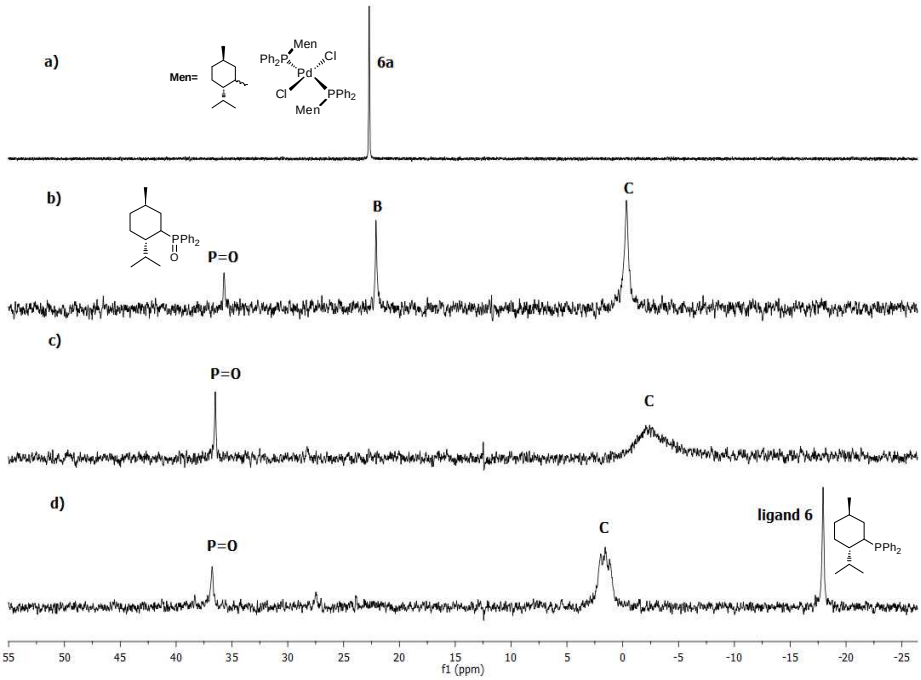


Figure 3.5 Sequence of $^{31}P\{^{1}H\}$ NMR spectra at variable temperature. a) **6a** in CD_3OD/THF at RT b) **6a** + 30 atm CO in CD_3OD/THF after 45 min at 343 K c) **6a** + 30 atm CO in CD_3OD/THF after 2 hours at 373 K d) **6a** + 30 atm CO in CD_3OD/THF at 183 K.

When a $^{31}P\{^{1}H\}$ spectrum was acquired at low temperature (183 K) (Figure 3.5, d), the signal **C** resolved into two distinct resonances at δ = 2.9 and -16.5 ppm. The latter signal was readily assigned to the free ligand **6**. The 1:1:1 multiplicity of the signal at δ = 2.9 ppm suggested that the corresponding species contained a P-D bond (J_{PD}= 72 Hz). When the temperature was raised back to room temperature, coalescence of the two signals was again observed, indicating that rapid interconversion between these two species was taking place at this temperature.

When the experiment was repeated under ^{13}CO-enriched mixture, only the singlet resonance corresponding to free CO was detected in the carbonyl region of the $^{13}C\{^{1}H\}$ NMR spectra.

It was therefore concluded that complex **6a** reacts with carbon monoxide in the presence of CD_3OD/THF, yielding the species corresponding to signals **B** and **C**. The signal **B** was not observed when the temperature was raised to 343 K, suggesting that this species reacts rapidly under these conditions. Furthermore, the failure in detecting CO-containing species by ^{13}C NMR corroborates this hypothesis. As only complex **6a**, CO and the solvent mixture were present, it was proposed that reaction with methanol could be taking place under these conditions and to confirm this hypothesis, the reaction was next repeated in neat THF-d_8.

e) Reaction of complex 6a in the presence of carbon monoxide (30 atm) in THF-d_8

A solution of the precursor **6a** in a mixture of THF-d_8 (Figure 3.6, a) was prepared and placed into a 10-mm high-pressure (HP) NMR tube. After pressurizing the tube with 30 atm of CO enriched with ^{13}CO, a $^{31}P\{^{1}H\}$ NMR spectrum was acquired at room temperature and the signal at δ= 22.7 ppm corresponding to the starting material **6a** was readily detected. Under these conditions, no others signals were observed. No changes were observed during

the following hours by ^{31}P NMR spectroscopy. However, after 14 hours, a new weak signal was detected at 30.7(**D**) ppm (Figure 3.6, b). At longer reaction time, this new signal did not increase significantly in intensity. The detection of this signal indicates that **6a** was reacting under these conditions. When the temperature was decreased to 193 K, the same two previously signals at δ= 22.7 (complex **6a**) and a singlet resonance at 30.7(**D**) ppm were again observed, together with a broad resonance at -16.5 ppm readily assigned to the free ligand **6**. The detection of free ligand **6** in solution suggested that a substitution reaction for **6a** was taking place. In the corresponding $^{13}C\{^{1}H\}$ NMR acquired at room temperature, two signals were detected in the carbonyl region of the spectrum at δ= 185 and 183 ppm. The former singlet signal was readily assigned to free CO. The latter signal was detected as a broad singlet and was attributed to a carbonyl ligand coordinated to palladium complex. The presence of the new ^{31}P signal at δ 30.7(**D**) suggested that the Pd-CO species contained a phosphorus ligand. Furthermore, the broad singlet multiplicity of the ^{13}C signal suggested the *cis* arrangement of the CO ligand and the PR_3 ligand.

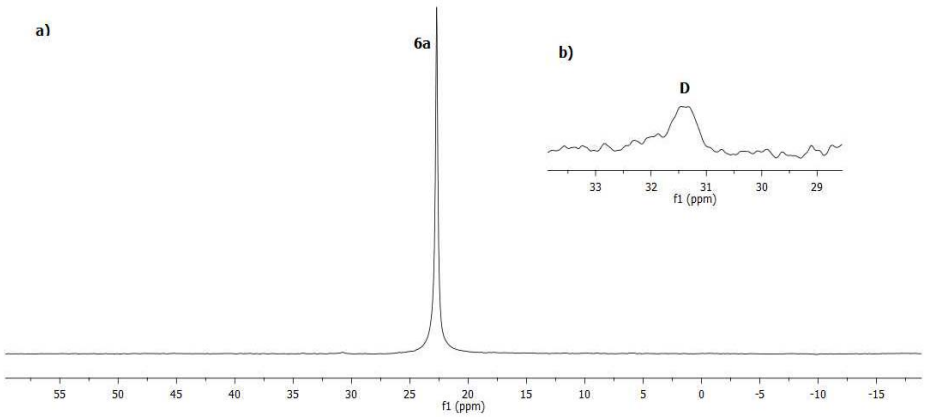
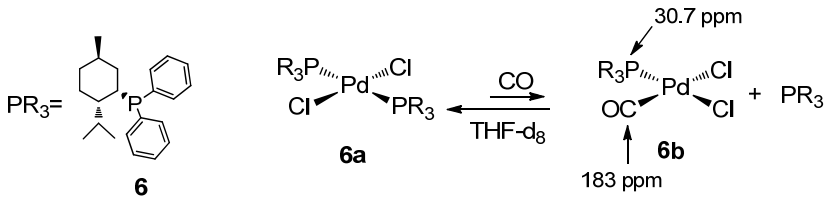


Figure 3.6. Sequence $^{31}P\{^{1}H\}$ NMR spectra. a) **6a** in THF-d_8 at RT b) **6a** + 30 atm CO in THF-d_8 after 14 hours at RT.

When the CO pressure was released from the NMR tube and a new spectrum was acquired, the signal at 30.7(**D**) ppm was not detected, suggesting that the formation of the corresponding species under CO pressure was reversible.

In view of these observations, the species resonating at δ 30.7(**D**) was identified as complex [$PdCl_2$(**6**)(CO)] **6b** (Scheme 3.8)



Scheme 3.8 Proposed structure for the complex [$PdCl_2$(**6**)(CO)] **6b**.

In section 3.2.1 (d), the formation of species containing a P-D(H) bond was proposed. In this section, experiments aiming at identifying this species are described.

f) Reaction of ligand 6 in the presence CD_3OD/THF-d_8

In order to probe if ligand **6** can be protonated in presence of methanol, the reactivity of this ligand was studied in presence of CD_3OD/THF-d_8 mixture. The presence of THF was required to solubilize ligand **6**.

However, no reaction was observed and it was concluded that this ligand was stable in methanolic solution.

g) Reaction of ligand 6 in the presence HCl (1 equiv.) in MeOH/THF

Next, the reaction of ligand **6** in presence of HCl was investigated. When a sample of ligand **6** was dissolved in a mixture MeOH/THF (Figure 3.7, a), 1 equiv. of HCl was added and the solution charged into a 5-mm NMR tube

fitted with Young's tap and a $^{31}P\{^{1}H\}$ NMR spectrum was acquired, only the signal **C** was detected at δ=0.79 ppm (Figure 3.7, b). When a $^{31}P\{^{1}H\}$ NMR spectrum was acquired at 183 K, two signals were then observed at 0.79 (**C**) ppm and at -16.5 ppm (Figure 3.7, c). The latter signal corresponded to the free ligand ligand **6**. The decoalescence of this signal at low temperature was previously described in section 3.2.1(d).

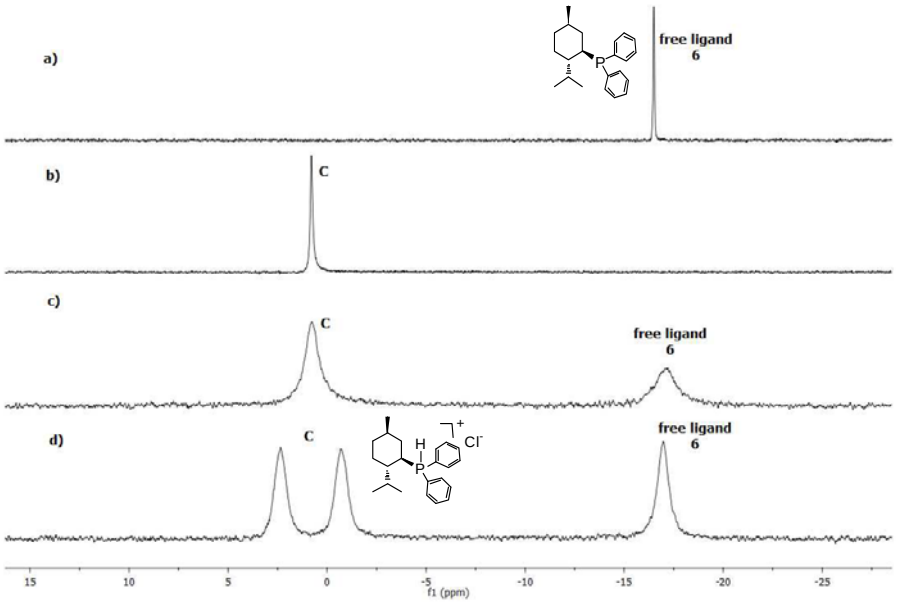
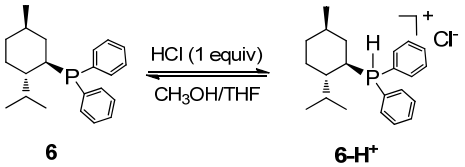


Figure 3.7 Sequence of ^{31}P NMR spectra. a) **6** in MeOH/THF at RT b) **6** + 1 equiv. HCl in MeOH/THF at RT c) **6** + 1 equiv HCl in MeOH/THF at 183 K d) ^{1}H coupled ^{31}P NMR spectrum of **6** + 1 equiv HCl in MeOH/THF at 183K.

When a ^{1}H coupled ^{31}P NMR spectrum was acquired at 183 K the ^{31}P signal resonating at δ= 0.79 ppm exhibited a doublet multiplicity J_{P-H}= 506 Hz (Figure 3.7, d). The value of the P-H coupling is characteristic of a P-H

moiety.[21,41] The species corresponding to signal **C** was therefore identified as the protonated monophosphine **6**-H$^+$ in equilibrium with monophosphine **6** (Scheme 3.9). It was then concluded that the protonated ligand **6**-H$^+$ is formed under methoxycarbonylation conditions, as described in Section 3.2.1(d).



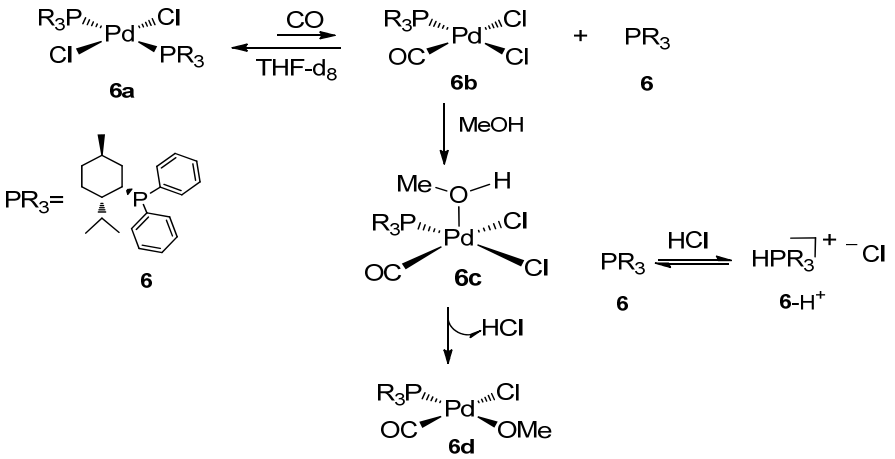
Scheme 3.9 Reaction of ligand **6** in the presence of HCl (1 equiv) in MeOH/THF.

Previous reports described the formation of protonated phosphine ligands under methoxycarbonylation conditions.[388,42] However, the protonation of the phosphine ligands usually occurs by reaction of the excess of acid which is usually used to produce the active species from the Pd precursors. In this system, no added acid was used. The detection of such a species therefore implied the in situ generation of acid from the catalytic mixture.

A solution of **6**-H$^+$ was again prepared in CH_3OH/THF and diethyl ether was added but no precipitation of the protonated phosphine was achieved. Hexane and pentane were also probed without success to precipitate the product **6**-H$^+$. After evaporation of the solution containing **6**-H$^+$ under vacuum, a white solid was isolated. Once re-dissolved in toluene-d_8, a new $^{31}P\{^1H\}$ NMR spectrum was acquired at room temperature and only one signal was observed at δ=-16.5 ppm and readily assigned to the free ligand **6**. The overall experiment was also performed in CD_2Cl_2 and identical results were obtained.

In view of these unsuccessful attempts to isolate the protonated phosphine, it was concluded that an equilibrium between the ligand **6** and its protonated form **6**-H^+ was taking place.

These experiments showed that the signal **C**, previously detected in Sections 3.2.1(a) and (d), corresponded to the average signal arising from the rapid interconversion between **6** and **6**-H^+ under these conditions. The signals corresponding to both species were detected at low temperature, apparently due to the lower rate of interconversion at 183 K. As ligand **6** was shown to be stable towards protonation in methanolic solution (Section 3.2.1(f)), the in situ generation of a stronger acid when complex **6a** is placed under CO pressure was indicated. The generation of HCl in methanol from a Pd complex containing a chloride ligand was previously reported.[43] We therefore concluded that similar reactivity was taking place in the presence of MeOH from the previously identified species [$PdCl_2$(**6**)(CO)] **6b**, which is generated from complex **6a** under CO (Scheme 3.10).



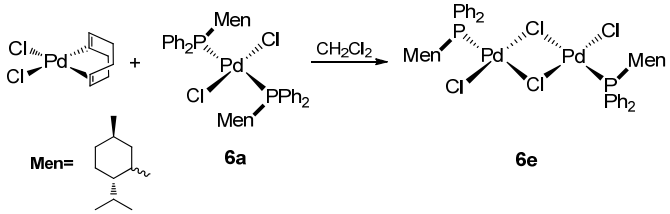
Scheme 3.10 Proposed mechanism for the formation of **6**-H^+.

Interestingly, the signal **A** at δ 27.3 ppm was also observed in weak intensity during this experiment. Although the low concentration of the corresponding species did not permit its identification, this observation indicated that this signal, previously described in section 3.2.1(a), was arising from a species that does not contain Pd.

Next, in order to investigate the identity of the species corresponding to the signal **B**, several experiments were carried out and are described in the following sections.

h) Synthesis of [Pd(μ-Cl)(Cl)(6)]$_2$ (6e)

As the detection of dinuclear palladium complexes of formula [Pd(μ-Cl)(Cl)(PR$_3$)]$_2$ was previously reported in related studies of palladium catalysed methoxycarbonylation reactions,[42] the synthesis of such dinuclear complex bearing the ligand **6** was carried out in order to investigate whether the signal **B** arose from such a species or from reaction products of this dinuclear complex under methoxycarbonylation conditions.



Scheme 3.11 Synthesis of [Pd(μ-Cl)(Cl)(**6**)]$_2$ (**6e**).

Complex **6e** was obtained by stirring a solution of [PdCl$_2$(COD)] and [PdCl$_2$(**6**)$_2$] (**6a**) overnight at room temperature (Scheme 3.11). The product was precipitated by addition of diethyl ether and obtained as a yellow powder in

48% yield. In the $^{31}P\{^{1}H\}$ NMR spectra of complex **6e**, a single resonance at δ=38.9 ppm was observed at room temperature. From this experiment, we concluded that the signal **B** at δ=22.1 ppm does not arise from the dimeric complex **6e**.

Next, the reactivity of the complex **6e** under CO in MeOH/THF was investigated.

i) Reactivity of dimer 6e and the protonated monophosphine 6-H$^+$ in the presence of carbon monoxide (30 atm) in CD_3OD/THF

When a sample of dimer **6e** was dissolved in CD_3OD/THF and 1 equiv. of protonated phosphine **6-**H$^+$ was added to the solution, the $^{31}P\{^{1}H\}$ NMR spectra acquired showed a singlet resonance at δ=22.7 ppm corresponding to the complex $[PdCl_2(\mathbf{6})_2]$ **6a** (Figure 3.8, a). The solution was then transferred into the 10-mm high-pressure NMR tube and charged with 30 atm of CO. A $^{31}P\{^{1}H\}$ NMR spectrum was acquired at room temperature and three signals were detected: the resonance arising from **6a**, a singlet resonance at 22.9(**E**) ppm (minor) and the signal corresponding to the phosphine oxide at δ=36.1 ppm (Figure 3.8, b). At longer reaction times, no changes in the spectrum were evident. After releasing the CO pressure, a new $^{31}P\{^{1}H\}$ NMR spectrum was recorded, and the same signals were observed. To verify the identity of the species arising from these signals, a sample of complex **6a** was added to the solution. In the corresponding $^{31}P\{^{1}H\}$ NMR spectrum, the signal at δ=22.7 ppm appeared significantly increased in intensity, indicating that complex **6a** was the main product of the reaction of the dimer **6e** in the presence of the protonated phosphine **6-**H$^+$ in CD_3OD/THF (Figure 3.8, c). However, the formation of the signal resonating at δ= 22.9(**E**) ppm under CO pressure was intriguing since no such signal was detected when the reactivity of **6a** under CO pressure was previously investigated. This observation suggested that this signal arose from a species formed through reaction of dimer **6e** with CO.

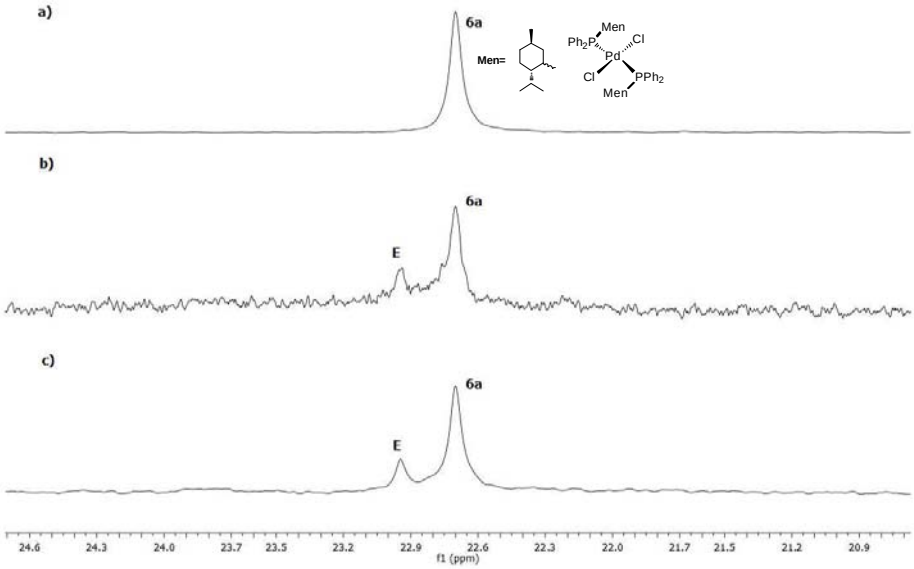


Figure 3.8 Sequence of ^{31}P NMR spectra. a) Complex **6e** and the protonated monophosphine **6-**H^+ in CD_3OD/THF at RT b) **6e** + 1 equiv **6-**H^+ + 30 atm CO in CD_3OD/THF at RT c) **6e** + 1 equiv **6**-H^+ after releasing CO pressure + 1 equiv **6a**.

When the reaction was repeated in a mixture of proteo methanol in THF-d_8 and 1 equiv. of protonated phosphine **6-**H^+ was added to the solution, and an ^1H NMR spectrum acquired at room temperature, one triplet signal ($J_{P\text{-}H}$= 13.6 Hz) was observed in the hydride region at δ= -13.9 ppm (Figure 3.9).

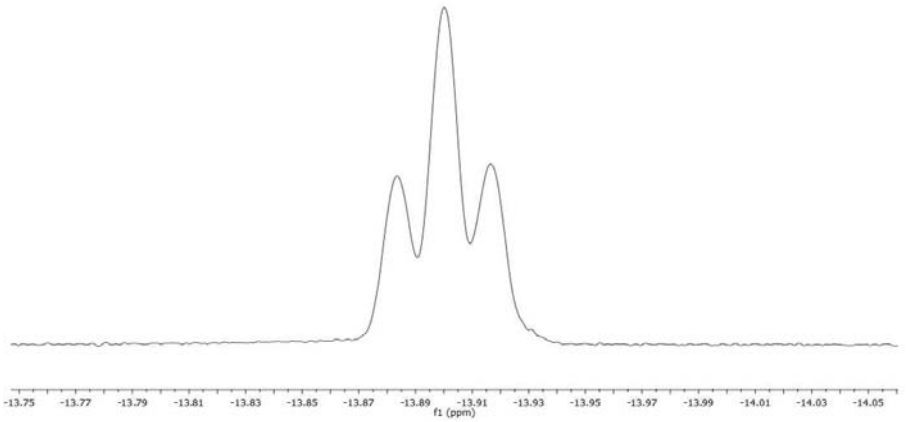
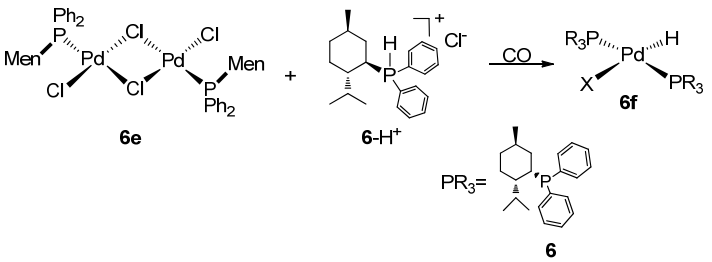


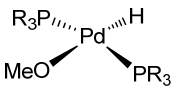
Figure 3.9 Selected region of ^{1}H NMR spectrum. Complex **6e** with protonated phosphine **6**-H^+ after releasing CO pressure in CD_3OD/THF at RT.

It was therefore concluded that species from the reaction of **6e** in the presence of **6**-H^+, CO and methanol leads to the formation of the hydride species **6f** containing two phosphine ligands in *trans* position to each other (Scheme 3.12). However, the nature of the fourth ligand (described as –X in Scheme 3.12) required to complete the coordination sphere of this species could not be identified.

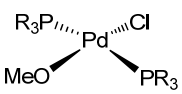


Scheme 3.12 Formation of [$PdHX(PR_3)_2$] (**6f**) from the reaction between dimer **6e** and the protonated phosphine **6**-H^+.

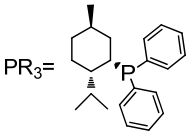
However, the similarity of the chemical shifts of the signals corresponding to species **6a**, **6f** and signal **B** indicated that these complexes present similar structures. As ^{31}P chemical shifts for cationic complexes would be expected to be rather distinct, we concluded that all three species could be neutral, which ruled out X= CO or MeOH. This proposal is in agreement with the non-detection of any carbonyl signal for the species corresponding to signal **B**. In view of these observations, we propose that these species contained a methoxy group, such as described in Scheme 3.13. Therefore the signal **B** was attributed to the species **6g**.



6f



6g



6

Scheme 3.13 Proposed structure for signals corresponding to species **6f** and **6g**.

In the Chapter 2, section 2.2, the norbornene concentration was shown to strongly affect the chemoselectivity of the methoxycarbonylation of norbornene reaction since at high concentration of this substrate, the formation of copolymers CO/NBN was significant. In view of these results, we decided to look at the reaction using HP NMR techniques at various norbornene concentrations and the results are described in the next section.

j) NMR study of the effect of the norbornene concentration in the methoxycarbonylation reaction using complex 6a

Three samples containing the complex **6a** in a mixture of CD_3OD/THF (ratio 1:1 in volume) were prepared with various amounts of norbornene (10, 50 and 100 equiv. with respect to Pd). The samples were pressurized with 30 atm of

CO and the reaction monitored by ^{31}P NMR spectroscopy. In all three samples, four signals were detected: a broad resonance at δ=0.79 corresponding to the protonated phosphine **6-**H^+, a singlet peak at 22.1 corresponding to species **6g**, at 22.7 ppm attributed to the starting material **6a**, and a singlet peak at 36.1 ppm corresponding to the phosphine oxide. No significant differences were observed by ^{31}P NMR for these samples.

However, when $^{13}C\{^1H\}$ NMR spectra of these samples were acquired at room temperature, important differences were observed: when only 10 equiv. of norbornene were present, only two singlet resonances were detected in the carbonyl region at δ=185 and 177 ppm, corresponding to free CO and the ester product, respectively (Figure 3.10, a). However, for the samples prepared with 50 and 100 equiv. of norbornene these two signals at 185 and 177 ppm were also observed but several signals at δ= 178.0-179.5 and 209.8-213-16 ppm were detected (Figure 3.10 b,c). The same trend was observed in presence of an excess of norbornene (Chapter 2, Table 2.16) during the catalytic experiments. The chemical shift of these signals indicates the presence of the copolymers CO-norbornene. Li and co-workers[44] and Takahashi and coworkers[45] previously reported the characterization of copolymers CO-norbornene and they proposed the structures in Figure 3.11. The chemical shifts for carbonyl groups are very similar to those detected here.

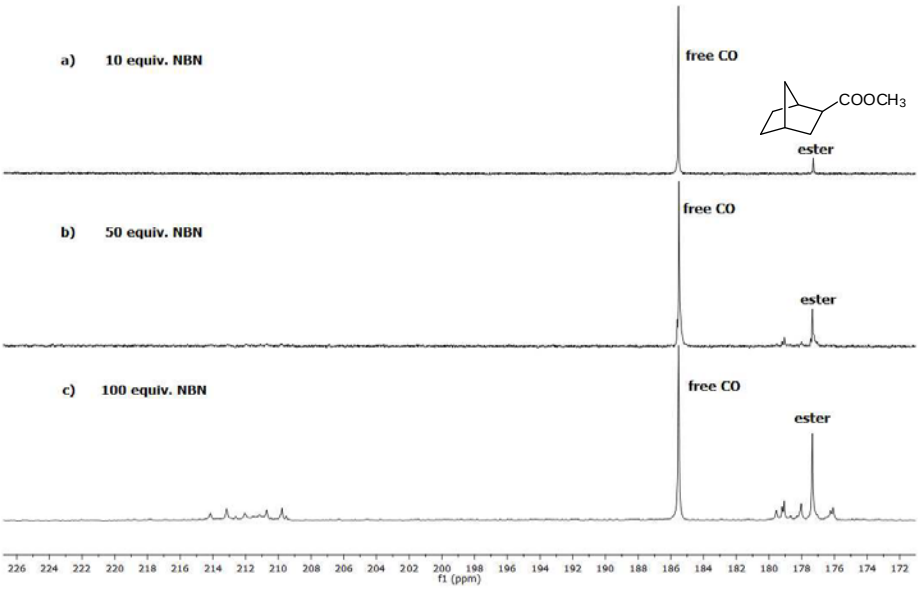


Figure 3.10 Sequence of $^{13}C\{^{1}H\}$ NMR spectra of complex **6a** in CD_3OD/THF + NBN + 30 atm CO at RT a) 10 equiv NBN b) 50 equiv NBN c) 100 equiv NBN.

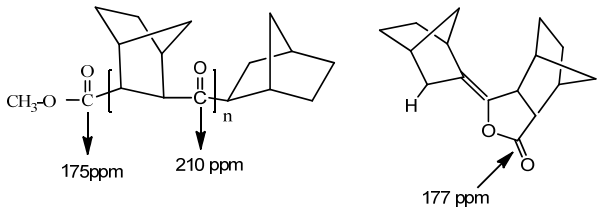


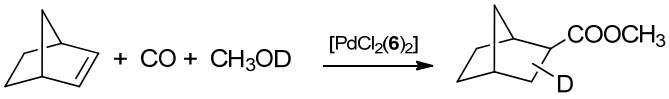
Figure 3.11 Copolymers CO-norbornene formed during the methoxycarbonylation of norbornene.

k) Deuterium labeling experiments in the methoxycarbonylation of norbornene using [$PdCl_2$(6)$_2$] (6a)

In order to gain information on the mechanism involved in this reaction, a set of catalytic experiments was completed using CH_3OD as the deuterated alcohol source at temperature ranging from 298 and 373 K. GC-MS analysis of reaction products was performed to evaluate the degree of deuterium incorporation into the ester products.

When complex **6a** was used as a catalyst precursor excellent conversion (99%) was achieved with total chemoselectivity to the ester product. The results obtained from GC-MS analysis of the ester were consistent in all cases with the incorporation of only one deuterium atom into this product (m/z = 155), from CH_3OD (Table 3.1). No further incorporation of deuterium was observed.

Table 3.1 Deuterium labeling experiments performed in CH_3OD in the methoxycarbonylation of norbornene using complex **6a**[a]



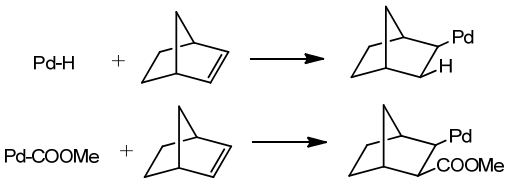
Entry	T (K)	m/z	No. D atom incorp.
1	298	155	1
2	313	155	1
3	343	155	1
4	373	155	1

[a]Reaction conditions: Pd (0.021 mmol), norbornene (0.21 mmol), MeOH/THF(1:1), 30 bars of CO.

These results thus indicated that the step involving the incorporation of the methanolic proton into the norbornene substrate, namely the insertion into Pd-H bond in the hydride based mechanism or the hydrolysis step in the Pd-

carbomethoxy mechanism (see Chapter 1) is not reversible under these conditions (Scheme 3.14).

These results are in agreements with previous reports which indicated that the insertion of norbornene into a M-H bond to form a M-norbornyl species takes place in an irreversible fashion.[4,40,46]



Scheme 3.14 Insertion of norbornene into the Pd-H and Pd-COOMe species.

Conclusions of this study

Several mechanistic aspects of the methoxycarbonylation of norbornene catalyzed by [$PdCl_2$(**6**)$_2$] (**6a**) were considered in detail and the following conclusions can be drawn:

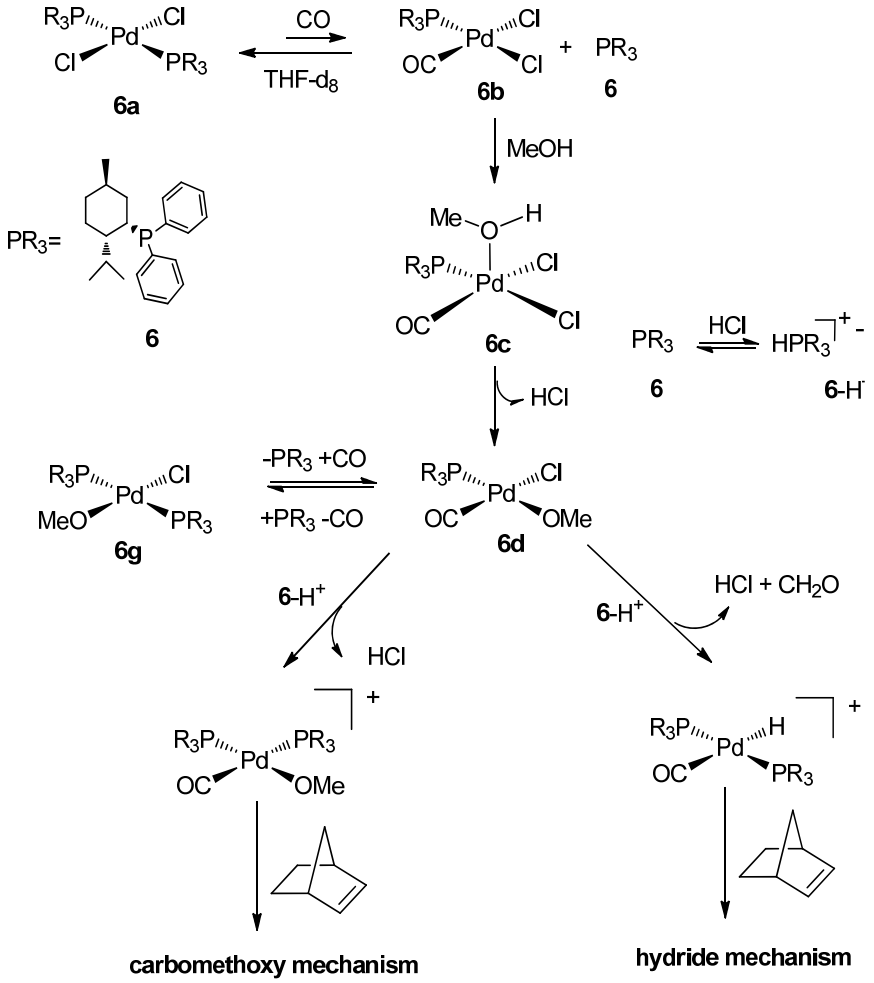
- When HP NMR experiments were completed in the presence of all the reagents contained in the catalytic mixture (**6a**, CO, norbornene and MeOH) no Pd species involved in the catalytic cycle of the process was detected. It was therefore deduced that the reaction was too fast on the NMR time scale.
- The HP-NMR study of the complete catalytic mixture containing **6a**, CO, norbornene in methanol/THF mixture led to the detection of three phosphorus containing species:
    - The protonated phosphine **6**-H^+ formed by reaction of the free ligand **6** and in situ generated HCl. These two compounds were shown to be in equilibrium.
    - The species **6g** which has been identified as *trans*-[PdCl(OMe)(**6**)$_2$].
    - An organophosphorus species that resonates at δ 27.3 ppm and which could not be undoubtedly identifies as this species was produced in low concentrations.
- The complex **6a** reacts under 30 atm pressure CO to form the complex [$PdCl_2$(**6**)(CO)] **6b** and free phosphine **6.** This reaction was shown to be reversible. In the presence of methanol, the Pd species **6b** rapidly reacts at room temperature to yield species **6g**. At higher temperature, **6g** was not detected, indicating that this species was rapidly reacting under these conditions. However, the product of this latter reaction could not be identified.

- The dimeric complex **6e** was synthesized and fully characterized by multinuclear NMR spectroscopy. This species reacts with **6**-H^+ to yield the hydride species [PdH(OMe)(**6**)$_2$] **6f**.
- Deuterium labeling experiments using CH_3OD as reagent revealed the incorporation of a single deuterium atom into the product when the catalytic runs were performed at temperature from 298 to 373 K. This indicates that the incorporation of the methanolic proton into the ester product involves an irreversible step of the mechanism.
- The variation of norbornene concentration (from 10 to 100 equiv.) did not lead to the detection any new organometallic species, although large differences in terms of chemoselectivity was evident by ^{13}C NMR analysis, in agreement with the catalytic results described in Chapter 2, Section 2.2.
- The presence of chloride ions in solution was shown to be crucial to obtain catalytic activity with this Pd system (Chapter 2, section 2.2). Our NMR investigations suggest that the role of the chloride could be related with the in situ formation of HCl in the catalytic solution, potentially leading to the formation of Pd-H.

From these conclusions, the mechanism of activation of **6a** in the absence of added acid shown in Scheme 3.15 was proposed.

The formation of species **6b** in Scheme 3.15 is attributed to the coordination of CO to **6a** and displacement of one neomenthylphosphine ligand **6**. Subsequent coordination of methanol leads to the formation of the intermediate species **6c** from which HCl and the Pd-OMe species **6d** are generated**.** Protonation of ligand **6** takes place by reaction with HCl. Reaction of species **6d** with ligand **6** would yield the species **6g** and liberate CO. Possible reaction of species **6d** with

the monoprotonated phosphine **6**-H$^+$ could generate active species to start both the hydride and carbomethoxy cycles.



Scheme 3.15 Proposed mechanism for the formation of Pd-species active in the methoxycarbonylation of norbornene from **6a** in the absence of added acid.

3.2.2 Study of the diphosphine system [$PdCl_2$(2)] (2a) under methoxycarbonylation conditions

As described in Chapter 2 (section 2.2), when the [$PdCl_2$(**2**)] (**2a**)/TFA system was used as catalyst precursor in the Pd-methoxycarbonylation of norbornene, practically total conversion (99%) and full chemoselectivity to the ester (100%) were achieved at room temperature.

In the following sections, the reactivity of the complex **2a** towards methanol, trifluoroacetic acid, CO and norbornene will be described.

The same methodology than in section 3.2.1 was used: first, the reactivity of complex **2a** towards all reagents present during catalysis was investigated using HP NMR techniques. Later, the reactivity of this complex towards methanol, TFA, CO, and norbornene was studied separately and in a stepwise fashion.

a) Reaction of complex 2a in the presence of TFA, norbornene, and carbon monoxide (30 atm) in CD_3OD/THF

First, the reactivity of complex **2a** in the presence of trifluoroacetic acid (TFA), norbornene and carbon monoxide in CD_3OD/THF was studied.

A 10-mm HP-NMR sapphire tube was charged with a solution of complex **2a** in CD_3OD/THF and a $^{31}P\{^1H\}$ spectrum was acquired (Figure 3.12, a). The signal corresponding to the starting material **2a** at δ=44.0 ppm was readily detected. Two broad signals at δ 19.1(**F**) and 37.7(**G**) ppm were also detected at this stage. At this point, 10 equiv of TFA, 50 equiv. of norbornene and 30 atm of CO were added and the reaction was monitored by ^{31}P NMR spectroscopy. In the first $^{31}P\{^1H\}$ NMR spectrum at room temperature (Figure 3.12, b), two signals at δ=36.9 (**H**) and 38.1(**I**) ppm with complex multiplicity, a broad resonance at 46.1(**J**) and a singlet resonance at δ=53.1 (**K**) ppm (major species) were observed (Figure 3.12, b). The coupling patterns of the signals **H** and **I**

suggested the formation of species containing a P-D coupling and will be investigated at a later stage.

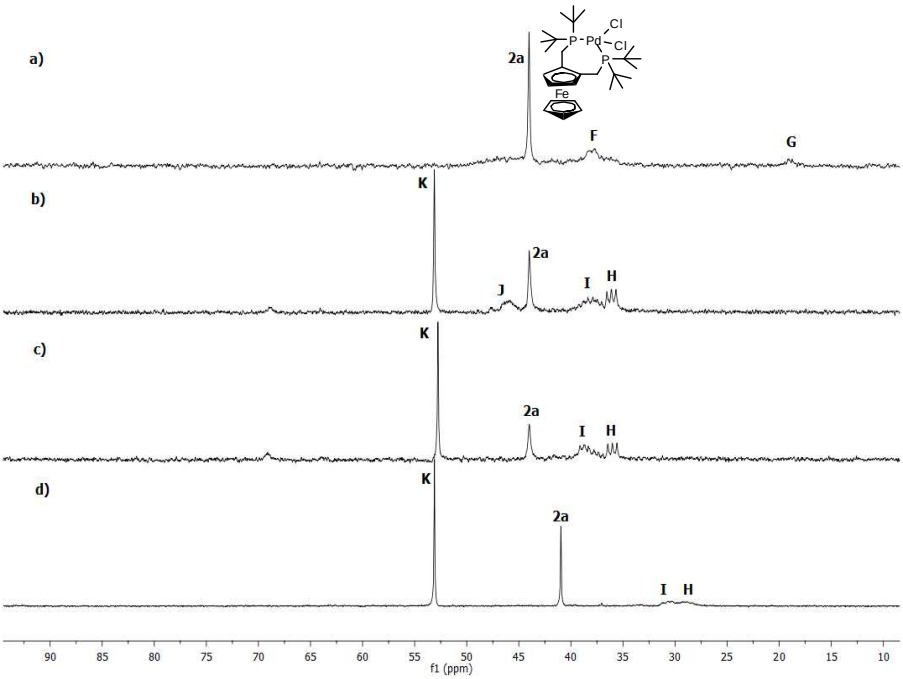


Figure 3.12 Sequence of $^{31}P\{^{1}H\}$ NMR spectra. a) **2a** in CD_3OD/THF at RT b) **2a** + 10 equiv TFA + 50 equiv NBN + 30 atm of CO in CD_3OD/THF at RT c) **2a** + 10 equiv TFA + 50 equiv NBN + 30 atm of CO in CD_3OD/THF after 12 hours at RT d) **2a** + 10 equiv TFA + 50 equiv NBN + 30 atm of CO in CD_3OD/THF at 213 K.

At longer reaction times, no significant changes in the spectra were observed. However, after 12 hours at room temperature, the signal at δ=46.1 ppm (**J**) was not observed anymore and the decrease in intensity of the signals corresponding to the starting material **2a** and signal **H** was significant (Figure 3.12, c). When the temperature was decreased to 213 K, four signals were

detected (Figure 3.12, d): the starting material **2a** at δ=41.5 ppm, a singlet resonance (**K**) now shifted at 56.1 (major species) ppm, two broad signals **H** and **I** shifted at 28.9 and 30.6 ppm, respectively (Figure 3.12, d). The decrease in intensity of both signals was significant. On warming the sample back to room temperature, identical spectrum to that presence in trace c was again obtained.

When the experiment was repeated using ^{13}CO, in the corresponding $^{13}C\{^{1}H\}$ NMR spectrum at room temperature, two singlet resonances were detected at δ= 185 and 177 ppm. The former signal was readily assigned to free CO. This signal appeared as a broad singlet suggesting that some fluxional behavior could be taking place. The latter signal was assigned to the ester product indicating that the methoxycarbonylation reaction was taking place under these conditions.

It was therefore concluded that four signals at δ 36.9 (**H**), 38.1(**I**), 46.1(**J**) and 53.1(**K**) ppm were detected by ^{31}P NMR when the reaction of complex **2a** in the presence of TFA, carbon monoxide and norbornene in CD_3OD/THF was studied. The coupling pattern of resonances at 36.9 (**H**) and 38.1 (**I**) ppm suggests the formation of species containing a P-D bond while the singlet multiplicity of the signal at 53.1(**K**) ppm indicated that the corresponding species presented high symmetry. By ^{13}C NMR, no signals corresponding to carbonyl containing Pd species could be detected although the signal for the ester product was readily observed, indicating that the methoxycarbonylation reaction had taken place under these conditions.

In order to gain information about the identity of these species, the reactivity of complex **2a** towards methanol, TFA, carbon monoxide and norbornene was investigated and the results are described in the next sections.

b) Reaction of Complex 2a in CD_3OD/THF

In a 5-mm NMR tube fitted with a Young's tap, a solution of complex **2a** in CD_3OD/THF as a mixture of solvents was prepared. In the corresponding $^{31}P\{^1H\}$ NMR spectrum at room temperature the signal at δ= 44.0 ppm (major), corresponding to the starting material **2a**, was readily detected (Figure 3.13, a). Under these conditions two broad resonances at δ= 19.1 (m, **F**) and 37.7 (m, **G**) ppm were also observed (Figure 3.13, a). At longer reaction times (up to 2 days), the presence of palladium black was observed but no significant changes were detected by ^{31}P NMR, except the progressive appearance of a new singlet resonance at δ= 64.2 (**L**) ppm (not shown in the Figure 3.13) that was assigned as the oxidized product of the free ligand **2**. This was confirmed when the free ligand purposely oxidized in the presence of H_2O_2.

When the experiment was repeated in neat THF, the $^{31}P\{^1H\}$ NMR spectrum acquired at room temperature showed the presence of only one singlet at δ= 44.0 ppm corresponding to the starting material **2a**. No others signals were detected under these conditions (Figure 3.13, b). It was therefore concluded that complex **2a** slowly reacts in presence of methanol and in eventually partly reduced to Pd(0).

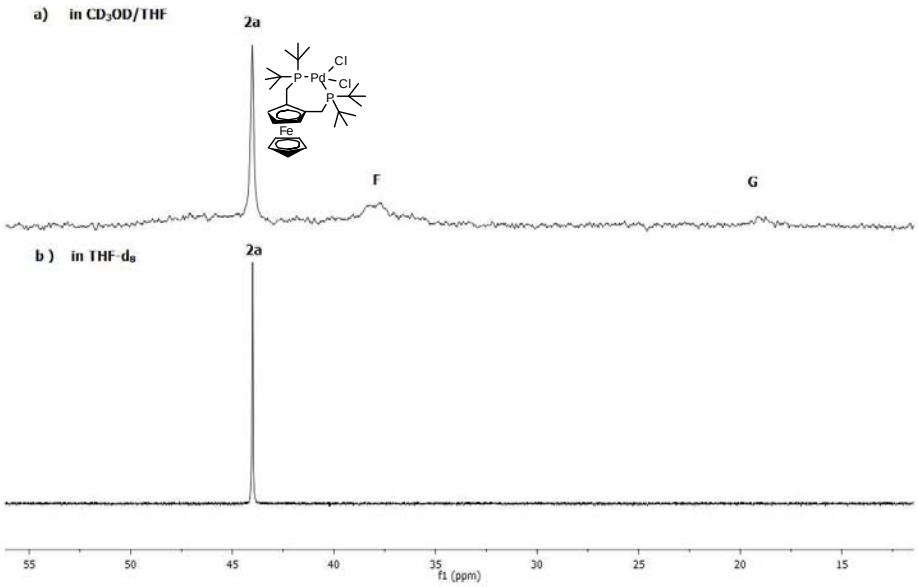


Figure 3.13 Sequence of $^{31}P\{^{1}H\}$ NMR spectra. a) Complex **2a** in CD_3OD/THF at RT b) Complex **2a** in THF-d_8 at RT.

c) Reaction of Complex 2a in the presence of TFA (10 equiv) in CD_3OD/THF

In this section, the reactivity of complex **2a** in CD_3OD/THF in the presence of TFA (10 equiv.) was investigated.

A solution of complex **2a** in CD_3OD/THF (Figure 3.14, a) was prepared and transferred into a 5-mm NMR tube and TFA (10 equiv.) was added. A $^{31}P\{^{1}H\}$ NMR spectrum was acquired and the signal at δ= 44.0 ppm, corresponding to the starting material **2a**, was readily detected. Under these conditions, the previously detected singlet resonance at δ= 36.9 (**H**) ppm was observed in high intensity (Figure 3.14, b), together with the broad resonance at δ= 38.1 (**I**), and a singlet resonance 48.1 (**J**) ppm. Furthermore, a new singlet resonance at 41.0

(**M**) ppm was also observed. The peak corresponding to the oxidized diphosphine **L** was also detected.

It was therefore concluded that the complex **2a** reacts in the presence of trifluoroacetic acid in CD_3OD/THF. In order to investigate whether the obtained signals corresponded to Pd species, the reaction of the free ligand **2** in presence of TFA under identical conditions was investigated.

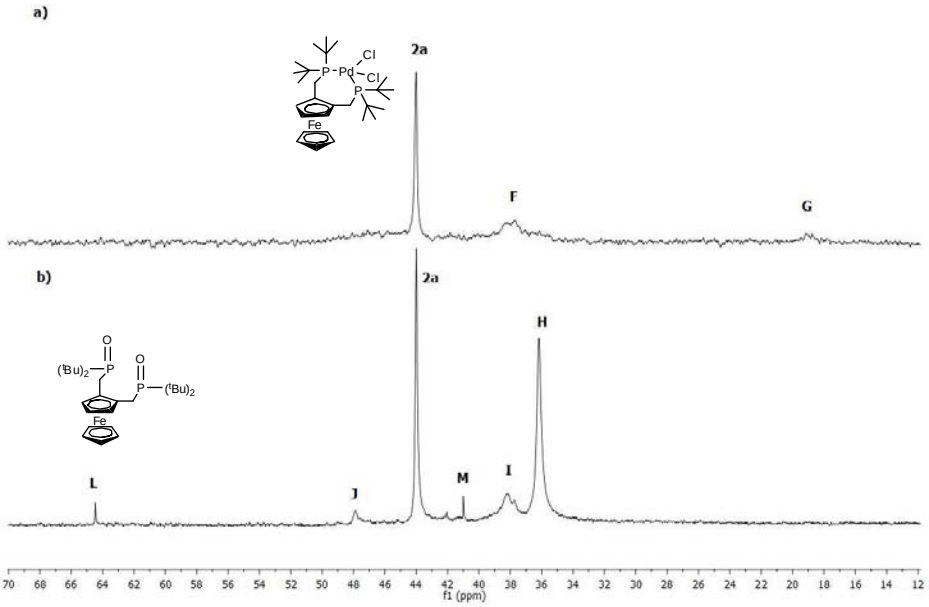


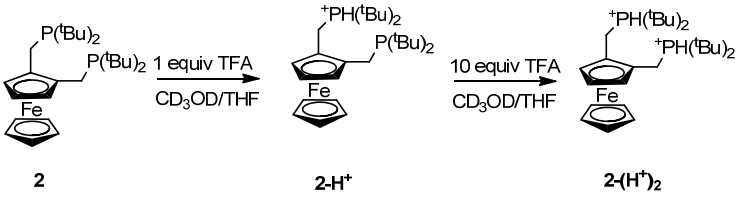
Figure 3.14 Sequence of $^{31}P\{^1H\}$ NMR spectra. a) Complex **2a** in CD_3OD/THF at RT b) Complex **2a** + 10 equiv TFA in CD_3OD/THF at RT.

d) Reaction of ligand 2 in the presence of TFA in CD_3OD/THF

As described in section 3.2.1, protonation of phosphine ligands can occur under methoxycarbonylation.[38,42] In this section, in order to confirm if ligand **2** is protonated we tested its reactivity in the presence of TFA in CD_3OD/THF.

When a sample of ligand **2** was dissolved in a CD_3OD/THF mixture (ratio 1:1 in volume) and charged into a 5-mm NMR tube fitted with Young's tap and a $^{31}P\{^1H\}$ NMR spectrum was acquired, one singlet resonance at δ= 22.8 ppm readily assigned to free ligand **2** was detected. When TFA (1 equiv.) was added, two previously observed broad signals at δ= 19.1(**F**) and 37.7(**G**) ppm were detected in high intensity in the ratio 1:1. The singlet resonance **H** at δ= 36.9 ppm was also detected as a minor product. It was thus concluded that the broad signals at δ= 19.1(**F**) and 37.7(**G**) ppm corresponded to a single species with two distinct phosphorus environments: the signal at δ 19.1 ppm was assigned to a phosphorus atom with similar environment to that of the free ligand (δ= 22.8 ppm) while the second signal was assigned to a protonated phosphorus atom. The corresponding species was therefore identified as the monoprotonated ligand **2**-H^+ [Fe(η^5-C_5H_5)-(η^5-C_5H_3)-($^+H(^tBu_2)_2P$-($^tBu_2$)$_2$P] (Scheme 3.16).

When 9 equiv. of TFA more were added to the solution, the singlet signal **H** at δ= 36.9 ppm was observed as the only signal at room temperature (Figure 3.15, a). When a $^{31}P\{^1H\}$ NMR spectrum was acquired at 193 K, the signal **H** appeared as a pseudo triplet with a 1:1:1 intensity pattern (Figure 3.15, b). The multiplicity of this signal suggests the formation of a species containing deuterium with a P-D bond of 69 Hz.



Scheme 3.16 Reactivity of ligand **2** in the presence of TFA in CD_3OD/THF.

The experiment was then repeated in a CH_3OH/THF mixture and, after evaporation of the solvent, the residue was re-dissolved in CD_2Cl_2. In the $^{31}P\{^1H\}$ NMR spectrum at 193 K, the signal **H** at 36.9 ppm was detected as a single resonance (Figure 3.15, c). In the ^1H-coupled ^{31}P NMR spectrum acquired at 193 K, this peak at 36.9 ppm exhibits a doublet multiplicity $J_{P\text{-}H}$= 460 Hz (Figure 3.15, d). The value of the P-H coupling is characteristic of a compound containing a P-H moiety. The species corresponding to this signal was therefore identified as the diprotonated diphosphine [Fe(η^5-C_5H_5)-(η^5-C_5H_3)-($^+$H(^{t}Bu$_2$)$_2$P)$_2$] **2**-(H^+)$_2$ (Scheme 3.16).

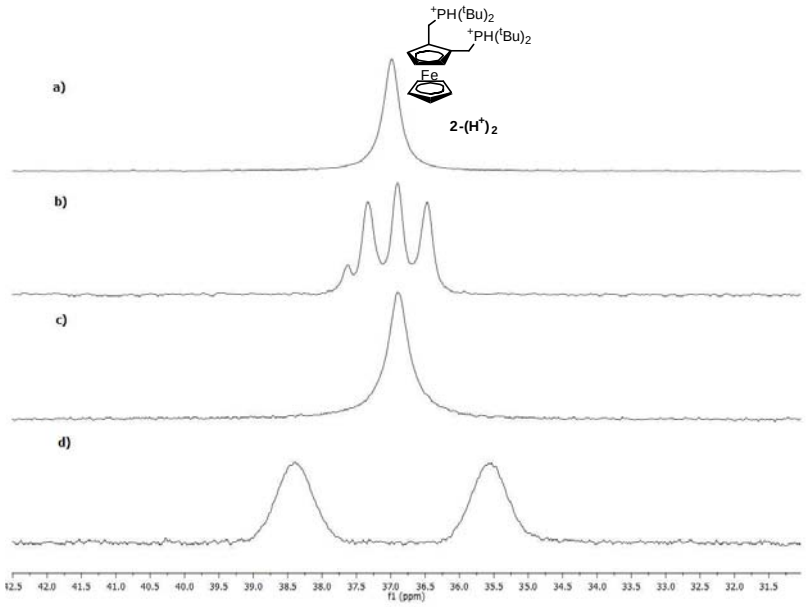
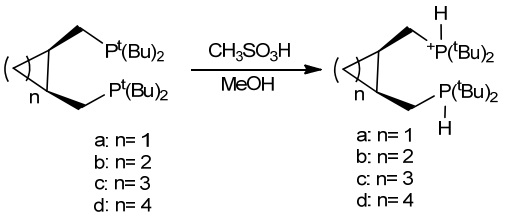


Figure 3.15 Sequence of $^{31}P\{^1H\}$ NMR spectra. a) Ligand **2** + 10 equiv TFA in CD_3OD/THF at RT b) **2** + 10 equiv TFA in CD_3OD/THF at 213 K c) **2** + 10 equiv TFA in CD_2Cl_2 at RT d) ^1H-coupled ^{31}P NMR spectrum of **2** + 10 equiv TFA in CD_2Cl_2 at 193 K.

Similar species were recently reported by Claver and co-workers who carried out a study of the protonation of basic cycloalkyl ligands (Scheme 3.17, **a-d**) in presence of 12.5 equiv of methanesulfonic acid (CH_3SO_3H).[38]



Scheme 3.17 Protonation of ligands **a-d** reported by Claver and coworkers.

These experiments showed that the previously observed resonances **H** and **F, G** arise from the products of the reaction between the ligand **2** and TFA, namely the di- and monoprotonated species **2**-$(H^+)_2$ and **2**-H^+, respectively. In contrast, the signals at δ 38.1(**I**), 46.1(**J**) and 40.1(**M**) ppm, previously detected by reaction of **2a** in the presence of TFA in MeOH/THF mixture (section 3.2.2(c)), were not detected in this section. These products could not be identified due to the low concentrations in which they were formed under these conditions.

In the next section, the reactivity of complex **2a** towards carbon monoxide will be described.

e) Reaction of complex 2a in the presence of TFA (10 equiv) and carbon monoxide (30 atm) in CD_3OD/THF

A solution of the precursor **2a** in CD_3OD/THF (ratio 1:1 in volume) was prepared (Figure 3.16, a). TFA (10 equiv.) was added and placed into a 10-mm high pressure NMR tube. After pressurizing the tube with 30 atm of CO, a $^{31}P\{^1H\}$NMR spectrum was acquired at room temperature. The previously observed signals at δ= 46.1 (**J**, br m), 44.0 (complex **2a**), 38.1 (**I**, br m) and 36.9

(diprotonated phosphine **2**-$(H^+)_2$) ppm were detected. One additional resonance was also observed at 53.1 (**K**, s) ppm (Figure 3.16, b) and it was therefore concluded that the corresponding species was formed due to the presence of CO. At longer reaction time, no significant changes were observed. However, when the CO pressure was removed, the signal at δ 53.1 (s, **K**) was not observed anymore. This indicated that the formation of this species involved a reversible reaction involving CO.

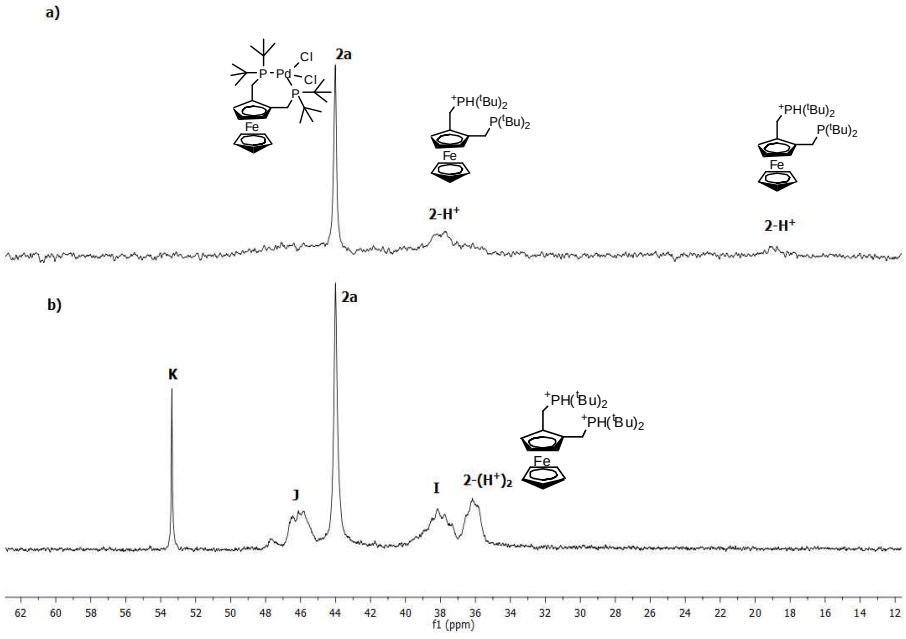
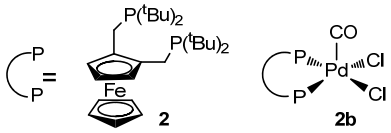


Figure 3.16 Sequence of $^{31}P\{^1H\}$ NMR spectra. a) Complex **2a** in CD_3OD/THF at RT b) **2a** + 10 equiv TFA+ 30 atm CO in CD_3OD/THF after 4 hours at RT.

When the experiment was repeated using ^{13}C-enriched CO, in the corresponding $^{13}C\{^1H\}$NMR spectrum recorded at 213 K, only the singlet resonance for free CO was detected at δ= 185 ppm.

When this experiment was repeated in neat THF-d_8, the formation of the species corresponding to signal **K** was again detected by ^{31}P NMR. However, when $^{13}C\{1H\}$ spectra were acquired, no carbonyl signal for this species could be detected. It was therefore concluded that species corresponding to signal **K** contains a very labile CO group, which could explain the failure in detecting the corresponding carbonyl signal. Therefore the signal **K** corresponding to species **2b**. The structures of species **2b** that could match these observations are described in Scheme 3.18.



Scheme 3.18 Proposed structure for species **2b**.

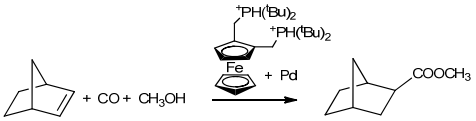
f) Reaction of complex 2a in the presence of TFA and norbornene (50 equiv) in CD_3OD/THF

The reactivity of complex **2a** in the presence of TFA (10 equiv) and norbornene (50 equiv) in CD_3OD/THF was investigated.

In a 5-mm NMR tube fitted with a Young's tap a solution of complex **2a** in CD_3OD/THF was prepared. Then, 10 equiv. of TFA and 50 equiv. of norbornene were added and the reaction was monitored by ^{31}P NMR. However, under these conditions, identical signals to those previously detected in the absence of norbornene were observed. It was thus concluded that CO was required to form a reactive species towards norbornene.

As described in Section 3.2.2(a), when the reactivity of complex **2a**, carbon monoxide and norbornene in CD_3OD/THF was studied, the presence of the diprotonated phosphine **2**-$(H^+)_2$ was detected. Interestingly, it was observed

that this species was consumed during the experiment sequence, which suggested that this species may play an important role in the catalytic reaction. To confirm this, species **2**-$(H^+)_2$ was tested in the methoxycarbonylation reaction of norbornene in presence of palladium precursor such as $[PdCl_2(COD)]$ and $[Pd(OAc)_2]$ under 30 bars of CO at room temperature during a period of 24 hours (Scheme 3.19). The catalytic results provided practically total conversion (99%) and high chemoselectivity (85%) when $[PdCl_2(COD)]$ was used as precursor. When $[Pd(OAc)_2]$ was used no catalytic activity was obtained. This indicated that the presence of chloride in solution is crucial to obtain catalytic activity with this system.



Scheme 3.19 Reaction of species **2**-$(H^+)_2$ in presence of palladium precursors under methoxycarbonylation conditions.

Furthermore, in view of the results obtained with the diprotonated ligand **2**-$(H^+)_2$, the catalytic reaction was performed using complex **2a** in presence of 2 equiv. of TFA, and identical results were obtained (conversion >99% and chemoselectivity >99%).

In view of the results obtained using $[PdCl_2(COD)]$/**2**-$(H^+)_2$ as catalytic system, we next performed its reactivity towards, methanol, carbon monoxide and norbornene.

g) Stability of the diprotonated diphosphine 2-$(H^+)_2$ in CH_3OH/THF-d_8

In order to probe the stability of compound **2**-$(H^+)_2$ in the solvent mixture used during the catalytic reaction a solution of the diprotonated diphosphine **2**-$(H^+)_2$

in $CH_3OH/THF\text{-}d_8$ was charged into a 5-mm NMR tube fitted with a Young's tap. The broad singlet corresponding to the starting material **2**-$(H^+)_2$ at δ= 36.9 ppm was readily detected in ^1H and $^{31}P\{^1H\}$NMR spectra that was acquired at room temperature. As the signal of diprotonated phosphine was detected as broad singlet, a $^{31}P\{^1H\}$NMR spectra was acquired a 193 K. No new signals were observed indicating that the compound **2**-$(H^+)_2$ was stable under these conditions.

In the next section, the reactivity of diprotonated diphosphine **2**-$(H^+)_2$ and $[PdCl_2(COD)]$ in $CH_3OH/THF\text{-}d_8$ in the presence of carbon monoxide (30 atm) will be studied.

h) Reaction of $[PdCl_2(COD)]$ and diprotonated diphosphine 2-$(H^+)_2$ in $CH_3OH/THF\text{-}d_8$

In a 5-mm NMR tube fitted with a Young's tap a solution of diprotonated diphosphine (**2**-$(H^+)_2$) and $[PdCl_2(COD)]$ (1 equiv.) in $CH_3OH/THF\text{-}d_8$ was prepared and the reaction was monitored by ^1H and ^{31}P NMR spectroscopy. When the sample was prepared at room temperature, the solution rapidly darkened. When a $^{31}P\{^1H\}$NMR spectrum was acquired, the resonance corresponding to the complex **2a** was readily detected together with several other signals which were attributed to decomposition products.

When the sample was prepared at 213 K and placed in the pre-cooled spectrometer, the signal corresponding to the diprotonated diphosphine (**2-$(H^+)_2$**) at δ=36.9 ppm was readily detected by ^{31}P NMR (Figure 3.17, a). No other signals were detected under these conditions.

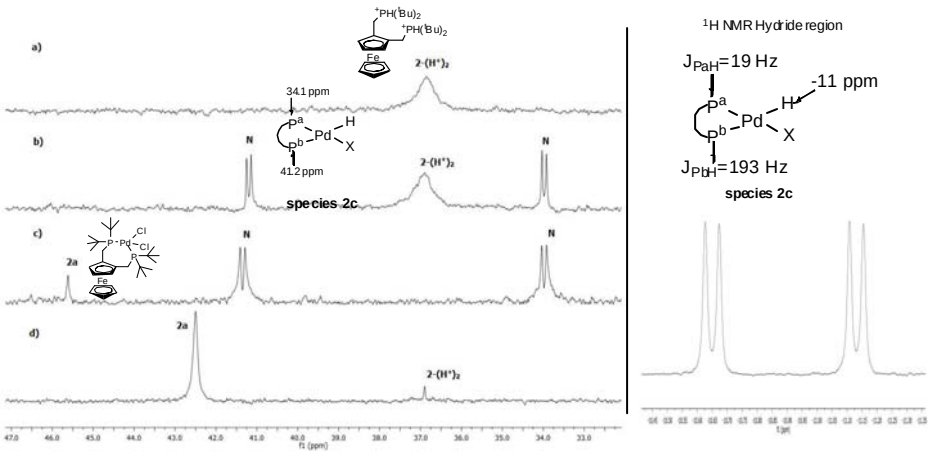


Figure 3.17 Sequence of $^{31}P\{^{1}H\}$NMR spectra. Reactivity of diprotonated diphosphine **2**-$(H^+)_2$ and $[PdCl_2(COD)]$ in $CH_3OH/THF\text{-}d_8$. a) Initial at 213 K b) at 233 K after a few minutes c) at 253 K after a few minutes d) back to RT.

When the temperature was raised to 233 K, two new signals were observed at δ= 34.0(**N**) and 41.2(**N**) ppm as two mutually coupled doublets (dd, $^{2}J_{PP}$=18 Hz) (Figure 3.17, b). It was therefore concluded that the corresponding species contained two inequivalent phosphorus environments. In the corresponding ^{1}H NMR spectrum, an hydride signal was detected as a doublet of doublet at δ=-11.0 ppm (dd, $^{2}J_{P^aH}$= 19 Hz and $^{2}J_{P^bH}$=193 Hz) (Figure 3.17, ^{1}H NMR hydride region). The coupling pattern of this signal clearly indicated that the corresponding hydride complex contained two inequivalent phosphorus centres. The values of these coupling constants are characteristic of *trans* ($^{2}J_{P^bH}$=193 Hz) and *cis* ($^{2}J_{P^aH}$= 19 Hz) couplings. The ^{31}P signals at δ 34.0(**N**) and 41.2(**N**) ppm were therefore assigned to the diphosphine Pd hydride species **2c** described in Figure 3.18. No information on the nature of the X ligand could be obtained by NMR techniques at this point. In this spectrum, a singlet resonance at 4.5 ppm was also observed and attributed to H_2.

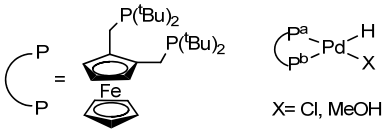


Figure 3.18 Proposed structure for species **2c**.

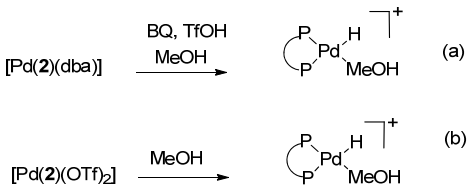
The sample was then slowly heated until 253 K and a new $^{31}P\{^{1}H\}$ NMR spectrum was recorded. At this temperature, the signal corresponding to the complex **2a** at δ= 44.0 ppm was detected and the signals at δ= 34.0(**N**) and 41.2(**N**) (dd, $^{2}J_{PP}$=18 Hz) remained unchanged (Figure 3.17, c). The resonance for the diprotonated phosphine **2**-$(H^{+})_2$ was not detected at this point. When the sample was heated to room temperature and a $^{31}P\{^{1}H\}$NMR spectrum acquired, the signals for species **2c** were not detected, in agreement with the previous experiment that was performed at room temperature. At this temperature, signals for **2a** and **2**-$(H^{+})_2$ were readily detected (Figure 3.17, d). At longer reaction times at this temperature (up to 7 days), no changes in the spectra were observed.

In the reaction between $[PdCl_2(COD)]$ and the diprotonated phosphine **2**-$(H^{+})_2$ in CH_3OH/THF-d_8, the formation of the Pd hydride complex **2c** was observed at low temperature and evolved towards the formation of the complex **2a** at room temperature. Such palladium hydride complexes of formula $[PdHX(P\text{-}P)]^{+}$ where X= MeOH, MeCN, THF were synthesised by Heaton and coworkers and used as intermediates in the methoxycarbonylation reaction of olefins [14,15,36].

In order to gain information on the nature of the ligand X in the complex **2c**, the hydride species [PdH(MeOH)(**2**)][TfO] was synthesised and its NMR features were compared to those of **2c**.

i) Synthesis of [PdH(2)(MeOH)][TfO] (2d)

The synthesis of similar Pd-H complexes have been previously reported.[14,15,36] Heaton and co-workers demonstrated that [PdH(d^{t}bpx)(MeOH)][TfO] can be obtained following different synthetic methodologies.[14]



Scheme 3.20 Formation of [PdH(**2**)(MeOH][TfO].

The reaction of [Pd(d^{t}bpx)(dba) and BQ in MeOH with the subsequent addition of TfOH is one of the route proposed (Scheme 3.20(a)). However, in our case, attempts to obtain the [PdH(**2**)(MeOH)][TfO] (**2d**) from [Pd(**2**)(dba)] were unsuccessful as decomposition of the palladium complex was immediately observed.

When the reaction was carried out using [Pd(**2**)(OTf)$_2$] in MeOH (Scheme 3.20, (b)), the formation of the complex [PdH(**2**)(MeOH)][TfO] (**2d**) was achieved. In the ^{1}H NMR spectrum of this species in MeOH at 213 K, the corresponding hydride signal was observed as a doublet of doublet at δ=-11.0 ppm (dd, $^2J_{P^aH}$= 19 Hz and $^2J_{P^bH}$=193 Hz) (Figure 3.19). These values were identical to those previously measured in this study for species **2c**.

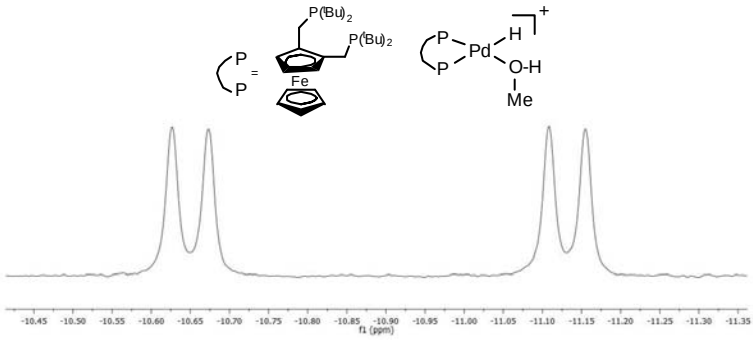


Figure 3.19 Selected region of the ^{1}H NMR spectra. Preparation *in situ* of [PdH(**2**)(MeOH)][TfO] **2d**.

However, when a $^{31}P\{^{1}H\}$ spectrum was acquired, two signals were observed at δ=30.1 and 76.1 ppm. These values are in agreement with those reported by Heaton and coworkers for similar hydride species with chloride coordinated.[14] The species **2c** was therefore identified as [PdH(Cl)(**2**)] (Figure 3.20)

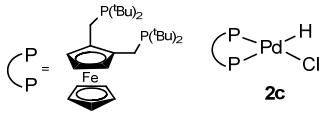
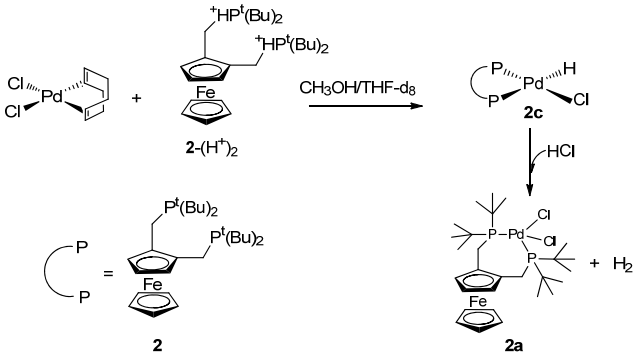


Figure 3.20. Proposed structure for complex **2c**.

The results obtained in the last two sections can then be rationalized in Scheme 3.21.



Scheme 3.21 Formation of [$PdCl_2$(**2**)] (**2a**) from the reaction of diprotonated diphosphine **2**-$(H^+)_2$ and [$PdCl_2$(COD)] in CH_3OH/THF-d_8.

In the reaction of [$PdCl_2$(COD)] in the presence of the diprotonated ligand **2**-$(H^+)_2$, the complex **2c** is first formed, and subsequent addition of HCl and elimination of H_2 yields the complex **2a**. This mechanism is in agreement with the detection of H_2 by ^{1}H NMR during the experiment. The formation of [$PdCl_2(PPh_3)_2$] from [PdH(Cl)$(PPh_3)_2$] in the presence of HCl was previously reported.[24,47] The mechanism was proposed to go through the formation of a Pd(IV) complex as intermediate, reductive elimination H_2 yielding the Pd dichloride product. However, there is no solid experimental evidence for the existence of Pd(IV)-H bond.

j) Reaction of [$PdCl_2$(COD)] and diprotonated diphosphine 2-$(H^+)_2$ in the presence of carbon monoxide (30 atm) in CH_3OH/THF-d_8

A solution of the diprotonated diphosphine **2**-$(H^+)_2$ and [$PdCl_2$(COD)] (1 equiv.) in a mixture of CH_3OH/THF-d_8 (ratio 1:1 in volume) was prepared at 213 K and placed into a 10-mm high-pressure NMR tube. After pressurizing the tube with 30 atm of CO, a $^{31}P\{^1H\}$NMR spectrum was recorded at 253 K and the signals corresponding to the species **2c** and **2a** were readily detected

(Figure 3.21, a). At longer reaction at 273 K, the resonances for species **2c** were not detected anymore, while the singlet resonance at δ 53.1(**K**) ppm corresponding to species **2b** was detected (Figure 3.21, b and c). When the CO pressure was released, only the signal corresponding to **2a** was observed (Figure 3.21, d).

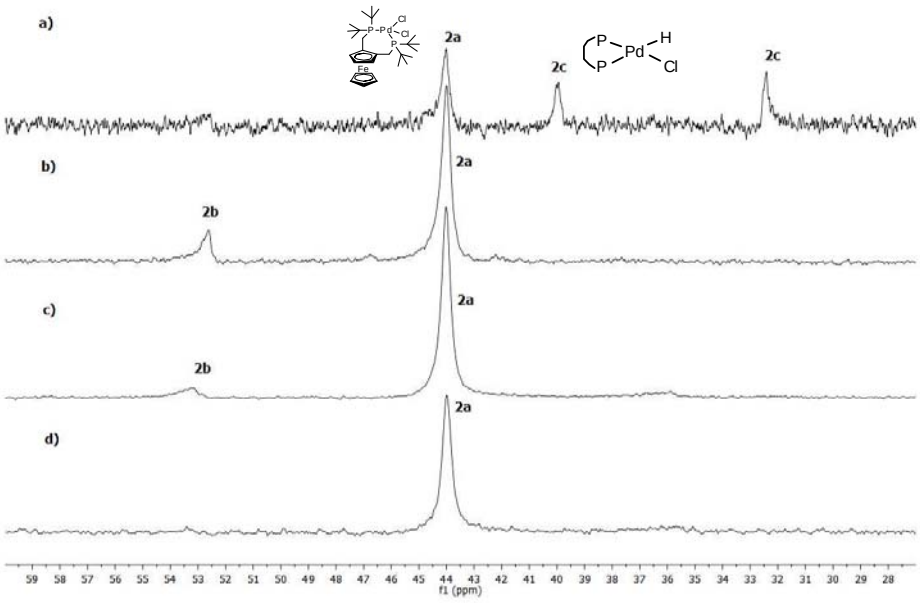


Figure 3.21 Sequence of $^{31}P\{^{1}H\}$NMR spectra. Reaction of diprotonated diphosphine **2**-$(H^+)_2$ and $[PdCl_2(COD)]$ in the presence of 30 atm of CO in $CH_3OH/THF\text{-}d_8$ a) Initial at 253 K b) After 30 min at 273 K c) After 1 hour at 273 K d) After releasing CO pressure at RT.

k) Reaction of [$PdCl_2$(COD)] and diprotonated diphosphine (2-(H^+)$_2$) in the presence of carbon monoxide (30 atm) and norbornene (50 equiv.) in CH_3OH/THF-d_8

A 10-mm HP-NMR tube was charged with a solution of the diprotonated diphosphine (**2**-(H^+)$_2$) and [$PdCl_2$(COD)] (1 equiv.) in CH_3OH/THF-d_8 at 213 K. Norbornene (50 equiv) and carbon monoxide (30 atm) were added at this temperature. At this point, the tube was rapidly transferred into the spectrometer and a first $^{31}P\{^1H\}$NMR spectrum was acquired at 213 K. The signals at δ= 34.0 and 41.2 ppm corresponding to the hydride species **2c** were readily detected (Figure 3.22, a).

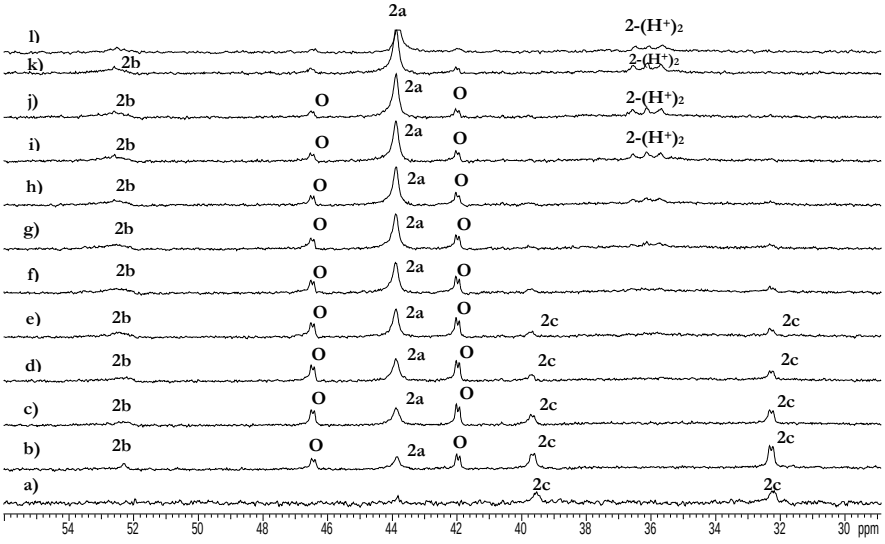


Figure 3.22 Sequence of $^1P\{^1H\}$NMR spectra. Reaction of [$PdCl_2$(COD)] and diprotonated diphosphine (**2**-(H^+)$_2$) in the presence of carbon monoxide (30 atm) and norbornene (50 equiv.) in CH_3OH/THF-d_8 a) initial at 213 K b) 15 min at 213 K c) 20 min at 213 K d) 25 min at 213 K e) 30 min at 213 K f) 40

min at 213 K g) 50 min at 213 K h) 60 min at 213 K i) 80 min at 213 K j) 100 min at 213 K k) 120 min at 213 K l) 150 min at 213 K.

After 15 minutes, the signal corresponding to complex **2a** was detected (Figure 3.22, b). The increase in the intensity of the signals corresponding to species **2c** was significant (Figure 3.22, b). The signal at 53.1 corresponding to species **2b** was detected as a minor resonance. However, at this point, two new mutually coupled doublets at δ= 42.2 (**O**) and 46.7 (**O**) ppm (dd, $^2J_{PP}$=15 Hz) were observed. These signals indicated that the corresponding species contained two phosphorus inequivalent centers. Interestingly, these resonances were not observed in the absence of norbornene and were attributed to the product of reaction of **2c** in the presence of norbornene. Possible structures for this complex that would match these NMR features are shown in Figure 3.23.

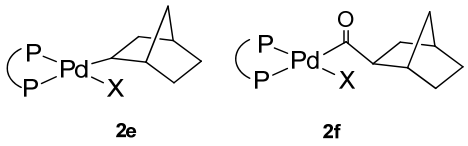


Figure 3.23 Possible structures for signals **O**.

Monitoring the reaction by ^{31}P NMR revealed that the signals corresponding to species **2c** rapidly decreased in intensity while the signal corresponding to complex **2a** increased in intensity (Figure 3.22, b-e) . The signals at δ= 42.2 (**O**) and 46.7 (**O**) ppm (dd, $^2J_{PP}$=15.2 Hz) first increased in intensity but after 50 min, they started to diminish significantly and after 100 min, they could not be detected anymore. The signals at δ=53.1 (**K**) ppm corresponding to species **2b** remained present throughout the experiment, although clear broadening of this

signal was evident with time. The signal assigned to the diprotonated diphosphine **2**-$(H^+)_2$ was observed after 80 minutes (Figure 3.22, i).

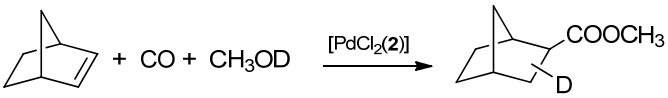
When a $^{13}C\{^1H\}$NMR spectrum was acquired, a singlet resonance at δ=185 ppm assigned to the free CO was detected. No other signals in the carbonyl region were detected. This observation indicated that the structure **2f** (Figure 3.23) for the signals **O** could be ruled out.

Interestingly, however, signals corresponding to norbornane were detected by ^1H NMR at δ= 1.1-1.3 (m, 4H, CH_2), 1.4 (m, 4H, CH_2), 1.5 (m, 2H, CH), 1.9-2.5 (m, 2H, CH_2) ppm and by ^{13}C NMR at δ=30.4 (CH_2), 37.3 (CH), 42.2 (CH_2) ppm. This product could be formed by protonolysis of species **2e** in the presence of HCl. Such reaction would yield the dichloride complex **2a**, which match the NMR observations described previously. It was concluded that the signals at 42.2 (**O**) and 46.7 (**O**) ppm corresponding to the norbornyl species **2e** in Figure 3.23.

l) Deuterium labeling experiments in the methoxycarbonylation of norbornene [$PdCl_2$(2)] (2a)

The same methodology than in section 3.2.1 (k) was used. A set of catalytic experiments was completed using CH_3OD as the alcohol deuterated source at temperature ranging from to 298 and 373 K. GC-MS analysis of reaction products was performed.

Table 3.2 Deuterium labeling experiments performed in CH_3OD in the methoxycarbonylation of norbornene using complex **2a**[a]



Entry	T (K)	m/z	No. D atom incorp.
1	298	155	1
2	313	155	1
3	343	155	1
4	373	155	1

[a]Reaction conditions: Pd (0.021 mmol), norbornene (0.21 mmol), MeOH/THF(1:1), 30 bars of CO.

When complex **2a** was used as a catalyst precursor excellent conversion (99%) was achieved with total chemoselectivity to the ester product. The results obtained from GC-MS analysis of the ester were consistent in all cases with the incorporation of only one deuterium atom into this product (m/z = 155), from CH_3OD (Table 3.2). No further incorporation of deuterium was observed.

These results as in the previous case (section 3.2.1 (k)) indicated that the step involving the incorporation of the methanolic proton into the norbornene substrate, into Pd-H bond or Pd-carbomethoxy mechanism is not reversible under these conditions.

Conclusions of this study

Several mechanistic aspects of the methoxycarbonylation of norbornene catalyzed by [$PdCl_2$(**2**)] (**2a**) were looked at in details in this study and the following conclusion can be drawn:

- The HP-NMR of the complete catalytic mixture containing **2a**, TFA, CO, norbornene in methanol/THF mixture led to the detection of three containing species:
  - The mono- **2**-H^+ and diprotonated **2**-$(H^+)_2$ phosphines formed by reaction of the free ligand with 1 and 10 equiv. of TFA, respectively. The diprotonated phosphine **2**-$(H^+)_2$ was synthesized and fully characterized by NMR spectroscopy and elemental analysis.
  - The formation of the species **2b** was formed from a reaction involving **2a** and CO. From these observations, a pentacoordinated structure of formula [$PdCl_2$(**2**)(CO)] is proposed for this species.
  - No Pd species involved in the catalytic cycle of the process was detected. It was therefore concluded that the reaction was too fast on the NMR time scale.
- The reaction of [$PdCl_2$(COD)] in the presence of the diprotonated species **2**-$(H^+)_2$ yields the hydride complex [PdHCl(**2**)] **2c** detected *in situ* in CH_3OH/THF-d_8 under methoxycarbonylation conditions. The formation of the [$PdCl_2$(**2**)] **2a** from the complex [PdHCl(**2**)] **2c** was observed.
- In the presence of norbornene, the complex **2c** reacts to form a norbornyl species **2e** that yield norbornane by protonolysis.

3.3 Experimental

3.3.1 General procedures

All palladium complexes were synthesised using standard Schlenk techniques under nitrogen atmosphere. Diethyl ether, toluene and THF were distilled over sodium-benzophenone and dichloromethane was distilled over P_2O_5. All solvents were deoxygenated before use. The palladium complexes $[PdCl_2(NCPh)_2]$,[48] $[PdCl_2(COD)]$,[49] were prepared according to literature methods. The ligand **2** was supplied gently by Dr. Graham Eastham from Lucite International. All other reagents were used as received from commercial suppliers. Deuterated solvents used for routine NMR measurements were dried over molecular sieves. ^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ NMR spectra were recorded on a Varian Mercury 400 spectrometer (400.14, 100.63 and 161.98 MHz respectively). Chemical shifts were referenced to either TMS as an internal standard (^1H, $^{13}C\{^1H\}$ NMR spectra) or 85% H_3PO_4 as an external standard ($^{31}P\{^1H\}$NMR spectra). High-pressure NMR experiments (HP NMR) were carried out in a 10 mm diameter sapphire tube with a titanium cap.

3.3.2 HPNMR measurements

In a typical experiment, the NMR tube was charged under N_2 with a solution containing the palladium precursor (0.021 mmol), TFA (when needed, 0.210 mmol) and norbornene (1.05 mmol) in a mixture of solvents CD_3OD/THF (ratio 1:1 in volume) (2 ml). The tube was then pressurized with CO to the desired pressure.

3.3.3 Synthesis of $[Pd(\mu\text{-}Cl)(Cl)(6)]_2$ (6e)

To a solution of complex **6a** (90.8 mg, 0.11 mmol) in dichloromethane (5 ml) was added a solution of $[PdCl_2(COD)]$ (31.4 mg, 0.11 mmol) in dichloromethane (5ml). The reaction was left to stir at room temperature overnight. The solution was concentrated under vacuum and diethylether (3ml)

was added to precipitate the complex as a yellow powder. Yield: 53.2 mg (48%). ^{1}H NMR (CD_2Cl_2, 400.14 MHz, ppm): δ 0.7 (d, J_{HH}= 8 Hz, CH_3), 1.04 (d, J_{HH}= 8 Hz, CH_3), 1.21 (d, J_{HH}= 8Hz, CH_3), 1.1 (m, CH_2), 1.3 (br s, CH_2), 1.4 (m, CH_2), 1.6 (m, CH_2), 1.9 (br s, CH), 2.70 (br s, CH), 2.78 (br s, CH), 3.60 (pseudo t, J_{HH}= 12 Hz, CH), 7.36-7.78 (m, Ar). ^{13}C{^{1}H} NMR (THF-d_8, 100.63 MHZ, ppm): δ 17.9 (m, CH_2), 20.46 (d, J_{PC}= 12.1 Hz, CH_2), 20.9 (s, CH_3), 24.6 (s, CH_3), 27.9 (d, J_{PC}= 9.1 Hz, CH), 28.5 (s, CH_2), 29.7 (s, CH_2), 31.7 (d, J_{PC}= 5.1 Hz, CH), 32.1 (br s, CH_2), 35.6 (br s, CH), 36.1 (br s, CH), 40.2 (br s, CH), 117.1 (s, Ar), 127.5 (d, J_{PC}= 11.1 Hz, Ar), 128.7 (d, J_{PC}= 12.1 Hz, Ar), 131,2 (m Ar), 131,5 (m Ar), 132. 7 (d, J_{PC}= 9.1 Hz, Ar), 135.5 (d, J_{PC}= 9.1 Hz, Ar). ^{31}P{^{1}H} NMR (CD_2Cl_2, 161.98 MHZ, ppm): δ 38.9 (s).

3.3.4 Synthesis of diprotonated phosphine 2-$(H^+)_2$

Bidentate ligand **2** (65.1 mg, 0.129 mmol) was dissolved in a mixture of solvents MeOH/THF (ratio 1:1 in volume) (2 ml) and TFA (100 μl, 1.29 mmol) were added to the solution. The reaction was stirred for a few minutes at room temperature. Then, the yellow solution was concentrated under vacuum and diethylether was added to precipitate compound **2**-$(H^+)_2$ as a yellow powder. Yield: 62.5 mg (96%). ^{1}H NMR (THF-d_8, 400.14 MHz, ppm): δ 1.3 (d, 18H, J_{HP}=13.2 Hz, CH_3), 1.4 (d, 18H, J_{HP}=13.2 Hz, CH_3), 3.3 (d, 4H, J_{HH}= 7.2 Hz, CH_2), 4.0 (t, 1H, J_{HH}= 2.8 Hz, C_5H_3-ring), 4.1 (s, 5H, C_5H_3-ring), 4.5 (d, 2H, J_{HH}= 2.4 Hz, C_5H_3-ring). ^{13}C{^{1}H} NMR (THF-d_8, 100.63 MHZ, ppm): δ 29.4 (d, J_{PC}= 9.1 Hz, CH_3), 20.0 (brs, CH_2), 33.4 (s, tert-C), 33.70 (s, tert-C), 66.6 (s, CH, Cp), 71.3 (s, CH, Cp), 71.8 (m, CH, Cp), 83.9 (m, C, Cp). ^{31}P{^{1}H} NMR (THF-d_8, 161.98 MHZ, ppm): δ 36.9 (s). . Calc. for $C_{28}H_{50}FeP_2$ (504.49 g/mol): Calc.: C, 66.66; H, 9.99 Found: C, 67.53; H, 10.83.

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Chapter 4

Asymmetric Rh-Catalyzed Hydroformylation of Norbornene

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4.1 Background

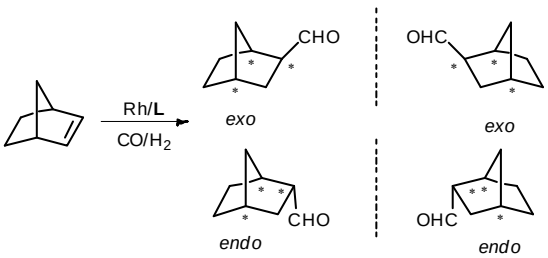
As mentioned in Chapter 1 (section 1.3), the hydroformylation of alkenes is nowadays one of the most important industrial applications of homogeneous catalysis.[1,2,3] Rhodium is currently the metal of choice to achieve high enantioselectivities in the hydroformylation of a relatively high variety of alkene substrates.[3,4] The elucidation of the different steps of the catalytic cycle and the characterization of the intermediates by HP NMR and IR studies, together with the discovery of several types of ligands that are able to provide high enantioselectivities, have made the rhodium-catalyzed hydroformylation a synthetically useful tool.[3a,4]

Ligands containing phosphite moiety such as diphosphites[5] and phosphine-phosphites[6] had been considered to be the most successful ligands to achieve high enantioselectivities in this process. Recently however, diphosphine[7] derivatives have shown to provide high levels of enantioselectivity in the Rh catalyzed asymmetric hydroformylation (see Chapter 1, Figure 1.5,)

Among the different diphosphite used as ligands in Rh catalyzed hydroformylation[3a] series of modular 1,3-diphosphite ligands derived from carbohydrates have been developed to be applied in the Rh-asymmetric hydroformylation of monosubstituted substrates such as styrene,[1,8] vinyl acetate,[5a,9] allyl cyanide[5a,9] and disubstituted internal substrates, such as 2,5-dihydrofurane[8,10] and 2,3-dihydrofurane.[8,10]

Much of effort in this field has been concentrated on the hydroformylation of vinylarenes, as a route to obtain enantiomerically enriched 2-aryl propionic acids, the profen class of nonsteroidal drugs.[11]

Among monocyclic 1,2-disubstituted alkene substrate, 5-membered ring heterocycles such as dihydrofurans and dihydropyrroles have been the most studied.[8,10] In the hydroformylation of these substrates, the simultaneous control of the chemo- regio- and enantioselectivity is a key issue since the presence of a heteroatom in the cycle favours in some cases an isomerisation process in the presence of a metal-hydride species. Among the bicyclic 1,2 disubstituted indene[12,13], norbornene[14] and its derivatives have received attention, although much less than their monosubstituted counterpart. Hydroformylation of norbornene (Scheme 4.1) is a challenging reaction that has been scarcely studied. Norbornene, which is a symmetrically disubstituted alkene, is an interested substrate to be hydroformylated because of the interest of the aldehyde derivatives as building blocks. It is important to note that the hydroformylation of this substrate does not present problems of regiocontrol.



Scheme 4.1 Rh-catalyzed hydroformylation of norbornene.

Because of the successful application of carbohydrate derivative diphosphites previously developed in our group[5a,8,10] (as indicated above) we considered of interest to explore the application of diphosphite ligands containing furanoside backbone (See Figure 4.1) in the Rh-asymmetric hydroformylation of norbornene. To the best of our knowledge, only two

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papers have been reported using phosphite ligands in the Rh catalyzed asymmetric hydroformylation of norbornene, achieving enantioselectivities up to 61 % with the *exo*-aldehyde being the major product. Recently the same authors have reported the preferential formation of *endo*-aldehyde, when water was used as solvent instead of toluene. However, the enantioselectivities obtained were moderate (up to 39%).

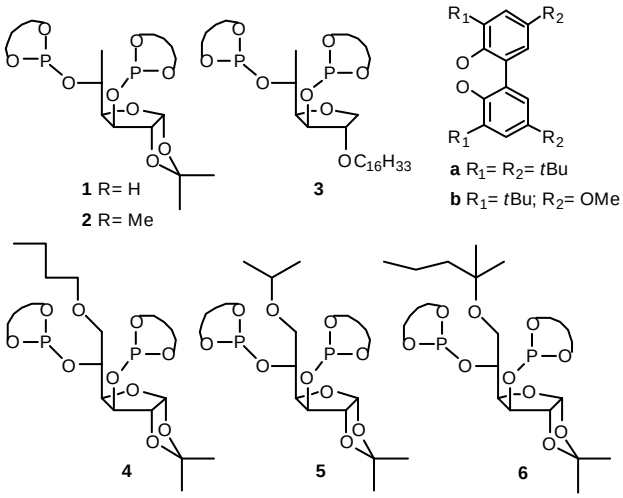
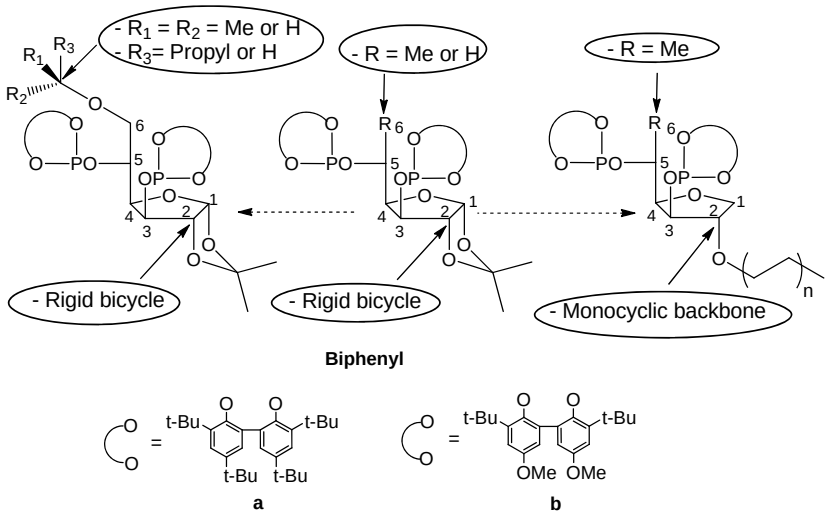


Figure 4.1 Diphosphite ligands derived for carbohydrates used in this study.

4.2 Results and discussion

The diphosphite ligands **1-6** (**a-b**) showed in Figure 4.1, were tested in the rhodium-catalyzed asymmetric hydroformylation of norbornene (Scheme 4.2). These ligands, reported in 2009, have been synthesized in the work of a previous doctoral thesis in our group.[8,15] Related to other carbohydrate ligands previously developed[16] these new ligands offer significant possibilities of modification: a) Introduction of *O*-alkyl substituents in the positions C-6 of the furanoside bicyclic backbone, and b) reduction of the 1,2-*O*-isopropylidene ring in order to obtain ligands with furanoside monocyclic backbone and introduction of *O*-alkyl substituent in the C-2 position. The bisphenyl moieties, **a** and **b** were selected because their versatility in several asymmetric processes[17,18] (Scheme 4.2). In the next sections the catalytic activity of the Rh systems containing these ligands in the hydroformylation of norbornene will be discussed.



Scheme 4.2 1,3-Diphosphite ligands derived from carbohydrates.

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Asymmetric hydroformylation of norbornene using diphosphites 1-6a

In order to know the effect of the described ligand modifications and to compare the efficiency of the different ligands, we first studied the activity of catalytic precursors containing ligands (**1-6a**). The catalytic reactions were performed using rhodium precursor [Rh(acac)$(CO)_2$] (1 equiv.) and diphosphite (1.1 equiv.) as a catalytic system under 18 bar of CO/H_2 (1:1) at 45°C during 24 hours. Similar conditions have been previously used in the hydroformylation of dihydrofurans.[15] The catalytic results are summarised in Table 4.1.

Total conversions (>99%) were obtained with Rh precursors containing ligands (**1-6a**) (Table 4.1, entries 1-6). Interestingly, the series of Rh/**1-6a** catalysts produced mainly the *exo*-product. Therefore, excellent *exo*-selectivities were obtained with ligands **2a**, **4-6a** (Table 4.1, entries 2, 4-6) and high values ranged between 93-97% were obtained with ligands **1a** and **3a** (Table 4.1, entries 1 an 3). In terms of enantioselectivity moderate values up to 42% were achieved with ligands **2a, 3a, 5a and 6a** (entries 2-3, 5-6). Low enantioselectivities (26 and 29%) (Table 4.1, entries 1 and 4) were obtained with ligands **1a** and **4a**, respectively.

Table 4.1 Asymmetric hydroformylation of norbornene catalyzed by rhodium/**1-6a**[a]

Entry	Ligand	C(%)[b]	exo(%)[b]	% (ee)[c]
1	**1a**	>99	97	26
2	**2a**	>99	98	40
3	**3a**	>99	93	38
4	**4a**	>99	>99	29
5	**5a**	>99	>99	42
6	**6a**	>99	99	38

[a] Reaction conditions: [Rh(acac)$(CO)_2$]= 0.012 mmol, Rh/**L**=1:1.1, Substrate/Rh

= 400:1, 18 bar of CO/H_2 (1:1), Toluene= 5 ml, T= 45 ºC, t = 24h. [b] Conversion and *exo*-selectivity determined by ^1H NMR and GC-MS. [c] Enantioselectivity of *exo*-product measured by GC.

As conclusion of this first screening, we found **5a** as the most efficient ligand, which provided excellent conversion (>99%) and *exo*-selectivity (>99%) although moderate enantioselectivity of 42%. Therefore, ligand **5a** was used as model to perform the study of reaction parameters of the Rh-catalyzed hydroformylation of norbornene. The results will be described in the next section.

Asymmetric hydroformylation of norbornene using diphosphite 5a. Study of the reaction parameters.

In view of the promising results obtained in terms of activity and selectivity with ligand **5a,** the catalytic system Rh/**5a** was selected to perform the optimisation of the reaction conditions by varying the substrate to metal ratio, the total and partial pressure, the metal to ligand ratio and the reaction temperature (Table 4.2, entries 1 *vs* 2-8).

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Table 4.2 Asymmetric hydroformylation of norbornene using diphosphite **5a**[a]

Entry[a]	Subst./Rh	T (°C)	Conv. (%)[b]	*Exo* (%)[b]	*ee* (%)[c]
1	400/1	45	>99	>99	42
2[d]	400/1	45	94	>99	40
3[e]	400/1	45	>99	>99	32
4[f]	400/1	45	>99	>99	39
5	800/1	45	>99	99	41
6	1600/1	45	>99	99	38
7	1600/1	20	36	99	61
8[g]	1600/1	0	<5	99	67

[a] Reaction conditions: $[Rh(acac)(CO)_2]$= 0.012 mmol, Rh/**L** = 1: 1.1, 18 bar of CO/H_2 (1:1), Toluene= 5 ml, t= 4h. [b] Conversion and *exo*-selectivity determined by ^1H NMR and GC-MS. [c] Enantioselectivity of *exo*-product measured by GC analysis. [d] P= 9 bar. [e] H_2/CO = 2.0. [f] Rh/L= 1: 2.0. [g] t = 24h.

When the reaction was carried out under 18 bars of CO/H_2 during a period of 4h at 45°C, the catalytic system Rh/**5a** produced total conversion with the exclusively formation of the *exo*-product and 42% of enantioselectivity (Table 4.2, entry 1). Then, to study the effect of the total pressure the Rh-asymmetric hydroformylation of norbornene was carried out at lower pressure. When the total pressure was decreased from 18 to 9 bars the conversion slightly decreased (94%) with no-effect on the *exo*-selectivity of the reaction (Table 4.2, entries 1 *vs.* 2). In terms of enantioselectivity, the results remained practically unaltered (40%). Then no clear effect on the selectivity of the reaction was observed. Interestingly, the increase of the

H_2/CO ratio from 1 to 2 did not produce any effect on the *exo*-selectivity (>99%) and conversion (>99%) of the reaction. However, an important decrease on the *ee* of the aldehyde product (Table 4.2, entries 1 *vs.* 3) was observed. Furthermore, no effect on the conversion and selectivity was observed when the L/Rh ratio was increased to 2 (Table 4.2, entries 1 *vs.* 4). Similar results were reported by Beller *at el*, who carried out the rhodium hydroformylation of styrene using phosphepine ligands. No noticeable effect on the ee value was observed when the L/Rh was increased.[19] When the substrate to metal ratios was increased from 400/1 to 800/1 and 1600/1, we did not observe noticeable effect on the catalytic results (Table 4.2, compare entries 1 *vs* 5-6). Conversion and *exo*-selectivity remained excellent. Finally, when the reaction temperature was decreased from 45 to 20°C with a substrate/Rh ratio of 1600, the enantioselectivity was significantly increased to 61% and the *exo*-selectivity was excellent 99% (entry 7). However, low conversion was obtained (36%) under these conditions (Table 4.2, compare entries 6 and 7). This is in agreement with the observations of Sémeril and co-workers on the rhodium catalyzed hydroformylation of norbornene using diphosphites, in which a significant increase in enantioselectivity from 22 to 41% was achieved when the reaction temperature was decreased from 80 to 55°C.[14d] A drastic decrease in conversion (<5%) was obtained when the reaction temperature was decreased from 20° to 0°C (Table 4.2, entries 7 and 8).

In summary, the highest enantioselectivity of 61% together with 99% *exo*-selectivity (99%) were obtained using a substrate/Rh ratio of 1600/1 under 18 bars CO/H_2 (1:1) at 20°C for 4 hours.

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Asymmetric hydroformylation of norbornene using diphosphites 1-6 a,b

The series of diphosphite ligands **1a** and **2-6 a,b** (Figure 4.2) were applied in the Rh-asymmetric hydroformylation of norbornene under the optimised reaction conditions. The results are summarised in Table 4.3.

In general, the conversiones obtained were moderate and the highest value of 36% was achieved with ligand **5a** (Table 4.3, entry 8). The lowest conversion of 8% was achieved for ligand **1a** (Table 4.3, entry 1). It is noteworthy that the incorporation of the *O*-alkyl group in the position C-6 of the glucofuranose backbone in ligands **4**-**6**, affects the activity (Table 4.3, entries 6-11). The order of activity found was Rh/**5a** (*O*-*iso*propyl) > Rh/**6a** (O-*sec*hexyl)> Rh/**4a** (*O*-*n*butyl). The highest activity, TOF 144h^{-1}, was therefore obtained with ligand **5a**. Here, it's really important to mention that although low conversions were obtained with these diphosphite ligands under the conditions studied, they provided catalytic systems 18 times more active and faster than those previously reported in the literature in the hydroformylation of norbornene using Rh systems containig diphosphine[14c] and diphosphite[14d,e] ligands (TOF up to 8h^{-1}).

In terms of stereoselectivity practically exclusive formation for *exo* product was obtained (>99%) with ligands **2a-b**, **5a** and **6a** (Table 4.3, entries 2, 3, 8 and 10) and up to 97% with ligands **1a**, **3a-b**, **4a-b**, **5b**, **6b** (Table 4.3, entries 1, 4-7, 9 and 11). When the biphenyl moietiy **b** containing -OMe groups as susbtituents in *para*-position was used instead of their counterpart with t-Bu groups **a**, a significant increase in enantioselectivity was observed (Table 4.3, entries 3, 5, 7, 9 11). Therefore, the highest enantioselectivity of 71% was achieved with ligand **6b** (Table 4.3, entry 11). As previously reported in the Rh-asymmetric hydroformylation of vinyl arenes and dihydrofurans, the ligands derived from xylofuranose **1a** produced lower enantioselectivities than those derived from glucofuranose **3a**-**6a** (Table 4.3, entries 1 vs. 2-11).[5c-d,8] The use of bicyclic ligand **2a-b** produced

comparable results to those obtained with monocyclic ligand **3a-b** (Table 4.3, entries 2-5).

Table 4.3 Rh-catalysed asymmetric hydroformylation of norbornene using diphosphites ligands **1-6 a,b**[a]

Entry	Ligand	Conv. (%)[b]	*Exo* (%)[b]	*ee* (%)[c]	TOF (h^{-1})
1	**1a**	8	87	41	32
2	**2a**	22	>99	63	88
3	**2b**	12	>99	70	48
4	**3a**	16	97	66	64
5	**3b**	18	97	70	72
6	**4a**	14	97	62	56
7	**4b**	11	97	69	44
8	**5a**	36	99	61	144
9	**5b**	30	95	68	120
10	**6a**	23	99	68	92
11	**6b**	13	96	71	52

[a] Reaction conditions: $[Rh(acac)(CO)_2]$= 0.012 mmol, Rh/**L**=1:1.1, Substrate/Rh = 1600:1, 18 bar of CO/H_2 (1:1), Toluene= 5 ml, T= 20 ºC, t = 4h. [b] Conversion and *exo*-selectivity determined by ^1H NMR and GC-MS. [c] Enantioselectivity of *exo*-product measured by GC.

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4.3 Conclusions

The use of Rh-1,3-diphosphite systems in the asymmetric hydroformylation of norbornene provided high activities (TOF up to 144 h^{-1}) with excellent *exo*-selectivities (up to >99%) and moderate enantioselectivities (*ee* up to 71%). It should to be noted that these systems are 18 times more active than those reported in the literature in the hydroformylation of norbornene. Excellent activity (TOF 120 h^{-1}), stereoselectivity (95% *exo*-aldehyde), and enantioselectivity (*ee* up to 68%) was obtained using the diphosphite ligand **5b**.

The modifications in the diphosphite ligand can be rationalized as follow:

- The incorporation of a stereocenter at position C-5 in ligands **2**, **4**, **5** and **6** provides an increase in both activity and enantioselectivity comparing with ligand **1**.
- No clear effect on the activity and enantioselectivity was observed when diphosphite ligands **2** and **3** containing bicyclic and monocyclic backbones, respectively, were used in the hydroformylation of norbornene.
- Pattern substitution at position C-6 of the sugar in ligands **2 4**, **5** and **6** which contain bicyclic backbone affects the activity of the hydroformylation reaction, however no effect on the enantioselectivity was observed.
- The presence of bicyclic backbone **b** in ligands **2**, **4**, **5** and **6** produces catalytic systems more enantioselective but less active that their counterpart containing bicyclic backbone **a**.

4.4 Experimental

4.4.1 General Procedures. All reactions and manipulations were carried out under a nitrogen atmosphere by using Schlenk-type techniques. The solvents were generally distilled over dehydrating agents and were deoxygenated before use. All ligands (**1-6**) were prepared according to literature methods. All other reagents were used as received from commercial suppliers. Deuterated solvents used for routine NMR measurements were dried over molecular sieves. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Varian Mercury 400 spectrometer (400.14, 100.63 and 161.98 MHz respectively). Chemical shifts were referenced to either TMS as an internal standard (^{1}H, $^{13}C\{^{1}H\}$ NMR spectra) or 85% H_3PO_4 as an external standard ($^{31}P\{^{1}H\}$NMR spectra). Gas chromatography analyses were performed using a Hewlett-Packard 5890 series II chromatograph with flame ionization detector and Ultra-2 (5% diphenylsilicone, 95% dimethylsilicone) (25m X 0.2 mm Ø) capillary column. Enantiomeric excesses were determined by GC analysis (Chiraldex-GTA capillar column 30m X 0.25mm X 0.12μm film thickness).

4.4.2 Catalysis

High-pressure experiments were carried out in a Berghof autoclave, and the reaction mixtures were magnetically stirred and electrically heated. In a typical experiment, the autoclave was purged three times with CO. The solution formed by $[Rh(acac)(CO)_2]$ (0.012 mmol), diphosphite (0.012 mmol) and norbornene (4.8 mmol) in toluene (5ml) was then introduced into the autoclave. Then, the autoclave was pressurized to the desired pressure of CO/H_2. After the desired reaction time, the autoclave was cooled to room temperature and depressurized. Conversions, chemo-, stereo-, and enantioselectivities were determined by GC, GC-MS and NMR analysis.

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Chapter 5

Concluding Remarks

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On the basis of the present work on the methoxycarbonylation of norbornene the following general conclusions can be drawn:

1. When triphenylphosphine was studied in various palladium systems under acidic conditions, a mixture of co-oligomers and esters were obtained. No suitable conditions were found to control the selectivity towards the ester formation.
2. The cationic complexes of the type $[Pd(OH_2)(OTs)(P\text{-}P)](OTs)$ bearing dppe, dppp, dppb diphosphine ligands were found to be preferably active for the copolymerization of norbornene.
3. Norbornene can be chemo- and stereoselectively functionalized to the ester in the presence of highly electron donating and bulky diphosphine ligands such as **1** and **2** (Figure 2.4, p53).
4. The palladium system containing the bulky and basic diphosphine **1** in the presence of TFA provided excellent conversions, chemoselectivities and stereoselectivities in the methoxycarbonylation of norbornene.
5. The palladium complex $[PdCl_2(\mathbf{2})]$ bearing the bidentate ligand **2** was active in the presence of trifluoroacetic acid providing at room temperature excellent conversion, chemo- and *exo*-selectivity.
6. The palladium complex $[PdCl_2(\mathbf{6})_2]$ bearing monodentate ligand **6** (Figure 2.4, p53) was found to be active for the methoxycarbonylation of norbornene, providing at room temperature excellent conversion, chemo- and *exo*-selectivity. The presence of acid was not required when this catalytic system was used.
7. Promising enantioselectivities (up to 46%) were obtained using palladium catalytic system containing monodentate ligand **7** (Figure 2.4, p53).

From the NMR studies of palladium systems modified with bidentate phosphine ligand **2** and monodentate phosphine ligand **6**, the following general conclusions can be drawn:

1. The catalytic system bearing the monophosphine **6** does not require the presence of acid for the methoxycarbonylation of norbornene because HCl is generated in situ in the solution.
2. The presence of the protonated phosphine was observed for both catalytic systems containing monophosphine **6** and bidentate phosphine **2**. In both cases, was demonstrated that these protonated phosphines could be involved in the catalytic reaction.
3. The diprotonated species **2**-$(H^+)_2$ was involved in the formation of the palladium hydride complex [PdHCl(**2**)] **2c**.

On the basis of the study of the asymmetric Rh-catalyzed hydroformylation of norbornene the following general conclusions can be drawn:

1. The catalytic systems containing 1,3-diphosphite ligands with a furanoside backbone **1**-**6a**,**b** (Figure 4.1, p155) were found to be active in the Rh-asymmetric hydroformylation of norbornene.
2. Excellent activity (TOF up to 144 h^{-1}) with practically total selectivity to the *exo*-product (>99%) and moderate to good enantioselectivity (up to 71%) were achieved for the rhodium-catalyzed hydroformylation of norbornene.

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Resumen

Las reacciones de carbonilación son importantes para la obtención de productos oxigenados a partir de hidrocarburos derivados del petróleo. En particular, la carbonilación de alquenos catalizada por complejos de metales de transición ha despertado un interés tanto a nivel científico como industrial ya que mediante este proceso se pueden obtener productos con un alto valor añadido (aldehídos, ésteres, ácidos carboxílicos, copolímeros, etc).

Dentro de las reacciones de carbonilación más significativas desde el punto de vista industrial figuran la alcoxicarbonilación y la hidroformilación. En estos dos procesos los sustratos más estudiados han sido los vinilarenos, especialmente estireno, debido a que permiten la obtención de productos intermedios en la síntesis de fármacos, cosméticos, agroquímicos, etc. Además de estireno, otros sustratos mucho menos estudiados, como el norborneno, pueden ser transformados mediante estas reacciones, con los sistemas catalíticos y condiciones de reacción adecuados, en productos intermedios con aplicación en química fina. En el caso particular de norborneno, el control de la selectividad hacia la formación del producto deseado es un punto clave ya que se ha visto que bajo condiciones de alcoxicarbonilación, es también posible la obtención de policetonas formadas mediante copolimerización alternada de monóxido de carbono con olefinas.

El conocimiento de los mecanismos operantes en este tipo de procesos es de gran importancia para el diseño de nuevos sistemas catalíticos altamente efectivos.

Basándose en las consideraciones anteriores, el primer objetivo de esta tesis se ha centrado en el estudio de las condiciones de reacción y factores que gobiernan la selectividad en la metoxicarbonilación de norborneno.

Un segundo objetivo, ha sido el estudio de sistemas catalíticos de paladio y su aplicación en la metoxicarbonilación asimétrica de norborneno. Para alcanzar el primer objetivo, se ha planteado la exploración de complejos de paladio

modificados con una fosfina monodentada, y fosfinas bidentadas (Capítulo 2, sección 2.1). Para lograr el segundo objetivo, se han sintetizado catalizadores de paladio modificados con monofosfinas y difosfinas voluminosas (Capítulo 2, sección 2.2). Estos catalizadores se emplearon en la reacción de metoxicarbonilación de norborneno.

Con el fin de racionalizar el comportamiento de los sistemas catalíticos con monofosfinas y difosfinas, se llevó a cabo un estudio mecanístico bajo condiciones similares a las catalíticas (Capítulo 3).

Después de revisar los antecedentes bibliográficos en la introducción y planteados los objetivos (Capítulo 1), en el Capítulo 2 "*Palladium-catalyzed carbonylation of norbornene*" en primer lugar se lleva a cabo un estudio de las condiciones de reacción empleando fosfinas mono- y bidentadas comunes (Figure 2.1). Se concluye sobre los parámetros de la reacción que influyen en la selectividad de la metoxicarbonilación de norborneno. El sistema modificado con la monofosfina, conduce a la formación de una mezcla de productos de metoxicarbonilación y copolimerización de norborneno. Los sistemas catiónicos de paladio con difosfinas favorecen la reacción de copolimerización y proporcionan altas conversiones.

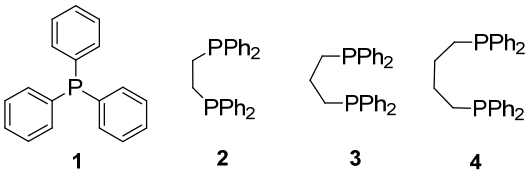

Figura 2.1 Ligandos utilizados en el estudio de las condiciones de reacción.

Capítulo 2, sección 2.1

En la segunda parte se presenta la síntesis y caracterización de complejos de paladio modificados con fosfinas mono- y bidentadas (Figura 2.4). En el caso

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del sistema catalítico que contiene el ligando monodentado (**6**), se obtienen excelentes conversiones, quimio- y estereoselectividades en ausencia de ácido. Excelentes conversiones, quimio- y estereoselectividades se obtienen con los sistemas catalíticos que contienen los ligandos bidentados (**1**,**2**) con grupos *tert*-butil enlazados al átomo de fósforo y forman un anillo quelato de 7-miembros con el centro metálico. Resultados prometedores en cuanto a enantioselectividad (46% *ee*) se obtienen con el sistema catalítico conteniendo el ligando **7**.

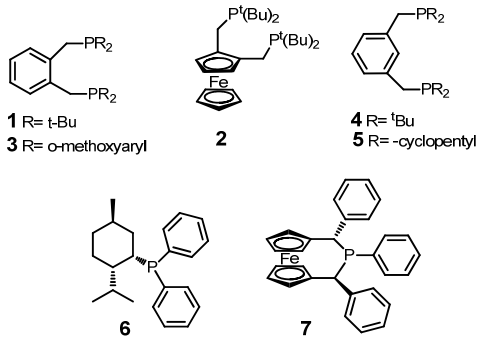

Figura 2.4 Ligandos utilizados en el Capítulo 2, sección 2.2.

En el capítulo 3 *"Mechanistic aspects of the Pd-catalyzed methoxycarbonylation of norbornene"* se discuten algunos aspectos mecanísticos de la metoxicarbonilación de norborneno, utilizando complejos de paladio con los ligandos **2** and **6** (Figura 2.4). La reactividad de los complejos con los diferentes componentes del sistema catalítico, se llevó a cabo paso a paso mediante experimentos *in situ* en condiciones similares a las empleadas en la catálisis. El estudio con el complejo de paladio modificado con el ligando **2** es interesante ya que proporcionó excelentes conversiones- quimio- y estereoselectividades a temperatura ambiente. Se observó protonación de la fosfina y presencia de una

especie Pd-H *in situ*. El estudio del sistema catalítico que contiene el ligando **6**, es interesante ya que no se requiere la presencia de ácido. Este estudio muestra la generación *in situ* de ácido clorhídrico promovida por reacción con monóxido de carbono y metanol. También se observa la protonación de la fosfina.

Finalmente, en el Capítulo 4 "*Asymmetric Rh-catalyzed hydroformylation of norbornene*" se estudia la aplicación de ligandos difosfitos derivados de carbohidratos (Figure 4.1) en la hidroformilación asimétrica de norborneno catalizada por rodio. Los sistemas catalíticos han resultados ser estereoselectivos y hasta 18 veces más activos que los publicados hasta el momento en la literatura. Sin embargo, las conversiones han sido moderadas. El mejor resultado de enantioselectividad ha sido de 71%.

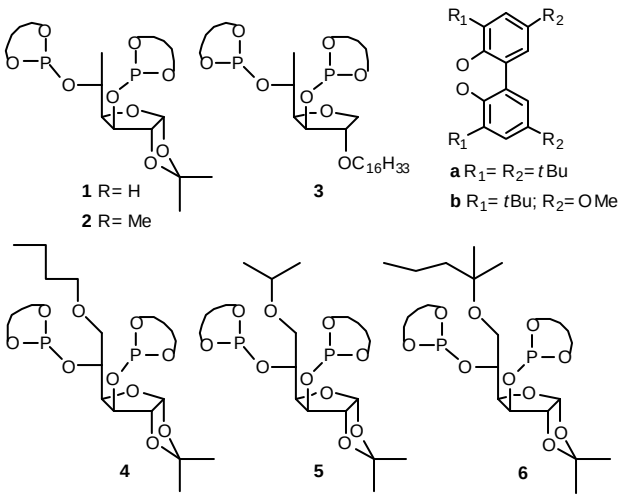

Figura 4.1 Ligandos utilizados en el Capítulo 4.

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CONGRESSES AND SCIENTIFIC MEETINGS

2006

XXII International Conference on Organometallic Chemistry (ICOMC), Zaragoza, Spain. July 2006. Poster Contribution.

2009

16th International Symposium on Homogeneous Catalysis, 6th-11th July 2008, Florence, Italy.
Poster Contribution: "Pd-Catalyzed Chemo- and Stereoselective Methoxycarbonylation of Norbornene Using Monodentate and Bidentate Phosphine Ligands".

International Symposium on Organometallic Chemistry and Catalysis (RENACOM 2009), 29th-30th April 2009, Tetouan, Morocco.
Poster Contribution: "Palladium-Catalyzed Methoxycarbonylation of Alkenes Using Monodentate and Bidentate Phosphine Ligands".

XXXII Reunión Bienal de la Real Sociedad Española de Química, 13th-18th September 2009, Oviedo, Spain.
Oral Contribution: "Rh-Catalyzed Asymmetric Hydroformylation of Norbornene Using Chiral Diphosphites".

PUBLICATIONS BASED ON THE CONTENT OF THE THESIS

Blanco, C.; Ruiz, A.; Godard, C.; Fleury-Brégeot, N.; Marinetti, A. and Claver, C.**"Unprecedent Chemo- and Stereoselective Palladium-Catalyzed Methoxycarbonylation of Norbornene**" C. *Adv. Synth. Catal.*, **2009**, 351, 1813.

Blanco, C.; Godard, C.; Zangrando, E.; Ruiz, A.; and Claver, C. "**Room Temperature Asymmetric Pd-Catalyzed Methoxycarbonylation of Norbornene. Highly Selective Catalysis and HP-NMR studies**" *Organometallics*, 2010, *in preparation.*

Blanco, C.; Gual, A.; Ruiz, A.; and Claver, C. **"Rh-Catalyzed Asymmetric Hydroformylation of Norbornene Using Chiral Diphosphites**" *Adv. Synth. Catal.* 2010 *in preparation.*

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