UNIVERSITAT ROVIRA I VIRGILI

LIGAND DESIGN FOR PALLADIUM AND IRIDIUM SELECTIVE CATALYSTS

Verónica de la Fuente Molina

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DOCTORAL THESIS

Supervised by

Prof. Dra. Carmen Claver Cabrero and Prof. Dr. Sergio Castillón Miranda

Departament de Química Física i Inorgànica

UNIVERSITAT ROVIRA I VIRGILI

Tarragona, 2011

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Prof. Dra. Carmen Claver Cabrero, catedràtica del Departament de Química Física i Inorgànica de la Universitat Rovira i Virgili,

CERTIFICO:

Que el present treball, titulat "**LIGAND DESIGN FOR PALLADIUM AND IRIDIUM SELECTIVE CATALYSTS**", que presenta Verónica de la Fuente Molina per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció i la co-direcció del Prof. Dr. Sergio Castillón Miranda, del Departament de Química Analítica i Orgànica de la Universitat Rovira i Virgili, al Departament de Química Física i Inorgànica i que acompleix els requeriments per poder optar a Menció Europea.

Tarragona, 25 de març de 2011

Prof. Dra. Carmen Claver Cabrero

Prof. Dr. Sergio Castillón Miranda

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"Las ciencias tienen las raíces amargas,
pero muy dulces sus frutos"
Aristóteles

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ACH: Acetone-cyanohydrin

ALPHA: 1,2-bis(di-*tert*-butylphosphinomethyl)benzene

[bmim][BF_4]: 1-butyl-3-methylimidazolium tetrafluoroborate

[bmim][PF_6]: 1-butyl-3-methylimidazolium hexafluorophosphate

[2,3-dmbim][BF_4]: 2,3-dimethyl-1-buthylimidazolium tetrafluoroborate

[2,3-dmbim][PF_6]: 2,3-dimethyl-1-buthylimidazolium hexafluorophosphate

BSA: N,O-bis(trimethylsilyl)acetamide

CAMP: Cyclohexyl(2-methoxyphenyl)(methyl)phosphine

Cy: Cyclohexyl

CO: Carbon monoxide

COD: 1,5-cyclooctadiene

δ: Chemical shifts

DABCO: 1,4-diazabicyclo[2.2.2]octane

BAr_F: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

Dba: dibenzylideneacetone

DBU: 1,8-Diazabicycloundec-7-ene

DCC: N,N'-diciclohexilcarbodiimida

Dcpp: 1,3-bis(dicyclohexylphosphinopropane

dd : doublet of doublet

ddd: doublet of doublet of doublet

DIOP: (-)-2,2-Dimethyl-4,5-diphenylphosphino)dimethyl)dioxolane)

Dipamp: Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]

DMF: Dimethylformamide

Dpfam: N,N-bis[(2-diphenylphosphino)phenylformamidinate

ee: Enantiomeric excess

GC: Gas Chromatography

GC-MS: Gas Chromatography Mass Spectrometry

HP: High-pressure Nuclear Magnetic resonance spectrometry

Hz: Hertz

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IR: Infrared

MeP: Methyl propionate

MMA: Methyl methacrylate

Nbd: Norbornadiene

NMR: Nuclear Magnetic Resonance

TBME: tert-butyl methyl ether:

THF: Tetrahydrofurane

TMS: Tetramethylsilane

TON: Turnover number

TOF: Turnover number frequency

PHOX: Phosphino-oxazoline

PHIM: Phosphino-imidazoline

VT-NMR: Variable temperature NMR

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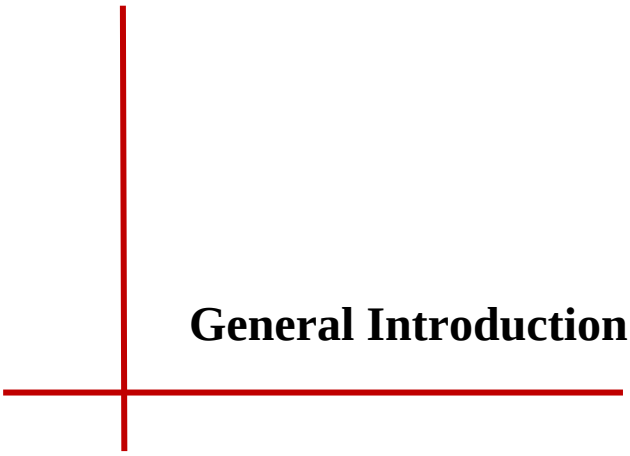

Chapter ***1***

General Introduction and Objectives

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1.1. Homogeneous catalysis and chemical industry applications

Organometallic complexes containing M-C bonds and coordination complexes containing ligands such as phosphorus donors and hydrides are often used as catalyst precursors for organic transformations. The reactivity of a complex with substrate molecules and the capability to catalyse chemical transformations are determined by the metal centre and the type of ligands in its coordination sphere.[1] A strategy to modify the properties of a catalyst thus consists in varying the ligand features. Over the last decades, the number of ligands available has grown impressively and largely contributed to the development of organometallic chemistry.[1] These catalyst features are crucial in order to design sustainable catalytic processes and can be defined as follow:

a) Activity: The rate of the reaction can be expressed as catalyst productivity and catalyst activity, defined as turnover number (TON) and turnover number frequency (TOF) respectively.

b) Selectivity: in catalytic processes, several types of selectivities can be encountered:

b.1) *Chemoselectivity:* the preferential reaction of one of the reactive functional groups of the substrate.

b.2) *Regioselectivity:* the preferential reaction at one of the reactive centres of a conjugated system.

b.3) *Stereoselectivity:* the preferential formation of one of the possible stereoisomers.

b.4) *Enantioselectivity:* the preferential formation of one enantiomer.

The presence of an organometallic complex in a reaction will affect the kinetics of this process since the substrates will be activated through coordination to the metal centre, providing an alternative mechanism which shows a different transition state with lower activation energy (Figure 1.1). As a result, the reaction using a catalyst becomes faster than the un-catalysed one. Moreover, the catalyst will be able to accelerate reactions that, albeit thermodynamically feasible, would not occur in the absence of a catalyst. This new pathway includes several new intermediates and steps which will configure the reaction mechanism. However, during the catalytic cycle, the catalyst can be involved in competitive reactions affecting the selectivity of the process.

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Generally, organometallic complexes are soluble in organic solvents and as such, can be used as homogeneous catalysts.[2] The study of their behaviour throughout the catalytic cycle by spectroscopic tools such as *in situ* HP NMR and IR techniques is therefore possible. On the contrary, the reaction involving a heterogeneous catalyst occurs at the interphase since the reagents and products are in a different phase than the catalyst.

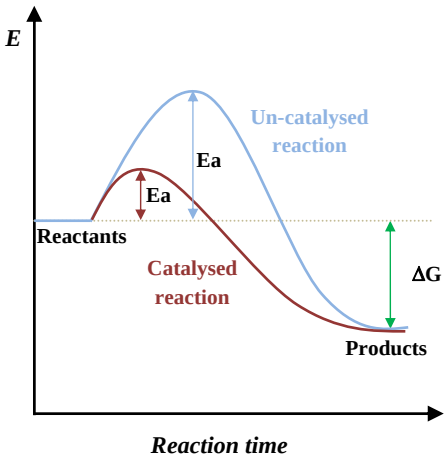

Figure 1.1. Comparison of the activation energy for a catalysed and an un-catalysed reaction.

Heterogeneous catalysts are more widely used in industrial processes than homogeneous catalysts due to the robustness and the possibility to reuse them. 85% of the industrial processes use a catalyst and in 75% of these processes, the catalyst is heterogeneous.[1]

In general, for homogeneous catalysts, activity and selectivity are higher than for the heterogeneous catalysts. When a catalytic process is transferred to an industrial scale, other aspects such as the catalyst recovery, catalyst life, susceptibility towards poisoning, diffusion and understanding of mechanism have to be considered. Regarding these aspects, the separation of the catalyst from the product is an issue where various strategies can be applied. Generally, distillation or crystallization of the product is useful, but other approaches such as phase separation, extraction or immobilization of a soluble catalyst into an insoluble support such as a polymer can also be used.

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Figure 1.2 shows some of the products formed in homogeneous catalysis. Most of these processes are manufacturated in a large scale except for the fine chemicals and intermediates.[3]

For instance, the synthesis gas is converted into methanol by a heterogeneous catalyst and then the carbonylation of methanol is performed by a homogeneous catalyst and produces acetic acid. The acetic anhydride is obtained by carbonylation of methyl acetate; both processes are carried out at a large scale. The hydroformylation of alkenes allows the formation of aldehydes which are hydrogenated to produce alcohols, which are used for the generation of plastics and detergents. Homogeneous catalysis is mainly used for small scale processes which yield high added value products, such as fine chemicals, intermediates, agrochemicals and pharmaceutical compounds.[4] Generally, these compounds are optically active, and in most of the cases, only one enantiomer presents the property of interest.

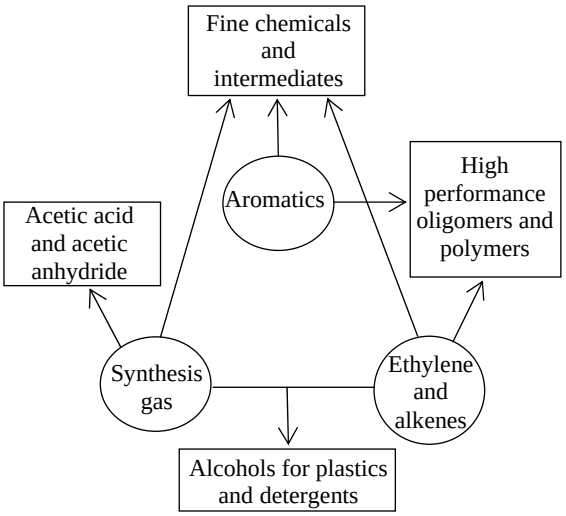

Figure 1.2. Chemicals and classes of chemicals that are manufactured by homogeneous catalytic processes.

For this reason, the pharmaceuticals, agrochemicals and flavours or fragrances companies usually prefer their enantioselective synthesis through the use of a metal catalyst bearing a chiral ligand.[5] Figure 1.3 shows the most representative class of chiral ligands which are successfully applied in asymmetric catalytic processes.[5]

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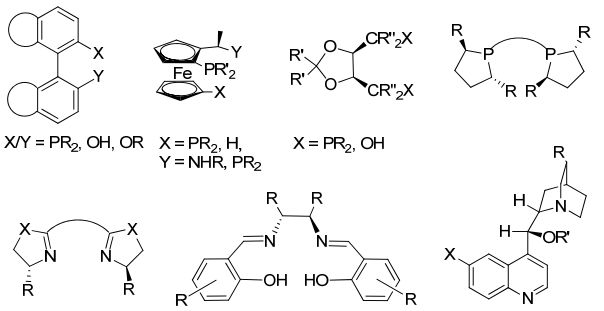
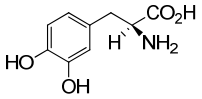
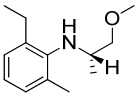
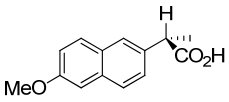
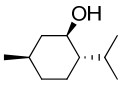
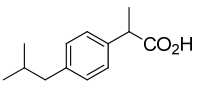
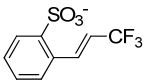


Figure 1.3. Versatile chiral ligand types.

Finally, Table 1.1 summarizes some of the most interesting added value products obtained via homogeneous catalysis.[3]

Table 1.1. Products obtained through homogeneous catalytic reactions.

Structure	Name	Use	Process
	L-Dopa	Drug for Parkinson's disease	Asymmetric hydrogenation
	(*S*)-Metolachlor	Grass herbicides	Asymmetric hydrogenation
	Naproxen	Antiinflammatory drug	Asymmetric hydroformylation, hydrocyanation or hydrogenation
	L-Menthol	Flavoring agent	Asymmetric isomerization
	(*R*)-Glycidol	One of the components of a heart drug	Asymmetric epoxidation
	Ibuprofen	Analgesic	Catalytic carbonylation
	Methyl Propanoate	Synthesis of methyl methacrylate	Methoxycarbonylation of ethene
	Intermediate for Prosulfuron	Herbicide	C-C coupling reaction

1.2. References

[1] P. W. N. M. van Leeuwen, *Homogeneous catalysis: Understanding the Art*, Kluwer, Dordrecht, **2004**.

[2] a) B. Cornils, W. A. Herrann, Eds., *Applied Homogeneous Catalysis with Organometallic compounds*, VCH, Weinhein, **1996**; b) L. A. Oro, E. Sola, Eds., *Fundamentos y aplicaciones de la Catálisis Homogénea*, Zaragoza, España, **2000**.

[3] S. Bhaduri, D. Mukesh, *Homogeneous catalysis: Mechanisms and Industrial Applications*, Wiley-Interscience, New York, **2000**.

[4] a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; b) A. zon Zelewsky, *Stereochemistry of Coordination Compounds*, Wiley, England, **1996**; c) I. Ojima, *Catalytic Asymmetric Synthesis*, VCH, New York, **2000**.

[5] H. U. Blaser, E. Schmidt, *Asymmetric Catalysis on Industrial Scale*, Wiley-VCH, Weinheim, Germany, **2004**.

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1.3. Objectives

This thesis focuses on the study of various catalytic reactions of industrial interest, aiming at the design of new and efficient catalytic systems for sustainable processes. The reactions that were studied can be divided into two groups:

a) Part I: Carbonylation reactions

a.1) Pd-catalysed methoxycarbonylation of ethene.
a.2) Pd-catalysed carbonylation of aryl iodides.

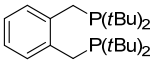
b) Part II: Asymmetric reactions

b.1) Ir-catalysed asymmetric hydrogenation of unfunctionalised olefins and imines.
b.2) Pd-catalysed asymmetric allylic substitutions.

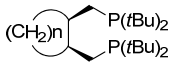
To achieve these goals the following objectives are proposed:

a) Carbonylation reactions

- To synthesise a new family of diphosphine ligands which are related to the ligand used at industrial level (ALPHA) but containing saturated cycloalkyl backbones to confer them flexibility.



Alpha ligand



n=1-4

- To prepare and characterise the corresponding palladium(II) phosphine complexes and compare the structural features of the complexes.
- To study the catalytic behaviour of these systems in the Pd-catalysed methoxycarbonylation of ethene.
- To perform a mechanistic study of this process using multinuclear NMR and HP-NMR techniques.

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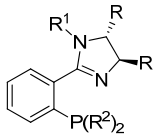
- To apply the diphosphine ligands previously synthesised in the Pd-catalysed aminocarbonylation and double carbonylation of aryl iodides.
- To investigate mechanistic aspects of the Pd-catalysed carbonylation reaction of aryl iodides using NMR techniques.

b) Asymmetric reactions

- To design and synthesise a new family of phosphino-imidazoline ligands modifying the substituents in the imidazole backbone, at the nitrogen atom of the imidazole ring and at the phosphorus moiety.



- To synthesise and characterise the corresponding palladium and iridium complexes.
- To test the Ir/phosphino-imidazoline catalytic systems in the enantioselective hydrogenation of unfunctionalised olefins and imines.
- To study the Pd/phosphino-imidazoline catalytic systems in the enantioselective allylic alkylation and amination reactions.
- To study the origin of the enantioselectivity by NMR spectroscopy and DFT calculations.
- To study the recovery of the catalyst in the Pd-catalysed allylic substitution reactions by using two different methods:
  - Anchoring the chiral phosphino-imidazoline ligand onto a polymer resin. This part has been carried out in collaboration of Prof. Dr. Miquel A. Pericàs and it takes part of the PhD thesis of Rocío Marcos.
  - Performing the reaction in ionic liquids.

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Part I

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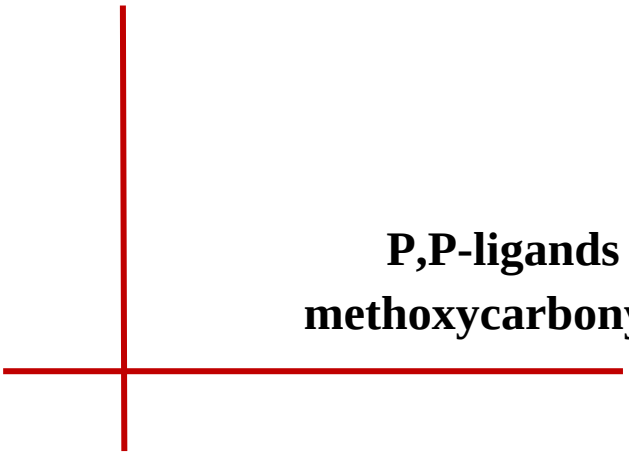

Chapter ***2***

P,P-ligands in Pd-catalysed methoxycarbonylation reaction

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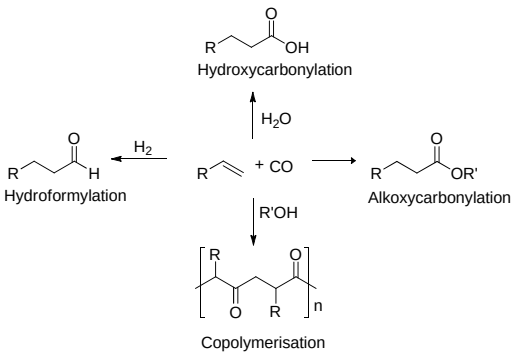
2. 1. Introduction to carbonylation reactions of olefins

As mentioned before, carbonylation reactions are among the most important homogeneous catalytic processes since they make use of carbon monoxide, an important C1 building block, to obtain products of industrial interest such as pharmaceuticals, polymers and building blocks for synthetic applications.[1]

The carbonylation of olefins, the basic raw materials for the chemical industry, was discovered in 1938 by Roelen and co-workers.[2] This reaction consists in the formation of aldehydes through the hydroformylation of an olefin in the presence of synthesis gas. Scheme 2.1 summarizes the different carbonylation reactions of olefins. The hydroxy- and alkoxycarbonylation reactions consist in the formation of acids or esters (from carbon monoxide and olefins) depending on whether the reaction is carried out in the presence of water or alcohol, respectively. Finally, the copolymerisation reactions which involve alternative insertions of carbon monoxide and olefin, produce polyketones, which can be used as thermoplastics.[3]



Scheme 2.1. Carbonylation reactions of olefins.

2.1.1 Pd-catalysed methoxycarbonylation of ethene

Lucite International is one of the major manufacturers of methyl methacrylate (MMA) in the world. Methyl methacrylate is used in a number of applications such as the production of the acrylic plastic Perspex and of corrosion casts for anatomical organs.[4]

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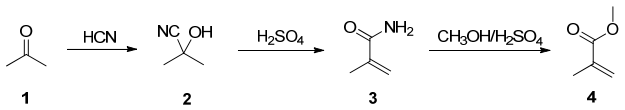
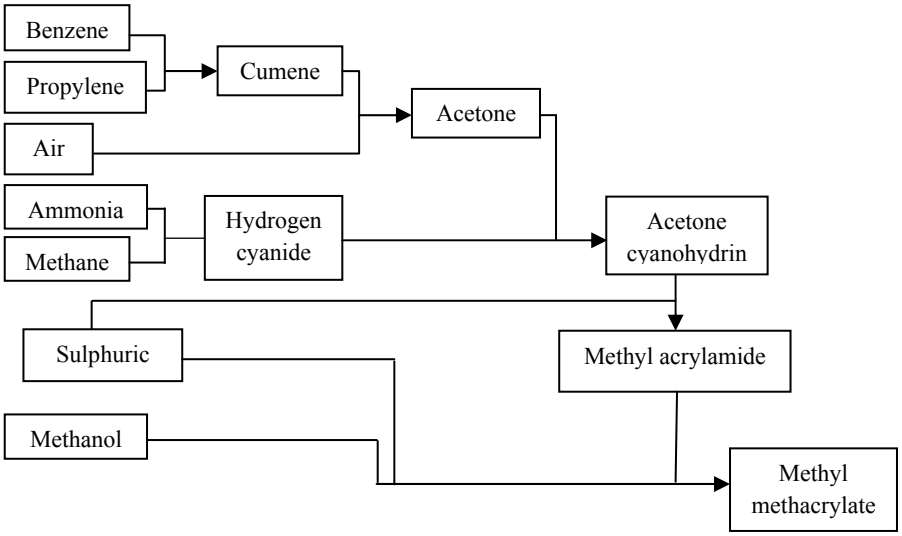
The method currently employed by the company for the manufacture of MMA is the acetone-cyanohydrin (ACH) route (Scheme 2.2). The two key reagents in the ACH route are hydrogen cyanide and acetone, as shown in Scheme 2.3.[5]



Scheme 2.2. Synthesis of methyl methacrylate.



Scheme 2.3. Scheme of the synthesis of methyl methacrylate.

Hydrogen cyanide reacts with acetone to give the cyanohydrin. MMA is then obtained by the hydrolysis of this addition product with sulphuric acid in the presence of methanol. The by-product of this step is ammonium hydrogensulfate, from which sulphuric acid is regenerated through pyrolysis at 1000 ºC to produce sulphur dioxide and subsequent hydrolysis.

The main drawbacks of the ACH process lie in the toxic nature of the hydrogen cyanide and also the requirement to recycle the sulphuric acid used in the process.

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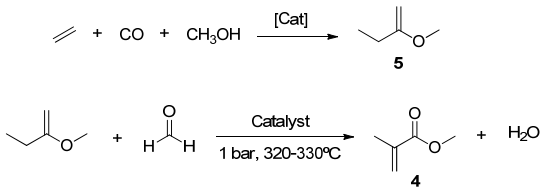
Lucite has developed a new process for the synthesis of MMA known as Alpha process.[6] This process overcomes the drawbacks of the ACH process providing a less toxic and more cost effective method for the synthesis of MMA. The two main steps in the process are shown in Scheme 2.4.



Scheme 2.4. Production of methyl methacrylate by the Alpha process.

In the first step, ethene reacts with carbon monoxide and methanol in the presence of a palladium phosphine catalyst to produce methyl propionate (MeP)

The catalytic system used in the synthesis of methyl propionate consists in:

a) A palladium source, usually $Pd_2(dba)_3$, where the palladium is in the zero oxidation state.
b) The bidentate phosphine 1,2-bis(di-*tert*-butylphosphinomethyl) benzene (ALPHA) (Figure 2.1).
c) A sulphonic acid, usually methanesulphonic acid.

In the second step, MMA is produced by an aldol reaction of MeP with formaldehyde.

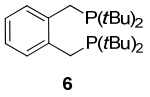


Figure 2.1. 1,2-bis-(di-*tert*-butylphosphinomethyl)benzene (ALPHA) ligand.

The Alpha process produces cheaper MMA than that prepared by the ACH route. Moreover, the reagents and by-products generated in the Alpha process are less toxic than those of the ACH route.[7]

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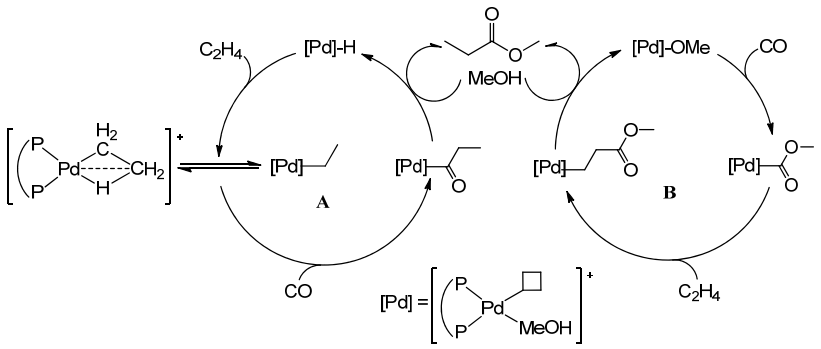
2.1.1.1.Mechanism

Both methoxycarbonylation and copolymerisation of ethene consist in the following steps: a) initiation, b) propagation and, c) termination.

The methoxycarbonylation of ethene is thought to occur by two possible mechanisms, the "hydride" (**A**) and the "carbomethoxy" mechanism (**B**), Scheme 2.5[8,9,10,11]



Scheme 2.5. Proposed mechanisms for the methoxycarbonylation of ethene: **A** Hydride cycle; **B** Methoxycarbonyl cycle. (□ Means different groups coordinated to palladium along the catalytic cycle).

The hydride mechanism (**A**) starts with a palladium hydride complex which is formed by the protonation of the palladium centre.[11] The Pd-alkyl complex is then formed by the coordination and insertion of ethene into the Pd-H bond. An acyl complex is then formed by the migratory insertion of CO.[8] The nucleophilic attack of methanol at the carbonyl leads to the formation of methyl propionate. The regeneration of the palladium hydride species completes the catalytic cycle.[12,13,14]

In the carbomethoxy mechanism (**B**)[1,15] the migratory insertion of CO into a Pd-OMe (the nucleophilic attack of the methanol on a coordinated CO was also proposed) leads to the formation of a methoxycarbonyl complex. Then the coordination and insertion of ethene takes place followed by methanolysis to yield the product.[15]

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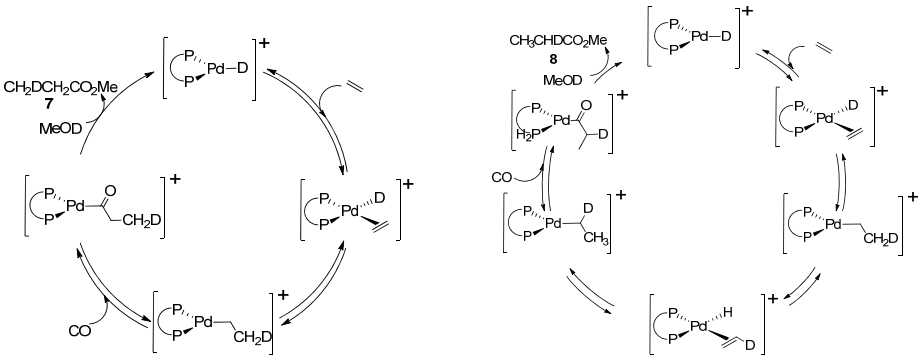
There is evidence and a general agreement that systems affording the ester product operate exclusively *via* the hydride catalytic cycle,[8] and that both cycles operate in copolymerisation catalysis.[15]

B. T. Heaton and co-workers reported deuterium labelling experiments carrying out the reaction in MeOD.[16] A control experiment of this solution was done to investigate the reaction between MeP and MeOD. The analysis of samples indicated that the results MeP was not deuterated, thus demonstrating that any deuterium found in the final product could only come from incorporation during the catalytic cycle and not after.

The analysis of the products obtained from the experiments using CO/ethene showed that the MeP obtained was mono-deuterated. The ^{13}C NMR showed that the MeP was present as two different isotopomers, $CH_2DCH_2CO_2Me$ (**7**) and CH_3CHDCO_2Me (**8**) in almost equal proportions (Scheme 2.6). Low levels of $C_2H_5CO_2Me$ (<10%) and $CH_2DCHDCO_2Me$ (4%) were also detected. The formation of $CH_2DCH_2CO_2Me$ and CH_3CHDCO_2Me can be explained by the hydride mechanism (as H/D exchange in methyl propionate does not occur) making the assumption that it takes place with rapid reversible migration of the hydride to the coordinated ethene molecule and coordination of CO occurs at a much higher rate than the exchange of Pd-H with MeOD. Scheme 2.6 shows both proposed routes for the formation of the products observed.



Scheme 2.6. Proposed mechanisms for the formation of $CH_2DCH_2CO_2Me$ and CH_3CHDCO_2Me.

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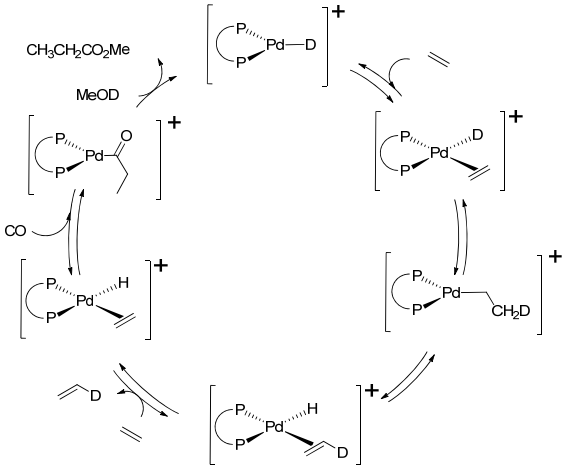
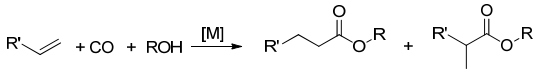
From these observations, it was concluded that the coordination of ethene is irreversible, since if it were reversible, significant amount of $C_2H_5CO_2Me$ would be expected from the loss of C_2H_3D followed by coordination of C_2H_4 to the Pd-H intermediate (Scheme 2.7).[16]



Scheme 2.7. Route to $CH_3CH_2CO_2Me$.

2.1.1.2. Background of ethene carbonylation

The earliest examples of the carbonylation of ethene catalysed by metal complexes appeared in the early 50s.[2] This reaction produces carboxylic acids or esters using carbon monoxide, and water or alcohols as starting materials (Scheme 2.8).



Scheme 2.8. Carbonylation of olefins.

In 1953, Reppe and co-workers reported that metal carbonyl hydrides were highly active catalysts for the carbonylation of acetylene with carbon monoxide, to afford acrylic acid.[2,17] The operating conditions were very mild (30 bar and 170ºC) compared with those used at that time. The ester of acrylic acid was synthesised under the same conditions using $NiBr_2$ and NiI_2 as catalysts.

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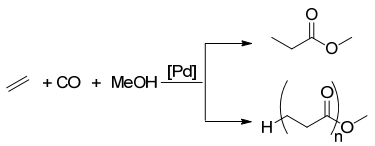
The results obtained by Reppe were applied in the carboxylation of alkenes, although reaction conditions were harsher than those used in the carbonylation of alkynes. The catalyst consisted in a nickel complex such as $Ni(CO)_4$. Other catalyst systems, constituted of metal carbonyls complexes of Ni[17], Co[18] and Pt[19] were also used. Nowadays, the most common system used contains palladium as the metal centre.

In the case of palladium catalysed alkoxycarbonylation of ethene, polyketones and/or low boiling liquids such as methyl propionate (n = 1) can be obtained (Scheme 2.9),[20,21] the selectivity of the reaction showing a marked dependence on the nature of the phosphine ligand employed. Many experimental[11-16,22-49] and theoretical[50-52] studies have been reported. Initially, it was concluded that monodentate phosphines favour alkoxycarbonylation of ethene to give methyl propionate while bidentate phosphines lead to polyketones.[20] Subsequently, van Leeuwen showed that the chemoselectivity of the reaction could be controlled by the appropriate choice of the diphosphine ligand, methoxycarbonylation being favoured by sterically hindered diphosphines.[50] Computational studies also concluded that bulky diphosphine ligands strongly favour ester formation over polymerization.[51] Extensive screening of monodentate and bidentate ligands has shown[21,53] that trialkyl phosphine ligands such as P(nBu$_3$), are more effective than aryl monodentate phosphines. Similarly, alkyl diphosphine ligands containing bulky end groups (**9-12**) are preferred, affording methyl propionate with 98% selectivity (Figure 2.2).[3]



Scheme 2.9. Methoxycarbonylation *versus* copolymerisation of ethene.

In the late 1990's, I.C.I synthesised a novel bidentate phosphine, 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (**6**) (known as Alpha ligand) which was used in the synthesis of methyl propionate. This ligand gave MeP with rates of 50,000 mol of MeP per mol of palladium per hour, and with an increased selectivity to MeP of 99.9%.[54-57]

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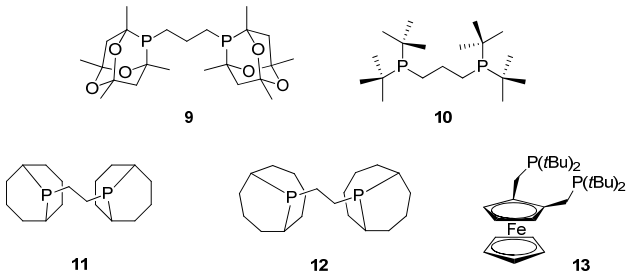
The catalytic system was formed by combining the Alpha ligand/ palladium dibenzylidene acetone in the presence of methanesulphonic acid. This catalytic system converts ethene, CO and MeOH to methyl propionate under mild conditions (100ºC and 10 bar).



9 10 11 12 13

Figure 2.2. Diphosphine ligands used in the methoxycarbonylation reaction.

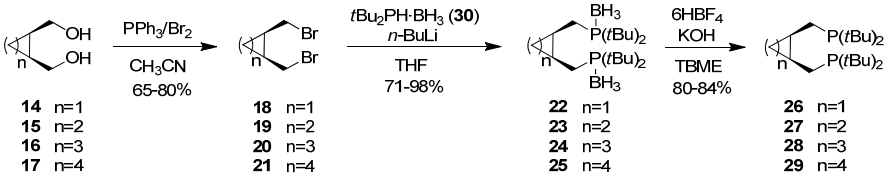
To determine the factors that make the 1,2-bis(di-*tert*-butylphosphinomethyl)benzene a specially suitable ligand for the palladium catalysed methoxycarbonylation of ethene, Lucite has developed a range of similar ligands. Modifications of the substituents on phosphorus produce a drastic decrease of both activity and selectivity.[8] Changing the ligand backbone from an aryl bridge to ferrocenyl[58] led to the discovery of a new family of bidentate phosphines, such as **13** (Figure 2.2) which is also highly active catalyst for the formation of methyl propionate with rates of 55,000 mol MeP per mol of palladium per hour and turnover numbers of 60,000 mol MeP per mol of palladium.

2. 2. Results and discussion

Based on the excellent results in terms of activity and selectivity obtained with the catalytic system Pd/ALPHA, modifications on the backbone of the ligand was proposed. The modification consisted in the substitution of the aryl group by cycloalkyl rings which will confer more flexibility to the ligand.

2.2.1 Synthesis of P,P-ligands

In this context, the syntheses of the bidentate phosphine ligands **26-29**, with a saturated alkyl ring backbone containing 3, 4, 5 and 6 carbon atoms, respectively, were carried out from the diols **14-17** in three steps (Scheme 2.10).



Scheme 2.10. Synthesis of phosphines **26-29** from diols **14-17**.

The diol *cis*-1,2-cyclohexanedimethanol (**17**) is commercially available, while the diols **14**[59,60] and **15**[59,60] were prepared by reduction of dimethyl *cis*-cyclopropane-1,2-dicarboxylate (**31**) and *cis*-cyclobutane-1,2-dicarboxylic acid (**32**), respectively, with lithium aluminium hydride (Scheme 2.11a). *Cis*-cyclopentane-1,2-dimethanol (**16**) [60,61] was prepared in three steps from ethyl 2-oxocyclohexanecarboxylate (**33**) by bromination to give compound **34**, followed by treatment in basic medium to induce a Favorskii[62] rearrangement affording the diacid **35** and finally reduction with lithium aluminium hydride (Scheme 2.11b).

The diols **14-17** were then converted in high yield to the dibromo compounds **18-21** by reaction with *in situ* prepared PPh_3Br_2.[63] The dibromides are easily separated from the triphenylphosphine oxide by-product by extraction into pentane (Scheme 2.10).

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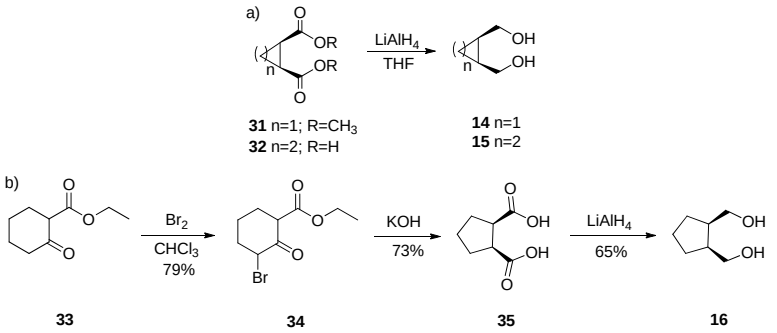

Scheme 2.11. Synthesis of diols **14-16**.

Reaction of the dibromides **18-21** with the lithium salt of the boron-protected secondary phosphine tBu$_2$PH·BH$_3$ (**30**) gave the boron protected bidentate phosphine ligands **22-25**.[64,65] De-boronation of the phosphines **22-25** was achieved by the addition of an excess of tetrafluoroboric acid to give an *in situ* prepared phosphonium salt which was then converted to the desired phosphine by the addition of potassium hydroxide.[64] The ^{31}P NMR spectroscopic data for the four novel diphosphine ligands **26**, **27**, **28** and **29** are given in Table 2.1.

Table 2.1. ^{31}P{^{1}H} NMR spectroscopic data for **6** and **26-29** and for the corresponding diselenides.

Entry	Ligand	Ligand Backbone	$\delta(^{31}P)$	Diselenide	
				$\delta(^{31}P)$	$J_{P\text{-}Se}$ (Hz)
1	**6**	Xylene	25.3	77.4	695
2	**26**	Cyclopropane	30.0	77.5	691
3	**27**	Cyclobutane	20.9	74.7	687
4	**28**	Cyclopentane	24.3	80.3	688
5	**29**	Cyclohexane	24.7	81.3	689

We have the phosphine diselenides of ligands **6** and **26-29** were also prepared to establish any differences in electronic properties of the ligands *via* the ^{31}P-^{77}Se coupling constant (Table 2.1). The variation in $J(^{31}P\text{-}^{77}Se)$ between **6** and **26-29** is small compared with the range of values for ^{31}P-^{77}Se coupling reported previously for other phosphine selenides,[66, 67] thus we concluded that

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all the diphosphines used in this study should have comparable electronic properties. However, a titrimetric study of the protonation of diphosphines **6** and **26-29** indicated that the basicity of the cycloalkyl diphosphines is significantly greater than that of ligand **6**. Thus, Table 2.2 reveals that di-protonation of the cycloalkyl ligands **26-29** occurs at higher pH than for ligand **6**, and that di-protonation of ligands **26** and **27** is favoured compared to di-protonation of ligand **6**.

The bite angles of the cycloalkyl ligands **26-29** and ligand **6** are listed in Table 2.3 and are practically identical. Differences in catalytic activity between **6** and **26-29** should, therefore, reflect the differences in basicity of the ligands and, possibly, the flexibility of the ligand backbone.

Table 2.2. Equilibrium constants of the ligands **6** and **26-29**.

Entry	Ligand	pk		Equilibrium constant	
		pK_1	pK_2	K_1	K_2
1	**6**	1.12	0.56	0.075	0.275
2	**26**	-	1.01	-	0.098
3	**27**	-	1.21	-	0.062
4	**28**	1.51	1.12	0.031	0.075
5	**29**	0.98	0.77	0.105	0.170

2.2.2 Synthesis and characterisation of the related Pd complexes (***41-44***)

The palladium complexes **41-44** containing ligands **26-29** have been prepared and the X-ray crystal structures of the complexes determined to compare the structural features of these complexes with those of the palladium complex of the reference ligand **6**, with the aim of establishing structure-catalytic performance correlations.

Direct reaction of diphosphines **26-29** with $[Pd_2(dba)_3]$ affords the [Pd(dba)(diphosphine)] complexes **37-40**. These complexes can then be oxidized (without prior isolation) in the presence of traces of O_2 to give the palladium(II) complexes[11] **41-44** by the addition of two equivalents of methanesulfonic acid (Scheme 2.12).

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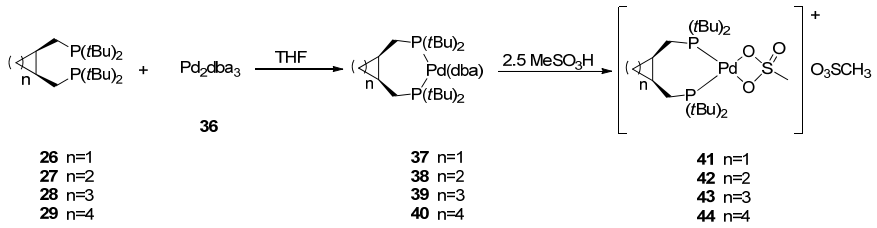

26 n=1
27 n=2
28 n=3
29 n=4

37 n=1
38 n=2
39 n=3
40 n=4

41 n=1
42 n=2
43 n=3
44 n=4

Scheme 2.12. Synthesis of Pd(II) complexes **41-44**.

Single crystals suitable for X-ray structure determinations were obtained by slow diffusion of diethyl ether (**41**, **42**, and **44**) or *tert*-butyl methyl ether (**43**) into tetrahydrofuran solutions of the complexes (Figure 2.3).

In the X-ray structure of the complexes **41-44**, two sulfonate ions (one coordinated and another as counterion) and one molecule of sulfonic acid are present. During the formation of the single crystals some palladium black precipitate, probably as a result of decoordination of sulfonate, which can provide the additional sulfonic acid molecule observed in the crystal structure. $[Pd(O_3SCH_3)(2\mathbf{6})][O_3SCH_3]$ (**41**) crystallizes in a monoclinic space group with unit cell parameters a = 9.8572(14) Å, b = 12.8636(18) Å, c = 26.605(4) Å and V = 3326.6(8) $Å^3$. The structure was solved in space group $P2_1/c$. The R1 value is 0.0449. The asymmetric unit of the structure contains one cation (with a single bidentate sulfonate ligand), one sulfonate anion and one sulfonic acid molecule (Figure 2.3). The palladium atom is coordinated in a distorted square planar geometry. There is disorder in the coordinated sulfonate, and in what is presumed to be the sulfonic acid molecule for which the acid H atom was not located and the assignment of oxygen and methyl was based on interatomic distances.

$[Pd(O_3SCH_3)(\mathbf{27})][O_3SCH_3]$ (**42**) crystallizes in a triclinic space group with a = 11.2245(12) Å, b = 13.0794(14) Å, c = 16.0019(17) Å and V = 2113.4(4) $Å^3$. The structure was solved in space group $P\bar{1}$. The R1 value is 0.0233. The asymmetric unit of the structure contains one cation (with a single bidentate sulfonate ligand), one sulfonate anion, one sulfonic acid molecule (hydrogen bonded to the sulfonate anion, with an essentially symmetrical hydrogen bond), and two molecules of THF (Figure 2.3). The palladium atom is coordinated in a distorted square planar geometry. There is no disorder in the structure.

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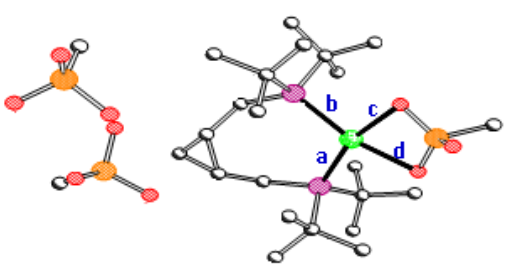
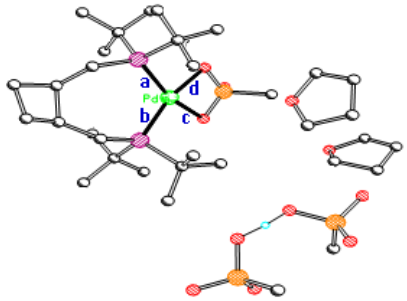
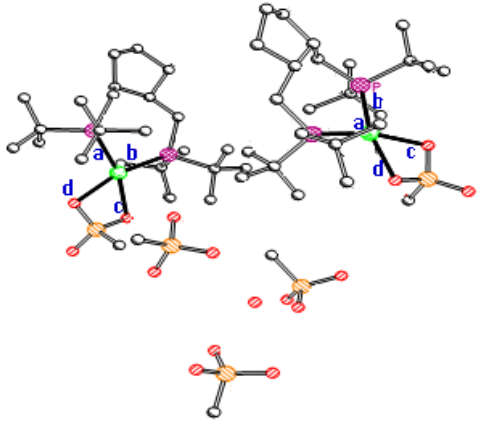


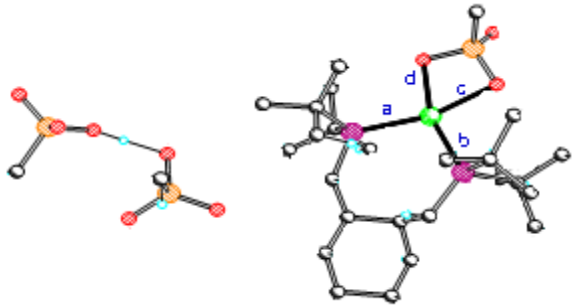
41
[Pd(O_3SCH_3)(**26**)][O_3SCH_3]

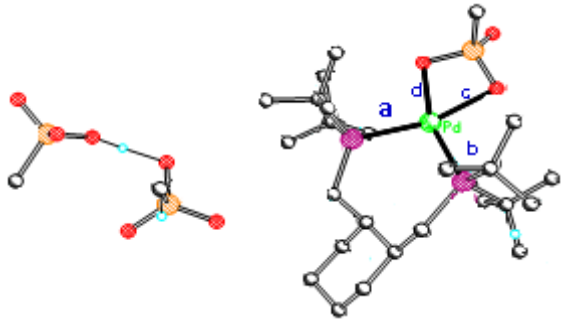


42
[Pd(O_3SCH_3)(**27**)][O_3SCH_3]



43
[Pd(O_3SCH_3)(**28**)][O_3SCH_3]





44
[Pd(O_3SCH_3)(**29**)][O_3SCH_3]

Figure 2.3. Molecular structure of complexes (**41-44**).

Hydrogen atoms omitted in this Figure, except for the one involved in the hydrogen bond.

Compound $[Pd(O_3SCH_3)(\mathbf{28})]O_3SCH_3$ (**43**) crystallizes in a triclinic space group with a = 10.8149(13) Å, b = 11.278(2) Å, c = 31.700(5) Å and V = 3376.7(9) $Å^3$. The structure was solved in space group $P\bar{1}$. The R1 value is 0.0396. The asymmetric unit contains two cations, two uncoordinated anions (one of which is disordered, the second component is not shown in the figure), a sulfonic acid molecule and a water molecule (these form hydrogen bonds). The palladium atom is coordinated in a distorted square planar geometry. The five-membered ring has an envelope conformation (Figure 2.3).

Compound $[Pd(O_3SCH_3)(\mathbf{29})][O_3SCH_3]$ (**44**) crystallizes in a monoclinic space group with a = 20.680(4) Å, b = 11.156(2) Å, c = 32.862(7) Å and V =7397(3) $Å^3$. The structure was solved in space group C2/c. The R1 value is 0.0353. The palladium atom is coordinated in a distorted square planar geometry. The six-membered ring has two disordered conformations in the structure, which represent the chair and boat conformations of the ligand (Figure 2.3). Only C and H atoms are affected, and the metal coordination remains the same. The uncoordinated anion and acid molecule are hydrogen bonded together.

The bond lengths, and interbond angles in **41-44** and those of the (1,2-bis(di-*tert*-butylphosphinomethyl)benzene) palladium(II) complex (**45**)[10] are listed in Table 2.3. The bond lengths and angles are broadly comparable across the five complexes. The (P-Pd-P) bite angles of the ligand in **41-44** are 101.23º, 100.55º, 99.09º and 99.42º for the two cations in **43**, and 100.94º, respectively. The palladium(II) complex of the cyclopentane based phosphine (**28**) has the smallest bite angle of the four cycloalkyl phosphines at (*av*. 99.25°) while the palladium(II) complex of the cyclopropane based phosphine (**26**) has the largest bite angle at (101.2°). The bite angle of the cyclobutane based phosphine (**27**) in **42** is similar to that of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene in **45**. We conclude that all these palladium complexes might be expected to show similar catalytic performance (*vide infra*) if this is determined by ligand bite angle.[68]

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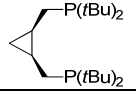
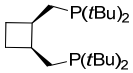
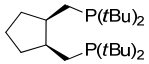
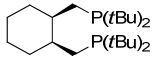
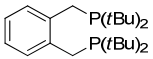
Table 2.3. Selected X-ray data of complexes **41-44**.

Complex		$[Pd(O_3SCH_3)$(**26**)$]^+$ (**41**)	$[Pd(O_3SCH_3)$(**27**)$]^+$ (**42**)	$[Pd(O_3SCH_3)$(**28**)$]^+$ (**43**)		$[Pd(O_3SCH_3)$(**29**)$]^+$ (**44**)	$[Pd(O_3SCH_3)$(**6**)$]^+$ (**45**)
(L-L)							
Ligand Bite Angle		101.2	100.6	99.4		100.9	100.6
Bond Lenghts	a	2.272(4)	2.262(10)	2.285(9)	2.267(8)	2.285(9)	2.273(8)
	b	2.276(4)	2.266(11)	2.283(10)	2.273(66)	2.283(10)	2.268(8)
	c	2.182(11)	2.194(3)	2.184(2)	2.172(80)	2.184(2)	2.174(2)
	d	2.197(11)	2.194(2)	2.187(2)	2.188(38)	2.187(2)	2.199(3)
Bond Angles	a-b	100.55(16)	99.09(4)	100.94(3)	100.58(7)	100.94(3)	101.23(3)
	a-c	160.57(3)	162.93(7)	161.97(6)	160.99(13)	161.97(6)	162.79(7)
	a-d	95.61(3)	97.83(7)	96.97(6)	95.82(13)	96.97(6)	97.29(7)
	b-c	98.48(3)	97.96(7)	97.08(6)	98.19(13)	97.08(6)	95.86(7)
	b-d	163.84(3)	163.05(7)	162.09(6)	163.21(14)	162.09(6)	161.21(7)
	c-d	65.38(4)	65.11(9)	65.01(8)	65.68(17)	65.01(8)	65.53(9)

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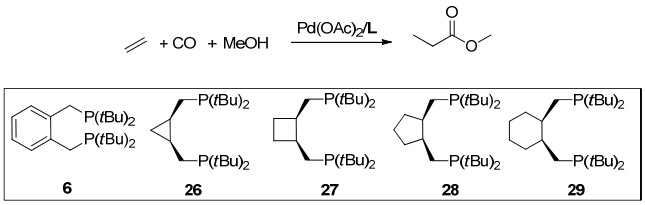
2.2.3 Application of the P,P- ligands in the Pd-catalysed methoxycarbonylation of ethene

Table 2.4 reports the catalyst performance for the diphosphines **26-29** (Scheme 2.10) in the palladium catalysed methoxycarbonylation of ethene to methyl propionate. The catalytic systems were prepared *in situ* by adding the diphosphine ligand (**6**, **26-29**) to a solution of $Pd(OAc)_2$ in MeOH/methyl propionate followed by addition of methanesulfonic acid to give the catalyst precursors **41-44**. The catalytic solutions were introduced into the autoclave under vacuum, which was then charged with 20 bar of ethene and 45 bar of carbon monoxide. The overall ratio $Pd/L/MeSO_3H$ was 1:3:2.5. Ligands **26-29** vary both in the size of the cyclic backbone, and consequently in the conformational freedom of the ligand, and in relative basicity (*vide supra*). The catalytic systems incorporating ligands **26**, **27** and **29**, with 3, 4 and 6 membered rings in the ligand backbone, were all more active than the catalytic system with ligand **6** albeit ligand **26** with only marginally more active (compare entries 2, 3, and 5 with 1, Table 2.4).

Table 2.4. Palladium catalysed methoxycarbonylation of ethene using diphosphines **6**, **26-29**.[a]



Entry	Ligand	X[b] (g)	TON[c]	Average rate[d]
1	**6**	21.1	630	315
2	**26**	21.6	646	323
3	**27**	33.4	997	499
4	**28**	8.2	245	123
5	**29**	25.4	758	379

[a] *Reaction conditions*: $Pd/L/MeSO_3H$=1:3:2.5; Substrate/Pd=1079, $Pd(OAc)_2$ $5.98\cdot10^{-4}$ mol, $MeSO_3H$ $1.50\cdot10^{-3}$ mol, ethene 0.65 mols, P_{ethene}=20 bar, P_{CO}=45 bar, 180 ml methyl propionate, 120 ml MeOH. Temperature=100ºC. [b]Grams of methyl propionate produced during the reaction. [c]Turnover number. [d]Average rate during the catalytic reaction (s^{-1}).

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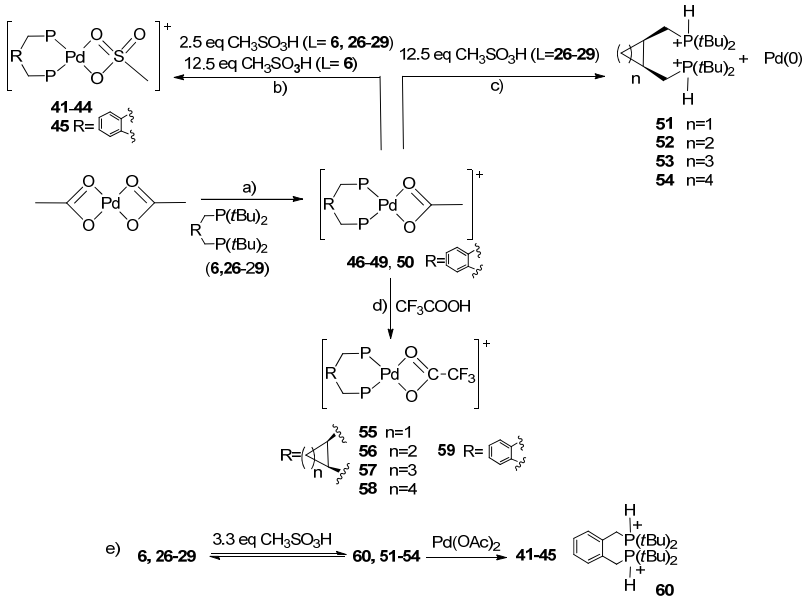
The catalytic systems incorporating ligands **26**, **27** and **29** are all significantly more active than that with ligand **28** containing a 5-membered ring (entry 4, Table 2.4). There is, thus, no clear correlation between flexibility in the chelate ring and catalyst performance. However, in contrast to the commercialised system incorporating ligand **6**, for which higher turnover numbers are obtained on increasing the amount of acid present,[59-60] we find that the $Pd(OAc)_2$/**26-29** systems are deactivated by excess of methanesulfonic acid. Thus, on changing the acid to palladium ratio from 2.5:1 to 12.5:1, low yields of methyl propionate, and large amounts of palladium black are observed. We attribute this to protonation of the more basic cycloalkyl ligands (Table 2.2).

Thus, in NMR experiments $Pd(OAc)_2$ was treated with ligands **26-29**, to give complexes **46-49**. When these complexes were treated with 12.5 equivalents of methanesulfonic acid, immediate formation of the protonated phosphines (**51-54**) and Pd metal was observed (Scheme 2.13c). However, when the protonated diphosphines **51-54**, obtained by adding 3.3 equivalents of methanesulfonic acid to ligands **26-29**, were allowed to react with $Pd(OAc)_2$, the catalyst precursors **41-44** were formed (Scheme 2.13e).



Scheme 2.13. Influence of acid on the formation of the catalyst precursors.

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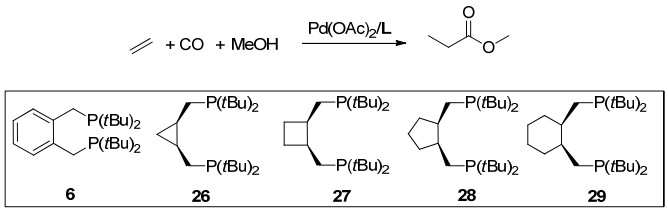
This is consistent with redistribution of the various equilibria involving protonated phosphine, free acid, and palladium coordinated phosphine, the differing basicities of **6** *vs* **26-29** resulting in differing concentration effects on the position of equilibrium.

When excess methanesulphonic acid is present the more basic ligands **26-29** remain protonated, and thus unable to complex Pd, while the less basic ligand **6** is partially deprotonated in the presence of palladium acetate leading to complex formation. However, when no excess of acid over ligand is present protonated phosphines can be deprotonated by the acetate ion, leading to complexes **41-44** (Scheme 2.13e).

Consistent with this hypothesis, good catalytic results were obtained using a large excess of the weaker acid, trifluroacetic acid (pKa = 0.5). Under these conditions the catalytic activity of the system $Pd(OAc)_2$/**6**/TFA is similar to that obtained in the presence of $MeSO_3H$ (*cf* Tables 2.4 and 2.5, entry 1).

Table 2.5. Palladium catalysed methoxycarbonylation of ethene using diphosphines **6, 26-29** and trifluoroacetic acid.[a]



Entry	Ligand	X (g)[b]	TON[c]	Average rate[d]
1	**6**	20.2	603	302
2	**26**	13.1	392	196
3	**27**	28.1	839	420
4	**28**	27.9	834	417
5	**29**	28.8	860	430

[a] *Reaction conditions*: Pd/L/CF_3CO_2H = 1:3:125; $Pd(OAc)_2$ $5.98 \cdot 10^{-4}$ mol, CF_3CO_2H 8.5 mol, P_{ethene} = 20 bar, P_{CO} = 45 bar, 180 ml of methyl propionate, 120 ml MeOH. Temperature = 100 ºC. [b] Grams of methyl propionate produced during the reaction. [c] Turnover number. [d] Average rate during the catalytic reaction (s^{-1}).

The systems with cycloalkyl ligands **27** and **29** are again slightly more active than the system with ligand **6** (entries 3 and 5 *versus* entry 1, Tables 2.4 and 2.5). However, ligand **28** affords significantly higher (entry 4, Tables 2.4 and 2.5) and ligand **26** significantly lower (entry 2, Tables 2.4 and 2.5) activity. These results illustrate the complexity of homogeneous catalysis and the dependence of each catalyst system on several factors.

As mentioned before, catalyst systems based on the more basic ligands (**26-29**) are inactive when run in the presence of excess methanesulphonic acid (as typically used commercial operation). For these ligands good activity in the presence of excess acid is only possible when an acid of lower pKa is employed. Drent and Pugh have previously noted the complex influence of ligand basicity and acid strength on catalyst selectivity in palladium-diphosphine carbonylation catalysis.[69] Further studies are required to fully understand the relationship between acid pKa, ligand basicity and catalyst activity (Scheme 2.13).

The differences in the catalytic performance of the catalysts used can thus not be attributed to the bite angles of the ligands. Furthermore, the catalytic systems containing ligands with high conformational mobility (**28**), or with a rigid backbone (**26**) afford lower activities than the systems containing ligands with somewhat intermediate flexibility. The combination of the basicity of the ligand and the strength of the acid used, however, is a key parameter to improve the catalyst performance. For instance, the Pd/**26-29** catalytic systems exhibited a very distinct behaviour with weak or strong acid. Indeed, these systems were activated by "weak" acids but were strongly inhibited by the use of strong acid. However, in the case of the Pd/**6** catalytic system, the presence of a strong acid is required to achieve high activities.

2.2.4 Mechanistic studies in the Pd-catalysed methoxycarbonylation of ethene

As noted above, Pd catalysed alkoxycarbonylation reactions normally show an acceleration of reaction rate on increasing the amount of strong acid present, which is attributed to the formation of the catalytically active Pd-H species being favoured.[70,71] In contrast, we observe the opposite trend for catalyst systems based on ligands **26-29**, which are deactivated by an excess of strong acid. We have, therefore, performed a mechanistic study by NMR

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and HP-NMR spectroscopy to establish if the hydride mechanism is indeed operating in this catalytic system.

2.2.4.1. Attempted preparation of palladium-carbomethoxy or palladium-hydride initiators from $[Pd(O_2CCF_3)$(**26-29**)$]^+$ (**55-58**)

No reaction was observed on heating a methanolic solution of $Pd(OAc)_2$/**29**/TFA with CO in a sapphire NMR tube (353 K, 20 bar CO) indicating the catalysis does not proceeded via a carbomethoxy complex (Scheme 2.5B).

Consistent with the report of Heaton and co-workers,[8,11] who found that $[Pd(O_3SCH_3)$(**6**)$]^+$ (**45**), is converted under catalytic conditions to the hydride complex $[Pd(H)(MeOH)$(**6**)$]^+$ (**62**) at 353 K (Scheme 2.14),[10] we find that $[Pd(O_2CCF_3)$(**6**)$]^+$ (**59**) is transformed into **62** on heating in methanol solution to 353 K in a sapphire NMR tube. However, we find that the isolated complexes $[Pd(O_2CCF_3)(L\text{-}L)]^+$ (L-L = **26**-**29**) (**55**-**58**) and the formed *in situ* are recovered unchanged following heating in methanol to 353 K, in the presence of stoichiometric amount or with an excess of acid a slight decomposition of the ligand is observed (Figure 2.4), with no evidence for formation of the hydride complexes $[Pd(H)(MeOH)$(**26**-**29**)$]^+$ (**64**-**67**) required for a hydride mechanism (Scheme 2.5A).

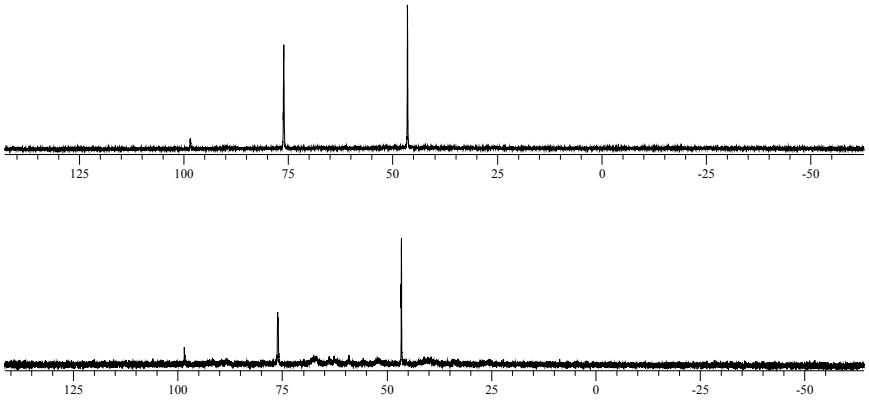

Figure 2.4. $^{31}P\text{-}\{^1H\}$ NMR at 193K a) $[Pd(O_2CCF_3)$(**29**)$]O_2CCF_3$ in MeOH. b) $[Pd(O_2CCF_3)$(**29**)$]O_2CCF_3$ in MeOH after 20 minutes at 353K.

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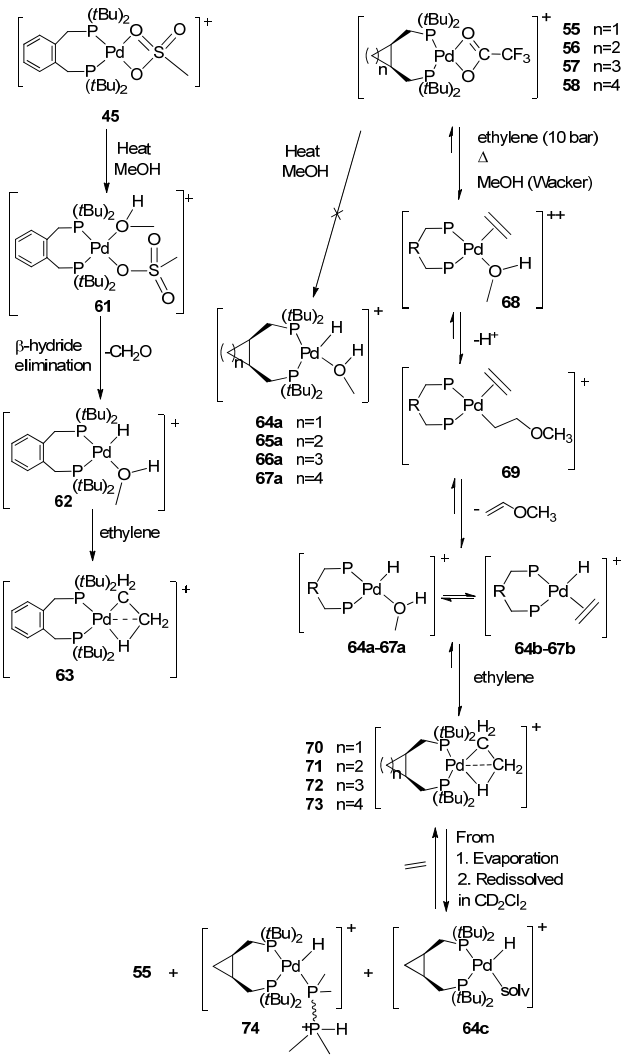

Scheme 2.14. Formation the palladium-hydride and palladium ethyl complex.

2.2.4.2 Reaction of [Pd(O_2CCF_3)(**26-29**)]$^+$ (**55-58**) with ethene (10 bar)

We next studied the direct reaction of the trifluoroacetate complexes [Pd(O_2CCF_3)(**26-29**)]$^+$ (**55-58**) with ethene in methanol and successfully generated the Pd-ethyl complexes required by the hydride pathway.

Thus, on heating methanolic solutions of **55-57** in a sapphire NMR tube in the presence of an excess of trifluoroacetic acid and ethene (10 bar) at 353 K for

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20 minutes, followed by cooling to 193 K, the $^{31}P\{^{1}H\}$ NMR spectra showed the presence of two new doublets which can be assigned (*vide infra*) to $[Pd(\mathbf{26\text{-}28})(CH_2CH_3)]^+$ (**70-73**) (Table 2.6, Scheme 2.14). When the experiment was repeated with complex **58**, two sets of doublets were observed corresponding to two conformers of the ethyl complex **73** (*vide infra*).

Table 2.6. Selected $^{31}P\{^{1}H\}$ NMR spectroscopic data for **70-73**.

Entry	Complex	$\delta P_1/P_2$	J_{PP} (Hz)
1	**70**	67.9/50.3	24.3
2	**71**	63.4/41.2	23.1
3	**72**	77.3/47.0	23.0
4	**73**	Major: 87.8/38.6	22.4
		Minor: 64.3/58.4	22.4

Attempts to isolate **71-73** were unsuccessful, thus on removal of methanol at reduced pressure and redissolution of the resulting residue in deuterated dichloromethane, the $^{31}P\{^{1}H\}$ NMR spectra revealed only the presence of the precursors **56-58**. However, for complex **70**, the $^{31}P\{^{1}H\}$ NMR spectrum showed, in addition to **55**, the presence of a new complex having two broad resonances at 70.4 and 37.9 ppm which can be assigned as the hydride-solvento complex **64**, (Scheme 2.14, Figure 2.5b). Thus, in the proton coupled ^{31}P NMR spectrum, recorded at 193 K, the signal at 70.4 ppm becomes a broadened doublet ($^2J_{PP}$ = 19.4 Hz) while the signal at 37.9 ppm shows an additional coupling due to a *trans* disposed hydride, (doublet of doublets, $^2J_{PP}$ = 19.4 Hz and $^2J_{PbH}$ = 193.8 Hz), (Figures 2.5a, 2.6). The resonance of the hydride ligand occurs in the ^{1}H NMR spectrum, recorded at 193 K, at -10.69 ppm (dd, $^2J_{PaH}$ = 13.6 Hz and $^2J_{PbH}$ = 193.8 Hz) (Figure 2.6). The resonances of a second, minor hydride complex can be seen at -10.47 ppm (ddd, $^2J_{PaH}$ = 22.4 Hz, $^2J_{PcH}$ = 36.0 Hz and $^2J_{PbH}$ = 188.4 Hz). The resonances of this new complex are not resolved in the $^{31}P\{^{1}H\}$ NMR spectrum making assignment of its structure problematic; we tentatively propose the structure **74** for this complex, consistent with the presence of an additional P-H coupling (Scheme 2.14). According to the law of microscopic reversibility the forward reaction must go by insertion of ethylene into the Pd-H bond. On pressurization of this

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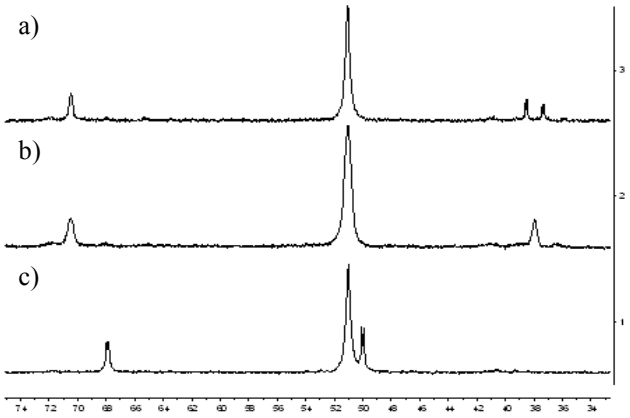

Figure 2.5. a) ^{31}P NMR spectra of a mixture of complexes $[Pd(O_2CCF_3)(\mathbf{26})]^+$ (**55**) and $[Pd(H)(MeOH)(\mathbf{26})]^+$ (**64**) at 193K, b) $^{31}P\{^1H\}$ NMR spectra of complexes $[Pd(O_2CCF_3)(\mathbf{26})]^+$ (**55**) and $[Pd(H)(MeOH)(\mathbf{26})]^+$ (**64**) at 193K, c) $^{31}P\{^1H\}$ NMR spectra of complexes $[Pd(O_2CCF_3)(\mathbf{26})]^+$ (**55**) and $[Pd(\mathbf{26})(CH_2CH_3)]^+$ (**70**).

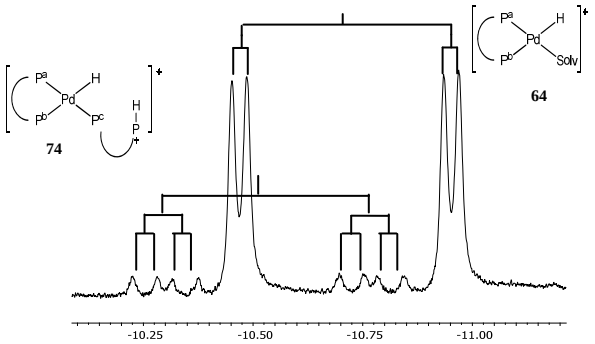

Figure 2.6. Selected region of the ^1H NMR spectra of $[Pd(H)(MeOH)(\mathbf{26})]^+$ (**64**).

solution with ethene at room temperature and cooling to 193 K, the $^{31}P\{^1H\}$ NMR spectrum showed the disappearance of the resonances of the hydride complex and the appearance of the resonances attributed to the ethyl complex $[Pd(\mathbf{26})(CH_2CH_3)]^+$ (**70**) (Figure 2.5c). We conclude that on heating methanolic solutions of $[Pd(O_2CCF_3)(\mathbf{26})]^+$ (**55**) in the presence of ethene, traces of the hydride complex $[Pd(H)(MeOH)(\mathbf{26})]^+$ (**64**) are formed, This complex reacts with ethene to give the ethyl complex $[Pd(\mathbf{26})(CH_2CH_3)]^+$ (**70**). However, in contrast to $[Pd(\mathbf{6})(CH_2CH_3)]^+$ insertion of ethene is readily

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reversible, giving the hydride complex **64** transiently on removal of ethene from solution. **64** itself is unstable and returns to the precursor complex $[Pd(O_2CCF_3)(\mathbf{26})]^+$ (**55**) (Scheme 2.14).

2.2.4.3 Conformational dynamic process in $[Pd(\mathbf{29})(CH_2CH_3)]^+$ (**73**)

We noted above that two conformers exist for the ethyl complex $[Pd(\mathbf{29})(CH_2CH_3)]^+$ (**73**). Thus, at 193 K two pairs of doublets are observed in the $^{31}P\{^1H\}$ NMR spectrum. Those of the major isomer occur at 87.8 ppm (d, $^2J_{PP}$ = 22.4 Hz, P^{1A}) and 38.6 ppm (d, $^2J_{PP}$ =22.4, P^{1B}), values similar to those of $[Pd(\mathbf{6})(CH_2CH_3)]^+$, (**63**) ($\delta$ = 67.7 ppm and 36.3 ppm ($^2J_{PP}$ = 31 Hz).[9-10] The resonances of the minor conformer occur at 64.3 ppm (d, P^{2A}) and 58.4 ppm (d, $^2J_{PP}$ = 22.4, P^{2B}).
The two isomers occur in the ratio 2.2:1. These conformers are in dynamic equilibrium. Figure 2.7 shows the variable temperature $^{31}P\{^1H\}$ NMR spectra of **73**, together with simulations performed using gNMR5.

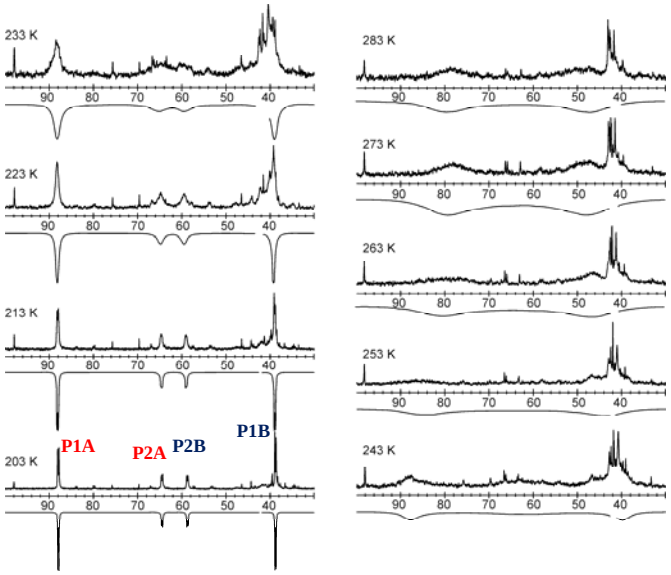

Figure 2.7. $^{31}P\{^1H\}$ NMR spectra and simulations at VT of the $[Pd(\mathbf{29})(CH_2CH_3)]^+$ (**73**).

The simulations reveal that concerted intermolecular equivalencing of P^{1A} with P^{2A} and P^{1B} with P^{2B} occurs, as would be expected for a chair to boat

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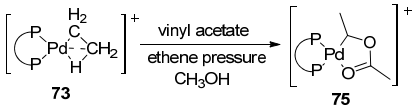
conformational flip. Intramolecular exchange of P^{1A} with P^{1B} and of P^{2A} with P^{2B} also occurs but at a slower rate and at different rates for the two isomers. The uncertainty in the exchange rate constants derived from the simulations is high, resulting in large uncertainties in the activation enthalpies and entropies obtained. Both processes appear to have similar activation enthalpies 45 $kJ.mol^{-1}$ and activation entropies close to 0 $J.mol^{-1}.K^{-1}$ as might reasonably be expected for the proposed exchanges.

Zacchini has previously reported that a rapid insertion-deinsertion fluxional process occurs in **63** in which the inequivalent phosphorus donors remain distinct. These donors are then equivalenced by a much slower fluxional process, in accord with our results.[9]

The chair and boat conformations of the ethyl complex **73** have been simulated in ArgusLab to determine the energy of each conformer. We find that the complex in which the ligand adopts the chair conformation is *ca.* 38 $kJ.mol^{-1}$ lower in energy than the boat conformer. Chair and boat conformers are also observed in the X-ray crystal structures of the precursor complex **44** (Figure 2.3).

2.2.4.4 Reaction of complex $[Pd(\mathbf{29})(CH_2CH_3)]^+$ in methanol in the presence of vinyl acetate

Due to the difficulty in isolating the hydride complexes **64**-**67** and ethyl complexes **70**-**73** (Scheme 2.14) we turned our attention to the vinyl acetate (VAM) insertion complex **75** (Scheme 2.15) since the *β*-chelate complex formed is more easily handled.



Scheme 2.15. Synthesis of $[Pd(\mathbf{29})(CH_2CH_2OC(O)CH_3)]^+$ (**75**).

Thus, the ethyl complex **73** was synthesised, and a solution of vinyl acetate in methanol was added under an ethene atmosphere to prevent back reaction to the trifluoroacetate complex **58**. Complex **75** was obtained as a mixture of two conformers (Scheme 2.15) presumably *via* an alkene exchange reaction that

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proceeds *via* β-hydride elimination, and decoordination of ethene, followed by VAM coordination and 2,1-insertion into the Pd-H bond.

Complex **75** was fully characterised by NMR spectroscopy. The $^{31}P\{^{1}H\}$ NMR spectrum, acquired at 193 K, (Figure 2.8a) shows two sets of signals, at 52.5 ppm and 51.3 ppm ($^{2}J_{PP}$ = 29.7 Hz) and at 70.2 and 30.5 ($^{2}J_{PP}$ = 27.7 Hz) (relative intensity of 4:1). When ^{13}C-labelled vinyl acetate was used, additional couplings are seen in the $^{31}P\{^{1}H\}$ NMR spectrum, the resonances at 52.5 and 30.5 ppm appearing as doublets of doublets ($^{2}J_{PC}$ = 95.6 Hz, J_{PP} = 30.5 Hz and $^{2}J_{PC}$ = 97.7 Hz, J_{PP} = 30.5 Hz, respectively) (Figure 2.8 b), values of $^{2}J_{PC}$ consistent with the proposed β-chelate structure.[72] The resonances of C^a and C^b of the major isomer occur at 23.9 ppm (d, J_{CC} = 32.5 Hz) and 96.2 (dd, J_{CC} = 32.6 Hz, J_{PC} = 94.7 Hz) in the $^{13}C\{^{1}H\}$ NMR spectrum (Figure 2.9b).

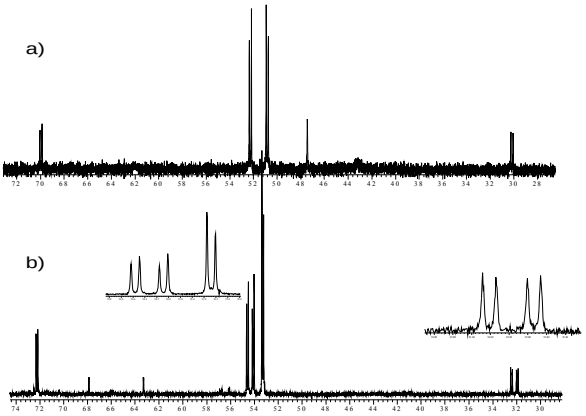

Figure 2.8. $^{31}P\{^{1}H\}$ NMR spectra. a) complex [Pd(**29**)(CH_2CH_3)]$^+$ (**73**) and vinyl acetate in methanol at 193 K, b) complex [Pd(**29**)(CH_2CH_3)]$^+$ (**73**) and vinyl-$^{13}C_2$ acetate in methanol at 193 K.

The resonance of C^a shows an additional quartet coupling (J_{CH} = 127.9 Hz) in the proton coupled ^{13}C NMR spectrum confirming its identity as a CH_3 group, while the resonance of C^b becomes a complex multiplet as expected for a methine carbon (Figure 2.9c). The methine resonance of the minor isomer is seen at 93.9 ppm (dd, J_{CC} = 31.2 Hz, J_{PC} = 94.3 Hz) in the $^{13}C\{^{1}H\}$ NMR spectrum and a poorly resolved doublet around 27.5 ppm may be assigned to the methyl carbon of the minor isomer (Figure 2.9b).

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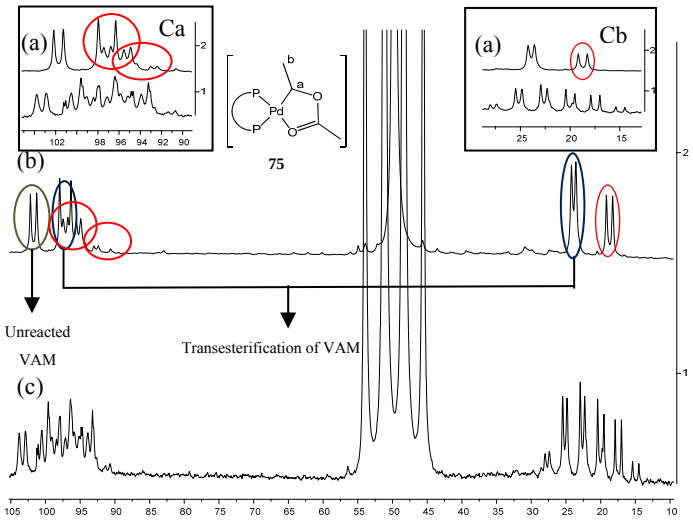

Figure 2.9. Spectrum of [Pd(**29**)($^{13}CH_2{}^{13}CH_2OC(O)CH_3$)]$^+$ (**75**) obtained by treating [Pd(**29**)(CH_2CH_3)]$^+$ (**73**) with vinyl-$^{13}C_2$ acetate in methanol at 193 K. a) Spectra b and c expanded. b) ^{13}C-{^1H} NMR spectra. c) ^{13}C NMR spectra.

Finally, a $^{31}P\{^1H\}$–$^{13}C\{^1H\}$ HMQC correlation spectrum was obtained and shows correlations between the ^{31}P signals at 23.9 and 52.5 and ^{13}C signals at 93.9 and 96.2 respectively (Figure 2.10). Thus, we can confidently assign **75** as two conformers or two diastereoisomers of the *β*-chelate complex resulting from the 2,1-insertion of VAM into the Pd-H bond of **67**. The two conformers or two diastereoisomers are proposed to arise from different conformations adopted by the backbone of the ligand, as previously observed. The Pd-H must originate by *β*-hydride elimination of ethene from the alkyl complex **73**.

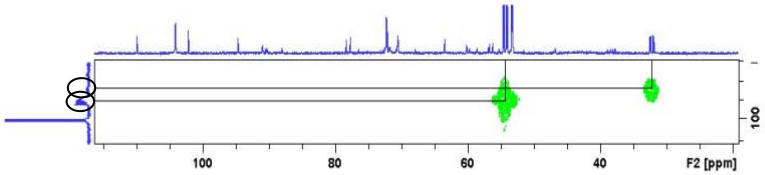

Figure 2.10. ^{31}P-{^1H}-^{13}C-{^1H} NMR correlation spectra of complex [Pd(**29**)($^{13}CH_2{}^{13}CH_2OC(O)CH_3$)]$^+$ (**75**).

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Using the systems containing ligands **26-29,** evidence for a hydride based pathway was indicated, similarly to the mechanism proposed by Heaton *et al*.[16] However, the equilibrium between the trifluoroacetate (**55-58**) and hydride (**64a-67a**) complexes was shown to be strongly shifted in favour of the trifluoroacetate complexes, in contrast with the results previously reported.

The ethyl complexes **70-73** revealed to be only stable in the presence of an overpressure of ethene. *In situ* NMR studies confirmed the presence of the ethyl complexes in the absence of CO, however, the resting state of the *operando* catalyst is the trifluoroacetate species **55-58** (Scheme 2.14, Figure 2.5).

Although the hydride pathway is shown to be dominant in palladium catalysed alkoxycarbonylation of alkenes using the ligands described here, the existence or not of a stable palladium-hydride catalyst precursor is no indication of the activity of the catalyst system. Detection and characterization of the catalytic intermediates can be successfully performed *in situ*, indeed isolation and conventional characterization of such intermediates may not be possible, particularly if the resting state of the catalyst lies outside the catalytic cycle, as here.

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2. 3. Experimental section

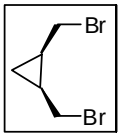
General Methods

All experiments were performed under an atmosphere of nitrogen using standard Schlenk line, cannula and glovebox techniques. All chemicals were obtained from Aldrich and used as supplied without further purification: (1*R*,2*S*)-cyclopropane-1,2-dicarboxylate, *cis*-cyclobutane-1,2-dicarboxylic acid, *cis*-cyclohexanedimethanol and ethyl 2-oxocyclohexanecarboxylate. NMR spectra were recorded using a Varian Mercury Spectrometer (400 M Hz) or Bruker Avance DPX400. HPNMR spectra were recorded on a Bruker AMX-II 200 spectrometer. The chemical shifts (δ) were reported in ppm and they are referenced to the tetramethylsilane (TMS). Methoxycarbonylation reactions were carried out in a 1L stainless steel autoclave.

Synthesis of *cis*-(1,2-dibromomethyl)cycloalkyl. General procedure

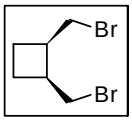
A solution of triphenyldibromophosphorane was prepared by adding bromine (141 mmol) dropwise to an ice-water-cooled solution of triphenylphosphine (141 mmol) in dry acetonitrile (200 mL). A solution of *cis*-1,2-cycloalkyldimethanol (70 mmol) in dry acetonitrile (100 mL) was added to the reaction mixture which was stirred under nitrogen overnight. The solvent was evaporated to yield an orange solid. The solid was finely dispersed in pentane (2 x 250 mL) and filtered to remove the triphenylphosphine oxide. The pentane solution was dried under vacuum to give the desired compound.

Synthesis of *cis*-1,2-(dibromomethyl)cyclopropane (18)



The synthesis of **18** was carried out from **14** (10.44 g, 102 mmol) in accordance with the general procedure. The product was isolated as a colourless oil. Yield = 18.59 g, 80%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 3.47 (m, 4H, CH_2); 1.61 (m, 2H, C*H cy*); 1.13 (m, 1H, CH*H cy*); 0.39 (m, 1H, CH*H cy*).

Synthesis of *cis*-1,2-(dibromomethyl)cyclobutane (19)



The synthesis of **19** was completed from **15** (4.02 g, 35 mmol) according to the general procedure previously described.

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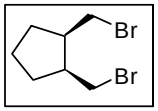
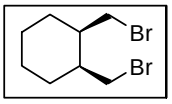
The product was isolated as a colourless oil. Yield= 6.68 g, 80%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 3.63 (m, 2H, CH_2); 3.45 (m, 2H, CH_2); 2.88 (m, 2H, C*H*); 2.15 (m, 2H, CH_2); 1.76 (m, 2H, CH_2). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 39.8 (s, *C*H *cy*); 34.0 (s, CH_2); 24.1 (s, CH_2 *cy*).

Synthesis of *cis*-(1,2-dibromomethyl)cyclopentane (20)



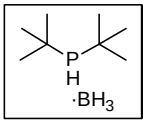
Diol **16** (16 g, 123 mmol) was treated following the general procedure to give compound **20** as a colourless oil. Yield = 23 g, 80%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 3.52- 3.41 (m, 2H, CH_2); 3.29 (m, 2H, CH_2); 2.46 (m, 2H, C*H cy*); 2.09- 1.85 (m, 4H, CH_2 *cy*); 1.63- 1.44 (m, 2H, CH_2 *cy*).

Synthesis of *cis*-(1,2-dibromomethyl)cyclohexane (21)



The synthesis of **21** was carried out from **17** (10 g, 70 mmol) according to the general procedure previously described. The product was isolated as a colourless oil. Yield = 11.81 g, 63%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 3.41 (m, 4 H, CH_2); 2.20 (m, 4 H, CH_2 *eq*); 1.64 (m, 2 H, C*H*); 1.56 (m, 4 H, CH_2 *ax*). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 33.7 (s, CH cy); 32.8 (s, CH_2 cy); 31.3 (s, $\underline{C}(CH_3)$); 29.7 (s, CH_3); 26.1 (s, CH_2 cy); 17.5 (s, CH_2)

Synthesis of di-*tert*-butylphosphine borane (30)



Di-*tert*-butylphosphine chloride (34g, 188.41mmol) was added to a schlenk flask followed by diethyl ether (200ml). The ether solution was cooled in a cold water bath and $LiAlH_4$ (1M in diethyl ether, 100ml, 100mmol) was added slowly. This gave a yellow suspension which was allowed to stir at room temperature overnight. The suspension was quenched by the addition of water (50ml, degassed with nitrogen for 20 minutes). This gave a biphasic solution. The upper (organic layer) was cannula transferred into a clean schlenk and the aqueous residues washed with a further 100ml of ether. The ether extracts were combined and dried with sodium sulphate. The ether extracts were then cannula transferred into a clean schlenk and the ether removed by distillation. This gave colourless oil**.** The colourless oil was then diluted with THF (200ml) and cooled to 0°C, to this was added BH_3 in THF (1M solution, 250ml, 250mmol). The resultant

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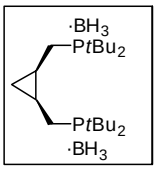
solution was then stirred at room temperature overnight. The solvent was then removed under vacuum to give a white crystalline solid which was then isolated in the glovebox. Yield = 22.1g, 73% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 3.9 (dq, $^{1}J_{H\text{-}P}$ = 345 Hz, $^{3}J_{H\text{-}H}$ = 6 Hz, 1H,); 1.2 (d, $^{3}J_{H\text{-}P}$ = 13.5 Hz, 18 H, CH_3); 0.4 (m br w, 3H, BH_3). **^{13}C NMR (**$CDCl_3$, 100.6 MHz, δ ppm): 38.2 (d, $^{1}J_{C\text{-}P}$ = 29 Hz, C(CH_3); 29.1 (d, $^{2}J_{C\text{-}P}$ = 1.6 Hz, CH_3). **^{31}P {^{1}H} NMR** (80 MHz, $CDCl_3$, δ ppm): δ 49.23 (m). **^{13}B NMR** ($CDCl_3$, 128.4 MHz, δ ppm): -43.7 (d, ^{1}J = 51.1 Hz).

Synthesis of boron-protected bidentate phosphine. General procedure

The *t*$Bu_2PH{\cdot}BH_3$ (**30**) (179 mmol) was dissolved in THF (200mL), and the solution was then cooled at 0ºC. To this solution was added Bu^nLi (2.5M in hexanes, 179 mmol), and was then stirred at room temperature for 1 hour. This was then added to a solution of corresponding cis-1,2-(dibromomethyl)cycloalkyl (82 mmol) in THF (200 mL) dropwise, and then the stirring was maintained overnight at room temperature. The solution was then dried under vacuum and the residue suspended in diethyl ether (400mL). Water was then added to give a bi-phasic mixture. The organic layer was collected by separation and the aqueous layer washed with diethyl ether (2 x 100ml). The organic layers were then combined and then washed with water (3 x 150 mL) and brine solution (3 x 100 mL). The organic layer was then dried over Na_2SO_4 and then filtered. The solution was evaporated under reduced pressure to give the desired compound.

Synthesis of boron-protected bidentate phosphine (22)



The synthesis of **22** was carried out from **18** (18.59 g, 82 mmol) according to the general procedure. The product was isolated as a white solid. Yield = 22.17 g, 71%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 1.99 (m, 2H, C*H*$_2$); 1.56 (s, 6H, B*H*$_3$); 1.43 (m, 2H, C*H*$_2$); 1.31 (d, $^{3}J_{H\text{-}P}$ = 17 Hz, 36H, C*H*$_3$); 1.24 (m, 2H, C*H cy*); 1.08 (m, 1H, CH*H cy*); 0.08 (m, 1H, CH*H cy*). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 46.6 (m). **HRMS** (ESI-TOF): m/z =387.3634, calcd for $[M]^+$: 387.3652. Anal. Calcd for $C_{21}H_{50}B_2P_2$: C, 65.31; H, 13.05; B, 5.60; P, 16.04. Found: C, 65.29; H, 13.09.

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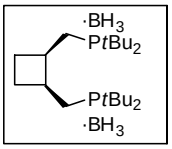
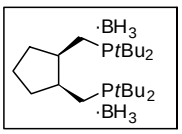
Synthesis of boron-protected bidentate phosphine (23)



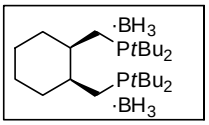
The synthesis of **23** was completed from **19** (6.68 g, 28 mmol) according to the general procedure previously described. The product was isolated as a white solid. Yield = 10.93 g, 98%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 2.85 (m, 6H, B*H*$_3$); 2.19 (m, 2H, C*H*$_2$); 1.99 (m, 2H, C*H*$_2$); 1.79 (m, 2H, C*H cy*); 1.61 (m, 2H, C*H*$_2$ *cy*); 1.49 (m, 2H, C*H*$_2$ *cy*); 1.30 (d, $^{3}J_{H\text{-}P}$ = 27 Hz, 18 H, C*H*$_3$); 1.26 (d, $^{3}J_{H\text{-}P}$ = 27 Hz, 18 H, C*H*$_3$). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 34.6 (d, $^{2}J_{C\text{-}P}$ = 7.64 Hz CH cy), 27.8 (d, $^{2}J_{H\text{-}P}$ = 3.82 CH_3), 27.4 (d, $^{3}J_{H\text{-}P}$ = 3.82 Hz CH_2 cy), 18.9 (s), 18.7 (s). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 44.3 (m). **HRMS** (ESI-TOF): m/z =401.3814, calcd for $[M]^+$: 401.3809. Anal. Calcd for $C_{22}H_{52}B_2P_2$: C, 66.02; H, 13.10; B, 5.40; P, 15.48. Found: C, 66.02; H, 13.15.

Synthesis of boron-protected bidentate phosphine (24)



The synthesis of boron-protected bidentate phosphine **24** was completed from **20** (23 g, 90 mmol) according to the general procedure previously described. The product was isolated as a white solid. Yield = 27.9 g, 75%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 2.30 (m, 2H, C*H*$_2$); 2.02 (m, 2H, C*H*$_2$); 1.97 (m, 2H, C*H cy*); 1.69-1.59 (m, 4H, C*H*$_2$ *cy*); 1.43-1.36 (m, 2H, C*H*$_2$ *cy*); 1.27 (d, $^{3}J_{H\text{-}P}$ = 26 Hz, 18H, C*H*$_3$); 1.21(d, $^{3}J_{H\text{-}P}$ = 23 Hz, 18H, C*H*$_3$). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 45.9 (m). **HRMS** (ESI-TOF): m/z =415.3889, calcd for $[M]^+$: 415.3965. Anal. Calcd for $C_{23}H_{54}B_2P_2$: C, 66.69; H, 13.14; B, 5.22; P, 14.95. Found: C, 66.69; H, 13.14.

Synthesis of boron-protected bidentate phosphine (25)



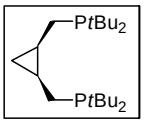
Following the general procedure, diol **21** (11.81 g, 44 mmol) was transformed in product **25** which was obtained as a white solid. Yield = 18.29 g, 97%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 2.95 (s, 3H, B*H*$_3$); 2.88 (s, 3H, B*H*$_3$); 1.81 (m, 4H, C*H*$_2$); 1.78 (m, 4H, C*H*$_2$ *eq*); 1.66 (m, 2H, C*H*); 1.45 (m, 4H, C*H*$_2$ *ax*); 1.30 (d, $^{3}J_{H\text{-}P}$ = 24 Hz, 18H, C*H*$_3$); 1.23 (d, $^{3}J_{H\text{-}P}$ = 24 Hz, 18H, C*H*$_3$). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 33.4 (s, CH cy); 33.1 (s, CH_2 cy); 30.5 (s, CH_2 cy); 29.1 (br s, $C(CH_3)_3$); 28.5 (d, CH_3, $^{2}J_{C\text{-}P}$ = 6.84); 28.1 (s, CH_2). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 46.71 (m). **HRMS** (ESI-TOF): m/z =429.4096, calcd

for $[M]^+$: 429.4122. Anal. Calcd for $C_{24}H_{56}B_2P_2$: C, 67.31; H, 13.18; B, 5.05; P, 14.46. Found: C, 67.26; H, 13.20

Synthesis of *cis*-1,2-bis(di-*tert*-butylphosphinomethyl)cycloalkyl. General procedure

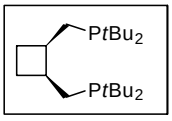
The corresponding boron-protected bidentate phosphine (42 mmol) was suspended in *tert*-butyl methyl ether (TBME) (300 mL) and to this was added tetrafluoroboric acid (54% in diethyl ether, 260 mmol). This gave a rapid gas evolution and the solution was heated to reflux overnight under nitrogen. The solvent was then removed under vacuum and the residue quenched with a solution (degassed with N_2 for 20 minutes) of potassium hydroxide in water (21 g, 200 mL, 651 mmol). The potassium hydroxide solution was added dropwise to the phosphine residue. This gave heat evolution and a white suspension. Pentane (2 x 250 mL) was added. The organic layers were removed by cannula to a separate schlenk. The organic extracts were then dried over Na_2SO_4, filtered, and evaporated under vacuum to give the desired compound in good yields.

Synthesis of *cis*-1,2-bis(di-*tert*-butylphosphinomethyl) cyclopropane (26)



Following the general procedure, the product **26** was obtained from **22** (22.17, 57 mmol) as a colourless oil. Yield = 17.23 g, 84%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 1.61 (m, 2H, C*H*$_2$); 1.50 (m, 2H, C*H*$_2$); 1.14 (d, $^3J_{H\text{-}P}$ = 21 Hz, 36 H, C*H*$_3$); 1.05 (m, 2H, C*H cy*); 0.88 (m, 1H, CH*H cy*); 0.05 (m, 1H, CH*H cy*). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 36.2 (d, $^1J_{C\text{-}P}$ = 7.8 Hz, $C(CH_3)_3$); 35.6 (d, $^1J_{C\text{-}P}$ = 7.8 Hz, $C(CH_3)_3$); 29.8 (br s, CH cy); 27.2 (br s, CH_3); 26.9 (br s, CH_3); 24.8 (m, CH_2 *cy*); 11.3 (m, CH_2). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 30.0 (s). **HRMS** (ESI-TOF): m/z = 357.2085, calcd for $[M]^+$: 358.2918.

Synthesis of *cis*-1,2-bis(di-*tert*-butylphosphinomethyl) cyclobutane (27)



The synthesis of **27** was carried out from **23** (10.93, 28 mmol) according to the general procedure previously described. The product was isolated as colourless oil. Yield = 8.5 g, 83%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 2.50 (m, 2H, C*H*$_2$ *cy*); 1.93 (m, 2H, C*H*$_2$ *cy*); 1.70 (m, 2H, C*H cy*); 1.42 (m, 2H, C*H*$_2$); 1.24 (m, 2H, C*H*$_2$);

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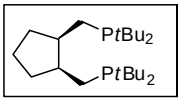
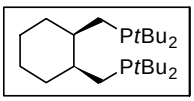
1.15 (d, $^{3}J_{H\text{-}P}$ = 27 Hz, 32 H, C*H*$_3$). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 37.6 (dd, $^{1}J_{C\text{-}P}$ = 21.08 Hz, $^{3}J_{C\text{-}P}$ = 9.4 Hz, $C(CH_3)_3$); 30.0 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz, CH_3); 29.9 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz, CH_3); 26.9 (s, CH_2 *cy*); 25.5 (d, $^{2}J_{C\text{-}P}$ = 11.5 Hz, CH); 22.1 (d, $^{1}J_{C\text{-}P}$ = 20.6 Hz, CH_2). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 20.9 (s). **HRMS** (ESI-TOF): m/z = 373.3137, calcd for $[M + H]^+$: 373.3153.

Synthesis of *cis*-1,2-bis(di-*tert*-butylphosphinomethyl) cyclopentane (28)



The synthesis of **28** was completed from **24** (27.9 g) according to the general procedure previously described. The product was isolated as yellow oil. Yield= 20.8 g, 80%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 1.99 (m, 2H, C*H*$_2$ *cy*); 1.83 (m, 2H, C*H*$_2$ *cy*); 1.64 (m, 2H, C*H*$_2$ *cy*); 1.60 (m, 2H, C*H cy*); 1.57-1.54 (m, 4H, C*H*$_2$); 1.12 (d, $^{3}J_{H\text{-}P}$ = 26 Hz, 36H, C*H*$_3$). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 43.9 (dd, $^{1}J_{C\text{-}P}$ =19.1 Hz, $^{3}J_{C\text{-}P}$ =8.3 Hz, $C(CH_3)_3$); 32.1 (d, $^{2}J_{C\text{-}P}$ = 22.1 Hz, CH); 31.5 (d, $^{3}J_{C\text{-}P}$ = 9.9 Hz, CH_2 *cy*); 30.2 (d, $^{2}J_{C\text{-}P}$ = 6.4 Hz, CH_3); 30.1 (d, $^{2}J_{C\text{-}P}$ = 6.4 Hz, CH_3); 22.4 (s, CH_2 *cy*); 21.6 (d, $^{1}J_{C\text{-}P}$ = 21.3 Hz, CH_2). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 24.33 (s). **HRMS** (ESI-TOF): m/z = 387.3310, calcd for $[M + H]^+$: 387.3309.

Synthesis of *cis*-1,2-bis(di-*tert*-butylphosphinomethyl)cyclohexane (29)



According to the general procedure the product **29** was obtained from **25** (18.29 g) as yellow oil. Yield = 14.37 g, 82%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 1.77 (m, 4H, C*H*$_2$ *eq*); 1.61 (m, 4H, C*H*$_2$ ax); 1.51 (m, 2H, C*H*); 1.35 (m, 4H, C*H*$_2$); 1.14 (d, $^{3}J_{H\text{-}P}$ = 18 Hz, 18H, C*H*$_3$); 1.12 (d, $^{3}J_{H\text{-}P}$ = 18 Hz, 18H, C*H*$_3$). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 41.0 (dd, $^{1}J_{C\text{-}P}$ = 21.2 Hz, $^{3}J_{C\text{-}P}$ = 7.8 Hz, $C(CH_3)_3$); 31.9 (d, $^{2}J_{C\text{-}P}$ = 21.4 Hz, CH); 31.3 (d, $^{3}J_{C\text{-}P}$ = 19.1 Hz, CH_2 *cy*); 30.0 (d, $^{2}J_{C\text{-}P}$ = 1.5 Hz, CH_3); 30.0 (d, $^{2}J_{C\text{-}P}$ = 1.5 Hz, CH_3); 29.9 (d, $^{4}J_{C\text{-}P}$ = 28.7 Hz, CH_2 *cy*); 23.7 (br s, CH_2). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 24.7 (s). **HRMS** (ESI-TOF): *m/z* = 401.3469, calcd for $[M + H]^+$: 401.3466.

Synthesis of palladium(II) complexes $[Pd(L\text{-}L)O_3SCH_3]O_3SCH_3$. General procedure

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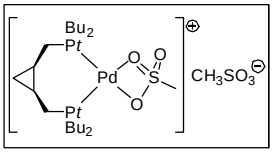
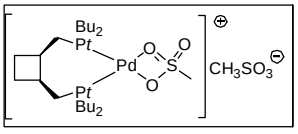
Bidentate phosphine ligand (1.30 mmol) and Palladium dibenzylidene acetone, $Pd_2(dba)_3$ (1.30 mmol) were combined in a schlenk flask. THF (50 mL) was then added and the resultant solution was stirred overnight at room temperature. Methanesulphonic acid was then added and the mixture reaction was then stirred for 2 hours. The solution was filtered under nitrogen and then dried under vacuum.

Synthesis of *cis*-1,2-bis(di-*tert*-butylphosphinomethyl)cyclopropane palladium(II) complex (41)



The synthesis of complex (**41**) was carried out from **26** (500 mg, 1.30 mmol) according to the general procedure previously described. Yield = 313 mg, 43%. The crystals are obtained after purification by the elimination of dba with diethyl ether (3 x 50 mL) and the solid was dissolved in THF (10 mL). 3 ml of this solution were put in a layer tub and diethyl ether was added carefully (20 mL) to form a biphasic solution. The solution was stood for 3 days which gave the formation of crystals. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 2.91 (s, CH_3); 2.80 (m, 2H, CH cy); 2.60-1.78 (m, 6H, CH_2 cy, CH); 1.55-1.17 (m, 38H, CH_3, CH_2). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 39.7 (s, CH_3); 36.7 (m, $C(CH_3)_3$); 28.9 (br s, CH_2 *cy*); 26.4 (m, CH *cy*); 23.7 (d, $^1J_{C-P}$ = 8.2 Hz, CH_2). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 77.64 (s). **HRMS** (ESI-TOF): *m/z*= 465.2043, calcd for $[M\text{-}CH_3SO_3 + H]^+$: 465.2051. Anal. Calcd for $C_{23}H_{50}O_6P_2PdS_2$: C, 42.17; H, 7.69; O, 14.65; P, 9.46; Pd, 16.24; S, 9.79. Found: C, 42.05; H, 7.74; S, 9.67.

Synthesis of *cis*-1,2-bis(di-*tert*-butylphosphinomethyl)cyclobutane palladium(II) complex (42)



The synthesis of complex (**42**) was carried out from **27** (1.30 mmol) according to the general procedure previously described. Yield = 350 mg, 47%. The crystals are obtained after purification by the elimination of dba with diethyl ether (3 x 50 mL) and the solid was dissolved in THF (10 mL). 3 ml of this solution was put in a layer tube and diethyl ether was added carefully (20 mL) to form a biphasic solution. The solution was stood for 3 days which gave the formation of crystals. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 2.90 (s, CH_3); 2.80 (m, 2H, CH cy); 2.05-1.59 (m, 4H, CH_2 cy); 1.55-1.17 (m, 40H, CH_3, CH_2). **^{13}C**

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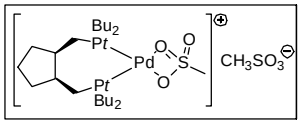
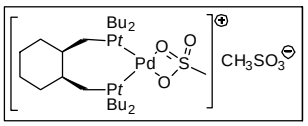
NMR ($CDCl_3$, 100.6 MHz, δ ppm): 40.8 (dd, $^1J_{C-P}$ = 18.8 Hz, $^3J_{C-P}$ =5.2 Hz, $C(CH_3)_3$); 39.7 (s, CH_3); 31.7 (br s, CH_3); 30.5 (br s, CH_3); 29.5 (br s, CH *cy*); 26.6 (m, CH_2 *cy*); 25.7 (d, $^1J_{C-P}$ = 10.8 Hz, CH_2). **$^{31}P\{^1H\}$ NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 73.3 (s). **HRMS** (ESI-TOF): *m/z*= 479.2147, calcd for $[M\text{-}CH_3SO_3 + H]^+$: 479.2188. Anal. Calcd for $C_{24}H_{52}O_6P_2PdS_2$: C, 43.08; H, 7.83; O, 14.35; P, 9.26; Pd, 15.90; S, 9.58. Found: C, 43.02; H, 7.86; S, 9.53

Synthesis of *cis*-1,2-(di-*tert*-butylphosphinomethyl)cyclopentane palladium(II) complex (43)



Following the general procedure the complex **43** was obtained from **28** (1.30 mmol). Yield = 321 mg, 42%. The dba was removed by diethyl ether (3 x 50 mL) and the solid was dissolved in THF (10 mL). 3 ml of this solution were put in a layer tube and tert-butyl methyl ether was added carefully (10 mL) to form a biphasic solution. The solution was stood for 3 days which gave the formation of crystals. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 2.93 (s, CH_3); 2.19 (m, 2H, CH cy); 2.11 (m, 4H, CH_2 cy); 1.93 (m, 2H, CH cy); 1.58 (d, $^3J_{H-P}$ = 15.2 Hz, 18H, CH_3); 1.52 (d, $^3J_{H-P}$ = 15.2 Hz, 18H, CH_3); 1.19 (m, 4H, CH_2). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 40.9 (dd, $^1J_{C-P}$ = 26.1 Hz, $^3J_{C-P}$ = 18.0 Hz, $C(CH_3)_3$); 39.6 (s, CH_3); 35.7 (br s, CH_2 *cy*); 35.6 (d, $^2J_{C-P}$ = 3.9 Hz, CH *cy*); 31.7 (d, $^2J_{C-P}$ = 2.3 Hz, CH_3); 30.4 (d, $^2J_{C-P}$ = 2.3 Hz, CH_3); 26.2 (m, CH_2 *cy*); 23.1 (dd, $^1J_{C-P}$ = 20.3 Hz, $^3J_{C-P}$ = 8.1 Hz, CH_2). **$^{31}P\{^1H\}$ NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 79.5 (s). **HRMS** (ESI-TOF): *m/z*= 493.2347, calcd for $[M\text{-}CH_3SO_3 + H]^+$: 493.2344. Anal. Calcd for $C_{25}H_{54}O_6P_2PdS_2$: C, 43.95; H, 7.97; O, 14.05; P, 9.07; Pd, 15.58; S, 9.39. Found: C, 43.82; H, 8.06; S, 9.42.

Synthesis of *cis*-1,2-bis(di-*tert*-butylphosphinomethyl)cyclohexane palladium(II) complex (44)



The synthesis of complex (**44**) was performed from **29** (1.30 mmol) according to the general procedure previously described. Yield = 399 mg, 51%. The crystals are obtained after purification by the elimination of dba with diethyl ether (3 x 50 mL and the solid was dissolved in THF (10 mL)). 3 mL of this solution were put in a layer tube and diethyl ether was added carefully (20 mL) to form a biphasic solution. The solution was stood for 3 days which gave the formation of crystals. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 2.93 (s, CH_3); 2.16 (br s, 2H,

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CH cy); 1.91 (m, 4H, CH_2 cy); 1.58 (d, $^3J_{H-P}$ = 15.2 Hz, 18H, CH_3); 1.52 (d, 15.2 Hz, 18H, CH_3); 1.34 (m, 4H, CH_2 cy); 1.32 (m, 4H, CH_2). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 41.5 (d, $^1J_{C-P}$ = 17.2 Hz, $C(CH_3)_3$); 40.8 (d, $^1J_{C-P}$ =17.2 Hz, $C(CH_3)_3$); 39.7 (s, CH_3); 34.3 (br s, CH *cy*); 31.3 (d, $^2J_{C-P}$ = 1.6 Hz, CH_3); 30.6 (d, $^2J_{C-P}$ = 1.6 Hz, CH_3); 27.4 (m, CH_2 *cy*); 26.3 (d, $_4J_{C-P}$ = 2.4 Hz, CH_2 *cy*); 23.3 (br s, CH_2). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, 193 K δ ppm): 94.4 (d, $^2J_{P-P}$ = 4.8 Hz); 63.3 (d, $^2J_{P-P}$ = 4.8 Hz). **HRMS** (ESI-TOF): *m/z* = 507.2527, calcd for $[M - CH_3SO_3 + H]^+$: 507.2501. Anal. Calcd for $C_{26}H_{56}O_6P_2PdS_2$: C, 44.79; H, 8.10; O, 13.77; P, 8.88; Pd, 15.26; S, 9.20. Found: C, 44.67; H, 8.21; S, 9.23

Methoxycarbonylation reactions

A 1L stainless steel autoclave was used to run these experiments. A standard catalyst solution is comprised of palladium(II) acetate, the bidentate phosphine ligand and methane sulphonic acid in a 1 Pd: 3(L-L): 2.5 $MeSO_3H$ ratio. $5.98 \cdot 10^{-4}$ mol of palladium is used in the catalyst experiment. Palladium acetate and the bidentate phosphine ligand ($1.83 \cdot 10^{-3}$ mol) are weighed into a flask in a glovebox, the flask is then transferred to a schlenk line. 180 mL of degassed methyl propionate and 120 mL of degassed methanol are then added. The reaction mixture was then stirred at room temperature for twenty minutes and methanesulphonic acid was then added by syringe to obtain the palladium(II) complexes $[Pd(O_3SCH_3)(L\text{-}L)]O_3SCH_3$. Then, the catalyst solution is added to the autoclave by vacuum transfer. The autoclave is then pressured with 20 bar of ethene and 40 bar of carbon monoxide. The autoclave is then heated to 100°C. After 3 hours at 100°C the autoclave is cooled to room temperature and the excess pressure vented. The catalyst exit solution is then collected, weighted and sampled for GC analysis.

NMR simulations of the VT ^{31}P{^{1}H} NMR spectra of 73

A 0.013 M solution of **73** in methanol was prepared following the general procedure below and $^{31}P\{^1H\}$ NMR spectra recorded at 10 K increments from 193 to 293 K. NMR simulations were performed using gNMR5. Several exchange models were tested including: intramolecular exchange of P^A and P^B in each isomer; pairwise intermolecular exchange of P^A in isomer 1 with P^A in isomer 2 and P^B in isomer 1 with P^B in isomer 2; pairwise intermolecular exchange of P^A in isomer 1 with P^B in isomer 2 and P^B in isomer 1 with P^A in

isomer 2; etc. The spectra are best modelled by three independent exchange processes involving pairwise intermolecular exchange of P^A in isomer 1 with P^A in isomer 2 and P^B in isomer 1 with P^B in isomer 2, in combination with intramolecular exchange of P^A with P^B in each isomer. The simulations are relatively insensitive to the intramolecular exchange rate for isomer 2. For simplicity, therefore, the exchange rate constants of the two intramolecular exchanges were set equal.

HP-NMR study

General method

All reactions and manipulations were carried out under dry oxygen-free nitrogen atmosphere using Schlenk techniques. All solvents were carefully purified by appropriate procedures. CD_2Cl_2 and CD_3OD were subjected to three freezepump thaw cycles and stored over 4 Å molecular sieves under nitrogen. Air sensitive compounds were stored under nitrogen at 243 K. ^{13}CO was purchased from ISOTEK, $^{13}CH_2=^{13}CHOC(O)CH_3$ from Aldrich. All other chemicals were purchased from Aldrich. Bis(ditertiarybutylphosphinomethyl)benzene (ALPHA) was donated by Lucite International. The sapphire tube was supplied by Saphikon. The recirculating pump by HiT-Hydraulik.[73]

HP-NMR measurements

In a typical experiments, the sapphire NMR tube was charged under N_2 with a solution containing the palladium precursor (0.048 mmol), the ligand (0.144 mmol), the corresponding acid CH_3SO_3H or CF_3CO_2H (0.12 mmol or 6 mmol respectively) in methanol. The tube was then pressurised with ethylene and carbon monoxide to the desired pressure. Most of the compounds reported below have not been isolated due to their instability or the reversible nature of the reaction involved. However, 1D and 2D NMR measurements and detailed isotopic labelling experiments allow all of these compounds to be assigned unambiguously.

Synthesis of $[Pd(O_2CCF_3)(L\text{-}L)]O_2CCF_3$ (55-58). General procedure
Bidentate phosphine ligand (0.144mmol) and palladium acetate, $Pd(OAc)_2$ (0.140 mmol) were combined in a schlenk flask. MeOH (3 mL) was then

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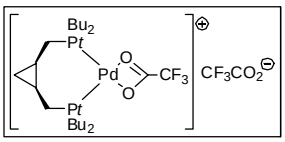
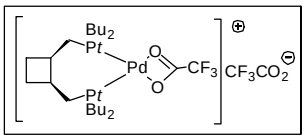
added and the resultant solution was stirred for 2 hours at room temperature. Trifluoroacetic acid was then added and the mixture reaction was then stirred for 2 hours. The solution was filtered under nitrogen and then concentrated under vacuum and diethylether (3mL) was added to precipitate the corresponding complex.

Synthesis of $[Pd(O_2CCF_3)(26)]O_2CCF_3$ (55)



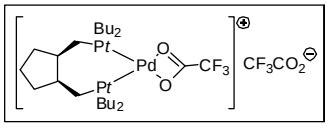
Following the general procedure the compound **55** was obtained from **26** (43 mg, 0.12 mmol) as a yellow powder. Yield = 56 mg, 63%. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 2.67 (m, 4H, CH_2); 1.68 (d, 18H, $^3J_{H-P}$= 14.4 Hz, CH_3); 1.46 (d, 18H, $^3J_{H-P}$= 14.4 Hz, CH_3); 1.31 (m, 2H, CH_2 cy); 1.13 (m, 1H, CH cy); 0.91 (m, 1H, CH cy). **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 162.9 (d, $^2J_{C-F}$= 39.5 Hz, CF_3); 117.5 (d, $^1J_{C-F}$= 285.2 Hz $C(CF_3)$); 39.3 (dd, $^1J_{C-P}$ = 18.4 Hz, $^3J_{C-P}$ = 9.2 Hz, $C(CH_3)_3$); 31.3 (br s, CH_3); 30.2 (br s, CH_3); 29.9 (s, CH_2 *cy*); 23.5 (d, $^2J_{C-P}$ = 20.6 Hz, CH *cy*); 17.6 (m, CH_2). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 51.0 (s). **HRMS** (ESI-TOF): *m/z*= 465.2043, calcd for $[M\text{-}CF_3CO_2 + H]^+$: 465.2051. Anal. Calcd for $C_{25}H_{44}F_6O_4P_2Pd$: C, 43.46; H, 6.42; F, 16.50; O, 9.26; P, 8.97; Pd, 15.40. Found: C, 43.33; H, 6.47.

Synthesis of $[Pd(O_2CCF_3)(27)]O_2CCF_3$ (56)



The synthesis of **56** was carried out from **27** (53 mg, 0.144 mmol) according to the general procedure previously described. Yield =67 mg, 66%. **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 49.0 (s). **HRMS** (ESI-TOF): *m/z*= 479.2178, calcd for $[M\text{-}CF_3CO_2 + H]^+$: 479.2188. Anal. Calcd for $C_{26}H_{46}F_6O_4P_2Pd$: C, 44.29; H, 6.58; F, 16.17; O, 9.08; P, 8.79; Pd, 15.10. Found: C, 44.21; H, 6.61.

Synthesis of $[Pd(O_2CCF_3)(28)]O_2CCF_3$ (57)



The synthesis of **57** was carried out from **28** (55 mg, 0.144 mmol) according to the general procedure previously described Yield = 62 mg, 59%.. **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 48.3 (s). **HRMS** (ESI-TOF): *m/z*= 493.2341, calcd for $[M\text{-}CF_3CO_2 + H]^+$: 493.2344. Anal. Calcd for $C_{27}H_{48}F_6O_4P_2Pd$: C, 45.10; H, 6.73; F, 15.85; O, 8.90; P, 8.62; Pd, 14.80. Found: C, 45.02; H, 6.78.

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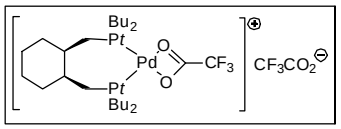
Synthesis of [Pd(O_2CCF_3)(29)]O_2CCF_3 (58)



The synthesis of **58** was carried out from **29** (105 mg, 0.26 mmol) in accordance with the general procedure. The product was isolated as a yellow-green solid. Yield = 148 mg, 77%. **^{1}H NMR** (CD_2Cl_2, 400 MHz, δ ppm): 1.63 (d, 18H, $^3J_{H\text{-}P}$= 14 Hz, CH_3); 1.54 (d, 18H, $^3J_{H\text{-}P}$= 14 Hz, CH_3); 1.48-1.18 (m, 14H). **^{13}C NMR** (CD_2Cl_2, 100.6 MHz, δ ppm): 162.7 (d, $^2J_{C\text{-}F}$= 38.9 Hz, CF_3); 116.0 (d, $^1J_{C\text{-}F}$= 291.4 Hz $C(CF_3)$); 41.8 (d, $^1J_{C\text{-}P}$ = 17.5 Hz, $C(CH_3)_3$); 40.5 (d, $^1J_{C\text{-}P}$ = 17.5 Hz, $C(CH_3)_3$); 38.2 (m, CH *cy*); 31.9 (m, CH_2 *cy*); 30.3 (m, CH_3); 26.8 (m, CH_2 *cy*); 16.9 (d, $^1J_{C\text{-}P}$ = 19.8, CH_2). **^{31}P{^{1}H} NMR** (CD_2Cl_2, 161.97 MHz, δ ppm (193K)): 76.2 (s); 46.9 (s). **HRMS** (ESI-TOF): *m/z*= 507.2527, calcd for [M-CF_3CO_2 + H]$^+$: 507.2501. Anal. Calcd for $C_{28}H_{50}F_6O_4P_2Pd$: C, 45.88; H, 6.87; F, 15.55; O, 8.73; P, 8.45; Pd, 14.52. Found: C, 45.51; H, 6.96.

Synthesis of [Pd(26-29)(CH_2CH_3)]O_2CCF_3 (70-73); General Procedure

Bidentate phosphine ligand (0.144mmol) and palladium acetate, $Pd(OAc)_2$ (0.140 mmol) were combined in a schlenk flask. MeOH (3 mL) was then added and the resultant solution was stirred for 20 minutes at room temperature. Trifluoroacetic acid (0.480 mmol) was then added and the mixture reaction was then stirred for 20 additional minutes. The solution was then transferred into the sapphire tube and it was charged with 10 bar of ethene at 353 K for 20 minutes.

Synthesis of [Pd(26)(CH_2CH_3)]O_2CCF_3 (70)

The synthesis of complex (**70**) was completed from **26** according to the general procedure previously described. **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 67.9 (d, $^2J_{PP}$ = 24.3 Hz); 50.3 (d, $^2J_{PP}$ = 24.3 Hz).

Synthesis of [Pd(27)(CH_2CH_3)]O_2CCF_3 (71)

The synthesis of complex (**71**) was completed from **27** according to the general procedure previously described. **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 63.4 (d, $^2J_{PP}$ = 23.1 Hz); 41.2 (d, $^2J_{PP}$ = 23.1 Hz).

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Synthesis of [Pd(28)(CH_2CH_3)]O_2CCF_3 (72)

The synthesis of complex (**72**) was completed from **28** according to the general procedure previously described. **^{31}P{H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): 77.3 (d, $^2J_{PP}$ = 23.0 Hz); 47.0 (d, $^2J_{PP}$ = 23.0 Hz).

Synthesis of [Pd(29)(CH_2CH_3)]O_2CCF_3 (73)

The synthesis of complex (**73**) was completed from **29** according to the general procedure previously described. **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 MHz, δ ppm): major isomer: 87.8 (d, $^2J_{PP}$= 22.4 Hz); 38.6 (d, $^2J_{PP}$= 22.4 Hz). Minor isomer 64.3 (d, $^2J_{PP}$= 22.4 Hz); 58.4 (d, $^2J_{PP}$= 22.4 Hz).

Synthesis of [Pd(29)(κ^2 -CH(Me)OAc)] O_2CCF_3 (75)

[Pd(**29**)(CH_2CH_3)]O_2CCF_3 (**73**) was synthesised as above. Then, 1.5 eq of CH_2=CHOC(O)CH_3 or $^{13}CH_2$=^{13} CHOC(O)CH_3 (10 μL) were added. A mixture of **75a** and **75b** formed immediately, as indicated by the ^{31} P{^{1} H} NMR spectrum. **75a** (major): **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 96.2 (dd, J_{CC} = 32.5 Hz, J_{PC} = 94.7 Hz), 23.9 (d, J_{CC} = 32.5 Hz). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 M Hz, δ ppm): 52. 5 (dd, $^2J_{PC}$ = 95.6 Hz, $^2J_{PP}$ = 30.5 Hz), 51. 3 (d, $^2J_{PP}$ = 29.7 Hz) **75b** (minor): **^{13}C NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 93.9 (dd, J_{CC} = 31.2 Hz, J_{PC} = 94.3 Hz), 27.5 (br s). **^{31}P{^{1}H} NMR** ($CDCl_3$, 161.97 M Hz, δ ppm): 70.2 (d, $^2J_{PP}$ = 29.7 Hz), 30.5 (dd, $^2J_{PC}$ = 97.7 Hz, $^2J_{PP}$ = 30.5 Hz).

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Chapter 3

P,P-ligands in Pd-catalysed aminocarbonylation and double-carbonylation reactions

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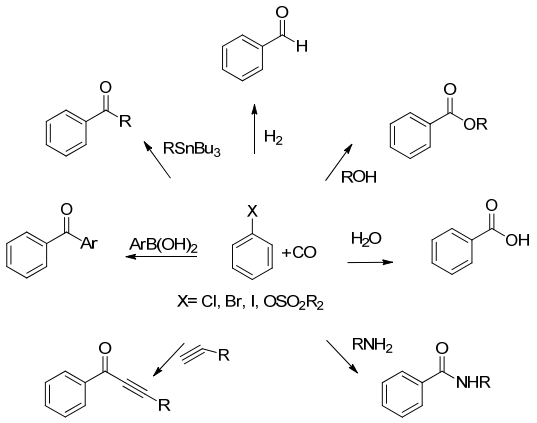
3. 1. Introduction to carbonylation reactions of aryl halides

Arenes and heteroarenes derivatives are important intermediates in the manufacture of agrochemicals, dyes, pharmaceuticals and other industrial products.[1] Nowadays, the most efficient procedure to obtain them is by transition metal catalysis.[1] Heck and co-workers developed the pioneering work in carbonylation reaction of aryl-X compounds to produce a wide range of products such as carboxylic acid derivatives, aldehydes, and ketones and this method is currently becoming a valuable tool in organic synthesis (Scheme 3.1).[2,3]



Scheme 3.1. Products obtained in the carbonylation of aryl halides.

These reactions consist in the incorporation of carbon monoxide into an aryl-, benzyl-, or vinylpalladium complex in the presence of a nucleophile (Scheme 3.1). Generally, the reaction conditions are 60-140ºC and 5-60 bar of carbon monoxide in the presence of a stoichiometric amount of base to regenerate the catalyst. The rate of the oxidative addition of the organic halide to an electronically unsaturated metal complex decreases in the order: C-I>C-OTf>C-Br>>C-Cl>>C-F.[2b]

Depending on the nucleophile used in the reaction, various products can be obtained such as: carboxylic acids by using water as nucleophile (hydroxycarbonylation), esters using alcohols (alkoxycarbonylation), amides using amines (aminocarbonylation), etc. Intramolecular reactions can also take place, thus forming heterocycles.[4]

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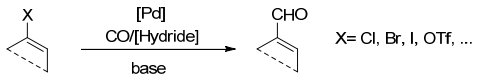
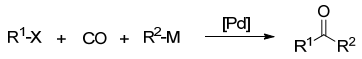
The Pd-catalysed reductive carbonylation of aryl halides or vinyl halides derivatives produce aromatic or α,β-unsaturated aldehydes (Scheme 3.2).[5]



Scheme 3.2. Palladium-catalysed reductive carbonylation reaction.

Finally, the palladium-catalysed carbonylative cross-coupling reaction use as nucleophile various organometallic reagents such as organoboranes or borates,[6] organoaluminum,[7] organosilane,[8] organoantimony,[9] and organozinc compounds (Scheme 3.3).[10]



Scheme 3.3. General scheme for the three-component cross-coupling reaction.

3.1.1. Pd-catalysed aminocarbonylation of aryl iodides

The synthesis of amides is one of the most sought-after goals in pharmaceutical chemistry.[11] In this context, the aminocarbonylation reaction represents a valuable and easy way to their synthesis. The aminocarbonylation reaction, where the nucleophile is an amine, has been less studied than the analogous alkoxycarbonylation reaction. Both reactions can be carried out under similar conditions. Heck reported the palladium complexes $[PdX_2(PPh_3)_2]$ (X= Br, I) which were active using various aryl bromides and iodides under 1atm of carbon monoxide at 100ºC.[12] However, there are only few reports on the reaction of aryl chlorides.

3.1.1.1. Mechanism

The palladium-catalysed carbonylation reaction of aryl or vinyl halides has been extensively studied although some uncertainty and disagreements in the later steps of the catalytic cycle can be found in the literature. Different pathways have been proposed depending on; a) the choice of catalyst precursor; b) the base, affecting the concentration of the nucleophilic anion and influencing reductive elimination of HX from palladium; c) the substrate; d) the solvent; and e) the carbon monoxide pressure.

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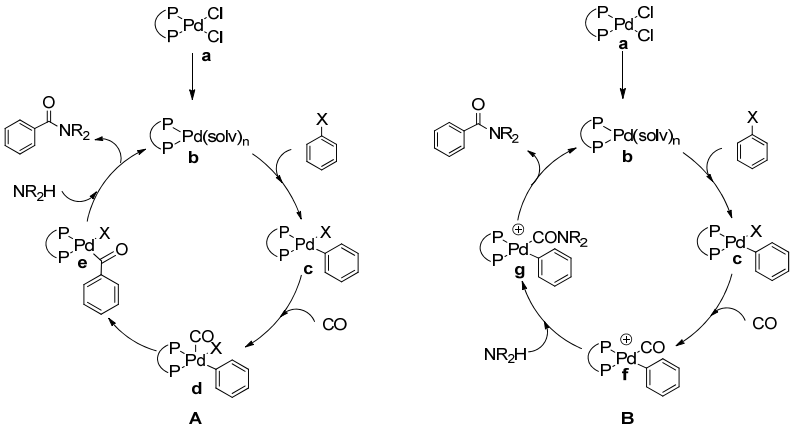
The most accepted catalytic cycle for the aminocarbonylation reaction of aryl halides is presented in Scheme 3.4A and consists in: a) the oxidative addition at Pd(0) to form Pd(II) species (**c**); b) the coordination of carbon monoxide to give a penta-coordinated intermediate (**d**), c) which undergoes carbonyl insertion to give an acyl palladium complex (**e**) and d) the nucleophilic attack into the acyl to produce the final product regenerating the catalyst. However, Yamamoto reported an alternative mechanism in which the nucleophilic attack occurs at Pd-CO (**f**) and reductive elimination in (**g**) produces the amide and regenerates the initial Pd(0) species (Scheme 3.4B).

The identification of the intermediate species was carried out by reaction of $[PdCl_2(PPh_3)_2]$ with methanol and amines under carbon monoxide in the absence of aryl halide.[13] The species formed under the conditions mentioned below produced esters when the corresponding aryl halide was added.[14]



Scheme 3.4. Proposed mechanisms for the aminocarbonylation reaction.

The catalytic species containing carbonyl ligands, as for instance $[PdL_2(CO)n]$, are less active towards the oxidative addition because the electron density of the metal is reduced by back-donation.[15] Bidentate phosphine ligands under carbonylation conditions, and in the presence or absence of monophosphine, give mixtures of palladium complexes (Figure 3.1).[15]

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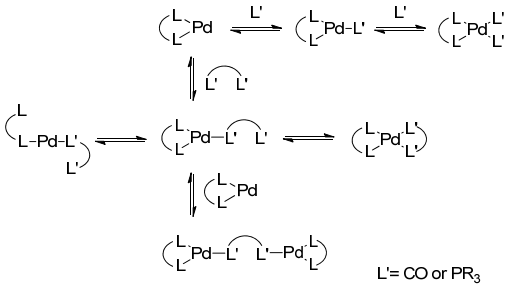


Figure 3.1. Precatalytic equilibria for PdL_2 systems.

Osborn studied the properties of monophosphine ligands to achieve good catalytic activity observing that the optimal range for phosphane cone angle was 160-180º.[16]

As such, the presence of alkyl-substituted phosphines was shown to accelerate the oxidative addition step. Aryl-substituted phosphine ligands are suitable for the aminocarbonylation of aryl iodides or bromides while the aryl chlorides require the presence of alkyl phosphine ligands.[15,17,18,19] However, the incorporation of alkyl substituents on the phosphorus atom disfavours the carbonylation step. For instance, carbonylation using $[PdBr(Ph)(PPh_3)_2]$ is 140 times faster than carbonylation with $[PdBr(Ph)(PEt_3)_2]$.[20] When diphosphine ligands are used, the coordination of carbon monoxide forms two isomeric species that were detected by IR (Figure 3.2).[20]

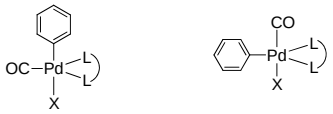


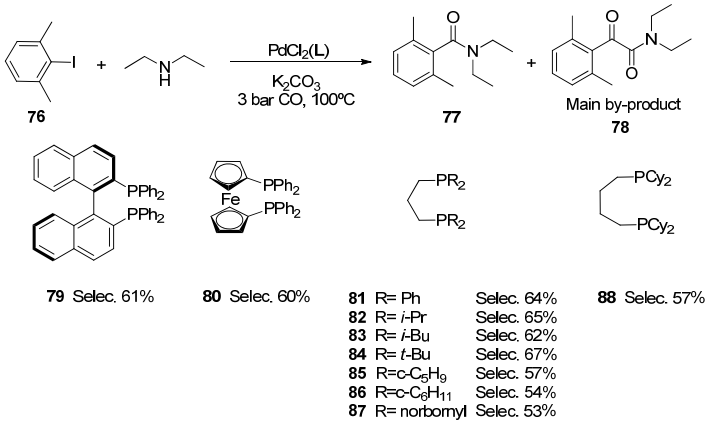
Figure 3.2. Isomeric intermediates preceding the carbonyl insertion.

After coordination of the carbonyl, two possible pathways are proposed. Heck proposed that the carbonyl insertion was irreversible. This proposal was demonstrated by Moser[21] with the palladium complex $[PdBr(COPh)(PPh_3)_2]$ and by Milstein[22] for $[PdCl(COCH_2Ph)(PMe_3)_2]$ using labelled carbon monoxide. However, Osborn studied this reaction using $[PdCl(COPh)(PCy_3)_2]$ as complex and observed a reversible reaction. This result was attributed to the electron and steric properties of the phosphine ligand.[16]

As mentioned before Yamamoto suggested a nucleophilic attack at the terminal carbonyl ligand rather than a carbonyl insertion, because of the higher reaction rates observed for more acidic alcohols.[23] However, Milstein found other evidence for the carbonyl insertion mechanism from the study of $[PdCl(CH_2Ph)(PMe_3)_2]$ which produces carbonyl insertion reactions very rapidly even at room temperature.[22] It is accepted that the carbonyl insertion reaction prevails over the nucleophilic attack at the terminal carbonyl ligand for single-carbonylation. Finally, the acyl complex reacts with the nucleophile via inter- or intramolecular attack.

3.1.1.2. Pd-catalysed aminocarbonylation of aryl iodides. Scope

As mentioned before, the aminocarbonylation of aryl halides has been less studied than the alkoxycarbonylation analogue. Scheme 3.5 summarizes some of the catalytic systems reported for the aminocarbonylation of aryl iodides. Barnard *et al.* were able to aminocarbonylate sterically hindered aryl iodides such **76** increasing the temperature at 100ºC. However, in some cases the α-ketoamide was formed as the main by-product.



Scheme 3.5. Pd-catalysed aminocarbonylation of 2,6-dimethyl-1-iodobenzene.

Kollár *et al.* have extensively studied the aminocarbonylation of aryl iodides with different catalytic systems. In particular, 2-iodo-anisole (**89**) reacted with carbon monoxide and different primary or secondary amines in the presence of $Pd(OAc)_2/PPh_3$ catalyst to give **90** (Scheme 3.6).[24]

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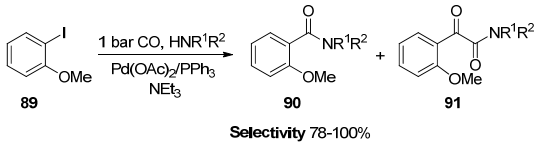
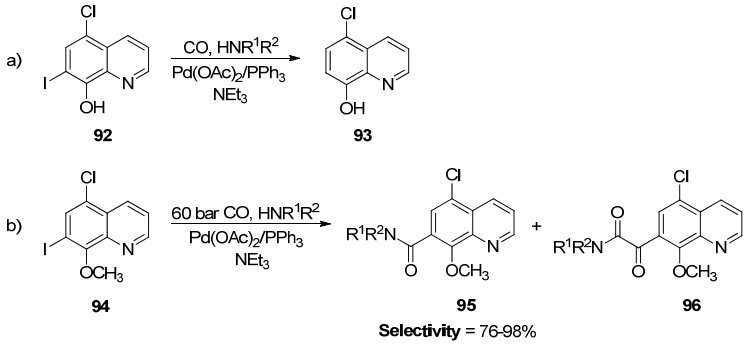


Scheme 3.6. Aminocarbonylation of 2-iodo-anisole (**89**) with $Pd(OAc)_2/PPh_3$.

The effect of the carbon monoxide pressure on the formation of the desired carboxamides or keto-carboxamides was also observed by the same authors.[24] In general, the amides were obtained under atmospheric carbon monoxide pressure and the α-ketoamides at 40 bars.

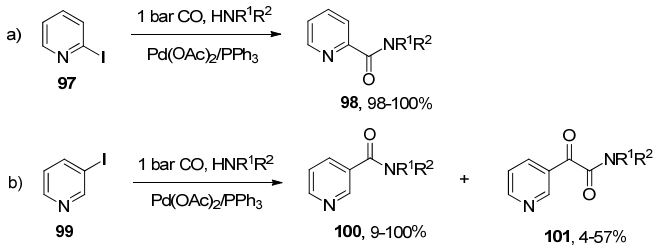
When the reaction was carried out with 5-chloro-7-iodo-8-hydroxy-quinoline (**92**), the expected amides were not detected. However, a selective dehydroiodination of **92** to produce 5-chloro-8-hydroxy-quinoline (**93**) was observed (Scheme 3.7a).[24] When 5-chloro-7-iodo-8-methoxy-quinoline (**94**) was used the monocarbonylation reaction was detected. Double-carbonylation was only observed in small amount (less than 15%) (Scheme 3.7b).



Scheme 3.7. Aminocarbonylation of 5-chloro-7-iodo-8-methoxy-quinoline (**94**).

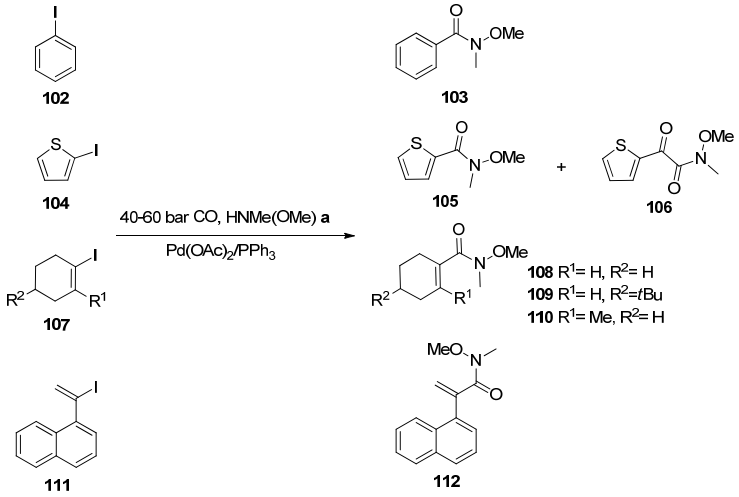
Various *N*-containing iodo-heteroaromatic substrates were aminocarbonylated using the catalyst system [$Pd(OAc)_2/PPh_3$] in the presence of a range of nucleophiles. The position of the iodo-substituent related to nitrogen determines the chemoselectivity towards mono- and di-carbonylated product. 2-iodopyridine affords the formation of carboxamides while 3-iodopyridine derivatives afford a mixture of carboxamides and keto-carboxamides. As previously described, the carbon monoxide pressure affects the

chemoselectivity of the process, with the formation of α-ketoamides favoured by high carbon monoxide pressures (Scheme 3.8).[25]



Scheme 3.8. Aminocarbonylation of 2- and 3-iodopyridines.

In 2010, Kollár reported the successful aminocarbonylation of several aryl iodides and iodoalkenes using the $Pd(OAc)_2/PPh_3$ system. The corresponding amides were obtained in 87% yield. The double-carbonylation products were only detected when 2-iodothiophene was the substrate (Scheme 3.9).[26]



Scheme 3.9. Palladium-catalysed aminocarbonylation of aryl iodides and iodoalkenes.

Furthermore, 1'-iodo-ferrocenecarboxamide- or 1'-iodo-ferroceneglyoxylic amide-type products were obtained in reasonable yields from the aminocarbonylation of 1,1'-diiodoferrocene (**113**) under carbon monoxide pressure. Later, some of these products **115** was used as substrates for another

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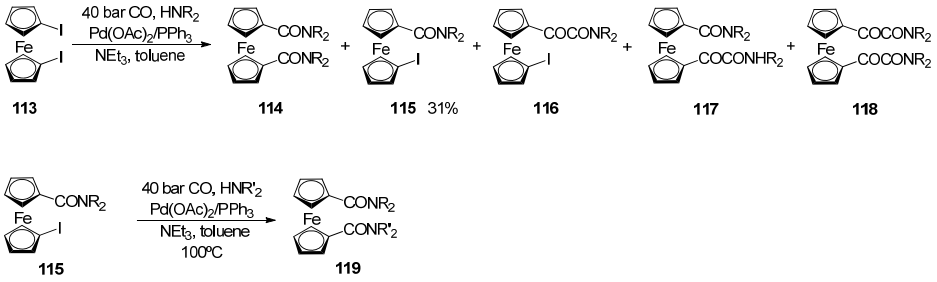
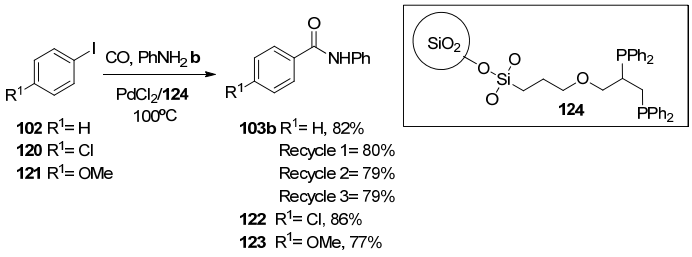
aminocarbonylation reaction affording unsymmetrical ferrocene 1,1'-diamides **119** (Scheme 3.10).[27]



Scheme 3.10. Pd-catalysed aminocarbonylation of 1,1'diiodoferrocene with $Pd(OAc)_2/PPh_3$.

Hang *et al.* reported the palladium-catalysed aminocarbonylation of aryl halides by silica-supported bidentate phosphine palladium complexes (Scheme 3.11). The results were in agreement with those reported by the analogous system $[Pd(PPh_3)_2Cl_2]$.[28]



Scheme 3.11. Pd-catalysed aminocarbonylation of aryl iodides with $PdCl_2$/**124**.

Perry *et al.* reported the addition of iodide as a promoter for the aminocarbonylation of electron-withdrawing substrates but this approach was not successful for electron-rich substrates.[29]

Milstein[30] and Sen[31] reported the aminocarbonylation of aryl chlorides with dippp ligand at 150ºC and 175ºC, respectively. Buchwald published in 1997 the formation of a phenyl ester by alkoxycarbonylation reaction and a subsequent transamination reaction using an excess of sodium phenoxide which acts as nucleophile and a base. The ligand used was dcpp (1,3-

bis(dicyclohexylphosphinopropane) and the reaction conditions were 1 bar of carbon monoxide and 100ºC.[32]

3.1.2. Pd-catalysed double-carbonylation of aryl iodides

Usually, as commented above the palladium-catalysed double-carbonylation of aryl iodides occurs under conditions very similar to those used for the monocarbonylation reaction, but using higher carbon monoxide pressures. The introduction of two carbon monoxides enables to form α-ketoacids, esters, or amides from (hetero)aryl, alkenyl, and alkyl halides.[33] This methodology was employed for the synthesis of many biologically active molecules.[34] The effect of the temperature and of the CO pressure on the aminocarbonylation of 3-iodoanisole and 4-bromobenzonitrile was reported by Buchwald and Jensen using $Pd(OAc)_2$/Xantphos as catalyst.[35] Their results indicated that the ratio of single- to double-carbonylation products decreases with higher CO pressure (from 5 to 15 bar) and increases with temperature (for 100-150ºC). The first reports dealing with the formation of α-ketoamides were dated in 1982[33s,33t,33r] and were soon followed by more detailed mechanistic studies.

3.1.2.1. Mechanism

Yamamoto and co-workers studied the mechanism for the Pd-catalysed double-carbonylation of aryl halides. [34e,343f,36] The initial studies focused on stoichiometric reactions of aryl and alkylpalladium halides with carbon monoxide, and amines (Scheme 3.12).

The proposed elementary steps of this catalytic cycle are: a) oxidative addition of aryl halide to the Pd(0) species **125** to give the arylpalladium halide **126**, b) carbon monoxide coordination and migratory insertion into the Pd-C bond to give the aroylpalladium species **127**, c) substitution of the halide ligand in **127** by carbon monoxide to give a cationic intermediate **128**, d) attack of the amine on the terminal CO ligand in **128** gives an aroyl and carbamoyl species **129**, and e) reductive elimination of the aroyl carbamoyl group forms the α-ketoamide and regenerates the initial Pd(0) species.

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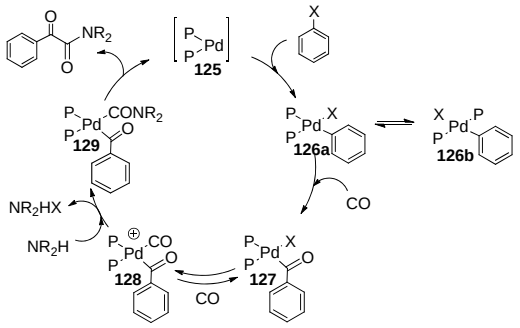
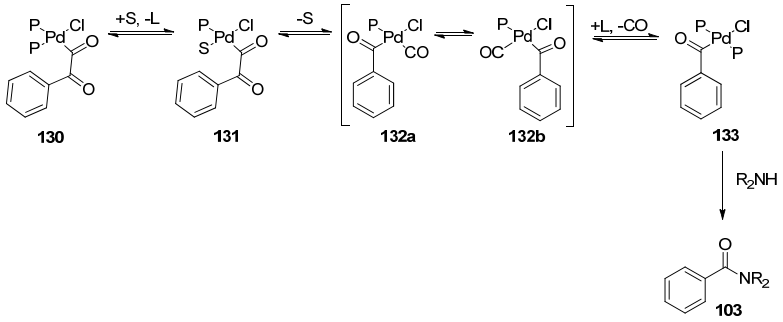


Scheme 3.12. Proposed mechanism for Pd-catalysed double-carbonylation of aryl halides.

The possibility of double CO insertion into the Pd-Ar bond in **126** was excluded on the basis of the reactivity of [PhCOCOPdCl(PPh_3)$_2$] (**130**), which decarbonylates at room temperature to the corresponding benzoyl compound, [PdCOPh(Cl)(PPh_3)$_2$] (**133**) (Scheme 3.13).[36,37]



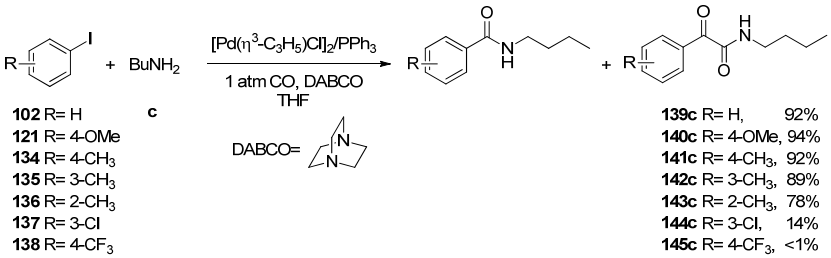
Scheme 3.13. Decarbonylation process of PhCOCOPdCl(PPh_3)$_2$ (**130**).

3.1.2.2. Pd-catalysed double-carbonylation of aryl iodides. Scope

There are few reports describing the selective Pd-catalysed double-carbonylation reaction of aryl halides. Some of the most efficient catalytic systems are commented below.

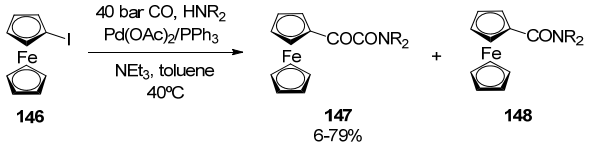
As mentioned above, the conditions required for the double-carbonylation reactions involve high CO pressures (40-70 bar) and high temperatures (100-150ºC).[34k,42,38] In 2001 Uozumi *et al.* observed that 1,4-diazabicyclo[2.2.2]octane (DABCO) was an excellent base for the highly

selective double-carbonylation of aryl iodides with primary amines (Scheme 3.14). The reaction was carried out under very mild conditions (1 bar CO, 25ºC) in the presence of Pd/PPh_3 as catalytic system.[39]



Scheme 3.14. Pd-catalysed double-carbonylation of aryl iodides with Pd/PPh_3 and DABCO.

The same year, Kóllar *et al.* reported the double-carbonylation of ferrocenyl iodides with Pd/PPh_3 in the presence of 40 bar of carbon monoxide and NEt_3 at 60ºC (Scheme 3.15).[40] A related work performing the reaction at atmospheric pressure has been published by the same authors.[27]



Scheme 3.15. Pd-catalysed double-carbonylation of iodoferrocene in the presence of secondary amines.

Dinuclear palladium complexes bearing a novel PNNP ligand, *N,N'*-bis[(2-diphenylphosphino)phenylformamidinate (dpfam), have been used in this reaction by Inoue.[33b] The optimal conditions involved K_3PO_4 as base and 1,4-dioxane as solvent. The best selectivity was 96% when *p*-iodoanisole was used as substrate (Scheme 3.16).

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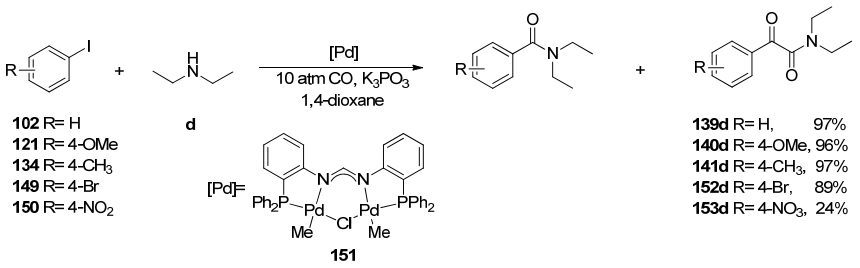
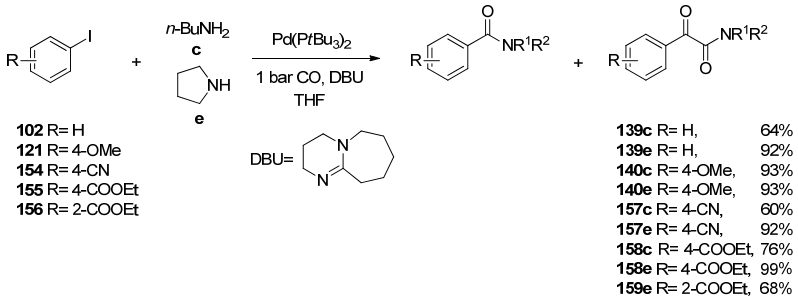


Scheme 3.16. Pd-catalysed double-carbonylation of aryl iodides with a Pd/PNNP complex.

In 2006, Kondo *et al*. reported the use of $Pd(PtBu_3)_2$ in the presence of atmospheric carbon monoxide pressure and DBU as a base.[41] This system was selective for the formation of α-ketoamides. The nucleophiles tested were *n*-butylamine and pyrrolidine achieving chemeoselectivities up to 99% (Scheme 3.17).



Scheme 3.17. Pd-catalysed double-carbonylation of aryl iodides with $Pd(PtBu_3)_2$.

More recently, high selectivities were achieved using $[Pd(PPh_3)_4]$ as catalyst precursor under 40 bar of CO using DBU as a base at 80ºC. Under these conditions the α-ketoamides were obtained with selectivities up to 96% (Scheme 3.18).[42]

Although no clear rationale on the selective formation of the double-carbonylation product can be deduced from literature reports, the nature of the base is critical and a large excess is always required.[33b,33o,34e,38a,38e] So far, only two main bases have been successfully utilised to obtain α-ketoamides, namely DBU and DABCO, although DBU is by far the most commonly used.[33n, 38a,38c,39,42]

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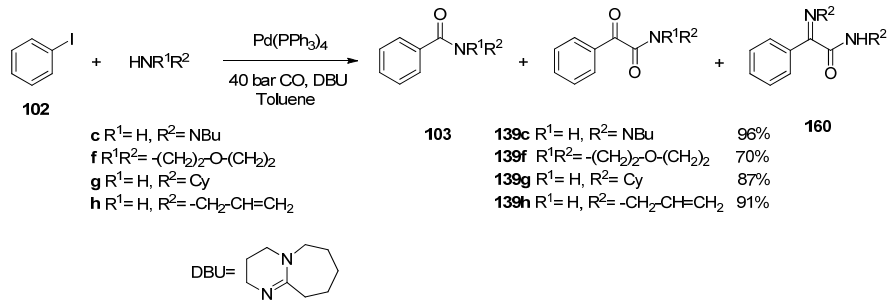

Scheme 3.18. Pd-catalysed double-carbonylation of aryl iodides with $Pd(PPh_3)_4$.

Furthermore, the chemoselectivity of the Pd-catalysed carbonylation reaction of aryl iodides towards α-ketoamides of amides seems to be influenced by: the nature of the catalyst, substrate, amine, carbon monoxide pressure, solvent and temperature.

a) Catalyst:

Generally, palladium complexes bearing monodentate tertiary phosphine ligands have shown to be the most efficient catalyst for the double-carbonylation reaction.[33,34e,34g] However, some efficient catalytic systems bearing bidentate ligands such as 1,4-bis(diphenylphosphino)butane (dppb) were also reported. Interestingly, poor results were obtained with PEt_3 or with PPh_3 although high selectivities were achieved when dialkylphenylphosphines such as ($PMePPh_2$) were used. The most efficient palladium precursors for this reaction are palladium (II) complexes which are reduced *in situ* to Pd(0) in the presence of carbon monoxide and amine.

b) Substrates:

The reactivity of the aryl halide decreases in the order of PhI > PhBr >> PhCl. Increasing the temperature accelerates the reaction rate but the selectivity for α-ketoamide decreases. The presence of substituents onto the phenyl rings modifies the reactivity of the aryl halides. Introduction of electron-withdrawing groups at the *para* position of the ring increases the reactivity but decreases the selectivity for α-ketoamide formation. For electron-donating groups the opposite effect was observed.

c) Carbon monoxide pressure:

The effect of carbon monoxide pressure is distinct for aryl iodides and aryl bromides, indicating a distinct rate determining step. When the carbon monoxide pressure is increased using PhI as substrate, the reaction rate increases and the formation for α-ketoamide is favoured. However, using phenyl bromide, the reaction is retarded suggesting that the rate-determining step may be the oxidative addition because under high CO pressures, the Pd(0) species will be coordinated by a greater number of CO molecules and its nucleophilicity will be reduced.[3f]

d) Solvent:

The more polar solvents favour the monocarbonylation reaction in contrast to the less polar solvents which produce the α-ketoamides in higher selectivities.

e) Amine:

The selectivity for the double-carbonylation of aryl halides is strongly affected by the nature of the amine used. Secondary amines of high basicity are suitable for this reaction but bulky amines are not very reactive and favour the formation of amides instead of α-ketoamide. In contrast, other amines with the similar basicity but less steric hindrance produce α-ketomides. The selectivity *versus* α-ketoamide product decreases in the order of Pr_2NH > Et_2NH > hexamethyleneimine > piperidine > Me_2NH > pyrrolidine. This tendency reveals that sterically demanding secondary amines give principally α-ketomides.

When primary amines afford the double-carbonylation product, by-products can be formed by reaction of the amine with the α-keto group affording a Shiff base.[42] Aniline which is the less basic amine among the amines explored; afford only the formation of amide product.[34f]

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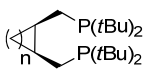
3. 2 Results and discussion

As mentioned above, bidentate ligands have received less attention than monoalkyl phosphines in the Pd-catalysed aminocarbonylation or double-carbonylation of aryl iodides. Different studies have shown that the presence of electron-rich ligands with high steric hindrance is required to achieve efficient catalytic systems. Thus, tri-*tert*-butylphosphine was the most efficient ligand reported for double-carbonylation process. Therefore, we considered that bulky and electron-rich bidentate phosphines (**26-29**) (Figure 3.3) that provided excellent results in alkoxycarbonylation of ethene (see previous chapter) could be appropriate ligands for the aminocarbonylation and double-carbonylation of aryl iodides



26 n=1
27 n=2
28 n=3
29 n=4

Figure 3.3. Bidentate phosphine ligands used for the Pd-catalysed aminocarbonylation and double-carbonylation reaction.

3.2.1. Pd-catalysed aminocarbonylation of aryl iodides

Initially, the Pd-catalysed aminocarbonylation reaction of 1-iodo-4-methoxybenzene was carried out in the presence of various palladium precursors and solvents using *n*-butylamine as nucleophile and **29** as ligand (Table 3.1). The reaction was performed under atmospheric carbon monoxide pressure in refluxing dichloromethane (entry 1, Table 3.1). The first experiment was carried out in the absence of base, achieving moderate conversion but excellent chemoselectivity to the aminocarbonylated product **123c** (entry 1, Table 3.1). Using pyridine as a base, excellent conversion and chemoselectivity to **123c** were obtained (entry 2, Table 3.1). The effect of the solvent was examined, observing the highest activity when dichloromethane was used and the chemoselectivity remained excellent in all the cases (entries 2-4, Table 3.1). Only a slight decrease in conversion was observed when toluene was used as solvent (entry 4, Table 3.1), which is in agreement with the observed in the previous works. Finally, all palladium precursors tested gave excellent conversions and chemoselectivities (entry 2 *vs.* 5-6, Table 3.1).

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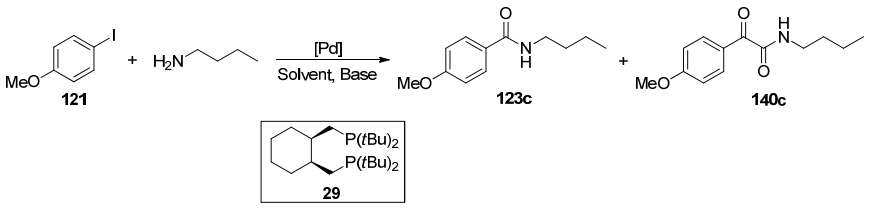
Table 3.1. Pd-catalysed aminocarbonylation of 1-iodo-4-methoxybenzene with *n*-butylamine: Optimization of reaction conditions.[a]



Entry	Pd precursor	Solvent	Base	Conv.[b] (%)	Sel. 123c/140c[b] (%)
1	Pd_2dba_3	CH_2Cl_2	-	31	99/1
2	Pd_2dba_3	CH_2Cl_2	Pyridine	96	99/1
3	Pd_2dba_3	THF	Pyridine	59	99/1
4	Pd_2dba_3	Toluene	Pyridine	76	94/6
5	$Pd(OAc)_2$	CH_2Cl_2	Pyridine	92	99/1
6	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	CH_2Cl_2	Pyridine	95	99/1

[a]*Reaction conditions*: [Pd] (0.01 mmol), ligand (0.011 mmol), aryl iodide (0.5 mmol), pyridine (1 mmol), *n*-butylamine (1.2 mmol), dichloromethane (1 mL), CO (1 bar), 45ºC and 14 hours. [b]Determined by ^{1}H-NMR and GC-MS.

Once optimised the catalytic conditions, a range of aryl iodides were used as substrates (Table 3.2). For *ortho*-, *meta*- and *para*-iodo anisoles (entries 1-3, Table 3.2), excellent chemoselectivities to the aminocarbonylated product were obtained (entries 1-3, Table 3.2), although the conversion decreases when the substituent is at the *meta*- or *ortho*- position. However, the reaction of the 2,4-dimethoxy derivative afforded exclusively the corresponding amide in excellent yield indicating that the steric hindrance from the methoxy group does not play a major role in terms of activity of the catalyst (entry 4, Table 3.2).

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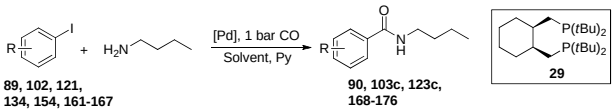
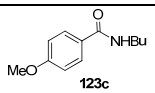
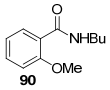
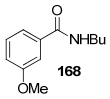
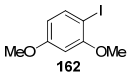
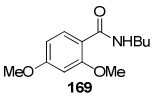
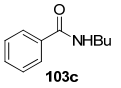
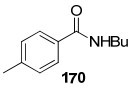
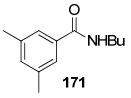
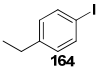
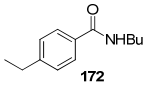
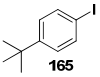
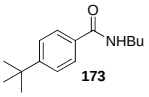
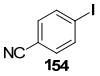
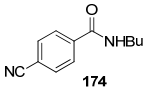
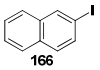
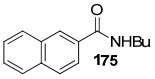
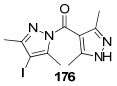
Table 3.2. Pd-catalysed aminocarbonylation of aryl iodides with *n*-butylamine.[a]



89, 102, 121, 134, 154, 161-167 → 90, 103c, 123c, 168-176

Entry	Aryl iodide	Product	Conv.[b] (%)	Selec.[b] (%)
1	 121	 123c	96	99
2	 89	 90	85	99
3	 161	 168	76	99
4	 162	 169	95	99
5	 102	 103c	95	99
6	 134	 170	91	99
7	 163	 171	85	99
8	 164	 172	92	99
9	 165	 173	99	99
10	 154	 174	94	99
11	 166	 175	77	99
12	 167	 176	96	99

[a]*Reaction conditions*: Pd_2dba_3 (0.005 mmol), ligand (0.011 mmol), aryl iodide (0.5 mmol), pyridine (1 mmol), *n*-butylamine (1.2 mmol), dichloromethane (1 mL), CO (1 bar), 45ºC and 14 hours. [b]Determined by ^{1}H-NMR and GC-MS.

When iodobenzene was used as substrate, excellent conversion and selectivity were achieved (entry 5, Table 3.2). When substrates with alkyl groups at the *para*- position of aryl group (entries 6, 8-9, Table 3.2) were used excellent results were obtained in terms of both conversion (91-99%) and chemoselectivity (99%). The conversion was slightly affected when 3,5-dimethyl-1-iodobenzene was used as substrate. However, the aminocarbonylated product was also formed selectively (99%) (entry 7, Table 3.2). With an electron-withdrawing substituent at the *para*- position, conversion and selectivity remained excellent (94%, 99%) (entry 10, Table 3.2). When 1-iodo-naphthalene was used as substrate the conversion dropped at 77% and the selectivity was unaltered (entry 11, Table 3.2). Finally, the aminocarbonylation of 1-iodo-2,5-dimethylpyrazole (**167**) was examined obtaining excellent conversion (96%), although the product formed was not the expected butyl amide but one incorporating two pyrazol units. This product results from the attack of pyrazol to the palladium-acyl intermediate complex (entry 12, Table 3.2) and was characterized by mass spectrometry.

To study the effect of the nucleophile, various amines were used (Table 3.3). Primary amines provided excellent conversions (89-96%) and chemoselectivities (96-99%) (entries 1-3, Table 3.3). The use of secondary amines lead to the corresponding amides in excellent conversions (>83%) and selectivities (99%) (entries 4, 6-8, Table 3.3).

However, when the diisopropylamine was used as nucleophile no reaction was observed (entry 5, Table 3.3). Low yields have been already reported for the formation of the aminocarbonylated product when diisopropylamine was used as nucleophile.[33b,33q,34f] This result shows the influence of the steric hindrance in the evolution of the reaction, resulting in this case in the inhibition of the aminocarbonylation reaction.

These results showed that palladium complexes bearing the bulky electron-rich bidentate phosphine ligand (**29**) constitute a very efficient catalytic system for the palladium-catalysed aminocarbonylation of a wide range of substrates and nucleophiles under mild conditions. It is important to mention that these results are among the best reported for this process.

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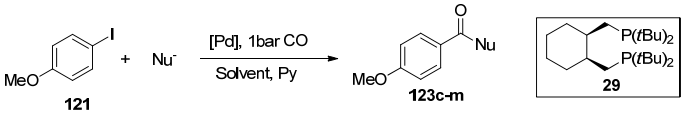
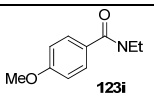
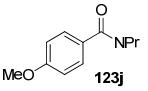
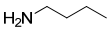
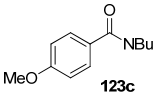
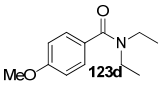
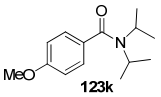
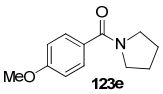
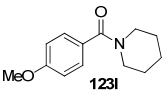
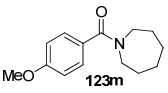
Table 3.3. Pd-catalysed aminocarbonylation of 1-iodo-4-methoxybenzene with different nucleophiles.[a]



Entry	Nucleophile	Product	Conv.[b] (%)	Selec.[b] (%)
1		 **123i**	89	99
2		 **123j**	91	96
3		 **123c**	96	99
4		 **123d**	99	99
5		 **123k**	0	-
6		 **123e**	92	99
7		 **123l**	97	99
8		 **123m**	83	99

[a]*Reaction conditions*: Pd_2dba_3 (0.005 mmol), ligand (0.011 mmol), aryl iodide (0.5 mmol), pyridine (1 mmol), nucleophile (1.2 mmol), dichloromethane (1 mL), CO (1 bar), 45ºC and 14 hours. [b]Determined by ^{1}H-NMR and GC-MS.

Since monocarbonylation of aryl iodide was successfully carried out under mild conditions using Pd/**29** catalytic system, the application of this catalytic system for the Pd-catalysed double-carbonylation reaction giving the formation of α-ketoamides was carried out.

To summarize, the Pd-catalysed aminocarbonylation of aryl iodides was studied using Pd/**29** as catalytic system. This catalytic system was shown to be very efficient since the reaction proceeds under mild conditions (atmospheric pressure of CO) and afford amides with excellent conversion (up to 99%) and selectivities (99%) for a broad range of substrates and amine nucleophiles.

To conclude this study, the trends that were observed to affect the activity and selectivity of this process can be summarized as follow:

- *Nature of the base*: no effect was observed. A wide range of bases can be used including organic or inorganic bases.
- *Palladium precursor:* no tendency was observed in terms of chemoselectivity although the use of a Pd(0) source such as Pd_2dba_3 was shown to increase the conversion.
- *Solvent*: polar solvents favour the chemoselectivity to the amide product.
- *Concentration of the catalytic mixture*: effects on the chemoselectivity since high concentrations were shown to favour the formation of the amide product.
- *Substituents at the aryl iodide substrate*: the presence of groups with distinct electronic and/or steric properties showed no effect on the chemoselectivity of the reaction.
- *Nature of the amine nucleophile*: no differences between the results obtained with primary or secondary amines were observed in terms of chemoselectivity although the use of bulky amines leads to a decrease of the activity.
- *Reaction temperature*: no effect on the selectivity of the reaction.

3.2.2. Pd-catalysed double-carbonylation of aryl iodides using P,P ligands

There are only a few papers dealing with palladium catalysed double-carbonylation of aryl iodides. Most of the reported catalytic systems required high CO pressure and high temperatures for achieving good selectivities to α-ketoamides. There are only two reports that describe the double-carbonylation reaction under 1 bar of CO.[39,41] In both, a large excess of base is required to perform the reaction. Then, it seems that the base has a strong influence in shifting the chemoselectivity of the reaction to the amide or to the α-

ketoamide. In both reports, the use of nitrogen bases namely DABCO or DBU and triphenylphosphine and tri-*tert*-butylphosphine as ligands, respectively. In this context, and despite that only monophosphines have been used in this process, we thought that since ligands **26-29** have provided excellent results in the carbonylation of aryl iodides, it deserved to be tested in the double-carbonylation reaction.

Initially, in order to modify the chemoselectivity of the carbonylation reaction *versus* the formation of α-ketoamide under mild conditions, different bases were tested (Table 3.4).

These experiments were carried out using 1-iodo-4-methoxybenzene as substrate to slow down the nucleophilic attack at the acyl because of the electron-donating effect of the substituent.

The first experiment was carried out using 1-iodo-4-methoxybenzene, pyrrolidine and Pd/**29** as catalytic system in absence of base (entry 1, Table 3.4), yielding conversion of 72% but with the exclusive formation of the aminocarbonylated product. Then, various pyridine derivatives were tested (entries 2-4) as bases, giving a wide range of values in terms of conversion (30-82%) and also the exclusive formation of the monocarbonylated product. Later, 2-methylquinoline and 2-methylquinoxaline were used as substrate affording again the amide product (entries 5 and 6, Table 3.4). When DABCO was used as a base (entry 7, Table 3.4), moderate conversion was obtained (64%) and no chemoselectivity to the formation of the α-ketoamide was achieved, in contrast with what is reported with the catalytic system Pd/PPh_3.[39] Imidazole was also tested under the same conditions obtaining high conversion (73%) but the amide product was again formed (entry 8, Table 3.4). Surprisingly, when DBU was used as a base, full conversion and high chemoselectivity to the α-ketoamide **140e**, (72%) were achieved (entry 9, Table 3.4). The use of triethylamine (entry 10, Table 3.4) produced poor conversion (31%) and no formation of the α-ketoamide. Finally, two inorganic bases (Cs_2CO_3 and K_3PO_4) were used (entries 11 and 12, Table 3.4), giving moderate conversion (63-75%) and very poor chemoselectivity to the formation of α-ketoamide (up to 9%).

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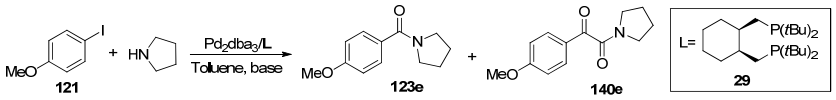
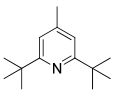
Table 3.4. Pd-catalysed double-carbonylation of 1-iodo-4-methoxybenzene with pyrrolidine: Effect of the base.



Entry	Base	Conv.[b] (%)	Selec.[b] 123e/140e (%)
1	-	72	100/0
2		79	100/0
3		30	100/0
4		82	100/0
5		74	100/0
6		40	100/0
7		64	100/0
8		73	100/0
9		99	28/72
10	NEt_3	31	100/0
11	Cs_2CO_3	63	91/9
12	K_3PO_4	75	95/5

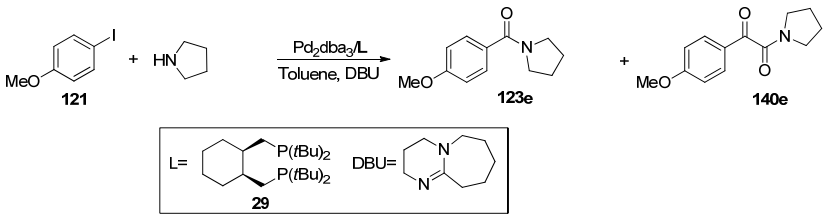
[a]*Reaction conditions*: Pd_2dba_3 (0.005 mmol), ligand (0.011 mmol), 1-iodo-4-methoxybenzene (0.5 mmol), base (1 mmol), pyrrolidine (1.2 mmol), toluene (5 mL), CO (1 bar), 60ºC and 14 hours. [b]Determined by ^{1}H-NMR and GC-MS.

To summarize, the screening of a number of bases was performed and showed that under atmospheric carbon monoxide pressure, the only base that provides a chemoselective reaction to the α-ketoamide is DBU (entry 9, Table 3.4).

Once demonstrated that DBU is the appropriate base for the Pd-catalysed double-carbonylation of aryl iodides with the catalytic system Pd/**29**, the other parameters affecting on the chemoselectivity of the reaction were studied.

First, the effect of the solvent was examined at 40ºC (entries 1-4, Table 3.5). The conversion obtained in all the cases was moderate (up to 63%). However, the chemoselectivity was improved when tetrahydrofurane or toluene were used as solvent (entries 1 and 2, Table 3.5).

Table 3.5. Pd-catalysed double-carbonylation of 1-iodo-4-methoxybenzene with pyrrolidine: Optimization of reaction conditions.



Entry	Pd precursor	Solvent	Temp. (ºC)	Conv.[b] (%)	Selec.[b] 123e/140e (%)
1	Pd_2dba_3	THF	40	26	10/90
2	Pd_2dba_3	Toluene	40	52	9/91
3	Pd_2dba_3	CH_2Cl_2	40	57	50/50
4	Pd_2dba_3	Toluene	rt	17	1/99
5	Pd_2dba_3	Toluene	40	53	9/91
6	Pd_2dba_3	Toluene	60	99	28/72
7	Pd_2dba_3	Toluene	80	99	37/63
8[b]	Pd_2dba_3	Toluene	60	99	37/63
9	$Pd(OAc)_2$	Toluene	60	85	36/64
10	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Toluene	60	71	60/40

[a]*Reaction conditions*: Pd_2dba_3 (0.005 mmol), ligand (0.011 mmol), 1-iodo-4-methoxybenzene (0.5 mmol), DBU (1 mmol), pyrrolidine (1.2 mmol), toluene (5 mL), CO (1 bar), 14 hours. [b]Pd/L ratio = 0.5. [c]Determined by ^{1}H-NMR and GC-MS.

Moderate chemoselectivities to the α-ketoamide formation were obtained in dichloromethane (entries 3, Table 3.5). Solvents with high dielectric constant

favour the formation of amide instead of α-ketoamide. In general, it can be suggested that polar solvents favour the nucleophilic attack to the acyl moiety in front of a second coordination of carbon monoxide which is apparently the crucial intermediate for the synthesis of the dicarbonylated product (See Scheme 3.4 and 3.12).

The optimization of the reaction temperature is described in Table 3.5 (entries 4-7). At low temperature poor conversions and excellent chemoselectivities were obtained (entries 4 and 5, Table 3.5). Raising the temperature at 60ºC yielded full conversion and high selectivity (72%, entry 6). When the temperature was increased to 80ºC, a decrease of the chemoselectivity was observed (entry 7, Table 3.5). It was therefore concluded that 60ºC could be the most appropriate reaction temperature, for achieving high conversion and selectivity towards the α-ketoamide product.

When the Pd/ligand ratio was decreased, the conversion was not affected but the chemoselectivity to the double-carbonylated product decreased to 63% (entry 8, Table 3.5). $Pd(OAc)_2$ and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ were also tested as catalyst precursors but in both cases, the chemoselectivity was poor (64 and 40 % of α-ketoamide respectively).

After this optimization of the reaction conditions, the family of bidentate ligands **6** and **26-29** was examined in the double-carbonylation of 1-iodo-4-methoxybenzene using *n*-butylamine as nucleophile (Table 3.6). Surprisingly, when the ligand **6** was used practically no activity and no chemoselectivity were observed even at 80ºC (entries 1 and 2, Table 3.6). Ligands **26-29** were also examined, achieving from good to excellent conversions (entries 3-6, Table 3.6) and excellent chemoselectivities in all the cases (up to 99%). The structural differences among these saturated cycloalkyl ligands lay on the size of the ring. No correlation between the size of the backbone and the activity can be extracted. It is interesting to mention the different catalytic behavior of the systems Pd/**6** which is practically inactive and no chemoselective *versus* the catalytic system Pd/**29** which afforded excellent results (entry 6, Table 3.6). The main difference between these two ligands is that the ligand **6** contains a rigid backbone while ligand **29** has a more flexible cyclohexyl backbone ring.

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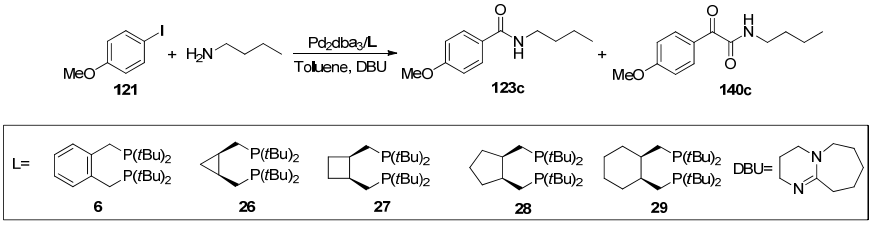
Table 3.6. Pd-catalysed double-carbonylation of 1-iodo-4-methoxybenzene with *n*-butylamine. Effect of the bidentate ligand.



Entry	Ligand	Conv.[c] (%)	Selec.[c] 123c/140c (%)
1	**6**	25	41/59
2[b]	**6**	27	73/27
3	**26**	82	7/93
4	**27**	60	1/99
5	**28**	72	12/88
6	**29**	99	4/96

[a]*Reaction conditions*: Pd_2dba_3 (0.005 mmol), ligand (0.011 mmol), 1-iodo-4-methoxybenzene (0.5 mmol), DBU (1 mmol), *n*-butylamine (1.2 mmol), toluene (5 mL), CO (1 bar), 60ºC and 14 hours. [b]Temperature = 80ºC. [c]Determined by ^{1}H-NMR and GC-MS.

Next, a number of aryl substrates and nucleophiles were tested with the catalytic system Pd/**29** under the previously optimized catalytic conditions (Table 3.7).

When the analogous 1-bromo or 1-chloro-4-methoxybenzene substrates were used, no catalytic activity was observed under 1 bar of carbon monoxide (entries 1 and 2, Table 3.7). Excellent results in terms of conversion and chemoselectivity were obtained with 1-iodo-4-methoxybenzene as substrate (entry 3, Table 3.7). This indicates that, in agreement with the previously reported, the oxidative addition is the rate determining step for aryl bromides and chlorides.[34f] When 1-iodo-2-methoxybenzene was used as substrate, high conversion was achieved but the amide product was formed instead of the α-ketoamide (entry 4, Table 3.7).

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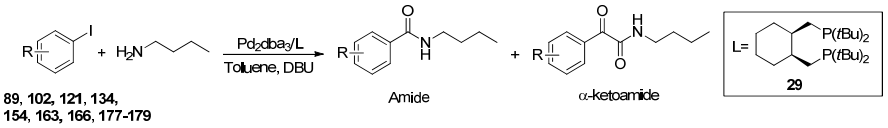
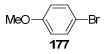
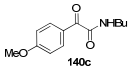
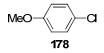
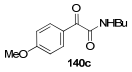
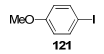
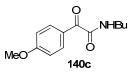
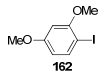
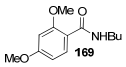
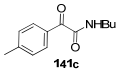
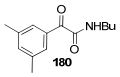
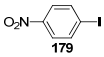
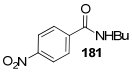
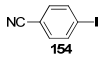
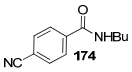
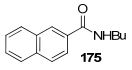
Table 3.7. Pd-catalysed double-carbonylation of different aryl iodides with *n*-butylamine.



89, **102**, **121**, 134, 154, **163**, **166**, 177-179

Entry	Substrate	Product	Conv.[b] (%)	Selec.[b] amide/ketoamide (%)
1	 177	 140c	0	-
2	 178	 140c	0	-
3	 121	 140c	99	4/96
4	 89	 90	73	100/0
5	 162	 169	99	100/0
6	 102	 103c	99	82/18
7	 134	 141c	81	15/85
8	 163	 180	54	30/70
9	 179	 181	89	100/0
10	 154	 174	80	70/30
11	 166	 175	99	75/25

[a]*Reaction conditions*: Pd_2dba_3 (0.005 mmol), ligand (0.011 mmol), aryl iodide (0.5 mmol), DBU (1 mmol), *n*-butylamine (1.2 mmol), toluene (5 mL), CO (1 bar), 14 hours. [b] Determined by ^{1}H-NMR and GC-MS.

Using 1-iodo-2,4-dimethoxybenzene as substrate, full conversion was obtained affording the amide product in 100% (entry 5, Table 3.7). In the case iodobenzene, excellent conversion was achieved and the chemoselectivity was affected, giving the α-ketoamide product in 18% (entry 6, Table 3.7). These results reveal how the absence of electron-donating group at the *para*-position of the aryl ring or the presence of bulky groups at the *ortho*- position makes the acyl group more electrophilic favouring the nucleophilic attack of the amine to this position instead of a second coordination of carbon monoxide. Later, the presences of methyl groups at the *para*- position (entry 7) and at *meta*- position (entry 8) were examined. In both cases, lower chemoselectivities were achieved (up to 85%) (entries 7 and 8, Table 3.7).

As expected, the presence of electron-withdrawing groups at *para*-position resulted in the selective formation of the amide, especially when a nitro group was present (entry 9, Table 3.7). The amide was formed in 70 or 75% selectivity when a 1-iodo-4-cyanobenzene or 1-iodonaphthalene was tested (entries 10 and 11, Table 3.7). These results confirmed that the monocarbonylation reaction is favored when electron-withdrawing groups are present in the substrate.

As the highest chemoselectivity was obtained when 1-iodo-4-methoxybenzene was used as substrate (entry 3, Table 3.7), various nucleophiles were tested using this substrate (Table 3.8). First, primary amines were examined. Under the same conditions ethylamine, *n*-propylamine and *n*-butylamine afforded excellent conversions (up to 99%) and excellent chemoselectivities towards the formation of corresponding α-ketoamide (up to 98%) (entries 1-3, Table 3.8). Unexpectedly, when the Pd/ligand ratio was increased to 2 the conversion decreased only slightly but the chemoselectivity remained excellent (entry 4, Table 3.8). However, when the less basic aniline was used, no reaction was observed (entry 5, Table 3.8), while the use of a chiral amine afforded low conversion (43%) but very high chemoselectivity (97%) (entry 6, Table 3.8).

When secondary amines were examined, lower chemoselectivities were obtained. Diethylamine produced the α-ketoamide with 56% of selectivity, however the more steric hindered diisopropylamine did not react under the same conditions (entry 7 *vs*. 8, Table 3.8). Cyclic secondary amines such as

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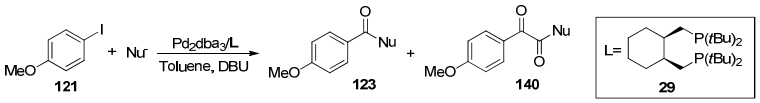
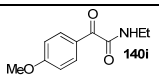
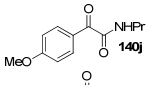
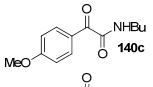
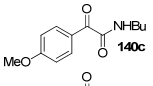
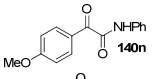
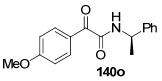
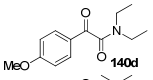
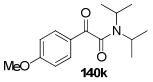
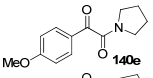
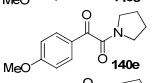
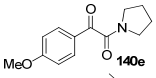
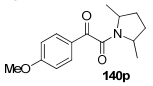
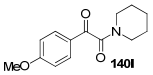
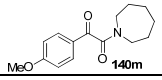
Table 3.8. Pd-catalysed double-carbonylation of 1-iodo-4-methoxybenzene with different nucleophiles.



Entry	Nucleophile (mmol)	Product	Conv.[c] (%)	Selec.[c] 123/140 (%)
1	 (1.2)	 **140i**	91	10/90
2	 (1.2)	 **140j**	78	12/88
3	 (1.2)	 **140c**	99	2/98
4[b]	 (1.2)	 **140c**	87	2/98
5	 (1.2)	 **140n**	0	-
6	 (1.2)	 **140o**	43	3/97
7	 (1.2)	 **140d**	62	44/56
8	 (1.2)	 **140k**	-	-
9	 (1.2)	 **140e**	99	28/72
10	 (2.0)	 **140e**	99	60/40
11	 (2.5)	 **140e**	99	65/35
12	 (1.2)	 **140p**	0	-
13	 (1.2)	 **140l**	99	45/55
14	 (1.2)	 **140m**	99	30/70

[a]*Reaction conditions*: Pd_2dba_3 (0.005 mmol), ligand (0.011 mmol), 1-iodo-4-methoxybenzene (0.5 mmol), DBU (1 mmol), *n*-butylamine (1.2 mmol), toluene (5 mL), CO (1 bar), 14 hours. [b]Pd/L ratio = 2. [c]Determined by ^{1}H-NMR and GC-MS.

pyrrolidine were tested under standard conditions (entry 9) and excellent conversion (99%) and high chemoselectivity (72%) were obtained.

The concentration of amine was then increased (entries 10 and 11, Table 3.8) and full conversions were obtained but the chemoselectivity was negatively affected, progressively favoring the formation of the amide. Entry 12 shows the result obtained when 2,5-dimethylpyrrolidine was used as substrate. Under the optimized conditions, no reaction was observed, probably due to the steric hindrance of this nucleophile. Using piperidine or azepane (entries 13 and 14, Table 3.8) excellent conversions were achieved together with moderate to high chemoselectivities (55-70 %).

To summarize, the Pd-catalysed double-carbonylation of aryl iodides under mild conditions (1 bar CO) was carried out using the Pd/**6,26-29** systems and DBU as a base with high conversion (up to 99%) and selectivity (up to 99%) towards α-ketoamides.

The following trends/observations drawn from this study are listed below:

- *Nature of the base*: very strong effect on the chemoselectivity since only DBU afforded high selectivity to the α-ketoamide products.
- *Palladium precursor*: effect on the chemoselectivity with Pd_2dba_3 being the most appropriate precursor for the double-carbonylation process.
- *Phosphine ligands***:** strong effect on the chemoselectivity since in the presence of DBU, the less coordinating ligands were the most appropriate to produce α-ketoamides.
- *Pd/L ratio:* ratios Pd/L > 1 (more metal than ligand) favor the double-carbonylation reaction.
- *Solvent*: apolar solvents favour the α-ketoamide products and toluene was the most appropriate under the conditions used in this study.
- *Concentration of the catalytic mixture*: high dilution favours the double-carbonylation process.
- *Substituents at the aryl iodide substrate*:
    - *Electronic effect*: electron-donating groups at the aryl ring favor the double-carbonylation reaction while electron-withdrawing substituents favor the aminocarbonylation.

- *Steric effect*: the presence of bulky substituents favor the aminocarbonylation.

- *Nature of the amine nucleophile*:
  - *Nucleophilicity*: the less nucleophile primary amines affords high selectivity to α-ketoamides while secondary amines are less selective under the same conditions.
  - *Nucleophile concentration*: at higher amine concentration, the monocarbonylation reaction is favored.

3.2.3. Mechanistic studies of the Pd-catalysed carbonylation reactions using P,P ligands

In order to gain information into the mechanism of the Pd-catalysed carbonylation reaction of aryl iodides using Pd/**29** an NMR study was carried out.

First, the palladium precursor (Pd_2dba_3) was reacted with ligand **29** in toluene at room temperature for 20 minutes and then, a ^{31}P-$\{^1H\}$ NMR spectra was recorded at room temperature observing a singlet at 22.5 ppm, corresponding to the free phosphine. When the temperature was decreased to -90ºC, two singlets were detected at 24.2 and 22.1 ppm, corresponding to the two conformations of the free ligand (boat and chair) (See Chapter 2, Figure 2.3).

Then, carbon monoxide was bubbled into a solution containing (Pd_2dba_3) and **29** (Scheme 3.19a), observing that the color of solution changed from purple to dark green. The ^{31}P-$\{^1H\}$ NMR spectrum of this solution at room temperature showed two broad signals at 68.0 and 51.2 ppm. In addition, resonances corresponding to the oxidized ligand (64.3-62.8 ppm) were detected. However, when the temperature was decreased at -90ºC the broad signals resolved into two doublets at 74.2 and 50.4 ppm ($^2J_{P\text{-}P}$= 11.2Hz) (Figure 3.4a), that were attributed to palladium complex containing two conformationally inequivalent phosphorus atoms (See Chapter 2, Figure 2.3). The two signals corresponding to the free ligand were also detected.

When a ^{13}C-$\{^1H\}$ NMR spectrum was recorded at -60ºC, a broad signal at 195.3 ppm was observed. The broad signal was assigned to a palladium carbonyl diphosphine complex (**182**) according to previous reports (Scheme 3.19a).[33q]

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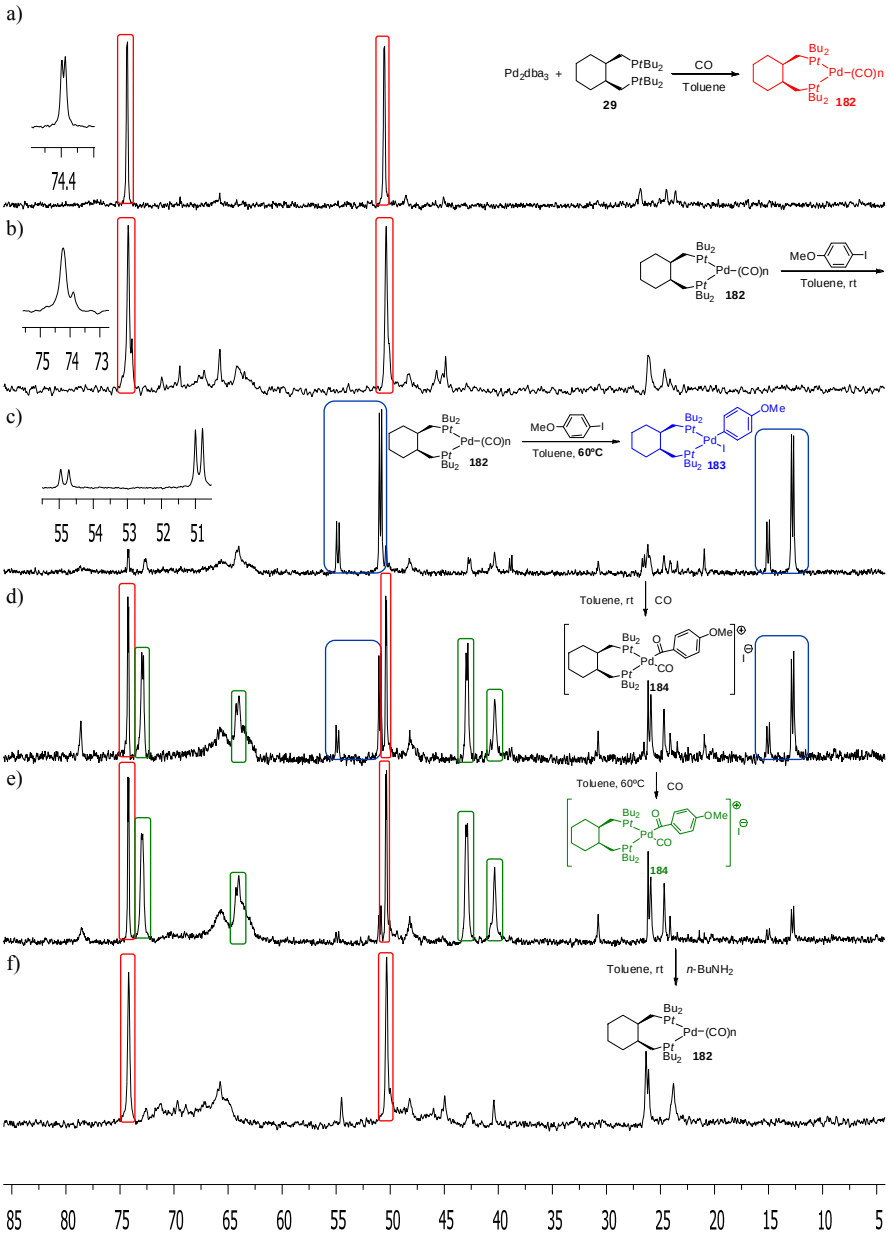
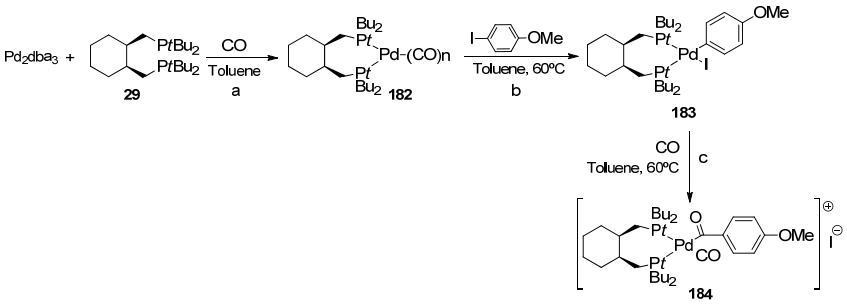


Figure 3.4. $^{31}P-\{^{1}H\}$ NMR spectra: a) of the Pd_2dba_3/**29** under 1 bar of CO in toluene at -90ºC. b) of the Pd_2dba_3/**29** under 1 bar of carbon monoxide plus addition of 1-iodo-4-methoxybenzene under nitrogen in toluene at -90ºC. c) of the Pd_2dba_3/**29** under 1 bar of carbon monoxide plus addition of 1-iodo-4-methoxybenzene under nitrogen in toluene at -90ºC after being heated for 1 h at 60ºC. d) The previous solution pressurized with 1 bar of CO at -90ºC. e) The previous solution pressurized with 1 bar of CO and heated at 60ºC for 15 minuts at -90ºC. f) Addition of *n*-butylamine to the previous solution at rt and acquired at -90ºC.

This experiment indicated that the presence of carbon monoxide favors the formation of the palladium complex **182**. In the absence of CO, no palladium/phosphine species were detected.

At this point, 20 equivalents of 1-iodo-4-methoxybenzene with respect to palladium were added, at room temperature and under nitrogen, to the solution mixture. The ^{31}P-{^{1}H} NMR spectra was recorded at low temperature (-90ºC) observing two broad signals at 74.3 and 50.6 ppm corresponding to **182** (Figure 3.4b), together with two new broad signals at similar chemical shift at 73.7 and 50.1 ppm (Figure 3.4b).



Scheme 3.19. Reaction carried out with Pd/**29**.

The solution was then heated for 1 hour at 60 ºC and again cooled to -90 ºC. The ^{31}P-{^{1}H} NMR spectra acquired at this temperature showed the complete disappearance of signals present in Figure 3.4b, while two new sets of two doublets at 54.8 and 15.0 ppm (^{2}J= 32.8 Hz) for the minor isomer and at 50.9 and 12.8 ppm (^{2}J= 32.8 Hz) for the major isomer (ratio 3.5:1), appeared (Figure 3.4c). These signals can be attributed to the boat and chair conformers of the cyclohexyl ring of the ligand in complex **183** (Scheme 3.19b).

These isomers could also be detected in the ^{1}H NMR spectrum by the presence in the aromatic region of two set of signals, at 8.18 and 6.46 ppm (^{3}J= 12.4Hz) for the major isomer and at 8.06 and 6.34 ppm (^{3}J= 12.4Hz) for the minor species. Additionally, in the ^{13}C-{^{1}H} NMR spectra recorded at -60ºC, in the high chemical shift region the four signals of quaternary aromatic carbons, also corresponding to two isomers, were detected at 164.2, 162.4, 161.8 and 161.1 ppm. No signals corresponding to species containing CO were detected.

Next, the solution was pressurized with 1 bar of carbon monoxide at room temperature. Immediately, a ^{31}P-{^{1}H} NMR spectrum was recorded at -90ºC and signals corresponding to species **182** (at 74.2 and 50.4 ppm, ^{2}J= 11.2 Hz) and **183** at 54.8 and 15.0 ppm (^{2}J= 32.8 Hz) and 50.9 and 12.8 ppm (^{2}J= 32.8 Hz) (ratio 3.5:1) were readily detected. Additionally, two new sets of doublets were detected. The first set of signals appeared at 72.9 and 42.8 ppm with a coupling constant of 26.4 Hz. The two others broad singlets appeared at 63.9 and 40.3 ppm (Figure 3.4d). When the solution was heated for 15 minutes at 60ºC, the signals corresponding to the complex **183** were not detected anymore (Figure 3.4e). A broad signal corresponding to the oxidation of the ligand at 65 ppm and one at 26 ppm were also present. The ^{1}H NMR spectrum showed two doublets at 7.91 and 6.33 ppm with a coupling constant of 13 Hz indicating the presence of a unique acyl species. Finally, ^{13}C-{^{1}H} NMR spectra showed two weak broad signals at 218 and 197 ppm, which is in agreement with the chemical shift of an acyl and terminal CO, respectively (Scheme 3.19c).[33q] In this context the two set of signals present in the ^{31}P-{^{1}H} NMR spectrum were attributed to the two conformers of carbonyl-acyl species **184**. The fact that when the solution containing **183** was pressurized with CO (1bar) species **182** was again observed suggests that the process between these two species is reversible.

Next, *n*-butylamine (20 eq) was added at room temperature to the solution which was immediately cooled down to -90ºC. The ^{31}P NMR of this solution showed the disappearance of all the signals except two doublets at 74.2 and 50.3, corresponding to the intermediate **182** (Figure 3.4f). No new palladium complexes were detected. The detection of **182** in the presence of all reagents used in catalytic reaction indicates that this species is the resting state of the catalytic cycle (Figure 3.4f).

Finally, a ^{1}H NMR spectrum was recorded at room temperature showed in the aromatic region, together with unreacted iodoarene, two doublets at 7.71 and 6.68 ppm (^{3}J= 8Hz) corresponding to the product **123c** resulting from the palladium-catalysed aminocarbonylation.

Aiming to know if oxidative addition was the rate determining step the solution was heated again at 60ºC for 30 additional minutes. The ^{31}P-{^{1}H} spectra recorded at -90ºC showed the presence of complexes **183** and **184**, but

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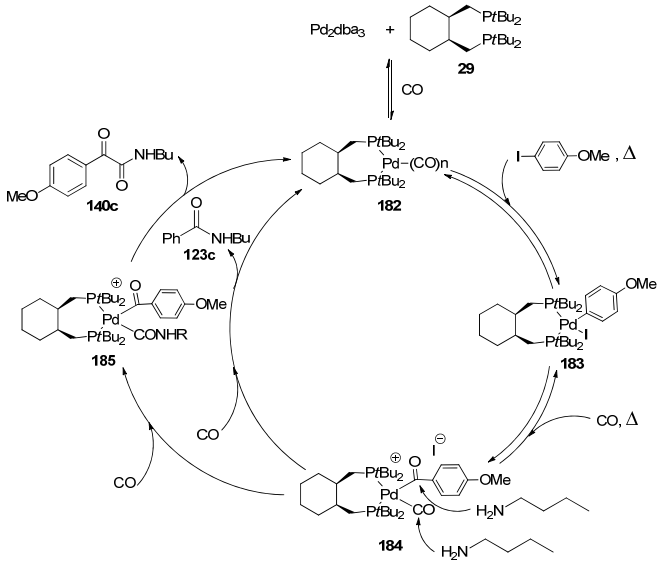
182 was still present, indicating that probably the oxidative addition is the rate determining step.

Based on these results, a possible mechanism for the Pd-catalysed carbonylation of aryl iodides with the catalytic system Pd/**29** is proposed (Scheme 3.20). The active catalytic species **182** is the resting state and undergoes oxidative addition affording the complex **183** at 60ºC. Then, carbon monoxide coordination and insertion into the Pd-Ar bond affords **184**, which can suffer the nucleophilic attack at the acyl group giving the aminocarbonylated product. If the nucleophilic attack occurs at the terminal CO ligand of **184**, the double-carbonylated product can be formed after a reductive elimination step.



Scheme 3.20. Proposed mechanism for the Pd-catalysed carbonylation of aryl iodides with the catalytic system Pd/**29**.

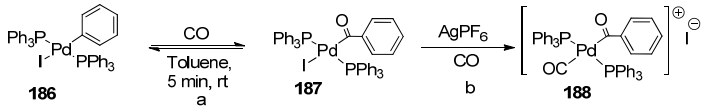
In the double-carbonylation process the presence of DBU was necessary to obtain the α-ketoamide product. An NMR study of the catalytic system Pd/**29** in the presence of DBU was carried out. Initially, the reaction was performed (ratio substrate:Pd = 20:1) in a 5mm NMR tube (Teflon cup), under the optimized catalytic conditions. Surprisingly, in the ^{31}P-{^{1}H} NMR spectrum only the signal corresponding to the free ligand was detected. Furthermore, the double-carbonylated product **140c** was detected in the ^{1}H NMR spectrum.

We decided to perform a step by step study, and since it was not possible to isolate the complex **183**, we decided to carry out the study with an analogous palladium complex bearing triphenylphosphine as ligand (**186**).

The palladium complex **186** was synthesized according to a literature procedure from $Pd(PPh_3)_4$ and iodobenzene in toluene at room temperature (Scheme 3.21a).[23] The ^{31}P-$\{^1H\}$ NMR spectra showed a singlet at 22.8 ppm which corresponds to a *trans* disposition of the two triphenylphosphine ligands as shown in Figure 3.5a.

Next, carbon monoxide was bubbled through the solution for 5 minutes, observing a change of color from transparent to orange. The ^{31}P-$\{^1H\}$ NMR spectrum recorded at room temperature showed a new signal at 18.9 ppm that was assigned to the complex **187** (Figure 3.5b, Scheme 3.21a).[33q] However, after a few minutes, the signal corresponding complex **186** progressively increased, indicating that the process is reversible (Figure 3.5c). When, the solution was again bubbled with carbon monoxide, the singlet corresponding to **187** was again detected (Figure 3.5d). Finally, under atmospheric carbon monoxide pressure, $AgPF_6$ was added to the solution at -60ºC, and was left to warm at room temperature (Scheme 3.21b).

Surprisingly, the ^{31}P-$\{^1H\}$ showed that the signal of the Pd-acyl complex **187** had disappeared and two new singlets at 33.1 and 23.9 ppm and a triplet signal at -11.2 (J= 970 Hz !!!) appeared (Figure 3.5e). The singlet at 23.9 ppm corresponded to **186** and the signal at 33.1 ppm was assigned to the cationic complex **188**, in agreement with the data reported for related complexes.[33q] The triplet observed at -11.2 ppm can be attributed to a "PF_2" fragment of an species that in the ^{19}F NMR appeared as a doublet at -77.9 ppm with a similar coupling constant (J= 968 Hz), and that was not fully characterized. Additionally, a signal at -138.6 ppm (heptuplete) attributed to PF_6^- counterion, and another at -143.8 ppm that that was not assigned, were detected. So, PF_6 degrades in the reaction medium affecting the stability of the catalyst.



Scheme 3.21. Reactivity of complex **186** with CO.

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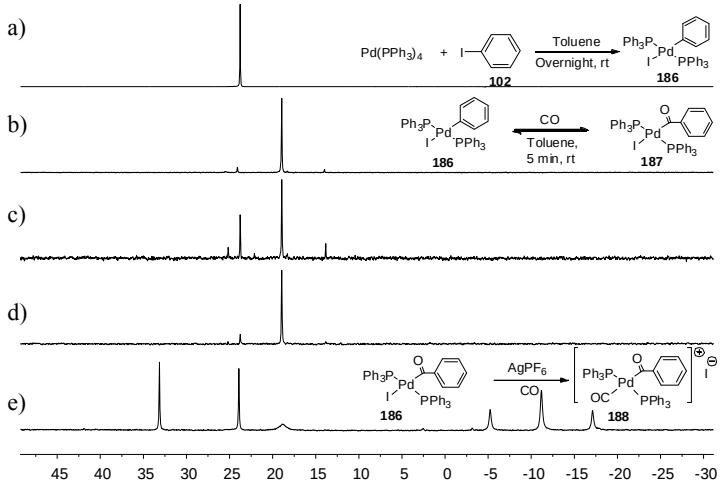

Figure 3.5. Reactivity of complex **186** with carbon monoxide.

Finally, the reactivity of complex **186** with DBU was examined by ^{31}P NMR (Scheme 3.22). The amount of DBU added to the solution was the same used under catalytic conditions. In the ^{31}P-{^{1}H} NMR spectrum, the fast disappearance of **186** was observed while two signals at 28.8 ($OPPh_3$) and -5.8 ppm (PPh_3) and three minor peaks at 31.8, 27.6 and 19.1 ppm, appeared (Figure 3.6). The signals of the minor peaks were not assigned but some of them could be attributed to complex **189** and its isomers *cis*/*trans*. Therefore, this experiment confirms that in the presence of DBU, the decoordination of the phosphine occurs, which is in agreement with the previous results obtained with the bidentate ligand (**29**). These experiments suggested that a phosphine free system where DBU acts as the real ligand could be active and selective to the double-carbonylation of aryl iodides.

Furthermore, when the reaction of $Pd(PPh_3)_4$ with 1-iodo-4-methoxybenzene was performed in the presence of 1 mmol of DBU under carbon monoxide (in the absence of butylamine), the NMR spectra were very complex and no clear information could be extrated; however, crystals suitable for X-ray diffraction were formed in the NMR tube and, the X-ray diffraction revealed the formation of product **193** (Figure 3.7), which contains a DBU fragment bonded to two acyl (-CO-*p*-anisole) units.

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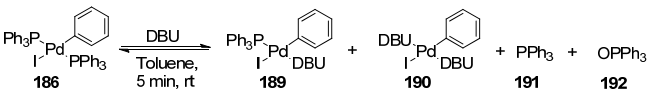

Scheme 3.22. Reactivity of complex **186** in the presence of DBU.

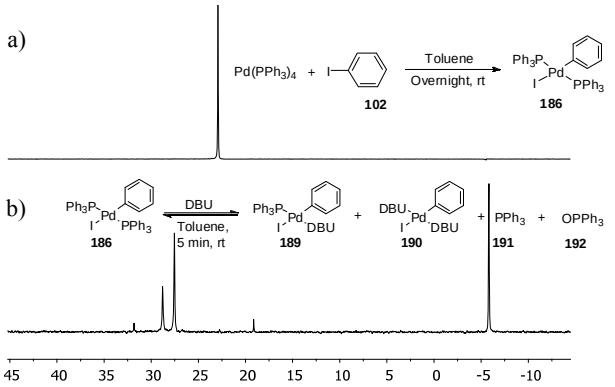

Figure 3.6. Reactivity of complex **186** in the presence of DBU.

The formation of the N-bonded acyl in product **193** can be explained by a nucleophilic attack of DBU at a Pd-acyl species and the release of the DBU-CO-*p*-anisole species. This nucleophilic attack can occur from a coordinated DBU molecule in an intramolecular manner or from a free DBU, thus giving rise to an external attack (Scheme 3.23).

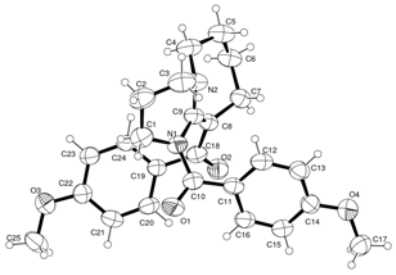

Figure 3.7. Molecular structure of product **193**. Ellipsoids drawn at 30% probability.

In the Pd-catalysed methoxycarbonylation reaction presented in the previous chapter it was already discussed the possible attack of MeOH at a Pd-acyl by an internal or external manner.[43] The DBU-CO-*p*-anisole product then reacts with a Pd(II) species via cyclometallation and reductive elimination, thus

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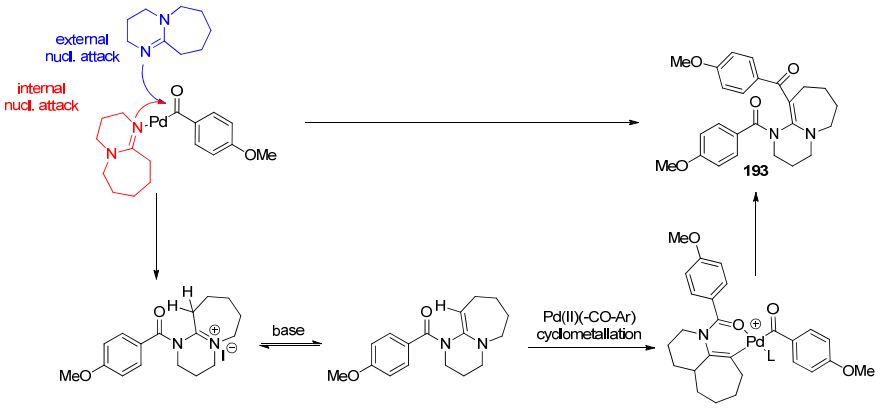
producing the product **193**.[44] The proposed mechanism is described in Scheme 3.23.

The formation of species **193** clearly indicates that DBU is also acting as a nucleophile under the reaction conditions and could therefore act in a similar way during the carbonylation process in the presence of the corresponding amine.

At that stage, we observed that DBU can have two additional roles apart of being a base such as ligand and nucleophile.



Scheme 3.23. Proposed mechanism for the formation of **193**.

The study of the reaction mechanism described here led to the identification of several Pd intermediates and a possible catalytic cycle is proposed.

One of the most striking observations is that in the presence of DBU, no phosphine containing palladium species (Pd/**29**) could be detected by NMR spectroscopy and only the free ligand was observed. These observations strongly indicated that the active Pd species under these conditions do not contain any phosphine ligand. This fact is in agreement with fact that when the ratio Pd/ligand increased the results were not practically affected (see entry 4, Table 3.8).

When the isolated complex **186** was reacted with DBU, free triphenylphosphine was also identified as major compound, which indicates that DBU is able to displace mono- and diphosphine ligands from the Pd

coordination sphere. Furthermore, it was observed that DBU can act as a nucleophile under the conditions studied.

3.2.4. Phosphine-free Pd-catalysed double-carbonylation of aryl iodides

From the previous mechanistic study, and from the analysis of parameters determining the selectivity in the synthesis of α-ketoamides it can be deduced that the phosphorus ligand it is not involved in the catalytic species. Furthermore, the fact that large excess of DBU, a coordinating base, is required respect to the catalyst (usually a DBU:substrate ratio of 2 :1) to achieve significant selectivity in the α-ketoamide prompted us to hypothesize that DBU was in fact the ligand, and consequently to investigate the role of this compound during the catalysis. Moreover, eventually for industrial applications, nitrogen donors are preferred to phosphorus based ligands due to their higher stability.[45]

Then, the influence of the nature of the base was investigated under conditions optimized in the previous section (toluene, 60 ºC, 14h) (entries 1-3, Table 3.9) using $Pd_2(dba)_3$ as catalyst precursor and in the absence of phosphine ligand. When DBU was used in a ratio 2:1 with respect to the substrate (entry 1), conversion was moderate but, interestingly, excellent selectivity to the double-carbonylation product **140c** was achieved. When other bases such as DMAP, DABCO were used under similar conditions, higher conversion was achieved in all cases but the monocarbonylation product was almost exclusively obtained. Such a striking effect is in agreement with previously reported results using phosphine containing catalysts.[38a,39] When the reaction was repeated in the presence of a smaller excess of DBU (entries 4-6), the conversion decreased dramatically and the selectivity to product **140c** was lowered to *ca*. 50%. It is noteworthy that in the absence of base, although the conversion was very low, the selectivity to **140c** remained at *ca*. 50 %, while the use of DABCO only yielded 3% of the double-carbonylation product (entries 7 *vs*. 3).

This indicated that under these conditions, the use of this latter base favoured the monocarbonylation process.

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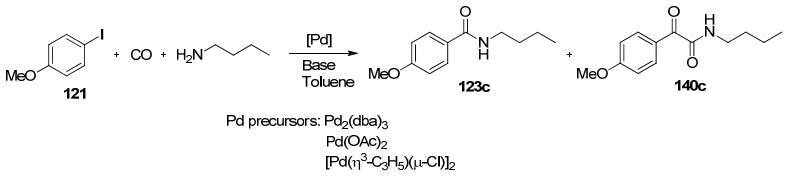
Table 3.9. Phosphine-free Pd-catalysed double-carbonylation of 1-iodo-4-methoxybenzene with *n*-butylamine: Optimization of reaction conditions.[a]



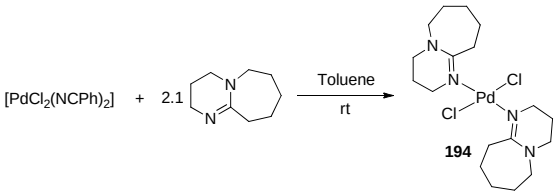
Entry	Pd precursor	T (ºC)	Base (mmol)	Conv.[b] (%)	Selec.[b] 123c/140c (%)
1	$Pd_2(dba)_3$	60	DBU (1)	56	<2/>98
2	$Pd_2(dba)_3$	60	DMAP (1)	19	89/11
3	$Pd_2(dba)_3$	60	DABCO (1)	92	97/3
4	$Pd_2(dba)_3$	60	DBU (0.05)	24	40/60
5	$Pd_2(dba)_3$	60	DBU (0.02)	21	50/50
6	$Pd_2(dba)_3$	60	DBU (0.01)	19	51/49
7	$Pd_2(dba)_3$	60	-	8	54/46
8	$Pd(OAc)_2$	60	DBU (1)	75	7/93
9	$[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$	60	DBU (1)	83	<5/>95
10	$PdCl_2(DBU)_2$ (**194**)	60	DBU (1)	56	8/92
11	$PdCl_2(DBU)_2$ (**194**)	60	-	17	18/82
12	$[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$	80	DBU (1)	>95	2/98
13[d]	$[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$	80	DBU (1)	91	2/98
14[c,d]	$[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$	80	DBU (1)	99	53/47
15	$PdCl_2(DBU)_2$ (**194**)	80	*t*BuOK (1)	23	72/28
16[e]	$PdCl_2(DBU)_2$ (**194**)	80	*t*BuOK (1)	91	10/90

[a]*Reaction conditions*: [Pd] (0.005 mmol), 1-iodo-4-methoxybenzene (0.5 mmol), base (1 mmol), butylamine (1.2 mmol), toluene (5mL), CO (1 bar), 14h. [b] Determined by ^{1}H-NMR and GC-MS. [c] + 0.01 mmol PPh_3.[d] 1h. [e] +5 equiv. respect to Pd of DBU.

The effect of the Pd precursor was then investigated (entries 1, 8-9). In all cases, the selectivity of the reaction remained unaltered, while the conversion

was found to increase up to 75 % and 83% when $Pd(OAc)_2$ and $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ were used.

To investigate the coordinating properties of DBU towards Pd, the complex $[PdCl_2(DBU)_2]$ (**194**) was synthesised from $[PdCl_2(NCPh)_2]$ and 2.1 equivalent of DBU in toluene and isolated in 71% yield as a yellow powder (Scheme 3.24). This species was fully characterised by NMR, MS and elemental analysis.



Scheme 3.24. Synthesis of complex **194**.

When **194** was used as precursor in the double-carbonylation of 1-iodo-4-methoxybenzene (entry 10), 56% conversion was achieved with excellent selectivity to **140c**. When the reaction was repeated using **194** in the absence of additional DBU (entry 11), the conversion decreased (17%) although the selectivity to **194** remained high. These results indicated that Pd species containing coordinated DBU are active in this catalytic process. Furthermore, the high selectivity to **194** in the absence of additional DBU suggests that the presence of DBU as ligand is responsible for the high selectivity to the double-carbonylation product. To improve the conversion the reaction conditions were optimized.

When the reaction was performed at 80 ºC using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as precursor and DBU as a base (entry 12), total conversion and selectivity to the product **140c** was achieved. When the reaction was stopped after 1h under the same conditions (entry 13), the conversion was found to only slightly decrease to 91%. The effect of additional phosphine was then investigated and when the experiment was repeated in the presence of 2 equivalents of PPh_3 per Pd (entry 14), the conversion remained very high but the selectivity decreased dramatically to 47 %. This result clearly indicated that the presence of PPh_3 strongly affects the selectivity of this process towards the production of the monocarbonylation product **123c**. Using $PdCl_2(DBU)_2$ as precursor with

*t*BuOK as a base, low conversion and chemoselectivity to **140c** were obtained (entry 15). However, when the reaction was repeated with a 5-fold excess of DBU with respect to the Pd precursor **194**, the conversion increased drastically to 91% while the selectivity remained excellent (entry 16). To the best of our knowledge, this is the first report of such selectivity in the absence of stoichiometric amounts of DBU (or DABCO). This demonstrated that in the presence of catalytic amounts of DBU, other bases such as *t*BuOK can be successfully used in this process (entry 16, Table 3.9). This indicated again that the presence of coordinated DBU is required to achieve high selectivity to the double-carbonylation product **140c**.

To enlarge the scope of the reaction, various aryl iodides were used as substrates with *n*-butylamine as nucleophile using the optimised conditions. The results are summarized in Table 3.10.

When *ortho*-, *meta*- and *para*-iodo anisoles were used as substrates (entries 1-3), high conversions were achieved in all cases (93-99%). However, clear differences in selectivity were observed. When *p*-iodo anisole was used, excellent selectivity to the double-carbonylation product was achieved (98%). However, when the *ortho*-substituted substrate was used, the selectivity was total to the monocarbonylation product, while with the *meta*-substituted substrate the selectivity to the double-carbonylation product was somewhat intermediate (65%).

These results clearly indicated that the selectivity of the reaction is strongly affected by the steric hindrance of the substrate.

When the *ortho*-, *para*-OMe disubstituted phenyl iodide was used as substrate (entry 4), the conversion was similar to those obtained with the monosubstituted substrates (95%) and the very low selectivity to the double-carbonylation product was similar to that of the *ortho*-iodo anisole. This result confirmed that the steric hindrance induced by the *ortho*-substituent controls the formation of the monocarbonylation product. When phenyl iodide was used as substrate (entry 5), 98 % of conversion and selectivity to **140c** (76%) were obtained at 60 ºC. When the reaction was carried out from alkyl-substituted phenyl iodides (entries 6-9), excellent conversions (94-99%) and selectivities to **140c** (90-99%) were obtained in all cases at 60 ºC. These

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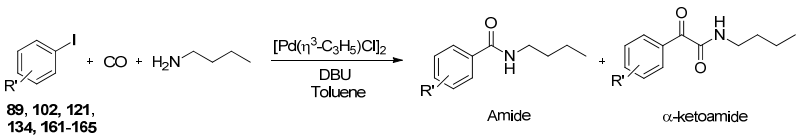
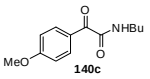
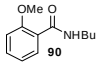
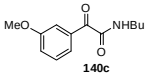
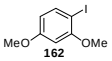
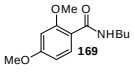
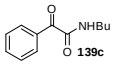
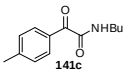
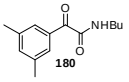
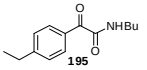
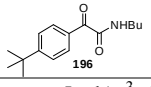
results indicated that the electronic properties of the substrate also strongly influence the chemoselectivity of the process. [38,39,41]

Table 3.10. Phosphine-free Pd-catalysed double-carbonylation of different aryl iodies with *n*-butylamine.[a]



Entry	Aryl iodide	Product	T (ºC)	Time (h)	Conv.[b] (%)	Selec.[b] Amide/α-ketoamide (%)
1	 121	 140c	80	1	99	2/98
2	 89	 90	80	1	93	98/2
3	 161	 140c	80	1	95	35/65
4	 162	 169	80	1	95	92/8
5	 102	 139c	60	14	98	24/76
6	 134	 141c	60	14	99	10/90
7	 163	 180	60	14	97	9/91
8	 164	 195	60	14	94	2/98
9	 165	 196	60	14	98	3/97

[a]*Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.005 mmol), aryl iodide (0.5 mmol), DBU (1 mmol), butylamine (1.2 mmol), toluene (5mL), CO (1 bar).[b] Determined by ^{1}H-NMR and GC-MS.

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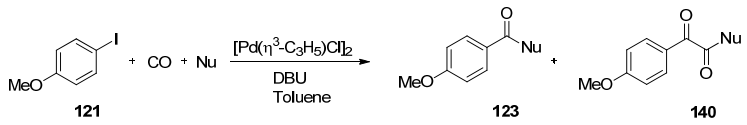
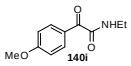
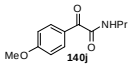
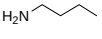
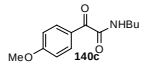
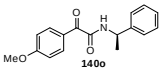
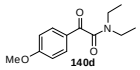
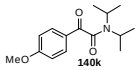
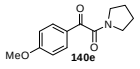
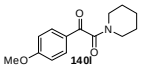
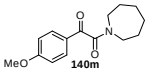
Next, the scope of the nucleophile was studied with primary and secondary amines. The results are listed in Table 3.11. When primary amines were used

Table 3.11. Phosphine-free Pd-catalysed double-carbonylation of 1-iodo-4-methoxybenzene with different nucleophiles.[a]



121 123 140

Entry	Nucleophile	Product	Temp. (ºC)	Time (h)	Conv.[b] (%)	Selec.[b] 123/140 (%)
1		 140i	80	1	90	2/98
2		 140j	80	1	93	6/94
3		 140c	80	1	99	2/98
4		 140o	60	14	99	1/99
5		 140d	60	14	82	4/96
6		 140k	60	14	-	-
7		 140e	60	14	93	11/89
8		 140l	60	14	96	8/92
9		 140m	60	14	87	5/95

[a]*Reaction conditions:* $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.005 mmol), 1-iodo-4-methoxybenzene (0.5 mmol), DBU (1 mmol), nucleophile (1.2 mmol), toluene (5mL), CO (1 bar).
[b] Determined by ^{1}H-NMR and GC-MS.

as nucleophiles (entries 1-4), conversions up to 99% and selectivities up to 99% to the products **140c, i-j** and **o** were obtained. In the case of (*R*)-methylbenzylamine (entry 4), the selectivity was improved when the reaction

was performed at 60 ºC. When secondary amines were used (entries 5-9), similar results were obtained with selectivities up to 96% to **140c** at 60 ºC, except in the case of the diisopropylamine for which no reaction product was detected. To the best of our knowledge, the double-carbonylation product has never been produced in this reaction in the presence of this amine as nucleophile and only the formation of the monocarbonylation product is reported in low yield.[33q,33o]

To summarize, the use of the first phosphine free catalyst for the double-carbonylation of aryl iodides was described and this new catalytic system was shown to be highly active (conv. up to 99%) and selective (up to 99%) to the α-ketoamide product. This catalyst was very efficient and highly selective for a wide range of aryl iodides and amine nucleophiles.

The following trends/observations drawn from this study are listed below:

- *Nature of the base*: strong effect on the chemoselectivity of the reaction since the desired product was formed in high yield only when DBU was used as base.
- *Palladium precursor*:
  - Effect on chemoselectivity with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ being the most appropriate under these conditions.
  - Noteworthy: when the complex $PdCl_2(DBU)_2$ was used as precursor, only catalytic amounts of DBU (5 equivalents DBU/Pd) were required and other bases such as *t*BuOK can be employed affording excellent chemoselectivity.
- *Phosphine ligand*: the presence of phosphine disfavours the formation of the α-ketoamides
- *Pd/DBU ratio*: higher Pd/DBU ratio produces a decrease of the chemoselectivity
- *Solvent*: apolar solvents favour de formation of α-ketoamide *vs* amide
- *Concentration of the catalytic mixture*: low concentration is required to achieve high chemoselectivity.
- *Substituents at the aryl iodide substrate*:
  - *Electronic effect*: electron-donating groups shift the chemoselectivity towards the double-carbonylation reaction

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while electron-withdrawing groups favors the formation of the amides.

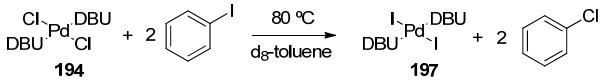
- *Steric effect*: the presence of bulky substituents favour the aminocarbonylation.

- *Nature of the amine nucleophile*:
  - *Nucleophilicity*: the less nucleophile primary amines affords high selectivity to α-ketoamides while secondary amines are less selective under the same conditions.
  - *Nucleophile concentration*: at higher amine concentration, the monocarbonylation reaction is favored.
- *Reaction temperature*: the selectivity of the reaction towards the double-carbonylation products can be increased by lower temperatures, indicating that the monocarbonylation reaction is kinetically favoured.

3.2.5. Mechanistic studies in phosphine free Pd-catalysed double-carbonylation of aryl iodides

First, a sample of **194** was dissolved in d_8-toluene and placed into a 5 mm NMR tube. At that point, 10 equivalents of phenyl iodide were added to the solution which was subsequently heated to 80 ºC and the reaction monitored by NMR spectroscopy. During this experiment, very little changes were observed by either ^{1}H or ^{13}C spectroscopy and no clear conclusions could be drawn.

However, small crystals suitable for X-ray crystallography were formed in the NMR tube on standing, and revealed that the iodide analogue of **194**, namely the species *trans*-$PdI_2(DBU)_2$ (**197**), was formed (Scheme 3.25). Phenyl chloride was also detected by GC as reaction product.



Scheme 3.25. Reactivity of complex **194** in the presence of phenyl iodide.

The formation of **197** can be explained by two successive oxidative addition of PhI and reductive elimination of PhCl. The oxidative addition of halide

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derivatives to Pd(II) were previously reported to yield Pd(IV) species under mild conditions.[46]

The molecular structure of the species **197** is shown in Figure 3.8. The complex presents a slightly distorted square planar geometry with characteristic bond lengths of Pd(II)-I containing species.[47] Full structural data for species **197** can be found in the experimental section. To the best of our knowledge, this is the first structurally characterised Pd complex containing coordinated DBU.

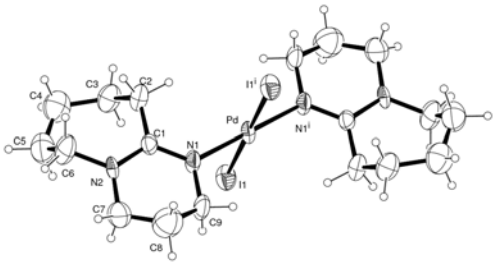

Figure 3.8. Molecular structure of complex **197**. Ellipsoids drawn at 30% probability.

Then, CO was bubbled into a solution of $PdCl_2(DBU)_2$ (**194**) for 5 minutes at room temperature, and the ^1H and ^{13}C-{^1H}NMR spectrums were recorded. The ^1H NMR spectra showed signals with a slight displacement on the chemical shift with regard to those of **194**. However, the ^{13}C-{^1H} NMR spectrum revealed new peaks at the aliphatic region and four new peaks at 228.0, 207.9, 164.5 and 158.3 ppm. The peak at 228.0 ppm can be assigned to a Pd-acyl species and the peak at 207.0 was assigned to a terminal Pd-CO. The peaks at 164.5 and 158.3 ppm were attributed to C=N bond in two different DBU units. With these data we proposed the structure **198**, shown in Scheme 3.26a, for the new species formed.

Next, the reaction of $PdCl_2(DBU)_2$ with 1-iodo-4-methoxybenzene under carbon monoxide pressure was studied. The ^1H NMR showed a complex spectrum on the aromatic region, where the substrate signals and other five compounds bearing an aryl group could be observed (Figure 3.9). Also, the ^{13}C-{^1H} NMR spectrum was acquired, observing that peaks from 177.4 to 161.1 ppm were lost. So, the reaction did not afford exclusively a complex as result of the oxidative addition, but other palladium complexes or organic compounds were also formed (Scheme 3.26b).

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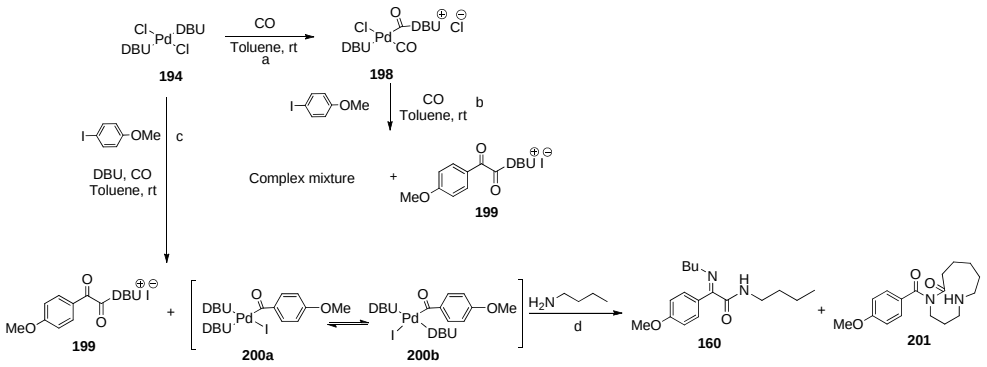


Scheme 3.26. Reactivity of complex **194** in carbon monoxide.

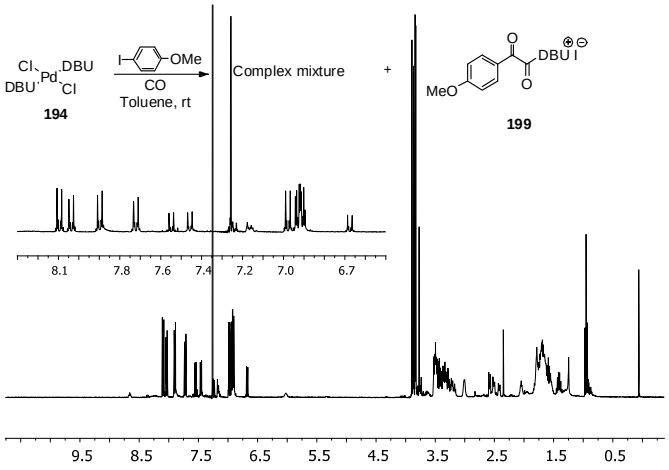


Figure 3.9. ^{1}H NMR spectrum of the reaction of $PdCl_2(DBU)_2$ with 1-iodo-4-methoxybenzene under atmospheric CO pressure.

As no clear conclusions could be extracted from these experiments, the reactivity of $PdCl_2(DBU)_2$ complex with 1-iodo-4-methoxybenzene and stoichiometric amount of DBU under ^{13}C-enriched carbon monoxide atmosphere, was examined (Scheme 3.26c). Interestingly, in the ^{13}C-{^{1}H} NMR spectrum was observed a new signal at 194.4 ppm, that can be assigned to a carbonyl group in the α-ketoamide compound, and that was attributed to **199**) (Figure 3.10). Furthermore, two peaks at the acyl region (226.7 and 226.1 ppm) were detected. By ^{1}H-^{13}C HMBC it was possible to assign these

two peaks to the isomers *cis*- and *trans*- because it was only observed a correlation peak with protons in the aromatic region of both acyl groups.

In order to confirm the structure of **199** an analogous α-ketoamide **203** containing a DBU fragment was synthesised by treating the keto-acid **202** with DBU in the presence of DCC (Scheme 3.27a). The ^{13}C-{^{1}H} NMR spectra of the isolated compound showed a signal at 194.9 ppm and another at 171.9 ppm assigned to the amide function, in concordance with the observed in the catalytic reaction. This result reveals that DBU also behaves as a nucleophile and attacks the Pd-CO terminal to triggering the double-carbonylation process and the formation of α-ketoamide **140c**.

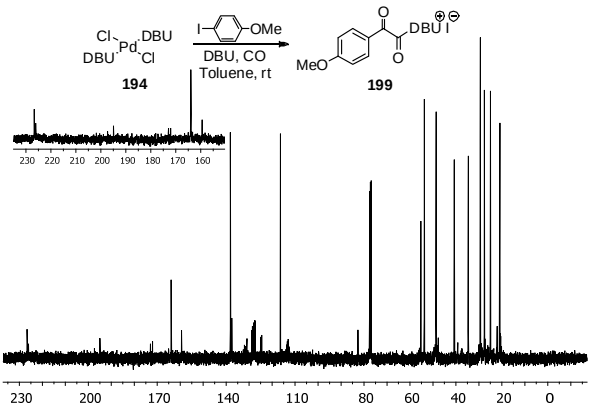
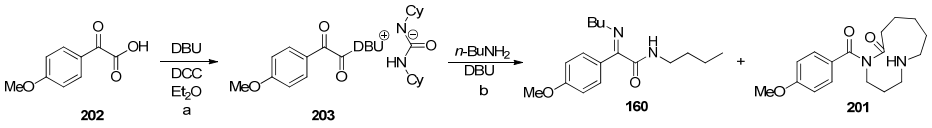


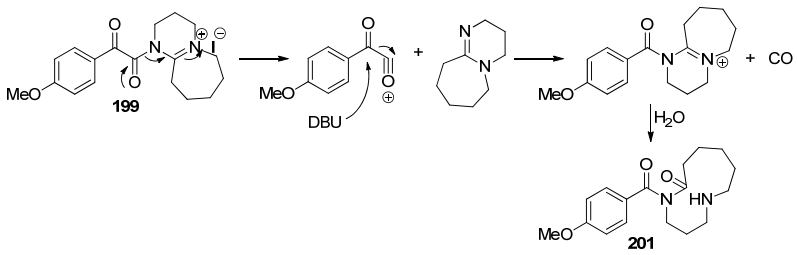
Figure 3.10. ^{13}C-{^{1}H} NMR spectrum of the reaction of $PdCl_2(DBU)_2$ with 1-iodo-4-methoxybenzene and DBU under atmospheric ^{13}CO pressure.



Scheme 3.27. Synthesis of compound **203** and its reactivity in front of *n*-butylamine.

In this context, the final α-ketoamide product could be formed by reaction of **199** with the amine present in the reaction medium, and consequently the amine would not take part of the catalytic cycle. To examine this hypothesis, to the previous solution containing **199**, and a mixture of the two complexes **200a** and **200b**, the *n*-butylamine was added at room temperature and then

heated at 60ºC overnight. Surprisingly, the expected product **140c** was not detected, and the imino amide **160**, that must be formed from **140c**, and the amide **201** (Scheme 3.26d), were instead formed. The formation of these compounds has already been observed by Skoda-Földes.[42] In order to confirm these results, the reactivity of the α-ketoamide **203** previously prepared,[48] in front of an amine was studied (Scheme 3.27b) by NMR spectroscopy and MS. The same compounds **160** and **201** were also detected under these conditions. Since neither **160** nor **201** were detected in the catalytic mixture, these results forced us to call into question the hypothesis that **199** was a precursor of the final α-ketoamide. The formation of **201** from **199** is more difficult to explain, and in Scheme 3.28 a mechanism for this process is suggested. It should involve a reversible reaction in which after the DBU release a decarbonylation induced by DBU takes place. The attack of water to the DBU-acyl intermediate will afford compound **201**, as it has been already reported.[42]



Scheme 3.28. Proposed mechanism for the decarbonylation process of **199** for giving **201**.

Based on these results, the mechanism described in Scheme 3.29 is proposed for the phosphine-free Pd-catalysed double-carbonylation of aryl iodide.

In this mechanism, the Pd precursor **194** is expected to be reduced to form a Pd(0) intermediate **204** under carbonylation conditions, which will react with an aryl iodide to form the oxidative addition product (**205**). After coordination and migratory insertion of CO Pd-acyl (**206**) is formed. This intermediate reacts with a second molecule of CO to form a cationic species containing a terminal CO and an acyl moiety with the iodide anion as counter-ion (**207**). The nucleophilic attack of amine at the terminal CO forms a Pd-acyl-amide species **208**. This step is thus crucial in order to achieve high selectivity to the double-carbonylation product. Alternatively DBU could attack the CO terminal in **207**, inter or intramolecularly, to generate species **209**. The

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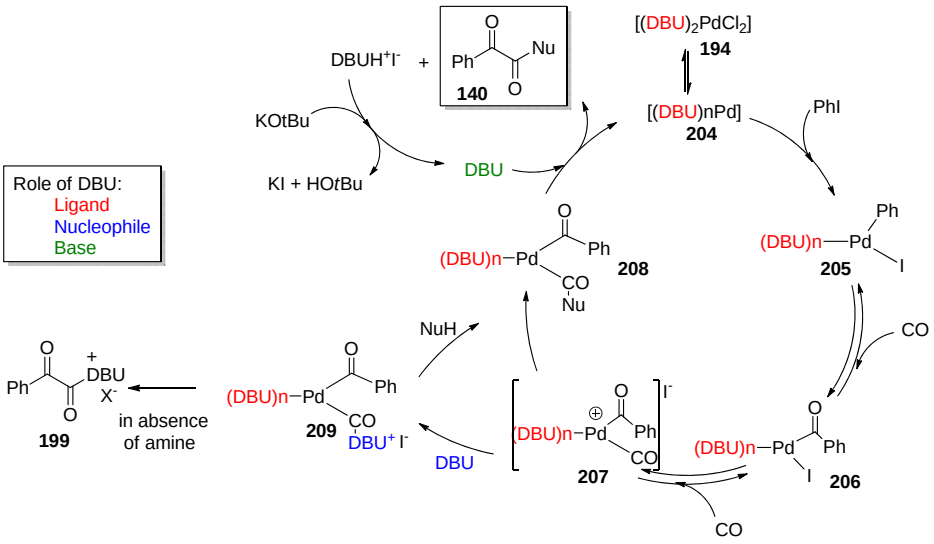
reductive elimination will afford the α-ketoamide **140c** and regenerate the active species (**204**) in the catalytic cycle. The reductive elimination in species **209** to afford **199** can take place in the absence of amine, but under normal catalytic conditions the attack of the amine affording **208** must be faster than the reductive elimination.



Scheme 3.29. Proposed mechanism for the phosphine-free Pd-catalysed double-carbonylation of aryl halide.

In summary, the success on the phosphine free Pd-catalysed double-carbonylation of aryl iodides lies in the role of DBU which is acting as a ligand, as a base, and probably as a nucleophile (or acyl transfer agent).

The evidence that we obtained from this study can be summarized as:

- *DBU as ligand:*
  - The phosphine free catalyst is highly selective to the double-carbonylation product.
  - The addition of phosphine to the reaction mixture produces a decrease in the chemoselectivity.
  - Isolation of $PdI_2(DBU)_2$ (**197**) and characterisation by X-ray diffraction.

- When NMR studies were performed using Pd/**29** or $PdIPhPPh_3$ (**186**) in the presence of DBU, only the presence of free ligand was detected.

- *DBU as nucleophile:*
  - Isolation of compound **193** and characterisation by X-ray diffraction.
  - Characterisation of compound **199** by NMR spectroscopy, resulting from the attack of DBU at the terminal Pd-CO.
  - The $PdCl_2(DBU)_2$ complex under 1 bar of carbon monoxide pressure produces the formation of a Pd-acyl complex containing the DBU fragment.
  - The presence of a catalytic amount (5 eq.) of DBU speeds up the double-carbonylation process and improves dramatically the chemoselectivity.

3.3. Experimental section

General Methods

All reactions were carried out under an argon atmosphere using Standard Schlenk techniques. Solvents were distilled and degassed prior to use. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini spectrometer at 300 and 400 MHz. Chemical shifts were reported relative to tetramethylsilane for ^{1}H and $^{13}C\{^{1}H\}$ as internal reference, H_3PO_4 85% for $^{31}P\{^{1}H\}$, and trichlorofluoromethane for $^{19}F\{^{1}H\}$ as external references. Elemental analyses were carried out on a Carlo Erba Microanalyser EA 1108. VG-Autospect equipment was used for FAB mass spectral analyses with 3-nitrobenzylalcohol as matrix. EI mass spectra were obtained on an HP 5989 A spectrometer at an ionizing voltage of 70eV. Conversion and chemoselectivity was measured by NMR spectrometry and GC-MS spectra. HP-FFAP Column of polyethylene glycol (30 m x 0.25 mm x 0.25 μm). Tª= 250 ºC injector. Flow 1.5ml/min. Initial Tª= 50ºC, for 3 min. 10ºC/min until 230ºC, for 15 min, 15ºC/min until 240ºC, for 40 min. Analysis time 76.67 min. m/z acquisition range: 43-600.

General procedure for Pd-catalysed aminocarbonylation of aryl iodides

A tube of multireactor was charged with the corresponding aryl iodide (0.5 mmol), Pd_2dba_3 (0.005 mmol), the bidentate ligand **29** (0.011 mmol) DBU (1 mmol) and the amine nucleophile (1.2 mmol) in dichloromethane (1 mL). Then, the tube was pressurized with 1 bar of carbon monoxide. The reaction was stirred at 45ºC for 14 hour. After the reaction, the mixture was filtered over Celite, and washed with water (3x5 mL). The organic phase was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The conversion and chemoselectivity were determined by GC-MS chromatography.

General procedure for Pd-catalysed double-carbonylation of aryl iodides

A tube of multireactor was charged with the corresponding aryl iodide (0.5 mmol), Pd_2dba_3 (0.005 mmol), the corresponding bidentate ligand (0.011mmol), DBU (1 mmol) and the amine nucleophile (1.2 mmol) in toluene (5 mL). Then, the tube was pressurized with 1 bar of carbon

monoxide. The reaction was stirred at 60ºC for 14 hour. After the reaction, the mixture was filtered over Celite, and washed with water (3x5 mL). The organic phase was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The conversion and chemoselectivity was determined by GC-MS chromatography.

General procedure for phosphine free Pd-catalysed double-carbonylation of aryl iodides

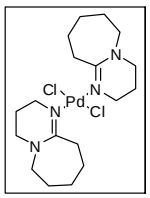
Primary amines:

A tube of multireactor was charged with the corresponding aryl iodide (0.5 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.005 mmol), DBU (1 mmol) and the primary amine desired (1.2 mmol) in toluene (5 mL). Then, the tube was pressurized with 1 bar of carbon monoxide. The reaction was stirred at 80ºC for 1 hour. After the reaction, the mixture was filtered over Celite, and washed with water (3x5 mL). The organic phase was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The conversion and chemoselectivity was determined by GC-MS chromatography.

Secondary amines:

A tube of multireactor was charged with the corresponding aryl iodide (0.5 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.005 mmol), DBU (1 mmol) and the secondary amine desired (1.2 mmol) in toluene (5 mL). Then, the tube was pressurized with 1 bar of carbon monoxide. The reaction was stirred at 60ºC for 14 hour. After the reaction, the mixture was filtered over Celite, and washed with water (3x5 mL). The organic phase was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The conversion and chemoselectivity was determined by GC-MS chromatography.

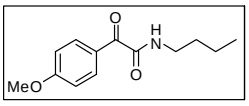
$PdCl_2(DBU)_2$ (194)



To a solution of $PdCl_2(PhCN)_2$ (300 mg, 0.79 mmol) in toluene was added 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (DBU) (1.65 mmol). The solution was stirred overnight at

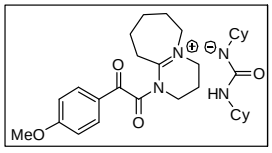
room temperature. A yellow precipitate was formed which was filtered and washed with fresh toluene. The complex **194** was obtained in 71% yield (269 mg). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 3.57-3.56 (m, 4H, CH_2), 3.46-3.31 (m, 4H, CH_2), 3.20-3.18 (m, 4H, CH_2), 3.25-3.12 (m, 4 H, CH_2), 1.90 (br s, 4 H, CH_2), 1.78 (m, 4H, CH_2), 1.64 (br s, 4H, CH_2), 1.51 (br s, 4H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 163.5 (C=N), 53.8 (CH_2), 47.8 (CH_2), 38.9 (CH_2), 38.1 (CH_2), 29.6 (CH_2), 27.9 (CH_2), 24.4 (CH_2), 22.3 (CH_2). **HRMS** (ESI-TOF): *m/z*=486.1617, calcd for $[(M\text{-}Cl)+CH_3CN]^+$: 486.1611. Anal. Calcd for $C_{18}H_{32}Cl_2N_4Pd$: C, 44.87; H, 6.69; Cl, 14.72; N, 11.63; Pd, 22.09. Found: C, 44.76; H, 7.01; N, 11.69.

N-butyl-2-(4-methoxyphenyl)-2-oxoacetamide (140c)



Following the general procedure for the synthesis of a-ketoamides using primary amines, compound **140c** was obtained in 87% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.40 (d, ^{3}J=9.2Hz, 2H, arom), 6.93 (d, ^{3}J=9.2Hz, 2H, arom), 3.87 (s, 3H, CH_3), 3.37 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 1.39 (m, 2H, CH_2), 0.94 (t, ^{3}J=7.2Hz, 3H, CH_3). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 186.1 (C=O), 164.6 (C, arom), 162.5 (C=O), 134.2 (CH, arom), 126.5 (C, arom), 113.9 (CH, arom), 56.8 (CH_3), 39.4 (CH_2), 31.5 (CH_2), 20.2 (CH_2), 13.9 (CH_3). **HRMS** (ESI-TOF): *m/z*=197.1290, calcd for $[M]^+$: 197.1287.

1-(2-(4-methoxyphenyl)-2-oxoacetyl)-2,3,4,6,7,8,9,10-octahydro-1H-pyrimido[1,2-a]azepin-5-ium cyclohexyl (cyclohexylcarbamoyl)amide (203)



50 mg of 2-(4-methoxyphenyl)-2-oxoacetic acid (0.278 mmol) were dissolved in 5 mL of diethylether. Then, 0.56 mmol of DBU and N,N'-dicyclohexylcarbodiimide (0.278 mmol) were added to the solution. The mixture was stirred for 2 hours and white salts precipitated immediately. The solution was filtered under nitrogen and the residue was washed with diethyl ether (3x10mL). The solvent was removed affording compound **203**. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.97 (d, ^{3}J=8.8Hz, 2H, arom), 6.84 (d, ^{3}J=8.8Hz, 2H, arom), 3.78 (s, 3H, CH_3), 3.40-3.32 (m, 6H, CH_2), 2.80 (br s, 2H, CH_2), 1.90 (m, 2H, CH_2), 1.65 (br s, 4H, CH_2), 1.57 (br s, 2H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 195.1

(C=O), 171.9 (C, arom), 165.7 (C=O), 163.2 (C=N), 132.1 (CH, arom), 127.5 (C, arom), 113.6 (CH, arom), 55.5 (CH_3), 54.2 (CH_2), 48.6 (CH_2), 38.5 (CH_2), 32.5 (CH_2), 29.1 (CH_2), 27.0 (CH_2), 24.3 (CH_2), 19.8 (CH_2).

Table 3.12. Experimental X-ray diffraction parameters and crystal data for **193**.

Empirical formula	$C_{25}\ H_{28}\ N_2O_4$
Formula weight	420.49
Temperature (K)	293(2)
Wavelength (Å)	1.54180 A
Crystal system	Triclinic
space group	P -1
Unit cell dimensions (Å)	a = 8.9060(10), alpha = 87.91(2) deg. b = 8.9930(11), beta = 78.441(16) deg. c = 13.7280(15), gamma = 85.870(14) deg.
Unit cell volume ($Å^3$)	1074.1(2)
Z, Calculated density (Mg/m^3)	2, 1.300
Absorption coefficient (mm^{-1})	0.713
F(000)	448
Theta range for data collection	3.29 to 61.09 deg.
Limiting indices	-9<=h<=9, -9<=k<=9, -15<=l<=15
Reflections collected / unique	12765 / 3165 [R(int) = 0.0625]
Completeness to theta = 61.22	96.2 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3165 / 0 / 282
Goodness-of-fit on F^2	0.960
Final R indices [I>2sigma(I)]	R_1 = 0.0563, wR_2 = 0.1400
R indices (all data)	R_1 = 0.0845, wR_2 = 0.1592
Largest diff. peak and hole ($e/Å^3$)	0.221 and -0.146

Table 3.13. Selected bond lengths and angles for crystal structure of compound **193**.

Bond lengths	
C(1)-N(1)	1.466(4)
C(3)-N(2)	1.471(4)
C(4)-N(2)	1.458(4)
C(9)-N(2)	1.376(4)
C(9)-N(1)	1.407(3)
C(10)-O(1)	1.227(3)
C(10)-N(1)	1.402(4)

C(14)-O(4)	1.345(4)
C(17)-O(4)	1.433(4)
C(18)-O(2)	1.229(4)
C(22)-O(3)	1.365(4)
C(25)-O(3)	1.415(4)

Bond angles	
N(1)-C(1)-C(2)	110.8(3)
N(2)-C(3)-C(2)	108.9(3)
N(2)-C(4)-C(5)	116.7(3)
C(8)-C(9)-N(2)	124.7(3)
C(8)-C(9)-N(1)	122.3(3)
N(2)-C(9)-N(1)	112.9(3)
O(1)-C(10)-N(1)	118.8(3)
O(1)-C(10)-C(11)	121.7(3)
N(1)-C(10)-C(11)	119.2(3)
O(4)-C(14)-C(13)	116.2(3)
O(4)-C(14)-C(15)	125.0(4)
O(2)-C(18)-C(8)	122.2(3)
O(2)-C(18)-C(19)	117.2(3)
O(3)-C(22)-C(23)	116.6(3)
O(3)-C(22)-C(21)	124.1(3)
C(10)-N(1)-C(9)	122.8(3)
C(10)-N(1)-C(1)	118.3(3)
C(9)-N(1)-C(1)	118.9(3)
C(9)-N(2)-C(4)	118.6(3)
C(9)-N(2)-C(3)	116.1(3)
C(4)-N(2)-C(3)	116.6(3)
C(22)-O(3)-C(25)	118.6(3)
C(14)-O(4)-C(17)	118.2(3)

Table 3.14. Experimental X-ray diffraction parameters and crystal data for **197**.

Empirical formula	$C_{18}H_{32}I_2N_4Pd$
Formula weight	664.68
Temperature (K)	293(2)
Wavelength (Å)	1.54180 A
Crystal system	Monoclinic
space group	P 21/c
Unit cell dimensions (Å)	a = 7.1690(9), alpha = 87.91(2) deg. b = 11.1380(11), beta = 78.441(16) deg.

	c = 14.9310(12), gamma = 85.870(14) deg.
Unit cell volume ($Å^3$)	1172.3(2)
Z, Calculated density (Mg/m^3)	2, 1.883
Absorption coefficient (mm^{-1})	27.115
F(000)	640
Theta range for data collection	4.99 to 63.33 deg.
Limiting indices	-8<=h<=8, -12<=k<=12, -17<=l<=17
Reflections collected / unique	1745 / 2044 [R(int) = 0.0000]
Completeness to theta = 61.22	96.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3165 / 0 / 282
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R_1 = 0.0768, wR_2 = 0.2125
R indices (all data)	R_1 = 0.0923, $_{wR2}$ = 0.23202
Largest diff. peak and hole ($e/Å^3$)	0.978 and -1.298

Table 3.15. Selected bond lengths and angles for crystal structure of compound **197**.

Bond lengths	
Pd-N(1)#1	2.004(9)
Pd-N(1)	2.004(9)
Pd-I(1)	2.6077(10)
Pd-I(1)#1	2.6077(10)
N(1)-C(1)	1.318(14)
N(1)-C(9)	1.455(18)
N(2)-C(1)	1.374(15)
N(2)-C(6)	1.429(19)
N(2)-C(7)	1.45(2)
C(1)-C(2)	1.47(2)
C(2)-C(3)	1.50(2)
C(3)-C(4)	1.51(2)
C(4)-C(5)	1.42(3)
C(5)-C(6)	1.56(3)
C(7)-C(8)	1.45(3)
C(8)-C(9)	1.46(3)

Bond angles	
N(1)#1-Pd-N(1)	180.0(6)
N(1)#1-Pd-I(1)	89.3(3)
N(1)-Pd-I(1)	90.7(3)
N(1)#1-Pd-I(1)#1	90.7(3)
N(1)-Pd-I(1)#1	89.3(3)
I(1)-Pd-I(1)#1	180.0
C(1)-N(1)-C(9)	118.1(10)
C(1)-N(1)-Pd	126.7(9)
C(9)-N(1)-Pd	115.1(7)
C(1)-N(2)-C(6)	120.6(13)
C(1)-N(2)-C(7)	120.1(11)
C(6)-N(2)-C(7)	118.8(13)
N(1)-C(1)-N(2)	123.3(11)
N(1)-C(1)-C(2)	119.8(11)
N(2)-C(1)-C(2)	116.9(11)
C(1)-C(2)-C(3)	115.7(14)
C(2)-C(3)-C(4)	115.8(16)
C(5)-C(4)-C(3)	118(2)
C(4)-C(5)-C(6)	110.3(18)
N(2)-C(6)-C(5)	116.2(15)
N(2)-C(7)-C(8)	112.8(16)
C(7)-C(8)-C(9)	112(2)
N(1)-C(9)-C(8)	116.1(14)

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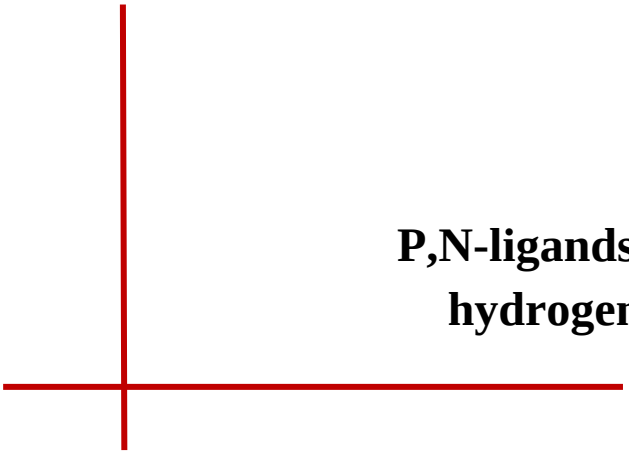

Chapter ***4***
P,N-ligands in Ir-catalysed hydrogenation reactions

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LIGAND DESIGN FOR PALLADIUM AND IRIDIUM SELECTIVE CATALYSTS
Verónica de la Fuente Molina
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4.1. Introduction

Ligands containing a P donor atom associated with a N, O or S moiety are of increasing interest as they can act as hemilabile ligands.[1,2] Transition metal complexes bearing chiral bidentate ligands containing two distinct coordinating atoms can induce enantioselective processes.[1,2]

Ligands containing the oxazoline moiety (**210**-**215**) have been widely explored and successfully used in asymmetric reactions (Figure 4.1), such as enantioselective copper and ruthenium cyclopropanation,[3] iron, magnesium and copper catalysed Diels Alder,[4] rhodium catalysed hydrosilylation,[5] iridium catalysed hydrogenation[6] and palladium catalysed allylic substitution.[7] More recently, ligands containing an imidazoline moiety (**216**-**218**) (Figure 4.1) have been used in palladium catalysed copolymerisation processes,[8] ruthenium Diels Alder reaction,[9] iridium catalysed enantioselective hydrogenation of prochiral olefins[10] and imines[11] and enantioselective diethyl zinc additions,[12] affording promising results.

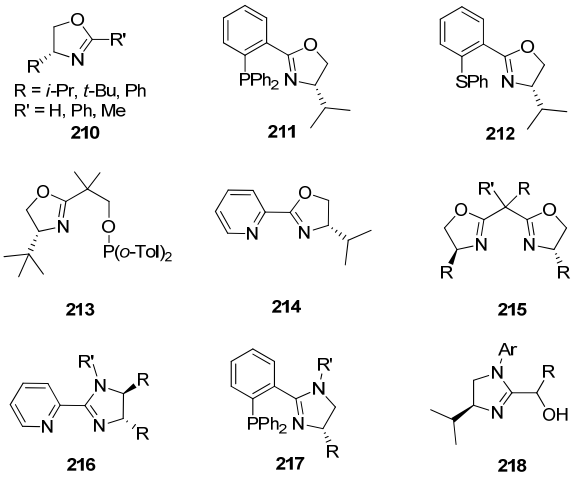

Figure 4.1. Oxazoline and imidazoline derivatives ligands tested.

Phosphino-oxazoline ligands have been extensively used in asymmetric hydrogenation reaction, achieving excellent enantioselectivities. For this reason, the replacement of the oxazoline ring by an imidazoline ring was considered and the similarities and differences are described below:

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Oxazoline and imidazoline ligands are structurally similar and show attractive features such as (Figure 4.2):

a) The versatility of the ligand design
b) The straightforward synthesis of ligands from readily available precursors
c) The modulation of the chiral centers

However, oxazoline and imidazoline ligands have some important differences:

a) The imidazoline ring is more basic[13]
b) The imidazoline allows the introduction of a variety of substituents into the aminic nitrogen, thus modifying its electronics and sterics properties

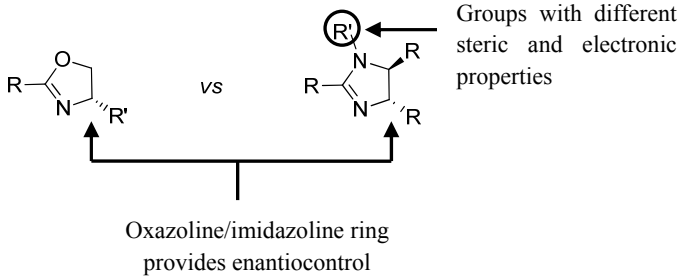

Figure 4.2. Oxazoline *versus* imidazoline ring.

The presence of an additional atom of nitrogen allows the possibility of modify the electronics and sterics properties of the ligand and furthermore, the anchoring into a polymer resin for instance by click chemistry.

In this context, the second part of this thesis focuses on the study of a new family of phosphino/phosphite-imidazoline ligands in the iridium catalysed asymmetric hydrogenation of unfunctionalised olefins and imines (Chapter 4) and the first application of this type of ligands in the palladium catalysed allylic substitution (Chapter 5).

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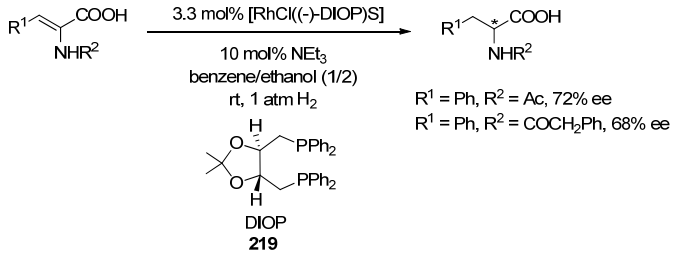
4.1.1. Ir-catalysed hydrogenation of unfunctionalised olefins

One of the most powerful catalytic methods for the preparation of enantiomerically pure compounds is the asymmetric hydrogenation.[14,15] In 1939, Iguchi reported the first rhodium catalysed hydrogenation reaction of a wide range of substrates using $RhCl_3$, $[Rh(NH_3)_5(H_2O)]Cl_3$ or $[RhCl_2(NH_3)_4]Cl$ as catalytic precursors.[16] Then, Wilkinson *et al.* carried out a study with the rhodium complex bearing triphenylphosphine as ligand $[RhCl(PPh_3)_3]$ which was a very efficient catalyst for the hydrogenation of alkenes under mild conditions.[17,18] This work was the starting poing of the development of chiral phosphine ligands which were applied in the asymmetric hydrogenation of alkenes, although low enantioselectivities were achieved (ee's up to 15%).[19,20,21,22,23] Kagan and Dang reported the first successful reduction of unsaturated acids and amino acids with enantioselectivities up to 72% with rhodium catalysts containing the bidentate ligand DIOP (**219**) (Scheme 4.1).

The first industrial application of homogeneous hydrogenation was developed by Knowles *et al.* using an air stable rhodium complex bearing CAMP (cyclohexyl(2-methoxyphenyl)(methyl)phosphine) (**220**) as ligand (Scheme 4.2). The hydrogenation of a prochiral enamide is the key step in the synthesis of L-DOPA, a drug used for the treatment of Parkinson disease. The monodentate ligand CAMP was rapidly replaced by the bidentate phosphine ligand DIPAMP (**221**) which gives the alkane with 95% of enantioselectivity (Scheme 4.2)[19,24,25]



Scheme 4.1. Asymmetric hydrogenation of dehydroamino acids with Rh/DIOP.

Several rhodium and ruthenium complexes have shown to be very efficient catalytic systems for the hydrogenation of substrates which contain a coordinating functional group adjacent to the C=C double bond such as

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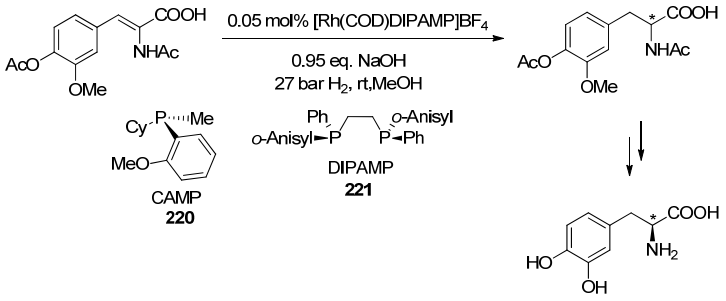
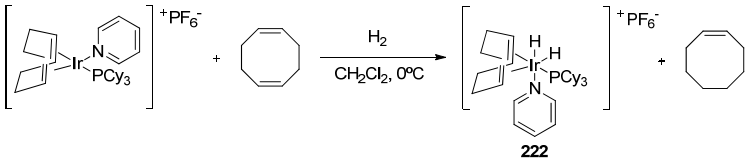
dehydroamino acids of allylic alcohols.[26] However, these catalysts are poor active and enantioselective when the substrates are not functionalised.[26] This limitation was overcome by Pfaltz's and co-workers who reported the asymmetric hydrogenation of unfunctionalised olefins with iridium complexes using chiral P,N ligands with excellent enantioselectivities.[17] These complexes were related to Crabtree's catalyst which is a very efficient catalytic system for the hydrogenation reaction of these substrates.[19]



Scheme 4.2. Synthesis of L-DOPA with Rh/DIPAMP.

4.1.1.1 Mechanism

The mechanism of olefin hydrogenation has been widely studied in the recent years employing the Crabtree's catalyst[27] and chiral analogues bearing P,N ligand such as phosphino-oxazoline ligands.[28] The first studies were carried out using the complex $[Ir(COD)(Py)(PCy_3)]PF_6$ in the hydrogenation of cyclooctadiene in dichloromethane.[29] The formation of the olefin dihydride complex **222** was observed by NMR (Scheme 4.3).[27,29] This intermediate was assumed to be the resting state of the catalytic cycle because the subsequent alkyl hydride species were not detected. The migratory insertion was therefore determined as the rate-limiting step.



Scheme 4.3. Olefin dihydride intermediate in the hydrogenation of cyclooctadiene with Crabtree's catalyst.

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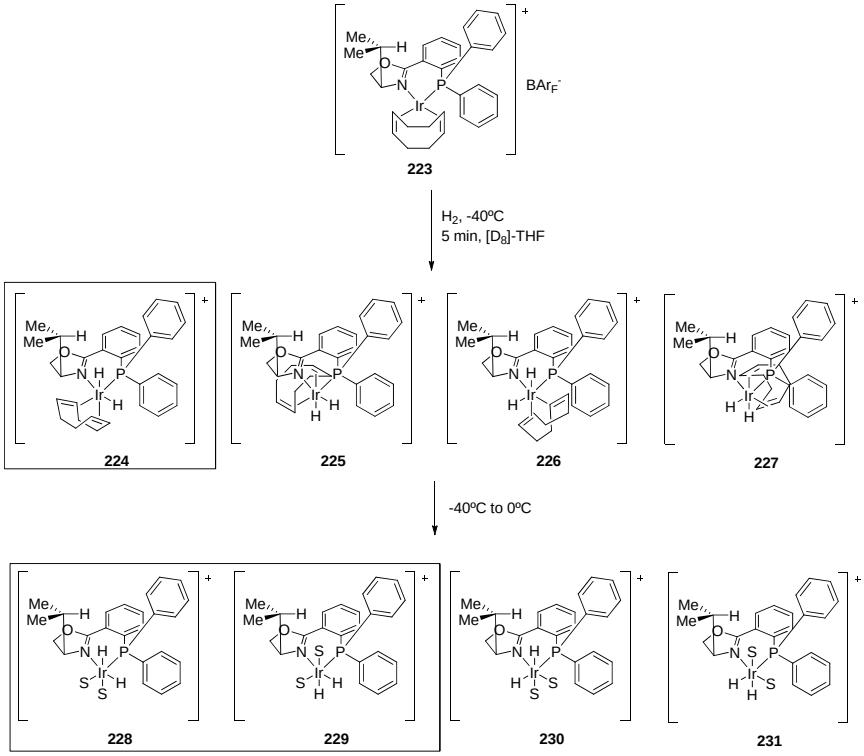
Later, Pfaltz and co-workers reported the reactivity of the [Ir(COD)(PHOX)]BAr_F complex **223** in the presence of hydrogen at -40ºC for 5 min in [D_8]-THF observing the formation of **224** as a main isomer.[31] The intermediate **224** was unambiguously identified. The formation of **224** instead of **225** is favoured due to the steric repulsion in complex **225** between the isopropyl group and the COD ligand. Therefore, the structures **226** and **227** are not formed because the formation of the Ir-H bond *trans* to the nitrogen atom is electronically favoured as it was previously reported by Crabtree.[30] When the sample was heated to 0ºC under hydrogen pressure two new iridium solvate hydride complexes (**228** and **229**) were detected together with the formation of cyclooctane (Scheme 4.4).[31]



Scheme 4.4. Stereoselective formation of olefin dihydrides and solvate dihydrides using a phosphino-oxazoline ligand.

Pfaltz *et al.* carried out a computational study to determine the reaction pathway in the hydrogenation of unfunctionalised olefins because of the difficulty of isolating the reactive intermediates. The results obtained were in

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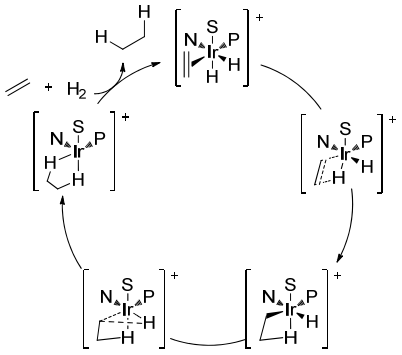
agreement with the experimental findings, in which the most stable isomers were complexes **228** and **229**.[32] Furthermore, Brandt also reported the same isomer ($[Ir(PN)(H_2)(CH_2Cl_2)_2]^+$ as the most stable species.[33]

These evidences allowed to establish the catalytic cycle involving Ir(I)-Ir(III) species as analogous to the mechanism for rhodium diphosphine-catalysed hydrogenation of olefins.[34] So, the $[Ir(PN)(H)_2(S)_2]^+$ cation is formed from the $[Ir(PN)(COD)]^+$ precatalyst and in the presence of the olefin, a solvent molecule is substituted by the substrate.

The olefin is located *trans* to the phosphorus atom and an hydride ligand migrates from the Ir(III) center to the olefin, giving and (alkyl)Ir(III) species. The reductive elimination of the alkyl group and a hydride ligand forms an Ir(I)(alkane) complex, and upon dissociation of the alkane, oxidative addition of H_2, and the coordination of another olefin regenerate the catalytic cycle (Scheme 4.5).[31]



Scheme 4.5. Catalytic cycle for olefin hydrogenation involving Ir(I)-Ir(III) intermediates.

Dieteker and Chen proposed a catalytic cycle involving pentacoordinated Ir(I)-Ir(III) intermediates without the coordination of solvent molecules. This mechanism was postulated based on gas-phase MS studies.[35]

In this context, Brandt and co-workers proposed a new pathway (Scheme 4.6A) involving Ir(III)-Ir(V) intermediates in which the complex $[IrL^*(H)_2(S)_2]^+$ (**228-231**) reacts with an olefin and a molecule of hydrogen, thus forming a dihydride/dihydrogen complex $[IrL^*(H)_2(H_2)(olefin)]^+$ (**232**).

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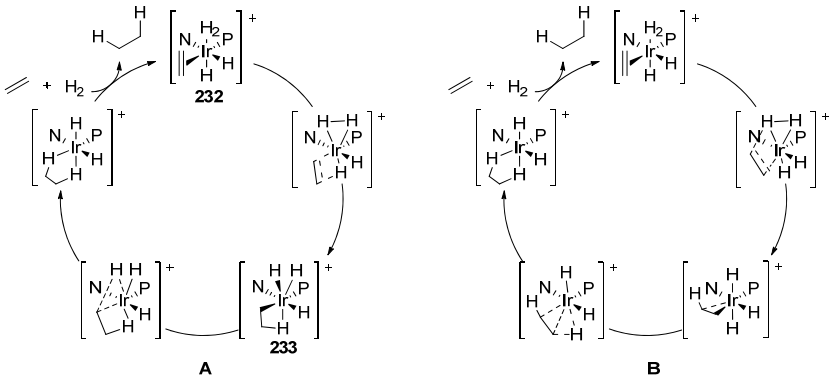
Then, the migratory insertion of one hydride into the olefin takes places and the cleavage of the H-H bond lead to the Ir(V) intermediate $[IrL^*(H)_3(alkyl)]^+$ (**233**). Subsequently, the reductive elimination of the alkyl group and one of the hydrides occurs. The regeneration of the catalytic cycle is produced by dissociation of the alkane and coordination of an olefin and H_2 (Scheme 4.6A).[33]



Scheme 4.6. Catalytic cycle for olefin hydrogenation involving Ir(III)-Ir(V) intermediates.

Finally, Burguess, Hall and co-workers proposed a mechanism for the asymmetric hydrogenation of olefins using a [Ir(oxazoline-NHC)(COD)]$^+$BAr$_F^-$ complex. Their computational study showed that the lowest-energy pathway was through Ir(III)-Ir(V) species. However, the mechanism involved for the first hydrogen transfer differs to the previous one because a metathesis reaction with coordinated H_2 is proposed instead of the migratory insertion. When the Ir(V) trihydride complex is formed a reductive elimination followed by a coordination of an olefin and H_2 produces the regeneration of the cycle (Scheme 4.6B).[36]

Recently, Andersson *et al.*[37] reported a computational study including the full system for the four catalytic cycles proposed. The results showed that the mechanism takes place through Ir(III) and Ir(V) intermediates and is consistent with the stereoselection observed experimentally. The most favoured pathway proceeds via migratory insertion instead of a metathesis reaction. However, as the energy difference between these two catalytic cycles is very small (4 Kcal/mol) both pathways could operate. Furthermore,

as they present the same cation, the major product predicted by both mechanisms is the same.

In the following sections some of the best results reported up to date in the field of the asymmetric hydrogenation of unfunctionalised olefins are described. The substrates are organised depending on their importance on this field.

4.1.1.2. Ir-catalysed hydrogenation of unfunctionalised olefins. Scope

This section describes the most relevant ligands used in the iridium catalysed hydrogenation of trisubstituted and 1,1-disubstituted olefins.[38] The main structure of the trisubstituted alkenes used in this process is summarized in Figure 4.3.

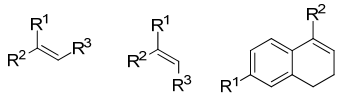


Figure 4.3. Trisubstituted alkenes used in Ir-catalysed hydrogenation reaction.

Cationic iridium complexes containing chiral ligand, diolefin (COD) and a counterion have been reported as most used catalyst. Originally, the counterion used was the hexafluorophosphate but several studies showed that the presence of this counterion leads to the deactivation of the catalysts *via* formation of hydride-bridged trinuclear complexes.[27] Some years later, Pfaltz *et al.* found how to avoid the deactivation of the catalyst by using the bulky tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F) as counterion. When the hydrogenation reaction of olefins was carried out with cationic iridium complexes having this bulky, apolar and extremely weakly coordinating anion, full conversions were obtained even at low catalyst loadings.[39,40]

In 1998, Pfaltz *et al.* reported the first enantioselective hydrogenation of unfunctionalised alkenes using a phosphino-oxazoline as ligand.[41] Complex **223** was active in hydrogenation of many trisubstituted aryl alkenes under 50 bar of hydrogen even at low catalyst loadings in a noncoordinating solvent such as CH_2Cl_2. The alkanes were produced in the hydrogenation of trisubstituted aryl alkenes with over 90% ee (Scheme 4.7).

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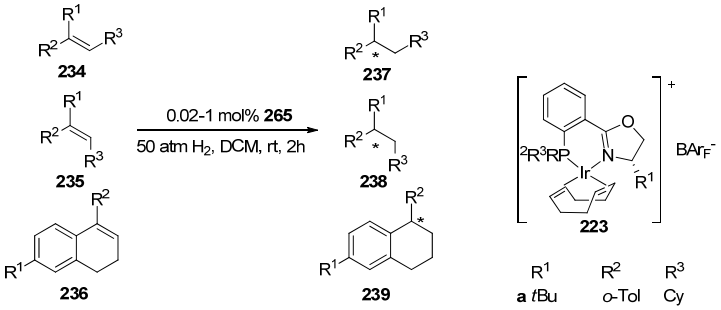

Substrate	R^1	R^2	R^3	Ee
234a	CH_3	Ph	Ph	97
234b	CH_3	CH_3	Ph	81
234c	CH_3	Ar	Ph	63
234d	CH_3	p-ClC_6H_5	Ph	72
234e	CH_3	CH_2OH	Ph	99
234f	CH_3	CH_2OAc	Ph	99
234g	CH_3	Ph	CO_2Et	96
235a	CH_3	Ar	CH_3	91
236a	OMe	CH_3	-	84

	R^1	R^2	R^3
a	*t*Bu	*o*-Tol	Cy
b	*t*Bu	Cy	Cy
c	*t*Bu	*t*Bu	*i*Pr
d	CH_2*t*Bu	Ph	Ph
e	*i*Pr	Ph	Ph

Scheme 4.7. Hydrogenation of trisubstituted alkenes using complex **223**.

Later, a set of variation of P,N ligands was reported where in all cases the P-center was a phosphine and the nitrogen group a oxazoline[42,43,44,45,46,47,48,49,50,51] imidazoline[52], pyridine,[53] quinoline[53] or sulfoximine[54] (Scheme 4.8).

Pfaltz and co-workers observed that the scope of trisubstituted alkenes hydrogenated by Ir(PHOX) complexes were limited. Therefore, they developed new oxazoline ligands replacing the phosphine moiety by a phosphinite unit. These new ligands were derived from serines and threonine (**254** and **255**) (Scheme 4.9)[55] and the corresponding iridium complexes allowed the enantioselective hydrogenation of challenging substrates such as (*E*)- and (*Z*)-2-aryl-2-butenes. Burgess and Richards also reported a phosphinite-ozaxoline ligand where the substituents at R^2 and R^3 were a proton. However, these modifications in the ligand backbone produced only moderate enantioselectivities in the Ir-hydrogenation of trisubstituted olefins.

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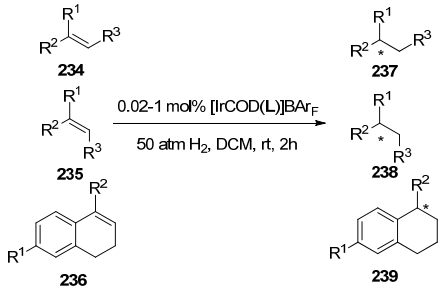
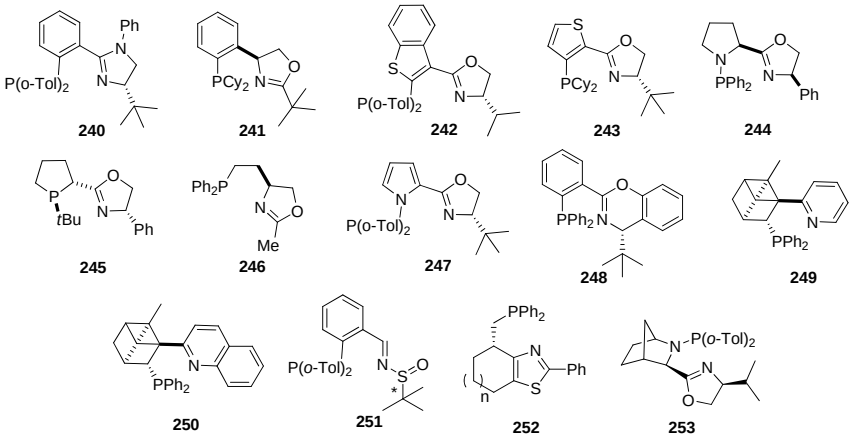


Substrate	R^1	R^2	R^3	Ee(**240**)	Ee(**241**)	Ee(**242**)	Ee(**243**)	Ee(**244**)
234a	CH_3	Ph	Ph	94	99	94	99	92
234b	CH_3	CH_3	Ph	90	-	-	-	76
234c	CH_3	Ar	Ph	88	-	-	-	56
234d	CH_3	p-ClC_6H_5	Ph	91	-	-	-	64
234e	CH_3	CH_2OH	Ph	-	97	-	-	94
234f	CH_3	CH_2OAc	Ph	-	-	-	-	-
234g	CH_3	Ph	CO_2Et	-	-	94	94	94
235a	CH_3	Ar	CH_3	-	-	-	-	-
236a	OMe	CH_3	-	-	-	-	-	88

Ee(**245**)	Ee(**246**)	Ee(**247**)	Ee(**248**)	Ee(**249**)	Ee(**250**)	Ee(**251**)	Ee(**252**)
95	95	99	78	95	94	94	94
-	93	75	37	-	-	-	-
-	75	70	-	-	-	-	-
-	-	92	-	-	-	-	-
91	-	-	90	95	-	-	-
90	-	-	73	-	-	-	-
-	67	-	77	69	70	70	70
-	72	-	-	-	-	-	-
-	-	92	72	58	65	65	65



Scheme 4.8. Asymmetric hydrogenation with phosphine-nitrogen ligands.

This new family of ligands showed to be efficient to induce enantioselectivity in the hydrogenation of cyclic substrates such as 6-methoxy-1-methyl-3,4-dihydronaphthalene (ee's up to 95%).

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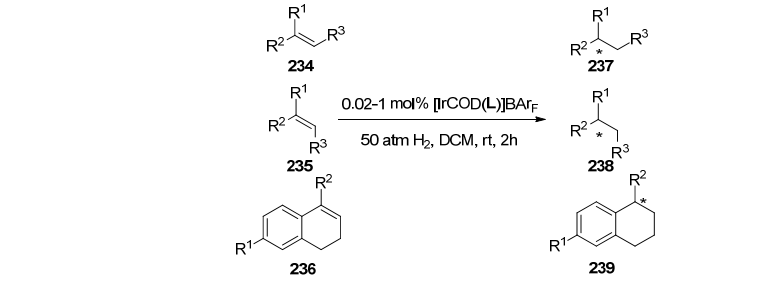
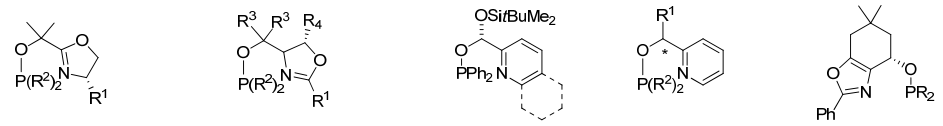
Scheme 4.9 summarizes the best results achieved for trisubstituted alkenes as substrate employing phosphinite-oxazoline ligands.[49,55a,56,57,58,59]



Substrate	R^1	R^2	R^3	Ee(**254**)	Ee(**255**)	Ee(**256**)	Ee(**257**)	Ee(**258**)
236a	CH_3	Ph	Ph	**a** 98	**a-c** 99	88	**a** 97	**a-c** 99
236b	CH_3	CH_3	Ph	**b** 91	**a-c, e** 99	-	**b** 87	**b** 96
236c	CH_3	Ar	Ph	**c** 89	**b** 92	-	**b** 90	-
236d	CH_3	p-ClC_6H_5	Ph	**a** 95	**d** 87	-	-	**b** 94
236e	CH_3	CH_2OH	Ph	-	-	-	-	-
236f	CH_3	CH_2OAc	Ph	-	-	-	-	-
236g	CH_3	Ph	CO_2Et	**a** 97	**a** 99	-	**c** 96	**b** 98
277a	CH_3	Ar	CH_3	-	-	-	-	**b** 99
236a	OMe	CH_3	-	**a** 94	**f** 96	-	**d** 95	**b** 93



254

	R^1	R^2
a	*t*Bu	*o*-Tol
b	*i*Pr	*o*-Tol
c	*i*Pr	Ph

255

a R^1= Ph, R^2= Ph, R^3= Bn, R^4= Me
b R^1=3,5-$Me_2C_6H_3$, R^2= Ph, R^3= Bn, R^4= Me
c R^1=3,5-*t*$Bu_2C_6H_3$, R^2= Ph, R^3= Bn, R^4= Me
d R^1= Ph, R^2= Ph, 2 x R^3= $(CH_2)_4$, R^4= H
e R^1= 3,5-$Me_2C_6H_3$, R^2= Ph, 2 x R^3= $(CH_2)_4$, R^4= H
f R^1= Ph, R^2= Cy, R^3= Bn, R^4=H

256

257

	R^1	R^2
a	*t*Bu	*t*Bu
b	Ph	Ph
c	*t*Bu	*o*-Tol
d	Ph	*t*Bu

258

	R^1
a	Ph
b	*o*-Tol
c	3,5-$Me_2C_6H_3$

Scheme 4.9. Phosphinite-oxazoline ligands used in unfunctionalised olefins.

Another type of P,N ligands are the phosphite-oxazoline which have been very successfully applied in the hydrogenation of unfunctionalised olefins by Diéguez and Andersson.[60] These ligands (**262** and **263**) afforded ee's up to 99% over a wide range of substrates (**234-236**).[60] The most important results obtained with these ligands are summarized in Scheme 4.10. [60,61,62]

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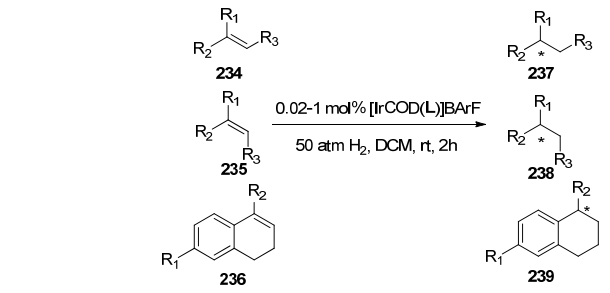
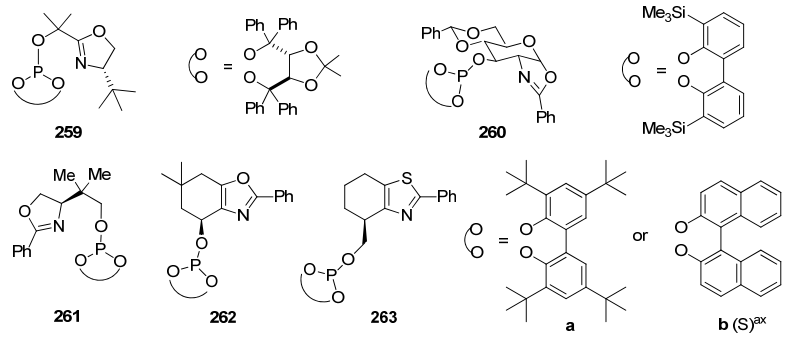


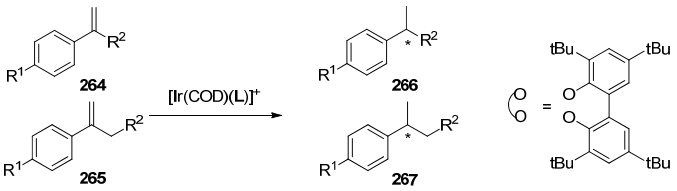
Substrate	R^1	R^2	R^3	Ee(**259**)	Ee(**260**)	Ee(**261**)	Ee(**262**/**263**)
234a	CH_3	Ph	Ph	-	>99	**b** 99	**263a** 98
234b	CH_3	CH_3	Ph	-	>99	**b** >99	**262b** 99
234c	CH_3	Ar	Ph	95	95	**a** 92	**263e** 90
234d	CH_3	*p*-ClC_6H_5	Ph	-	-	**b** 96	**263a** 99
234e	CH_3	CH_2OH	Ph	-	-	-	-
234f	CH_3	CH_2OAc	Ph	78	-	-	-
234g	CH_3	Ph	CO_2Et	-	92	**a** 93	**263a** 96
234h	CH_3	Ph	TMS	-	-	-	**263a** 98
234i	$P(O)Ph_2$	Ph	CH_3	-	-	-	**262a** 91
234j	$P(O)Ph_2$	Ph	COOEt	-	-	-	**262a** 92
235a	CH_3	Ar	CH_3	-	-	**a** 95	**263a** 95
236a	OMe	CH_3	-	-	99	**b** >99	**263a** 99



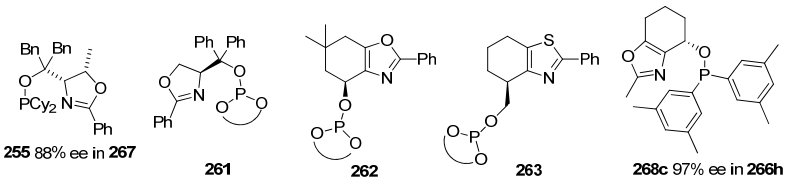
Scheme 4.10. Phosphite-oxazoline ligands used in trisubstituted olefins.

There are only a few iridium catalysts tested in the hydrogenation of these substrates, **264** and **265**. The most common substrates tested are 2-aryl-1-butenes, (**264**), and the allylic alcohol, (**265**) (Scheme 4.11). The conversions reported are excellent because they are less hindered than the trisubstituted one but the enantioselectivities vary from low to high depending on the catalyst. The benchmark substrate has a *p*-methoxy substituent in the aryl group and the enantioselectivitites achieved 97% with the catalyst bearing ligand **268**. The hydrogenation of this substrate was observed to be hydrogen pressure dependent and the optimal results were obtained at atmospheric

pressure and room temperature (Scheme 4.11). The most extensive work developed in this area was carried out by Diéguez and Andersson using the iridium catalytic systems (**261**-**263**).[63,64] Scheme 4.11 shows the results obtained in the hydrogenation of a wide range of 1,1-disubstituted olefins.



Substrate	R^1	R^2	Ee(**261**)	Ee(**262**/**263**)
264a	H	Et	99	**263** 94
264b	H	Bu	94	**263** 95
264c	H	2-Mepropyl	93	**263** 94
264d	H	2,2-diMepropyl	90	**263** 85
264e	H	i-Pr	97	**263** 95
264f	H	Cy	97	**263** 94
264g	H	$P(O)Ph_2$	-	**262** 82
264h	OMe	Et	>99	**263** 97
264i	CF_3	Et	96	**263** 94
264j	Py	Et	99	**263** 99
264k	Py	t-Bu	>99	**263** 96
265a	H	OH	95	**263** 87
265b	H	OAc	91	**263** 83
265c	H	TMS	96	**263** 93



Scheme 4.11. Asymmetric hydrogenation of 1,1-disubstituted alkenes with Ir/phosphite ligands.

4.1.2. Ir-catalysed asymmetric hydrogenation of imines

Chiral amines are important synthetic intermediates due to their application in the pharmaceutical, agrochemical and fine chemical industries.[65] One of the most useful method for their preparation is the asymmetric hydrogenation of C=N double bonds using chiral transition metal complexes as catalysts.

However, it is well known that the asymmetric hydrogenation of imines presents important drawbacks such as, for instance, the coordination of

substrate which can take place through both the nitrogen donor atom and the double bond, the *E/Z* isomeric mixture present in acyclic imines, and the poisoning effect of the resulting amines on the catalysis. Despite of these problems, recent progress in the field of asymmetric hydrogenation of imines led to the discovery of new catalytic systems providing high activities and enantioselectivities (in some cases up to 99%).[65] A relevant example is the iridium-ferrocenyl diphosphine complexes, which in the presence of both acetic acid and iodine constitute a stable and highly active catalytic system for imine hydrogenation. This is one of the most important homogeneous processes, being the key step in the industrial production of the chiral herbicide (*S*)-Metolachlor which is produced in more than 10000t per year with 79% of enantioselectivity.[65d]

The interest of both academic and industrial research groups in asymmetric hydrogenation of imines has increased over the last years, focusing on the discovery of catalytic systems active under low hydrogen pressures and providing high to excellent enantioselectivities. In parallel, the scope of this reaction has been extended, and more challenging C=N containing substrates were transformed using this asymmetric process.[65a]

This chapter describes the recent advances in the asymmetric hydrogenation of acyclic or cyclic imines.

4.1.2.1 Mechanism

Several mechanisms have been proposed for the hydrogenation of imines since slight modifications of the substrate, addition of additives, solvent used or acid medium produce remarkable effects on the catalytic activity.

One of the first mechanism proposed was based on a kinetic study of the hydrogenation of N-(β-naphthylmethylene) aniline using the iridium cationic complex $[IrCOD(PPh_3)_2]PF_6$ **269** as catalytic precursor in which reductive elimination was determined as the rate determining step.[66] As a conclusion of this study, the catalytic cycle shown in Scheme 4.12 was proposed. The catalytic precursor reacts with hydrogen to afford complex **270** which is the initial complex entering the catalytic cycle. Next, the coordination of the substrate occurs through the nitrogen atom (η^1) or the C=N (η^2) to form the species **271a-c**. Then, hydride transfer to the imine in **271a** generates the

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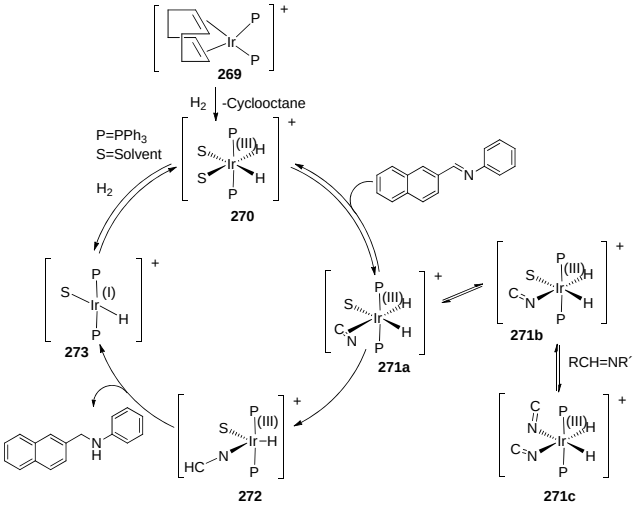
iridium-alkylaminium intermediate **272**, which undergoes reductive elimination to afford the desired amine and the intermediate **273**, from which the starting species **270** can be regenerated.



Scheme 4.12. Catalytic cycle for the hydrogenation of *N*-(β-naphthylmethylene)aniline proposed by Canudas.[66]

One of the main disadvantages of this reaction is the deactivation of the catalyst due to the formation of hydride-bridged structures analogue to those proposed by Crabtree.[67,68] In order to prevent the deactivation of the catalyst various additives, particularly iodine or iodides, were tested. However, the deactivation of the catalysts can also be due to the strong donor character of the NH group of the product.[69]

Zhang *et al.* reported a highly enantioselective catalytic system for the hydrogenation of hindered imines based on an Ir-ferrocene binaphane complex (Scheme 4.13).[70] The activity and enantioselectivity of the reaction were increased in the presence of I_2 as additive. The oxidative addition of iodine to the initial Ir(I) complex gives an Ir(III) Ir-f-binaphane-I_2 system (Scheme 4.13). Then, after hydrogen coordination the heterolytic cleavage of hydrogen favors the formation of Ir(III)-H intermediates related to those reported by Osborn, as well as the other intermediates in the catalytic cycle.[71]

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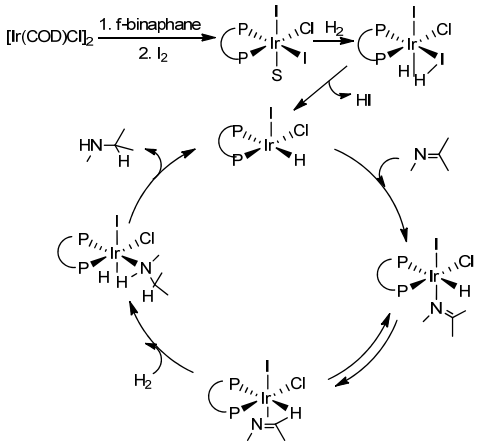
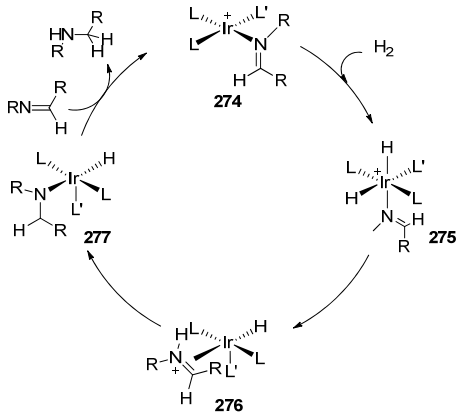


Scheme 4.13. Catalytic cycle for the hydrogenation imines catalysed by Ir(III)/I_2 complexes proposed by Zhang.[70]

Recently Oro and Sola reported a mechanistic study of imine hydrogenation using cationic and dinuclear iridium complexes observing that the key species is short-lived η^2-coordinated iminium species **276** which are hydrogenated very rapidly to produce the desired amine (Scheme 4.14).[72]



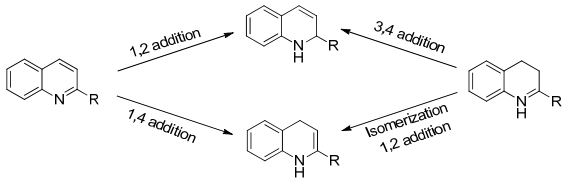
Scheme 4.14. Catalytic cycle for the hydrogenation of imines proposed by Oro.[73]

The catalytic cycle starts with an iridium cationic complex bearing two phosphine ligands, the imine and the other vacant site can be ocuppied by a solvent molecule or by an amine formed by previous imine hydrogenation or from the imine hydrolysis. The intermediate **275** is formed through the

oxidative addition of dihydrogen to the intermediate **274**. Then, a hydrogen atom transfer takes place on the nitrogen atom of the imine giving the formation of the η^2-iminium intermediate **276**. The second hydrogen atom transfer is an intrasphere nucleophilic attack on the carbon atom of the N^+=C double bond producing the pentacoordinated intermediate **277**. Finally, the regeneration of the catalytic cycle occurs through the release of the desired amine and the coordination of a new imine producing intermediate **274** (Scheme 4.14).[73]

The hydrogenation of 2 alkyl-quinoline derivatives was reported by Zhou and Li in 2009[74] who proposed two possible hydrogenation pathways depending of the 1,2 or 1,4 initial hydrogen addition (Scheme 4.15).

Their mechanistic studies indicated that hydrogenation of quinolines followed a "1,4 hydride addition, isomerization, 1,2 hydride addition" pathway. It was also proposed that the role of iodine was to oxidize the Ir(I) catalyst precursor to an Ir(III) complex, which in the presence of hydrogen affords a highly active Ir(III)-H species (Scheme 4.16). Subsequently, after quinoline coordination, 1,4 hydride transfer takes place to form an amino-iridium intermediate. Then, heterolytic cleavage of H_2 regenerates the active Ir(III) species and the product of 1,4 addition. This product undergoes an HI mediated isomerization, and coordination of the resulting enamine to the Ir(III) active species, followed by insertion and σ-bond metathesis yield the 1,2,3,4-tetrahydroquinoline.



Scheme 4.15. Possible pathways for the hydrogenation of quinolines.

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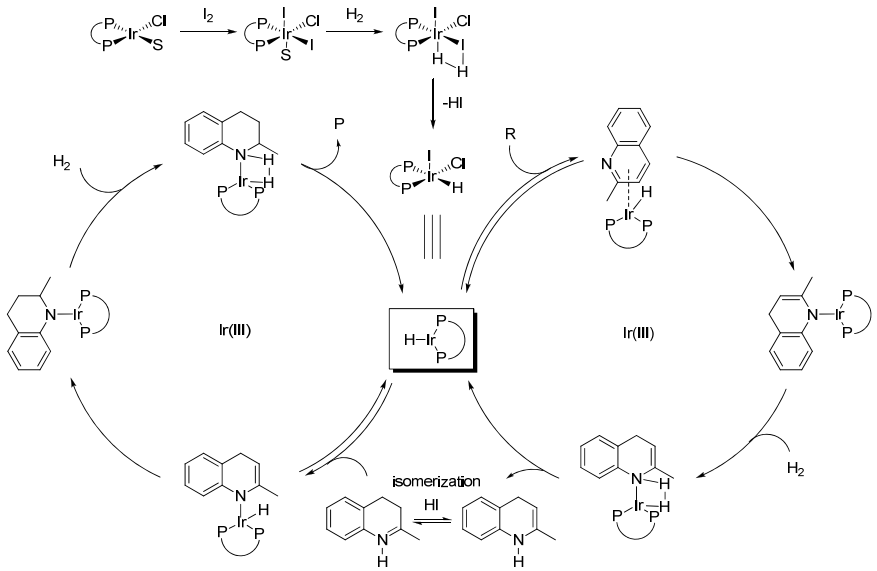

Scheme 4.16. Postulated mechanism for the hydrogenation of quinolines.

Apart from the case of iodine, the specific role of the additives and the reaction conditions is very rarely fully understood. It is obvious that further efforts to understand the mechanism of this transformation will lead to important discoveries in the future.

4.1.2.2. Asymmetric Hydrogenation of Imines. Scope

The general structures of acyclic imines used as substrates to be hydrogenated are collected in Figure 4.4.

It is not easy to extract general trends from the results published in this field, due to variety of substrates, catalysts, and reaction mechanisms involved. As usual, the efficiency of a catalytic system is specific for a particular substrate.

In the case of imine hydrogenation this fact is particularly relevant since hydrogenation of acyclic substrates, which exists as *Z/E* mixtures, and cyclic imines, where only a configuration imposed by the cycle exists, present quite different problems. Thus, catalytic systems used in the hydrogenation of cyclic or heteroaromatic imines are usually distinct from those used in acyclic imines.

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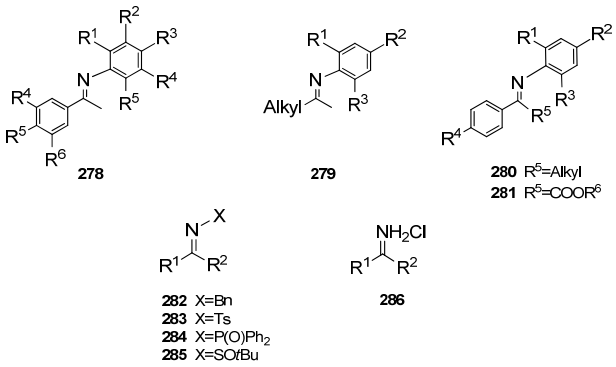


Figure 4.4. Acyclic imines studied in asymmetric hydrogenation.

Excellent results in the hydrogenation of acyclic imines were described using several catalysts based on Ir, Rh, Ru and Pd, although Ir complexes are still the most widely studied catalysts, and comparison of the different parameters influencing the catalytic results are easier to make in this case. In general, two types of iridium precursors are used, cationic $[Ir(COD)_2]X$ or neutral $[Ir(\mu\text{-}Cl)(COD)]_2$, in the presence of bidentate phosphorus ligands (diphosphines,[75,76,70,77,78,79,80] diphosphinites, diphosphites,[81,82] phosphine-phosphite[83]) as well as monodentate P ligands[84,85,86] (phosphoroamidites, phosphines) and phosphorus-nitrogen ligands, in particular phosphino-oxazoline derivatives.[28b,87] Cationic complexes are more common and BAr_F is the anion of choice. The use of additives such as I_2 yields Ir(III) species, thus modifying the catalytic cycle.

Concerning the substrates, much research has been oriented towards the preparation of primary amines, that is, the group linked to the nitrogen atom was considered as a protecting group, and consequently should be easily removed. For this reason, benzyl derivatives were initially explored. It is now established that these imines are particularly challenging, and there are only a few catalytic systems able to provide high enantioselectivities ([Ir]/spiranic phosphino-oxazoline) with these substrates.[88]

The hydrogenation of cyclic imines with Ir catalysts is mainly carried out using neutral precursors in the presence of iodine as additive.

Cyclic imines, quinolines and unfunctionalised N-H imines have been successfully transformed into enantiomerically enriched amines. The

asymmetric hydrogenation of heteroaromatic compounds, in particular cyclic imines, requires in general stronger reaction conditions, because of the high stability of the aromatic ring and the facile poisoning of the catalyst. Relevant results have been however obtained in the hydrogenation (Figure 4.5).

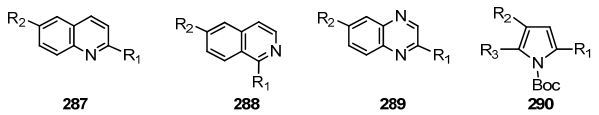
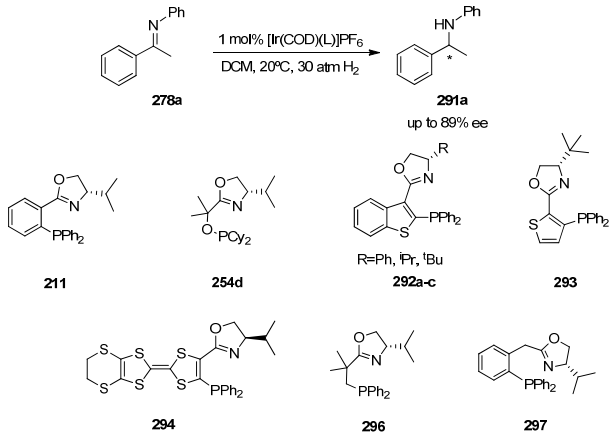


Figure 4.5. Cyclic imines and heteroaromatic compounds studied in asymmetric hydrogenation.

In 1997, Pfaltz *et al.* reported the first iridium complexes containing chiral phosphino-oxazolines **211** (PHOX), **292** and **293**, in the hydrogenation of imines (ee's up to 89% using ligand **211**) (Scheme 4.17).[89]

Cationic iridium(I) complexes with the PHOX ligand (**223**) modified with perfluoroalkyl chains on the phenyl groups of the phosphine moiety, have shown to be efficient catalysts in $scCO_2$, achieving 89% ee and full conversion in the hydrogenation of **278a**. Hydrogenation of imine **282b** gave very low conversions. Both the side chains and the lipophilic anions increased the solubility of the complex into the $scCO_2$, but the choice of the anion had also a dramatic effect on the enantioselectivity with BAr_F leading to the best results (ee's up to 81%).[90]



Scheme 4.17. Enantioselective hydrogenation of substrate **278a** with [Ir]/**223**, **254d, 292-294**, **296-297**.

Recently, Pfaltz *et al.* have reported a screening of various iridium complexes derived from chiral oxazoline-based P,N ligand discovering three efficient ligands (**254d**, **296** and **297**) which are air and moisture stable. The iridium catalysts containing these ligands are the best reported to date in terms of activity, enantioselectivity and turnover number even at low catalyst loading, low temperature, and moderate hydrogen pressure achieving enantioselectivities up to 95% (Scheme 4.17).[91] The catalyst bearing the ligand **297** has been reported by Hou and co-workers showing high activities and enantioselectivities in the hydrogenation of several acyclic imines (ee's up to 88%).[92]

Related catalytic systems have been prepared *in situ* by addition of phosphino-imidazoline **299**[11] or oxazoline-thioether **300**[93] ligands to the iridium precursor $[Ir(COD)_2]BF_4$. In both cases the enantioselectivities achieved were moderate (up to 50% for phosphino-imidazoline ligands). The addition of additives had a negative effect on the enantioselectivity and the use of cationic precursors provided better results than those obtained with the neutral dinuclear $[Ir(\mu\text{-}Cl)(COD)]_2$/L (Scheme 4.18).

Related ligands incorporating aminophosphino-oxazoline functionalities **301-305**, containing two stereocenters, were also applied in the Ir-asymmetric hydrogenation of **278a** with enantioselectivities up to 90%. The hydrogenation of the benzyl derivative **282b** was achieved with 82% ee (Scheme 4.18). The stereogenic center of the oxazoline unit has a considerable impact on the enantioselectivity of the reaction. Thus, the iridium catalyst containing ligand **301**, with a (*R*) configuration on the oxazoline ring and (*S*) configuration on the aminophosphine moiety induced a higher enantioselectivity (90% ee) than its diastereomer containing ligand **302**, which has a (*S*) configuration on the oxazoline ring (14% ee).[94]

Andersson *et al.* reported a new class of aminophosphino-oxazoline ligands **305** with a 2-aza-norbornane backbone that provided high ee's in the iridium-catalysed hydrogenation of acyclic *N*-arylimines. The *N*-(1-phenylethylidene)aniline (**278a**) was hydrogenated with 98% conversion and 90% ee. The introduction of substituents on the aromatic ring attached to the phosphorus atom had a very moderate effect on the resulting enantioselectivity. However, the structure of the substrate had a strong effect. The best results were obtained when R^1=R^2=Ph, while replacement of R^2 by

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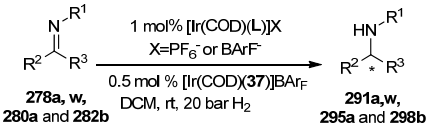
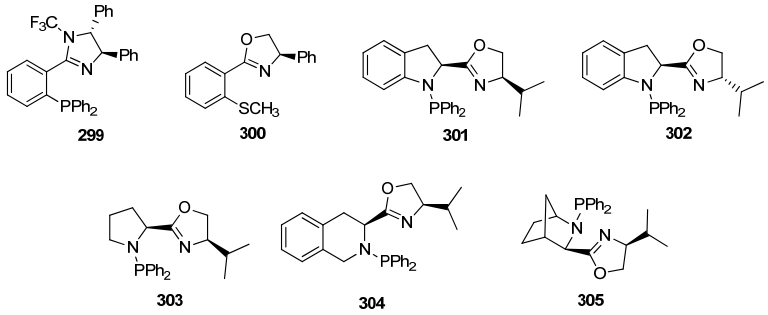
cyclohexyl or *tert*-butyl, or R^3 by groups different than methyl had a detrimental effect on the enantioselectivity (Scheme 4.18).[51]



Substrate	R^1	R^2	R^3	Ee(**299**)	Ee(**300**)	Ee(**301**)	Ee(**302**)	Ee(**303**)	Ee(**304**)	Ee(**305**)
278a	Ph	Ph	CH_3	51	-	90	14	85	68	90
278w	Ph	Cy	CH_3	-	-	-	-	-	-	30
280a	Ph	Ph	Et	-	-	-	-	-	-	78
282b	Bn	Ph	CH_3	11	15	82	-	62	60	-



Scheme 4.18. Enantioselective hydrogenation of **278a** and **282b** with [Ir]/**299**-**304** and **278a**, **278w** and **280a** with [Ir]/**305**.

Phosphino-oxazoline ligands containing a spiranic backbone provided the best enantioselectivity of this family of ligands. Thus, spirobiindane based ligand (SIPHOX) **306** have been used in the asymmetric hydrogenation of **278a,h-i** and **278p-v** at ambient hydrogen pressure with enantioselectivities up to 97%. The enantioselectivity increased when the reaction was carried out in weakly polar solvents such as CH_2Cl_2, toluene, ether and *tert*-butyl methyl ether. The presence of 3,5-dimethyl groups on the P-phenyl ring had a positive effect on the conversion but the enantioselectivity was not affected. The introduction of electron-donating or electron-withdrawing groups on the α-phenyl ring of the ketimine slightly increased the enantioselectivity. Furthermore, iridium complexes bearing SIPHOX ligand **306** have shown to be resistant to the formation of inactive trimers under hydrogenation conditions (Scheme 4.19).[95]

Zhang, Ding and co-workers recently reported a related phosphino-oxazoline ligand with a spiro[4,4]-1,6-nonadiene backbone called SpinPHOX **307**

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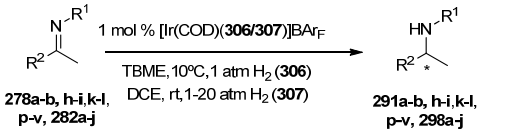
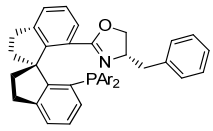
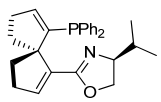
(Scheme 4.19). The Ir/**307** catalytic system was successfully used in the asymmetric hydrogenation of challenging *N*-alkyl ketimine substrates, such as **282a-h** achieving ee's up to 93%.



Substrate	R^1	R^2	Ee(**306**)	Ee(**307**)
278a	Ph	Ph	93	91
278b	4-$MeOC_6H_4$	Ph	-	90
278h	Ph	4-$MeOC_6H_4$	94	-
278i	Ph	4-ClC_6H_4	90	92
278p	Ph	4-BrC_6H_4	91	91
278q	Ph	3,4-$(CH_3)_2C_6H_3$	94	95
278r	Ph	3-ClC_6H_4	93	93
278s	Ph	3-BrC_6H_4	92	93
278t	4-ClC_6H_4	Ph	97	-
282a	Bn	4-$MeOC_6H_4$	-	90
282b	Bn	Ph	-	91





Scheme 4.19. Enantioselective hydrogenation of substrates **278a, 278h-i** and **278p-v** with [Ir]/**306** and **278a,b**, **278i**, **278k-l**, **278p-s** and **282a-h** with [Ir]/**307**.

The chirality on the spiro backbone in ligands **306** and **307** has a significant impact on the asymmetric induction. The matched combination is obtained with an *R* configuration on the spiro backbone and *S* configuration on the oxazoline moiety. The *i*Pr group appears to be the substituent of choice (Scheme 4.19).[88] The Ir-catalysed enantioselective hydrogenation of a range of *N*-(3,5-dimethyl-4-methoxy)phenylimines (**278x-z** and **278a'-h'**) was performed under mild conditions (10 bars) in the presence of the isolated P,N-ferrocenyl iridium complex [Ir(COD)(**308**)]BAr_F^-, producing chiral amines in high yields and enantioselectivities (up to 99%) (Scheme 4.20).

The solvent has a strong effect on the catalysis. It was observed that the use of toluene affords excellent conversion but poor enantioselectivites (11%). In contrast, if the reaction is carried out in methanol poor conversions and moderate enantioselectivites are achieved. The optimised mixture of solvent toluene/MeOH 4:1 provides full conversion and enantioselectivity up to 84%.

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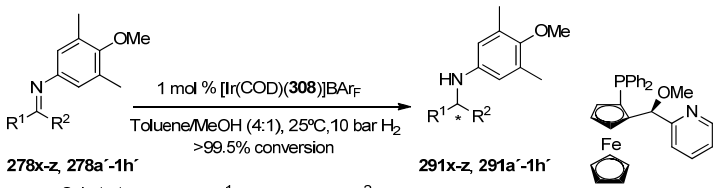

Substrate	R^1	R^2	Ee
278x	3-$CH_3C_6H_4$	CH_3	93
278y	4-PhC_6H_4	CH_3	92
278z	4-$CF_3C_6H_4$	CH_3	89
278a´	4-ClC_6H_4	CH_3	92
278b´	4-$CH_3CO_2C_6H_4$	CH_3	94
278c´	3-FC_6H_4	CH_3	93
278d´	2-$CH_3C_6H_4$	CH_3	94
278e´	2-naphthyl	CH_3	93
278f´	Ph	Et	94
278g´	Ph	Pent	95
278h´	Ph	$-(CH_2)_3COPh$	99

Scheme 4.20. Enantioselective hydrogenation of substrates **278x-z** and **278a´-h´** with [Ir]/**308**.

The deprotection of the 3,5-dimethyl-4-methoxyphenyl moiety of amines was performed under smooth conditions with cerium ammonium nitrate[96] in a 6:1 MeOH/H_2O mixture, providing the corresponding primary amines in good yields. To extend this protocol, the authors carried out the asymmetric synthesis of chiral γ- and δ-lactams[97,98] achieving 92-97% ee.[99] The highest ee's were obtained with substrates bearing a remote carbonyl group (**278h´**).

The asymmetric hydrogenation of cyclic imines, and particularly heteroaromatic compounds, although less explored than their acyclic analogue, was reviewed in 2007.[100]

Bolm and co-workers reported a series of naphthalene-bridged phosphino-sulfoximine ligands that provided 92% ee in the iridium–catalysed hydrogenation of quinoline **287**. Other alkyl substituted quinolines were hydrogenated in lower ee's.[101]

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4. 2 Results and discussion

Based on the excellent results reported in the Ir-catalysed asymmetric hydrogenation of olefins and imines using especially phosphino-oxazoline ligands, we encouraged to study analogous iridium catalytic systems bearing phosphino-imidazoline as ligands.

4.2.1 Synthesis of P,N-ligands

4.2.1.1. Synthesis of phosphino-imidazoline ligands

According to the previous indicated objectives, this work starts with the synthesis of P,N-ligands. Phosphino-imidazoline ligands were prepared as indicated in Scheme 4.21. Starting from 2-fluorobenzoylchloride (**309**) by treatment with the sodium salt of methanethiolate afforded 2-fluoro-thiobenzoic acid *S*-methyl ester (**310**). The product **311** was obtained by the subsequent treatment of **310** with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide) (Scheme 4.21).[11,102]

The imidazoline ring was formed by condensation of **311** with a chiral diamine, either (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (**312**) or (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (**313**) to give compounds **314** and **315**, respectively. The driving force of the reaction is the precipitation of HgS by using the desulfurizing agent mercury (II) oxide.[103] Compounds **314** and **315** reacted with Ph_2PK in THF at room temperature overnight affording the phosphino-imidazoline ligands **316** and **317** in 94% and 86% yield, respectively.

Changing the electronic properties of the ligands has a dramatic effect on the enantioselectivity of metal-catalysed reactions.[104] Aiming to study these effects phosphino-imidazoline ligands can be modified by introducing different substituents in the phosphorus atom, but also in the NH of the imidazoline ring.

Thus, compound **319** with cyclohexyl groups linked to phosphorus was synthesised by reaction of **314** with $(Cy)_2PH{\cdot}BH_3/NaH$[105] to afford compound **318**, which was then treated with DABCO to give **319**.[106]

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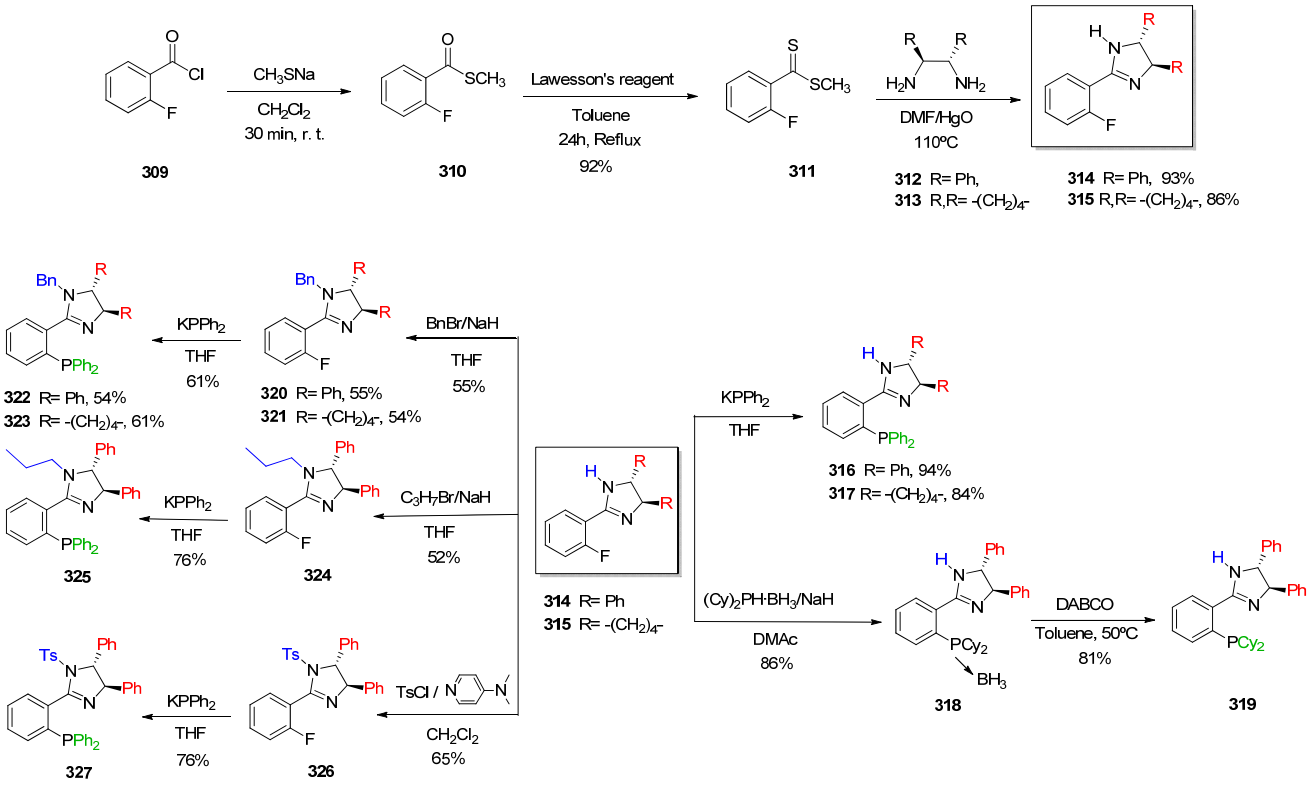

Scheme 4.21. Synthesis of the phosphino-imidazoline ligands **316**, **317**, **319**, **322**, **323**, **325** and **327**.

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Accordingly, a series of derivatives of compounds **316**, **317** in which the NH of the imidazoline ring was functionalised with aryl or alkyl substituents were also synthesised. Thus, imidazoline **314** was treated with benzyl bromide, propyl bromide and tosyl chloride to afford imidazolines **320**, **324** and **326**. A single crystal of the intermediate **326** was suitable for X-ray crystal (Table 4.1). The molecular structure of this compound is described in Figure 4.6.

The structure shows that the tosyl group is *trans* with respect to the phenyl moiety of the imidazoline ring (Figure 4.6). Selected bond lengths and angles are listed in Table 4.2. Similarly, compound **315** was reacted with benzyl bromide to give **321**. All these reactions were conducted a room temperature to avoid possible racemization processes.[104] Finally, these compounds were treated with $KPPh_2$ to yield the phosphino-imidazoline ligands **322**, **323**, **325**, and **327** (Scheme 4.21). All the ligands were characterised by multinuclear NMR spectroscopy and mass spectrometry (MS).

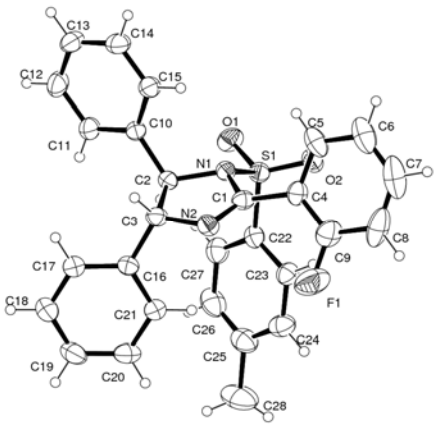

Figure 4.6. X-Ray structure of intermediate **326**.

4.2.1.2. Synthesis of phosphite-imidazoline ligands

Due to the excellent results published with phosphite-oxazoline ligands (See section 4.1.1.2) we were interested in phosphite-imidazoline ligands and their application in the asymmetric hydrogenation reactions. The formation of an alcohol-imidazoline intermediate is required to introduce a phosphite moiety in the backbone of the ligand. This compound was synthesised according to a previously described method for analogous compounds.[107]

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Table 4.1. Experimental X-ray diffraction parameters and crystal data for **326**.

Empirical formula	$C_{28}H_{23}FN_2O_2S$
Formula weight	470.54
Temperature (K)	293(2)
Wavelength (Å)	1.54180
Crystal system	Orthorhombic
space group	P 21 21 21
Unit cell dimensions (Å)	a = 9.6470(13), alpha = 90 deg. b = 10.0780(13), beta = 90 deg. c = 23.959(3), gamma = 90 deg.
Unit cell volume ($Å^3$)	2329.4(5)
Z, Calculated density (Mg/m^3)	4, 1.342
Absorption coefficient (mm^{-1})	1.538
F(000)	984
Theta range for data collection	3.69 to 61.22 deg
Limiting indices	-10<=h<=10, -11<=k<=11, -27<=l<=27
Reflections collected / unique	11058 / 3474 [R(int) = 0.0450]
Completeness to theta = 61.22	98.5 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3474 / 0 / 309
Goodness-of-fit on F^2	1.068
Final R indices [I>2sigma(I)]	R_1 = 0.0411, wR_2 = 0.1031
R indices (all data)	R_1 = 0.0429, wR_2 = 0.1044
Absolute structure parameter	0.08(2)
Extinction coefficient	0.0127(7)
Largest diff. peak and hole ($e/Å^3$)	0.554 and -0.188

Table 4.2. Selected bond lengths and angles for compound **326**.

Bond lengths (Å)		Bond angles (º)	
S(1)-O(2)	1.423(2)	O(2)-S(1)-O(1)	120.43(13)
S(1)-O(1)	1.424(2)	O(2)-S(1)-N(1)	107.22(12)
S(1)-N(1)	1.668(2)	O(1)-S(1)-N(1)	104.75(12)
S(1)-C(22)	1.753(3)	O(2)-S(1)-C(22)	109.57(12)
N(1)-C(1)	1.439(3)	O(1)-S(1)-C(22)	108.72(14)
N(1)-C(2)	1.490(3)	N(1)-S(1)-C(22)	104.99(12)
N(2)-C(1)	1.268(4)	C(1)-N(1)-S(1)	120.90(18)
N(2)-C(3)	1.471(4)	C(2)-N(1)-S(1)	116.39(17)
F(1)-C(9)	1.325(5)	N(2)-C(1)-N(1)	116.2(2)

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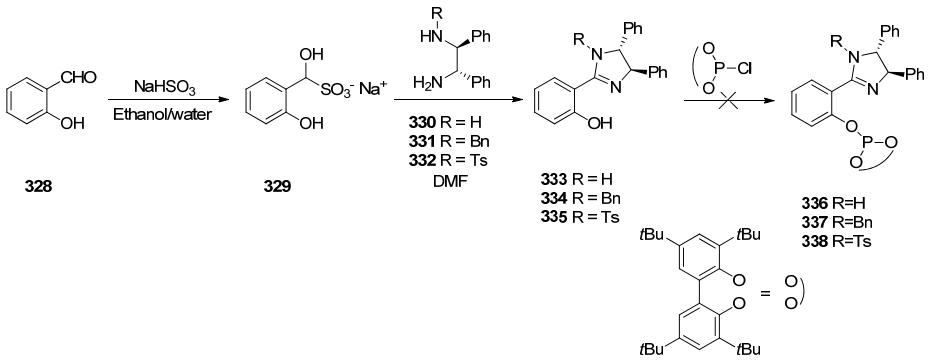
The 2-hydroxybenzaldehyde (**328**) was reacted with sodium bisulfite in a mixture of ethanol and water affording the intermediate **329** which reacted with the corresponding diamine in dimethylformamide (DMF). The (1*R*,2*R*)-N^1-benzyl-1,2-diphenylethane-1,2-diamine (**331**) had been previously synthesised starting from the (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine and benzyl chloride in the presence of a base. [108] However, in our hands, this procedure only afforded to the dialkylated product. The procedure was optimised modifying the reaction temperature and the equivalents of benzyl chloride, obtaining a mixture of the monoalkylated and dialkylated diamine in a ratio 7:1. The desired amine was then purified by column chromatography. Diamines **330** and **332** were commercially available and the condensation reaction with sodium hydroxyl (2-hydroxyphenyl)methane sulfonate salt afforded the alcohol-imidazoline intermediates **333** and **335** in good yields. The synthesis of phosphite **336** was attempted using the procedures reported by our group (Scheme 4.22).[109] However, the triethylamine or pyridine abstracts the acidic proton at nitrogen atom of the imidazoline ring instead of the alcoholic proton. In view of this result, we focused on the intermediates which have a substituent at that position. The alcohol **334** was treated with the previously synthesised phosphorochlorhydrite in toluene in the presence of triethylamine at room temperature but unfortunately the desired ligand was not obtained. Other bases were tested such as pyridine, 4-dimethylaminopyridine, sodium hydride, pyrrolidine. The reaction temperature was optimised but in all the cases the alcohol did not react with the corresponding phosphorochlorhydrite.



Scheme 4.22. Attempts of synthesising phosphite-imidazoline ligands.

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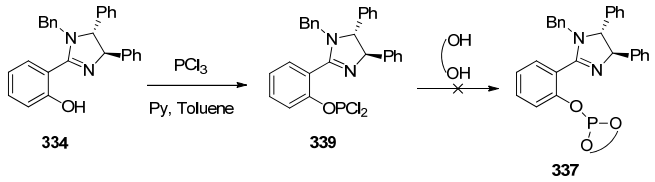
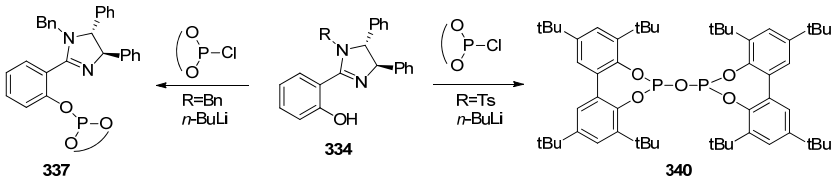
Later, it was decided react the alcohol-imidazoline ligand with PCl_3, obtaining compound **339** and then the introduction of the biaryl group. This procedure afforded to the formation of compound **339** in good yields but the further reaction with the diol did not afford the phosphite **337** (Scheme 4.23).



Scheme 4.23. Alternative synthetic pathway proposed for the synthesis of phosphite-imidazoline ligand **337**.

Finally, the desired ligand was successfully obtained by treating **334** with of *n*-butyl lithium, *N*,*N*,*N*,*N*-tetramethylethylenedimine and the phosphorochlorhydrite in tetrahydrofurane.[58] Ligand **337** was fully characterised by NMR and MS techniques. The $^{31}P\{^{1}H\}$ NMR spectrum of ligand **337** in deuterated dichloromethane at room temperature showed a broad signal at 143.6 ppm. When the temperature was decreased at -90ºC the broad signal resolved into two singlets in the ratio 1:1 at 152.0 and 138.9 ppm respectively which was attributed to two rotameric isomers. The same procedure was carried out with intermediate **335** but the desired phosphite was not obtained and instead the formation of diaryl phosphite **340** was observed (Scheme 4.24).[110]



Scheme 4.24. Synthesis of ligand **337** and the formation of the diaryl phosphite ligand **340**.

4.2.2. Synthesis of Cationic Iridium Complexes

The corresponding cationic iridium (I) complexes **341**-**346** were synthesised by reaction in dichloromethane of $[Ir(\mu\text{-}Cl)(COD)]_2$ with ligands **316**, **317**,

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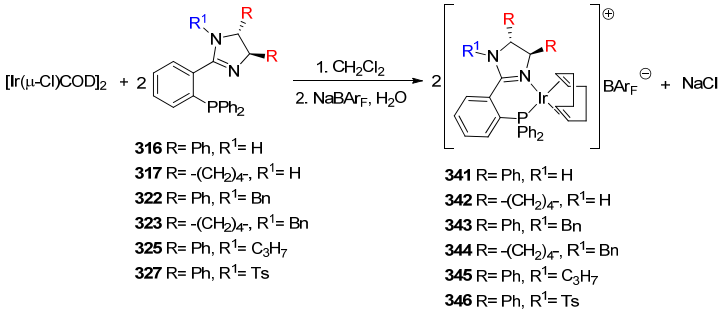
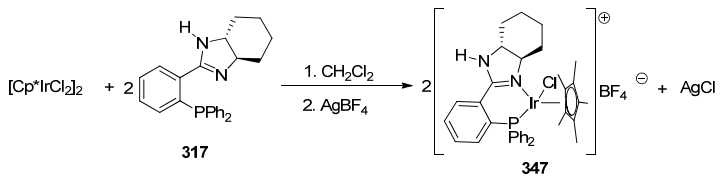
322, **323**, **325** and **327** (Scheme 4.25). The complexes were characterised by multinuclear NMR spectroscopy and MS analysis.[10,111] The VT-NMR spectra showed two isomers in solution. At room temperature, a broad peak at 14.5-15.5 ppm was resolved in two well defined singlets at (16.7 and 14.9 ppm) at -60ºC. The two isomeric species could be attributed as conformers containing the chelate ring with in a boat or chair conformation.



Scheme 4.25. Synthesis of iridium complexes **341-346**.

To compare the influence of the cationic iridium precursor in hydrogenation reactions, the new cationic iridium (III) complex [Cp*IrCl(**317**)]BF_4 (**347**) bearing the phosphino-imidazoline ligand (**317**) was synthesised (Scheme 4.26). This complex was characterised by NMR and MS analysis. The $^{31}P\{^1H\}$ NMR spectrum shows a singlet at -3.1. After a few days at room temperature in the NMR tube, yellow crystals appeared from the solution. Figure 4.7 shows a view (30% probability ellipsoid) of one of the two independent complex cations observed, which only differ in the orientation of the phenyl rings of the phosphorus atom. Figure 4.8 shows the view of the two independent complex cations along the Cl-Ir bond direction, observing the variations in the orientations mentioned before. Table 4.3 summarizes the bond lengths and angles of this complex.



Scheme 4.26. Synthesis of cationic iridium (III) complex **347**.

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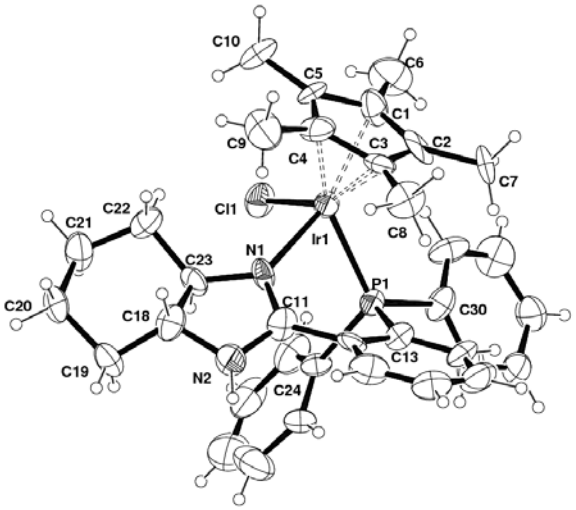

Figure 4.7. X-Ray structure of complex **347**.

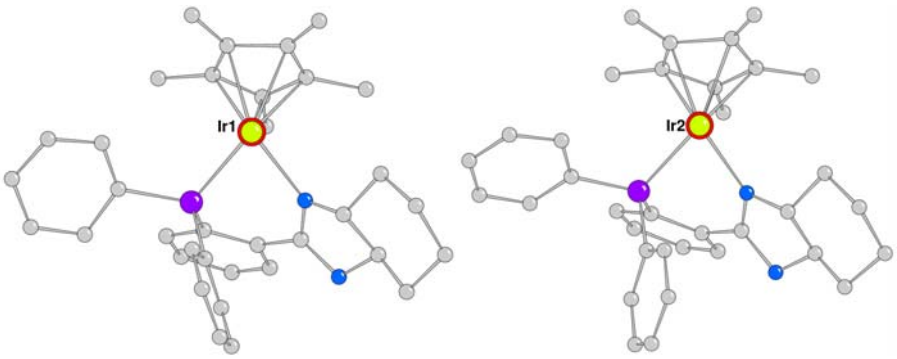

Figure 4.8. View of the two independent complex cations along the Cl-Ir direction.

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Table 4.3. Selected bond lengths (Å) and angles (°) for complex **347**.

	Cation **347a**		Cation **347b**	
Bond lengths	Ir(1)-N(1)	2.152(14)	Ir(2)-N(3)	2.104(12)
	Ir(1)-P(1)	2.303(4)	Ir(2)-P(2)	2.301(5)
	Ir(1)-Cl(1)	2.420(5)	Ir(2)-Cl(2)	2.440(4)
	Ir(1)-C(1)	2.23(2)	Ir(2)-C(41)	2.367(15)
	Ir(1)-C(2)	2.283(16)	Ir(2)-C(42)	2.246(15)
	Ir(1)-C(3)	2.220(16)	Ir(2)-C(43)	2.277(17)
	Ir(1)-C(4)	2.252(16)	Ir(2)-C(44)	2.207(17)
	Ir(1)-C(5)	2.330(16)	Ir(2)-C(45)	2.310(17)
Bond Angles	N(1)-Ir(1)-P(1)	78.6(4)	N(3)-Ir(2)-P(2)	77.5(5)
	N(1)-Ir(1)-Cl(1)	93.4(4)	N(3)-Ir(2)-Cl(2)	94.3(4)
	N(1)-Ir(1)-C(1)	155.9(7)	N(3)-Ir(2)-C(41)	124.6(7)
	N(1)-Ir(1)-C(2)	135.5(8)	N(3)-Ir(2)-C(42)	162.9(5)
	N(1)-Ir(1)-C(3)	100.5(6)	N(3)-Ir(2)-C(43)	135.5(6)
	N(1)-Ir(1)-C(4)	94.1(8)	N(3)-Ir(2)-C(44)	101.0(5)
	N(1)-Ir(1)-C(5)	119.0(7)	N(3)-Ir(2)-C(45)	97.6(7)
	P(1)-Ir(1)-Cl(1)	91.34(16)	P(2)-Ir(2)-Cl(2)	94.74(16)
	C(1)-Ir(1)-P(1)	123.4(6)	P(2)-Ir(2)-C(41)	157.5(5)
	C(2)-Ir(1)-P(1)	100.5(6)	C(42)-Ir(2)-P(2)	116.8(5)
	C(3)-Ir(1)-P(1)	110.5(4)	C(43)-Ir(2)-P(2)	97.5(5)
	C(4)-Ir(1)-P(1)	146.6(6)	C(44)-Ir(2)-P(2)	111.6(5)
	P(1)-Ir(1)-C(5)	161.6(5)	P(2)-Ir(2)-C(45)	147.4(5)
	C(1)-Ir(1)-Cl(1)	95.6(5)	C(41)-Ir(2)-Cl(2)	88.2(5)
	C(2)-Ir(1)-Cl(1)	131.0(7)	C(42)-Ir(2)-Cl(2)	93.6(4)
	C(3)-Ir(1)-Cl(1)	156.0(5)	C(43)-Ir(2)-Cl(2)	130.1(5)
	C(4)-Ir(1)-Cl(1)	121.8(6)	C(44)-Ir(2)-Cl(2)	151.8(4)
	C(5)-Ir(1)-Cl(1)	92.6(6)	C(45)-Ir(2)-Cl(2)	117.8(5)

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4.2.3. Asymmetric Hydrogenation of Unfunctionalised Olefins

The P,N ligands and the iridium complexes prepared in the previous section 4.2.1 and 4.2.2 were synthesised to be used as catalysts in the asymmetric hydrogenation of unfunctionalised olefins and imines. An optimization of the reaction conditions was carried out with iridium complexes bearing ligand **316** in the asymmetric hydrogenation of *E*-1,2-diphenylpropene (Table 4.4).

Our initial studies showed that under the same catalytic conditions the complex [Ir(COD)**316**]BAr_F (**341**), gave total conversion in front of the 87% obtained with the complex [Ir(COD)**316**]BF_4 (**348**) using substrate/Ir ratio of 50 (entry 1 *vs* 5). When this ratio was modified to 100 the activity of the complex **341** remained practically the same but the complex [Ir(COD)**316**]BF_4 was completely inactive (entry 2 *vs* 6). However, the enantioselectivity obtained with [Ir(COD)**316**]BF_4 complex was slightly higher (entry 1 *vs* 5).

The experiments were performed at 50 bars, as it is used for related catalytic systems.[55] When the hydrogen pressure was decreased from 50 to 40 bars a negative effect on the activity was observed while the enantioselectivity remained the same (entries 3,4 *vs* 5,6). No significant effect was attributed to the addition of 10% mol of ligand **316** to the isolated complex (entry 7). Finally, the reaction time was decreased and small decrease in conversion was observed (entry 8, Table 4.4) and also when the substrate/Ir ratio is increased produces a loss in the activity. (entries 8-10). The optimal catalytic conditions thus were 50 bars of hydrogen, room temperature during 24 hours for having full conversion.

Introduction of a benzyl group at the nitrogen atom produced a negative effect on the activity and enantioselectivity (entry 2, Table 4.5). However, when an alkyl chain was introduced the activity remained constant and the enantioselectivity was slightly increased (ee's up to 57%) (entries 2 *vs*. 3, Table 4.5).

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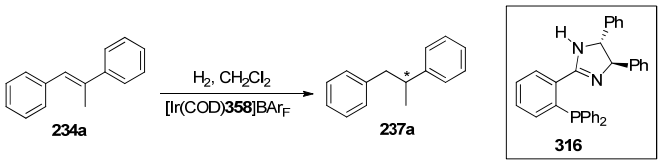
Table 4.4. Optimization of reaction conditions in the asymmetric hydrogenation of *E*-1,2-diphenylpropene with complex [Ir(COD)**316**]BAr_F (**341**).[a]



Entry	Iridium precursor	Substrate/Ir	Ligand excess	PH_2 (bar)	Reaction time	Conv.[b] (%)	ee[c] (%)
1	[Ir(COD)**316**]BF_4	50	-	50	24h	87	49
2	[Ir(COD)**316**]BF_4	100	-	50	24h	0	-
3	[Ir(COD)**316**]BAr_F	50	-	40	24h	60	35
4	[Ir(COD)**316**]BAr_F	100	-	40	24h	41	40
5	[Ir(COD)**316**]BAr_F	50	-	50	24h	100	38
6	[Ir(COD)**316**]BAr_F	100	-	50	24h	92	39
7	[Ir(COD)**316**]BAr_F	100	10%	50	24h	100	42
8	[Ir(COD)**316**]BAr_F	50	-	50	8h	86	42
9	[Ir(COD)**316**]BAr_F	100	-	50	8h	73	39
10	[Ir(COD)**316**]BAr_F	200	-	50	8h	42	40

[a]*Reaction conditions:* Catalyst = 0.01 mmol, 5 mL CH_2Cl_2, rt. [b] Conversion determined by ^{1}H NMR and GC. [c] Enantioselectivities determined by chiral HPLC. The main enantiomer has (*S*) configuration.

The different behaviour of these two electron-donating groups can be due to the difference in their steric hindrance. In contrast, the introduction of an electron-withdrawing group at the same position had a very negative effect on the activity (entry 4). These results could suggest that the oxidative addition step is rate determining step under the tested conditions. Under these conditions, the most efficient catalytic system in the asymmetric hydrogenation of *E*-1,2-diphenylpropene was the isolated complex **345**, which contains ligand **325** with an alkyl chain at the nitrogen atom of the imidazoline ring.

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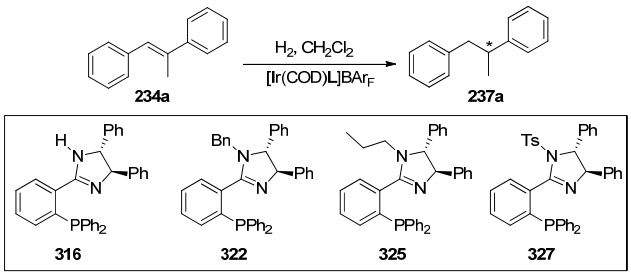
Table 4.5. Asymmetric hydrogenation of *E*-1,2-diphenylpropene with complexes **341**, **343**, **345** and **346**.[a]



Entry	Iridium precursor	Conv.[d] (%)	ee[c] (%)
1	[Ir(COD)**316**]BAr_F, (**341**)	99	50
2	[Ir(COD)**322**]BAr_F, (**343**)	61	32
3	[Ir(COD)**325**]BAr_F, (**345**)	97	57
4	[Ir(COD)**327**]BAr_F, (**346**)	15	57

[a]*Reaction conditions:* Catalyst = 0.01 mmol, Substrate/Ir= 100, PH_2=50 bars, 5 mL CH_2Cl_2, rt. [b] Conversion determined by ^1H NMR and GC. [c] Enantioselectivities determined by chiral HPLC. Product has (*S*) configuration.

The asymmetric hydrogenation of trisubstituted olefins is thus strongly dependent on the nature of the substituent at the nitrogen atom of the ligand. Excellent conversion with moderate enantioselectivity (up to 57%) was obtained in the hydrogenation of **234a** using complex [IrCOD(**325**)]BAr_F (**345**). However, the use of the analogous complex [IrCOD(**327**)]BAr_F (**346**), which contain an electron-withdrawing group at the nitrogen atom, namely tosyl, resulted in a significant decrease in conversion. However, the presence of this group did not affect the enantioselectivity.

The catalytic systems **341**, **343**, **345** and **346** were tested in the asymmetric hydrogenation of 2-(4-methoxyphenyl)-1-butene and even under 10 bars of hydrogen, good to excellent conversion were obtained (entries 2, 5, 8 and 11, Table 4.6). When the hydrogen pressure was decreased to 1 bar, only moderate conversions were achieved (entries 2, 5, 8 and 11 *vs*. 3, 6, 9 and 12). The same tendency than in the previous substrate was observed. The presence of an electron-withdrawing substituent at the nitrogen atom led to a decrease

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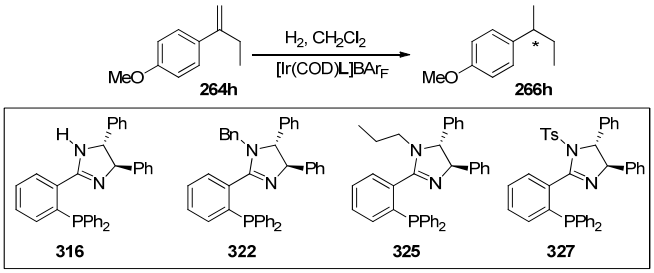
in the conversion (entries 10-12). However, using these catalytic systems, poor enantioselectivities were obtained (ee's up to 18%, Table 4.6, entry 9).

Table 4.6. Asymmetric hydrogenation of 2-(4-methoxyphenyl)-1-butene with Ir complexes containing ligands **316**, **322**, **325** and **327**.[a]



Entry	Iridium precursor	PH_2 (bar)	Conv.[b] (%)	ee[c] (%)
1	[Ir(COD)**316**]BAr_F, (**341**)	50	100	6
2	[Ir(COD)**316**]BAr_F, (**341**)	10	100	9
3	[Ir(COD)**316**]BAr_F, (**341**)	1	65	17
4	[Ir(COD)**322**]BAr_F, (**343**)	50	100	5
5	[Ir(COD)**322**]BAr_F, (**343**)	10	64	7
6	[Ir(COD)**322**]BAr_F, (**343**)	1	43	15
7	[Ir(COD)**325**]BAr_F, (**345**)	50	100	7
8	[Ir(COD)**325**]BAr_F, (**345**)	10	96	13
9	[Ir(COD)**325**]BAr_F, (**345**)	1	62	18
10	[Ir(COD)**327**]BAr_F, (**346**)	50	87	6
11	[Ir(COD)**327**]BAr_F, (**346**)	10	42	9
12	[Ir(COD)**327**]BAr_F, (**346**)	1	29	11

[a]*Reaction conditions:* Catalyst = 0.01 mmol, Substrate/Ir= 100, 5 mL CH_2Cl_2, rt. [b] Conversion determined by ^1H NMR and GC. [c] Enantioselectivities determined by chiral HPLC. Product has (*S*) configuration.

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To summarize:

- The asymmetric hydrogenation of 1,1-disubstituted olefins was carried out under 1 bar of hydrogen pressure and conversions up to 99% were achieved with most of the new catalytic systems. However, the enantioselectivity was very low in all the cases.
- Lower hydrogen pressure improved the enantioselectivity of the reaction: the ee increased from 7% under 50 bar of H_2 to 18% at atmospheric pressure.

Finally, the iridium complexes with the new family of phosphino-imidazoline ligands are efficient catalysts for the reduction of unfunctionalised olefins although they afford the corresponding alkanes in poor or moderate enantioselectivities, achieving ee's up to 57% in the substrate *E*-1,2-diphenylpropene. Ee's up to 99% have been reported for the hydrogenation of the same substrate with a wide range of catalyst for example Ir/**255**, **257**, **260**, etc...(See section 4.1.1.2).

4.2.4. Asymmetric Hydrogenation of Imines

Although, the asymmetric hydrogenation of acyclic imines has been extensively studied using phosphino-oxazoline ligands, only preliminary results with phosphino-imidazoline ligands were reported by our group in 2003.[11] Most of the published examples use isolated iridium complexes for the reduction of acyclic imines and the combination of the neutral iridium dimer precursor with stoichiometric amount of the corresponding ligand for the cyclic substrates.[112] When the reaction was carried out with complex **341**, total conversion was obtained but without enantioselectivity (entry 1, Table 4.7). When, the reaction was repeated in the presence of catalytic amount of iodine (0.1mmol) the conversion and the enantioselectivities obtained were 99% and 3 %, respectively (entry 2, Table 4.7). When the catalytic precursor was formed *in situ* by reaction of the iridium dimer in the presence of stoichiometric amount of ligand **316,** no conversion was obtained (entry 3). This result suggests that the active catalytic species generated *in situ* is not the same than those obtained starting from the isolated complex **341**. When 0.05 mmol of iodine were added to the catalytic solution, the conversion increased up to 43% but the amine obtained was as a racemic mixture (entry 4, Table 4.7). Total conversion to the corresponding amine was obtained using 0.01 mmol of iodine although the enantioselectivity could not be improved (entry

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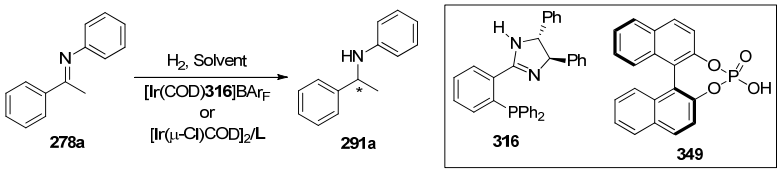
5, Table 4.7). When the catalytic system was prepared *in situ*, iodine addition is required to form the Ir(III) species which are responsible of the catalytic activation[70,72b] In 2008, Xiao and co-workers published a cooperative effect between a chiral metal catalyst and a bulky phosphoric acid in the hydrogenation of a wide range of imines.[113] The effect of phosphoric acid **349** in the asymmetric hydrogenation of N-(β-phenylethylidene)aniline with Ir/**316** was therefore tested. However, only hydrolysis of the imine was achieved under these conditions (entry 6, Table 4.7).

Table 4.7. Optimization of reaction conditions in the asymmetric hydrogenation of N-(β-phenylethylidene)aniline with complex **341** or Ir/**316**.[a]



Entry	Iridium precursor	Solvent	Additive	Conv.[b] (%)	ee[c] (%)
1	[Ir(COD)**316**]BAr_F, (**341**)	Toluene	-	99	4
2	[Ir(COD)**316**]BAr_F, (**341**)	Toluene	I_2	99	3
3	[Ir(μ-Cl)COD]$_2$/**316**	Toluene	-	0	-
4	[Ir(μ-Cl)COD]$_2$/**316**	Toluene	I_2	43	4
5[d]	[Ir(μ-Cl)COD]$_2$/**316**	Toluene	I_2	99	6
6[e]	[Ir(μ-Cl)COD]$_2$/**316**	Toluene	**349**	0	-
7[d]	[Ir(μ-Cl)COD]$_2$/**316**	CH_2Cl_2	I_2	85	2
8[d]	[Ir(μ-Cl)COD]$_2$/**316**	Toluene/MeOH	I_2	47	0
9[d]	[Ir(μ-Cl)COD]$_2$/**316**	CH_2Cl_2/MeOH	I_2	64	3

[a]*Reaction conditions:* Catalyst = 0.01 mmol, Substrate/Ir= 100, I_2=0.05 mmol, 2 mL solvent, rt. [b] Conversion determined by ^{1}H NMR and GC. [c] Enantioselectivities determined by chiral HPLC. Product has (*S*) configuration. [d] I_2=0.1 mmol. [e] 37% hydrolysis.

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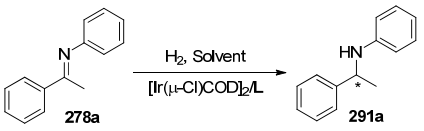
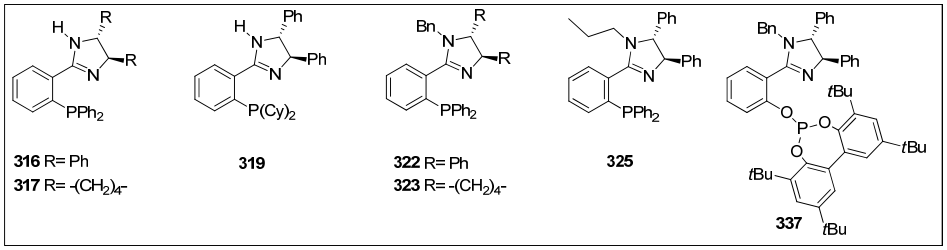
Finally, various solvents were tested and toluene was observed to be the best solvent (entry 5 *vs* 7-9, Table 4.7).

When the reaction conditions were optimised, a screening of the family of phosphino-imidazoline ligands was carried out (Table 4.8).

Table 4.8. Asymmetric hydrogenation of N-(β-phenylethylidene)aniline with Ir/**316**, **317**, **319**, **322**, **323**, **325**, **337**.[a]





Entry	Iridium precursor	Conv.[b] (%)	Ee[c] (%)
1	[Ir(μ-Cl)COD]$_2$/**316**	99	6
2	[Ir(μ-Cl)COD]$_2$/**317**	99	24 (*R*)
3	[Ir(COD)**317**]BAr$_F$, (**342**)	99	21 (*R*)
4	[Cp*IrCl(**317**)BF$_4$, (**347**)	31	5
5	[Ir(μ-Cl)COD]$_2$/**319**	99	3
6	[Ir(μ-Cl)COD]$_2$/**322**	99	2
7	[Ir(COD)**322**]BAr$_F$, (**343**)	99	4
8	[Ir(μ-Cl)COD]$_2$/**323**	99	4
9	[Ir(μ-Cl)COD]$_2$/**325**	98	2
10	[Ir(μ-Cl)COD]$_2$/**337**	99	0

[a]*Reaction conditions:* Catalyst = 0.01 mmol, Substrate/Ir= 100, I_2=0.01 mmol, 2 mL toluene, rt. [b] Conversion determined by ^{1}H NMR and GC. [c] Enantioselectivities determined by chiral HPLC.

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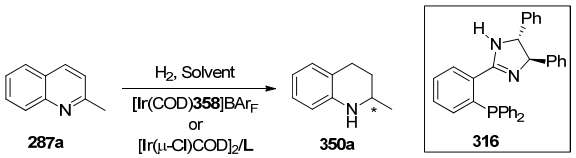
The enantioselectivity could be increased up to 24% by replacing the phenyl groups by a cyclohexyl ring (entry 1 *vs* 2, Table 4.8). The complex **342** was tested under the previous conditions but no positive effect on the catalysis was observed. When **347** was used as catalyst both activity and enantioselectivity decreased (entries 2-4, Table 4.8). Because of the introduction of cyclohexyl substituents on the imidazoline ring improves the enantioselectivity, various electron-donating groups were introduced at the nitrogen atom. However, not effect was observed by introduction of a benzyl or an alkyl chain in the ligands bearing a phenyl groups in the imidazoline ring (**322** and **325**) did not produce any effect on the enantioselectivity. However, when electron-donating groups were introduced on the imidazoline's backbone with a cyclohexyl ring, the enantioselectivity dropped (ee's up to 7%) (entries 6, 8 and 9, Table 4.8). Finally, the effect of the substituents at the phosphorus atom was studied. In this context, the phenyl groups of the phosphine were replaced by cyclohexyl which did not give any enantioselectivity (entry 6, Table 4.8). The same tendency was observed when the phosphine was replaced by phosphite (**337**) which showed high activity in the reduction of the N-(β-phenylethylidene)aniline but no enantioselectivity (entry 10).

Iridium catalysts containing the phosphino-imidazoline ligands (**316**, **317**, **319**, **322**, **323**, **325** and **337**) were then applied in the hydrogenation of substrates **287a** (Tables 4.9 and 4.10). The optimization of reaction conditions was performed with complex **341** or using the catalytic system Ir/**316**. It is interesting to mention that the complex **341** was not active in the hydrogenation of 2-methylquinoline in contrast with the results obtained in the hydrogenation of N-(*β*-phenylethylidene)aniline, for which full conversion was achieved. When 0.05 mmol of iodine was added to the complex **341**, complete conversion was obtained without enantiodescrimination (entries 1 and 2, Table 4.9). The Ir/**316** system was not active in the absence of iodine which is in agreement with previous results (entry 3, Table 4.9) (See entry 3, Table 4.7).

When 0.05 mmol of iodine were added to the mixture of $[Ir(\mu\text{-}Cl)COD]_2$/**316**, full conversion to the corresponding amine was achieved and the enantioselectivity increased up to 22%. In this context, for the complete hydrogenation of 2-methylquinoline only 0.05 mmol of iodine was necessary while 0.1 mmol of iodine were required for the full hydrogenation of N-(*β*-phenylethylidene)aniline. When the solvent was varied from toluene to

dichloromethane or mixtures of toluene/methanol and dichloromethane/methanol a decrease on the enantioselectivities was observed (Table 4.9, entry 4 *vs.* 5-7).

Table 4.9. Optimization of reaction conditions in the asymmetric hydrogenation of 2-methylquinoline with complex **341** or Ir/**316**.[a]



Entry	Iridium precursor	Solvent	Additive	Conv.[b] (%)	ee[c] (%)
1	[Ir(COD)**316**]BAr_F, (**341**)	Toluene	-	0	-
2	[Ir(COD)**316**]BAr_F, (**341**)	Toluene	I_2	99	14
3	[Ir(μ-Cl)COD]$_2$/**316**	Toluene	-	0	-
4	[Ir(μ-Cl)COD]$_2$/**316**	Toluene	I_2	98	22
5	[Ir(μ-Cl)COD]$_2$/**316**	CH_2Cl_2	I_2	95	13
6	[Ir(μ-Cl)COD]$_2$/**316**	Toluene/MeOH	I_2	89	3
7	[Ir(μ-Cl)COD]$_2$/**316**	CH_2Cl_2/MeOH	I_2	93	5

[a]*Reaction conditions:* Catalyst = 0.01 mmol, Substrate/Ir= 100, I_2=0.005 mmol, 2 mL solvent, rt. [b] Conversion determined by ^{1}H NMR and GC. [c] Enantioselectivities determined by chiral HPLC. Product has (*S*) configuration.

The phosphino or phosphite-imidazoline ligands were tested in the hydrogenation of 2-methylquinoline under the previously mentioned conditions (Table 4.10). The systems Ir/**316** and Ir/**317** provided conversions up to 98% and the same values of enantioselectivity (ee's 23%) (entries 1 and 2, Table 4.10). The introduction of various substituents at the nitrogen atom of the imidazoline ring produced a decrease in ee values (entries 4, 6-9, Table 4.10). This effect is independent of the substituent on the imidazoline ring. These results suggest that the acidic proton of the imidazoline ring can be abstracted in the presence of substrate giving the protonated 2-

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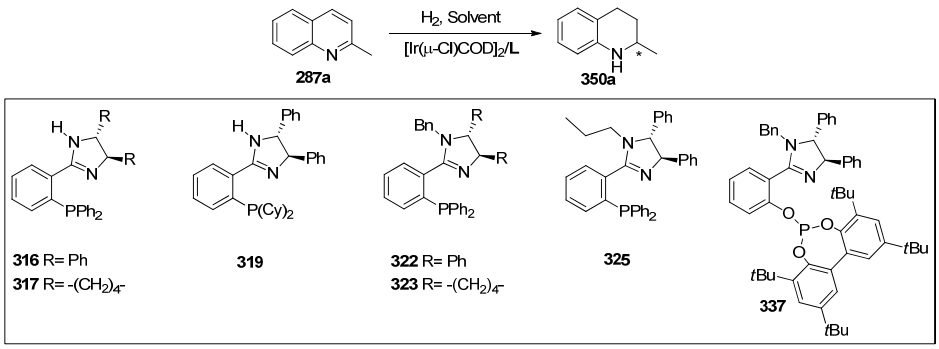
methylquinoline which is involved in the catalytic cycle, as mentioned in the introduction section of this chapter (Scheme 4.14). The corresponding ligand could be coordinated by the sp^3 nitrogen instead of the sp^2 (ligands **316** and **317**) or other coordination modes. However, ligands having a substituent at the nitrogen atom (**322**, **323** and **325**) force the coordination to the metal centre through the sp^2 nitrogen atom (Scheme 4.27).

Table 4.10. Asymmetric hydrogenation of 2-methylquinoline with Ir/**316**, **317**, **319**, **322**, **323**, **325** and **337**.[a]



Entry	Iridium precursor	Conv.[b] (%)	ee[c] (%)
1	[Ir(μ-Cl)COD]$_2$/**316**	98	22 (*S*)
2	[Ir(μ-Cl)COD]$_2$/**317**	96	23 (*R*)
3	[Ir(μ-Cl)COD]$_2$/**319**	99	60 (*S*)
4	[Ir(μ-Cl)COD]$_2$/**322**	94	7
5	[Ir(COD)**322**]BAr$_F$, (**343**)	11	2
6	[Ir(μ-Cl)COD]$_2$/**323**	99	3
7	[Ir(μ-Cl)COD]$_2$/**325**	99	9
8	[Ir(μ-Cl)COD]$_2$/**337**	53	44 (*S*)

[a]*Reaction conditions:* Catalyst = 0.01 mmol, Substrate/Ir= 100, I_2=0.01 mmol, 2 mL toluene, rt. [b] Conversion determined by ^{1}H NMR and GC. [c] Enantioselectivities determined by chiral HPLC.

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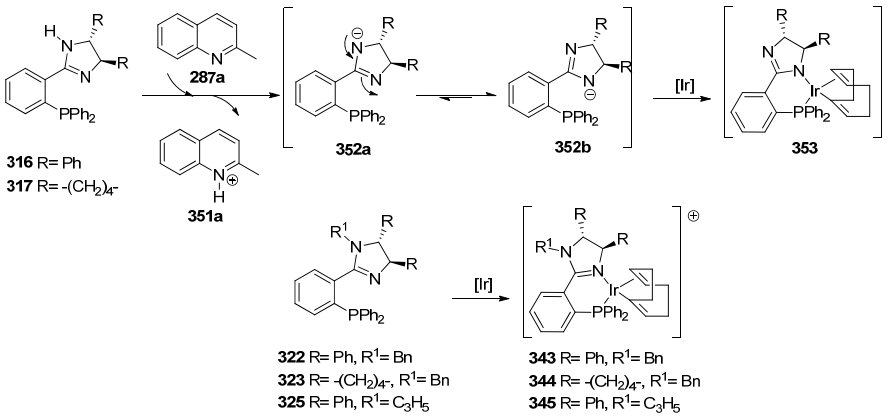
When the isolated complex **343** was used under the same conditions, the activity decreased (entry 5). The catalyst formed by Ir/**319** containing cyclohexyl rings showed high activity and an important increase in enantioselectivity (ee's up to 60%) (entry 3). In order to know if that behaviour was due to steric or electronic effects, the phosphite-imidazoline ligand **337** was tested under the same conditions. Comparing the result obtained with the phosphino-imidazoline ligand **322** (ee's up to 7%) with the result obtained with the catalytic system Ir/**337** the increase in the enantioselectivity is really significant (ee's up to 44%) (entry 4 *vs*. 8, Table 4.10).



Scheme 4.27. Proposed mechanism for the different behaviour of alkylated phosphino-imidazoline ligands and those without any substituent at the nitrogen atom.

Comparing the results obtained with Ir/**319** and **337**, it is obvious that in both cases an improvement on the enantioselectivity was achieved and the most important factor seems to be the steric hindrance that produces the cycloalkyl or the substituted biaryl with respect to the aryl groups in the conventional phosphino-imidazoline ligand.

Different additives were tested with the catalytic system formed by Ir/**319** in the asymmetric hydrogenation of **287a-c**. Entry 1 of Table 4.11 shows the result obtained in the presence of iodine which will be used as reference to compare the values obtained with various additives. Various iodide sources were tested such as NBu_4I, which has been extensively used as additive in the asymmetric hydrogenation of imines.[89]

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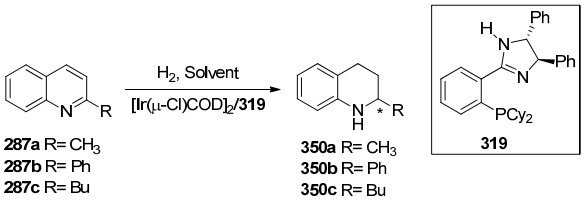
The catalytic system Ir/**319** did not show any activity in the presence of NBu_4I (entry 2, Table 4.11). When *N*-iodosuccinimide was used as the source of iodide, total conversion was achieved. In contrast, the enantioselectivity decreased in comparison with the ee achieved with iodine (entry 3 *vs*. 1, Table 4.11). Potassium iodide and a tridecafluorononyl iodide were also tested as iodide source but no activity was obtained. The effect of a combination of iodine and 10 mmol % of hydrochloric acid was also explored. However, no significant effect on the activity or enantioselectivity was observed.

Table 4.11. Asymmetric hydrogenation of quinoline derivatives with the catalytic system Ir/**319**.[a]



Entry	Substrate	Additive	Conv.[b] (%)	ee[c] (%)
1	**287a**	I_2	99	60
2	**287a**	NBu_4I	0	-
3	**287a**	N-Iodosuccinimide	99	43
4	**287a**	KI	0	-
5	**287a**	Tridecafluorononyl iodide	0	-
6	**287a**	I_2/HCl	99	56
7	**287a**	HCl	32	12
8[d]	**287a**	I_2	87	57
9	**287b**	I_2	99	15
10	**287c**	I_2	99	11

[a]*Reaction conditions:* Catalyst = 0.01 mmol, Substrate/Ir= 100, I_2=0.005 mmol, 2 mL toluene, rt. [b] Conversion determined by ^{1}H NMR and GC. [c] Enantioselectivities determined by chiral HPLC. [d] Reaction temperature= -10ºC. Product has (*S*) configuration.

As a conclusion, under these conditions the best additive is iodine. When the reaction was performed at -10ºC the conversion was slightly decreased at 87%

and the enantioselectivity practically remains the same 57% (entry 8, Table 4.11).

Even though the enantioselectivity achieved with the catalytic system Ir/**319** is modest, there is only one efficient catalytic system bearing a P,N ligand published for this substrate up to date.[101]

Furthermore, two different quinoline derivatives (**287b** and **287c**) were hydrogenated with the catalytic system Ir/**319** in the presence of iodine in toluene under 40 bars of hydrogen pressure. Both amines were obtained with poor enantioselectivities (up to 15%) (entry 9 and 10, Table 4.11).

When the hydrogenation of 2-methylquinoxaline was carried out in toluene at room temperature under 40 bars of hydrogen, the catalytic system Ir/**316** was not active even in the presence of iodine as additive (entries 1 and 2, Table 4.12). Various solvents were tested at room temperature or at 50ºC. When the reaction was performed in methanol at 50ºC, this catalytic system was very active and an additive was not required to obtain practically full conversion (entries 7 and 8). When the hydrogen pressure was decreased to 15 bars, the desired amine was produced with excellent conversion but low ee's (entry 9). When the complex **341** was used, no improvement in enantioselectivity was detected (entry 10). Modifying the phenyl groups of the imidazoline ring **316** by a cyclohexyl **317** gave very high conversion but no enantioselectivity (entry 11). The catalytic system Ir/**319** did not afford any improvement in the enantioselectivity (entry 12). The isolated complex **347** gave very low conversions and enantioselectivities (entries 13-15).

Summarising the results obtained in the Ir-catalysed asymmetric hydrogenation of imines, we can conclude that cationic complexes [Ir(COD)**L**]BAr_F were very active in the hydrogenation of N-(β-phenylethylidene)aniline but not enantioselective. It should be noted that the catalytic systems Ir/**L** requires the addition of iodine as additive to be active. The replacement of phenyl groups by cyclohexyl rings on the imidazoline ring produces a slight increase in enantioselectivity (from 6 to 24%) with Ir/**316** and Ir/**317** respectively. The introduction of substituents at the nitrogen atom of the imidazoline ring did not improve the catalytic results.

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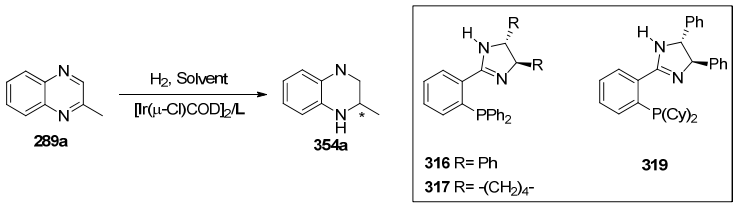
Table 4.12. Asymmetric hydrogenation of 2-methylquinoxaline with Ir/**316**, **317**, **319** and **341** and **347** complexes.[a]



Entry	Iridium precursor	Solvent	Temp. (ºC)	PH_2	Additive	Conv.[b] (%)	ee[c] (%)
1	[Ir(μ-Cl)COD]$_2$/**316**	Toluene	rt	50	-	0	-
2	[Ir(μ-Cl)COD]$_2$/**316**	Toluene	rt	50	I_2	0	-
3	[Ir(μ-Cl)COD]$_2$/**316**	CH_2Cl_2	rt	50	I_2	0	-
4	[Ir(μ-Cl)COD]$_2$/**316**	THF	rt	50	I_2	0	-
5	[Ir(μ-Cl)COD]$_2$/**316**	MeOH	rt	50	I_2	0	-
6	[Ir(μ-Cl)COD]$_2$/**316**	THF	50	50	I_2	0	-
7	[Ir(μ-Cl)COD]$_2$/**316**	MeOH	50	50	I_2	92	1
8	[Ir(μ-Cl)COD]$_2$/**316**	MeOH	50	50	-	99	2
9	[Ir(μ-Cl)COD]$_2$/**316**	MeOH	50	15	-	99	5
10	[Ir(COD)**316**]BAr_F, (**341**)	MeOH	50	15	-	99	3
11	[Ir(μ-Cl)COD]$_2$/**317**	MeOH	50	15	-	89	0
12	[Ir(μ-Cl)COD]$_2$/**319**	MeOH	50	15	-	97	2
13	[Cp*IrCl(**317**)BF_4, (**347**)	MeOH	50	15	-	27	3
14	[Cp*IrCl(**317**)BF_4, (**347**)	CH_2Cl_2	50	15	-	0	-
15	[Cp*IrCl(**317**)BF_4, (**347**)	MeOH/ CH_2Cl_2	50	15	-	13	0

[a]*Reaction conditions:* Catalyst = 0.01 mmol, Substrate/Ir= 100, I_2=0.01 mmol, 2 mL toluene, rt. [b] Conversion determined by ^{1}H NMR and GC. [c] Enantioselectivities determined by chiral HPLC.

The asymmetric hydrogenation of 2-methylquinoline and their derivatives requires the addition of additives to the iridium precursor to achieve catalytic

activities. Different additives were tested obtaining the best results with iodine. Poor enantioselectivities were obtained with the systems Ir/**316** and Ir/**317** (up to 24%). The introduction of electron-donating groups at the nitrogen atom of the imidazoline ring produced racemic amines. The introduction of a bulkier and electron-rich substituent at the phosphorus atom gave an important rise on the enantioselectivity (Ir/**319**) (up to 60%). If the phosphine function is substituted by a phosphite Ir/**337**, an improvement in ee (40%) was observed but the activity was lower. It was therefore concluded that the presence of bulky substituents at the phosphorus atom is required to achieve moderate to good enantioselectivities, when the phosphorus function is a phosphine or a phosphite.

As previously mentioned in the introduction, there are only a few examples of the use of P,N-ligands in the asymmetric hydrogenation of cyclic imines.[112] Furthermore, to the best of our knowledge, the hydrogenation of 2-methylquinoline or 2-methylquinoxaline using phosphino-imidazoline or phosphite-imidazoline ligands has not been reported.

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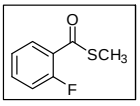
4.3. Experimental section

General Methods

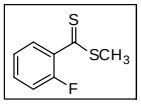
All reactions were carried out under an argon atmosphere using Standard Schlenk techniques. Solvents were distilled and degassed prior to use. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini spectrometer at 300 and 400 MHz. Chemical shifts were reported relative to tetramethylsilane for ^{1}H and $^{13}C\{^{1}H\}$ as internal reference, H_3PO_4 85% for $^{31}P\{^{1}H\}$, and trichlorofluoromethane for $^{19}F\{^{1}H\}$ as external references. Elemental analyses were carried out on a Carlo Erba Microanalyser EA 1108. VG-Autospect equipment was used for FAB mass spectral analyses with 3-nitrobenzylalcohol as matrix. EI mass spectra were obtained on an HP 5989 A spectrometer at an ionizing voltage of 70eV. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Conversion was measured by NMR spectrometry or GC chromatography. The enantiomeric excesses were measured by HPLC (OJ-H and OD-H chiral columns)

2-Fluoro-thiobenzoic acid *S*-methyl ester (310)[11]



2-fluorobenzoylchloride (1.96 ml, 15 mmol) was added dropwise at 0ºC to a suspension of 1.20 g (17 mmol) of methanethiolate sodium salt with 17 ml of dichloromethane. After 1 hour at room temperature, the reaction mixture was quenched with water (20 ml). After several extractions with dichloromethane, the combined organic layers were dried and concentrated to afford 3.5g (99 % yield) of compound **310** as a yellow liquid, which was used without purification in the next reaction. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.82 (m, 1H, arom.); 7.45 (m, 1H, arom.); 7.18-7.08 (m, 2H, arom); 2.45 (s, 3H, CH_3). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 188.6 (C=O); 159.9 (d, ^{1}J=257.1 Hz, C, arom.); 134.2 (d, ^{3}J=8.8 Hz, CH, arom.); 129.5 (CH, arom.); 125.2 (d, ^{2}J=11.3 Hz, C, arom.); 124.1 (d, ^{3}J=3.4 Hz, CH, arom.); 116.6 (d, ^{2}J=22.2 Hz, CH, arom.); 12.0 (CH_3).

2-Fluoro-dithiobenzoic acid *S*-methyl ester (311)[11]



Lawesson's reagent (2 g, 5.4 mmol) was added under argon to a solution of **310** (325 mg, 1.4 mmol) in dry toluene (17 ml) and the mixture

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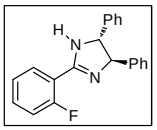
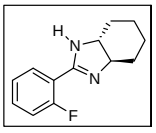
was heated to reflux. The reaction was monitored by TLC. When no starting material could be detected (ca. 24 hours), the reaction mixture was allowed to cool, and filtered. The solid was washed with toluene and the combined toluene solutions were evaporated and purified by flash column chromatography to afford 318 mg (92 % yield) of compound **311** as a red liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.56 (m, 1H, arom.); 7.34 (m, 1H, arom.); 7.13-7.03 (m, 2H, arom); 2.71 (s, 3H, CH_3). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 224.2 (C=S), 157.3 (d, ^{1}J=253.1 Hz, C, arom.), 134.5 (d, ^{2}J=12.4Hz, C, arom.), 132 (d, ^{3}J=8.5 Hz, CH, arom.), 129.5 (CH, arom), 123.9 (d, ^{3}J=3.7 Hz, C, arom.), 116.3 (d, ^{2}J=22.2 Hz, CH, arom.), 20.9 (CH_3).

(4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydroimidazole (314) [11]



A solution of 2-fluoro-dithiobenzoic acid *S*-methyl ester (**311**) (326 mg, 1.75 mmol) in dimethylformamide (3ml) was added to a suspension of (1*R*,2*R*)-diphenylethylene diamine (**312**) (407 mg, 1.92 mmol) and red mercury (II) oxide (414 mg, 1.9 mmol) in dimethylformamide (2 ml) at room temperature and vigorously stirred. The solution was heated at 110ºC for 30 minutes. Then, the reaction mixture was filtered, concentrated under reduced pressure and purified by flash column chromatography to afford 509 mg (93% yield) of compound **314** as a white powder. **$[\alpha]_D^{20}$=** + 0.485º (c=0.811, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.28 (dt, 1H, J=7.6 Hz, J=1.6 Hz, arom.), 7.49-7.12 (m, 13H, arom.), 5.99 (s, 1H, NH), 4.89 (s, 2H, CH). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 162.1 (C=N), 159.4 (d, ^{1}J=32.9 Hz, C, arom.), 143.3 (C, arom.), 132.6 (d, ^{3}J=9.15 Hz, CH, arom.), 131.3 (d, ^{4}J=2.3 Hz, CH, arom.), 128 (CH, arom.), 127.5 (CH, arom.), 126.6 (CH, arom.), 124.6 (d, ^{3}J=3.1 Hz, CH, arom.), 117.6 (d, ^{2}J=10.6 Hz, C, arom.), 116.1 (d, ^{2}J =23.6 Hz, CH, arom.). **^{19}F NMR** ($CDCl_3$, 332.5 MHz, δ ppm): -114.2 (m). **HRMS** (ESI-TOF): *m/z*= 316.1365, calcd for [M^+]: 316.1327. Anal. Calcd for $C_{21}H_{17}FN_2$**:** C, 79.72, H, 5.42; N, 8.85. Found: C, 79.67; H, 5.60; N, 8.89.

(3a*R*,7a*R*)-2-(2'-Fluorphenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazol (315)



Following the previous procedure, a solution of 2-fluoro-dithiobenzoic acid *S*-methyl ester (**311**) (326 mg, 1.75 mmol)

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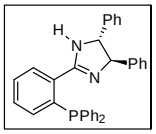
in dimethylformamide (3ml) was added to a suspension of (1*R*,2*R*)-cyclohexane-1,2-diamine (219 mg, 1.92 mmol) and red mercury (II) oxide (414 mg, 1.9 mmol) in dimethylformamide (2 ml) at room temperature and vigorously stirred. The solution was heated at 110ºC for 30 minutes. Then, the reaction mixture was filtered, concentrated under reduced pressure and purified by flash column chromatography to afford 314 mg (86% yield) of compound **315** as a white powder. **[α]$_D^{20}$=** + 116º (c=1.00, CH_2Cl_2).[111] **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.10 (dt, 1H, ^{3}J=7.8 Hz, ^{4}J=1.9 Hz, arom.), 7.40 (m, 1H), 7.18 (dt, 1H, ^{3}J=7.6 Hz, ^{3}J=1.1 Hz, arom.), 7.09 (ddd, 1H, ^{3}J= 12.1Hz, ^{3}J= 8.3 Hz, ^{4}J= 1.1 Hz, arom.), 5.67 (br s, 1H, NH), 3.11 (m, 2H, CH), 2.30 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 1.35 (m, 2H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 162.2 (C=N), 161.0 (d, ^{1}J=25.0 Hz, C, arom.), 116.2-132.4 (arom), 69.2 (CH), 30.9 (CH_2), 25.1 (CH_2). **^{19}F NMR** ($CDCl_3$, 332.5 MHz, δ ppm): -114.4 (m).[111] **HRMS** (ESI-TOF): *m/z*= 219.1295, calcd for [M^+]: 219.1298. Anal. Calcd for $C_{13}H_{15}FN_2$**:** C, 71.53; H, 6.93; F, 8.70; N, 12.83. Found: C, 71.48; H, 7.01; N, 12.89.

(4*R*,5*R*)-2-[(2-diphenylphosphine)phenyl]-4,5-diphenyl-4,5-dihydroimidazole (316) [11]



A mixture of 150 mg (0.475 mmols) of (4*R,5R*)-2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydroimidazole (**314**) in 40 µl of anhydrous tetrahydrofuran and 1.04 ml (0.522 mmols) of potassium diphenylphosphide (0.5 M in tetrahydrofuran) was heated at 60ºC for 1 hour. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography under argon to give 226 mg (99% yield) of compound **316** as a white solid. **[α]$_D^{20}$=** -0.192º (c=0.57, CH_2Cl_2). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.80 (m, 1H, arom.), 7.32-7.11 (m, 22H, arom.), 6.80 (m, 1H, arom), 5.86 (s broad, 1H, NH), 4.73 (m, 1H, CH), 4.48 (m, 1H, CH). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 164.2 (C=N), 143.3-126.7 (arom), 80.3 (CH), 71.3 (CH). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): -10.3. **HRMS** (ESI-TOF): *m/z*= 483.1988, calcd for [M^+]: 483.1990. Anal. Calcd for $C_{33}H_{27}N_2P$**:** C, 82.14; H, 5.64; N, 5.81; P, 6.42. Found: C, 82.09; H, 5.71; N, 5.87.

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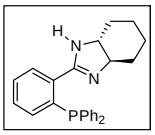
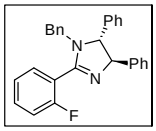
(3a*R*,7a*R*)-2-(2'-Diphenylphosphanylphenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazol (317)



Following the previous procedure, a mixture of 104 mg (0.475 mmols) of (3a*R*,7a*R*)-2-(2'-Fluorphenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazol (**315**) in 40 µl of anhydrous tetrahydrofuran and 1.04 ml (0.522 mmols) of potassium diphenylphosphide (0.5 M in tetrahydrofuran) was stirred at room temperature for 12 hours. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography under argon to give 154 mg (84% yield) of compound **317** as a white solid. $[\alpha]_D^{20}$= +57.8 (*c* = 1.02, CH_2Cl_2) **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.65 (m, 1H, arom.), 7.37-7.26 (m, 12H, arom.), 6.88 (m, 1H, arom), 5.24(br s, 1H, NH), 2.75 (br s, 2H, CH), 2.12 (m, 2H, CH_2); 1.73 (m, 2H, CH_2); 1.33 (m, 2H, CH_2); 1.21 (m, 2H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 166.2 (C=N), 137.7-128.4 (arom), 69.7 (CH), 30.8 (CH_2); 25.4 (CH_2). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): -9.8.[111] **HRMS** (ESI-TOF): *m/z*= 341.1840, calcd for [M^+]: 341.1834. Anal. Calcd for $C_{25}H_{25}N_2P$**:** C, 78.10; H, 6.55; N, 7.29; P, 8.06. Found: C, 78.08; H, 6.71; N, 7.33.

(4*R*,5*R*)-1-benzyl-2-[(2-fluorophenyl)phenyl]-4,5-diphenyl-4,5-dihydroimidazole (320)



A total of 125 mg (0.395 mmol) of (4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydroimidazole (**314**) in 1 ml of anhydrous tetrahydrofuran was added to a cooled solution (0ºC) of 17.4 mg (0.43 mmol) of NaH (60% in oil suspension) and 0.5 ml of anhydrous tetrahydrofuran. The mixture was stirred for 30 min and then benzyl bromide (47 µl, 0.395 mmol) was added dropwise. After 3 hours, the reaction was stopped by adding a few drops of methanol and further purification gave 88.5 mg (55% yield) of compound **320** as a pale yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.70 (m, 1H, arom.), 7.48 (m, 1H, arom), 7.47-7.19 (m, 15H, arom.), 6.90 (m, 2H, arom), 5.00 (d, ^{3}J=8.2 Hz, CH), 4.44 (d, ^{2}J=15.6 Hz, CH_2), 4.36 (d, ^{3}J=8.2 Hz, CH), 3.90 (d, ^{2}J=15.6 Hz, CH2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 161.9 (C=N), 159.4 -116.1 (arom**.**)**,** 78.4 (CH), 72.2 (CH), 49.0 (CH_2). **^{19}F NMR** ($CDCl_3$, 332.5 MHz): -112.9. **HRMS** (ESI-TOF): *m/z*= 407.1929, calcd for [M^+]: 407.1924. Anal. Calcd for $C_{28}H_{23}FN_2$**:** C, 82.73; H, 5.70; F, 4.67; N, 6.89. Found: C, 82.64; H, 5.79; N, 6.92.

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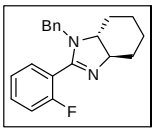
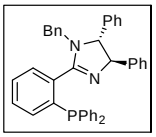
(3aR,7aR)-1-benzyl-2-(2-fluorophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzo[d]imidazole (321)



Following the previous procedure: a total of 86 mg (0.395 mmol) of (3a*R*,7a*R*)-2-(2'-Fluorphenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazol (**315**) in 1 ml of anhydrous tetrahydrofuran was added to a cooled solution (0ºC) of 17.4 mg (0.43 mmol) of NaH (60% in oil suspension) and 0.5 ml of anhydrous tetrahydrofuran. The mixture was stirred for 30 min and then benzyl bromide (47 µl, 0.395 mmol) was added dropwise. After 3 hours, the reaction was stopped by adding a few drops of methanol and further purification gave 66 mg (54% yield) of compound **321** as a pale yellow solid. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.43 (m, 1H, arom.), 7.35-6.95 (m, 8H, arom), 4.36 (d, ^{2}J=15.6 Hz, 1H, CH_2), 3.83 (d, ^{2}J=15.6 Hz, CH_2), 3.14 (m, 1H, CH), 2.67 (m, 1H, CH), 2.31 (m, 1H, CH_2), 1.74-1.60 (m, 2H, CH_2), 1.40-1.07 (m, 4H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 164.8 (C=N), 160.6-115.9 (arom.)**,** 71.9 (CH), 71.6 (CH), 52.0 (CH_2), 31.3 (CH_2), 30.4 (CH_2), 25.7 (CH_2), 24.7 (CH_2). **^{19}F NMR** ($CDCl_3$, 332.5 MHz, δ ppm): -111.6. **HRMS** (ESI-TOF): *m/z*= 309.1762, calcd for [M^+]: 309.1767. Anal. Calcd for $C_{20}H_{21}FN_2$**:** C, 77.89; H, 6.86; F, 6.16; N, 9.08. Found: C, 77.57; H, 6.93; N, 9.12.

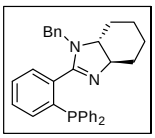
(4*R*,5*R*)-1-benzyl-2-[(2-diphenylphosphine)phenyl]-4,5-diphenyl-4,5-dihydroimidazole (322)



A mixture of 88.5 mg (0.218 mmols) of (4*R*,5*R*)-1-benzyl-2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydroimidazole **320** and 0.5 ml (0.239 mmols) of potassium diphenylphosphide (0.5 M in tetrahydrofuran) was heated at 60ºC for 1 hour. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography under argon to give 68 mg (54% yield) of compound **322** as a white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.70 (m, 1H, arom.), 7.44 (m, 1H, arom), 7.38-7.10 (m, 25H, arom.), 6.90 (m, 2H, arom), 4.93 (d, ^{3}J=9.8 Hz, CH), 4.44 (d, ^{3}J=9.8 Hz, CH), 4.28 (d, ^{2}J=17 Hz, CH_2), 3.70 (d, ^{2}J=17 Hz, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 164.9 (C=N), 143.9-126.8 (arom), 78.8 (CH), 72.8 (CH), 49.3 (CH_2). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): -12.3. **HRMS** (ESI-TOF): *m/z*= 573.2492, calcd for [M^+]: 573.2460. Anal. Calcd for

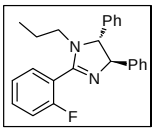
$C_{40}H_{33}N_2P$**:** C, 83.89; H, 5.81; N, 4.89; P, 5.41. Found: C, 83.92; H, 5.89; N, 4.23.

(3a*R*,7a*R*)-1-Benzyl-2-(2'-diphenylphosphanylphenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazol (323)



A mixture of 67 mg (0.218 mmols) of (3a*R*,7a*R*)-1-benzyl-2-(2-fluorophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzo[d]imidazole **321** and 0.5 ml (0.239 mmols) of potassium diphenylphosphide (0.5 M in tetrahydrofurane) was heated at 60ºC for 1 hour. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography under argon to give 56 mg (54% yield) of compound **323** as a white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.41-7.02 (m, 19 H, arom), 4.32 (d, ^{2}J=15.7 Hz, 1 H, CH_2), 3.56 (d, ^{2}J= 15.7 Hz, 1 H, CH_2), 2.96 (m, 1 H, CH), 2.40 (m, 1H, CH), 2.26 (m, 1H, CH_2), 1.71 (d, J= 12.8 Hz, 1 H, CH_2), 1.59 (d, J= 12.9 Hz, 1 H, CH_2), 1.55 (dd, J= 11.5 Hz, ^{3}J= 3.0 Hz, 1 H, CH_2), 1.42-0.96 (m, 4H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 167.6 (C=N), 139.1-127.1 (arom), 71.8 (CH), 71.4 (CH), 51.8 (CH_2), 31.4 (CH_2), 30.2 (CH_2), 25.6 (CH_2), 23.9 (CH_2).[111] **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): –10.3 ppm. **HRMS** (ESI-TOF): *m/z*= 573.2492, calcd for [M^+]: 573.2460. Anal. Calcd for $C_{32}H_{31}N_2P$**:** C, 80.99; H, 6.58; N, 5.90; P, 6.53. Found: C, 80.86; H, 6.63; N, 5.95.

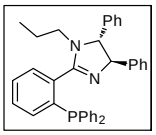
(4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-1-propyl-4,5-dihydro-1H-imidazole (324).



A solution of (4*R*,5*R*)-2-(2-fluoro-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazole (**314**) (170 mg, 0.54 mmol) in 1mL of anhydrous tetrahydrofurane was added to a cooled solution (0ºC) of 23.57 mg (0.59 mmol) of NaH (60% in oil suspension) and 0,5 mL of anhydrous tetrahydrofurane. The mixture was stirred for 30 min and then propylbromide (49.2 µl, 0.54 mmol) was added drop wise. After 3h, the reaction was stopped by adding a few drops of methanol. Purification by column chromatography (hexane/ethyl acetate 1:1 (5% NEt_3)) to give compound **324** as a yellow oil (100 mg, 52%). **$[\alpha]_D^{20}$= -61.86º** (c=1.01, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.31 (m, 1H, arom); 7.70 (m, 1H, arom); 7.50-7.17 (m, 12H, arom); 5.02 (d, ^{3}J=8.8Hz, 1H, CH); 4.55 (d, ^{3}J=7.2 Hz, 1H, CH); 3.04-2.88 (m, 2H,

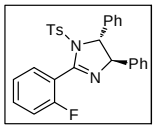
CH_2); 1.41-1.22 (m, 2H, CH_2); 0.65 (t, ^{3}J=7.6Hz, CH_3). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 162.2 (C=N), 144.6-116.1 (arom); 78.5 (CH); 73.5 (CH); 47.1 (CH_2); 20.9 (CH_2); 11.3 (CH_3). **^{19}F NMR** ($CDCl_3$, 332.5 MHz): -113.9 (m); **HRMS** (ESI-TOF): *m/z* = 315.1928, calcd for $[M]^+$: 315.1924. Anal. Calcd for $C_{24}H_{23}FN_2$: C, 80.42; H, 6.47; F, 5.30; N, 7.82. Found: C, 80.38; H, 6.56; N, 7.85.

(4*R*,5*R*)-2-(2-diphenylphosphanyl-phenyl)-4,5-diphenyl-1-propyl-4,5-dihydro-1H-imidazole (325).



Compound **324** (100 mg, 0.279 mmol) was added to a solution of potassium diphenylphosphide (0.61mL, 0.307 mmol, 0.5M in THF) and the resulting mixture was stirred overnight at room temperature. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography under nitrogen (hexane/ethyl acetate 1:1(5% NEt_3)) to give compound **325** as a white solid (111 mg, 76%). **[α]$_D^{20}$=** -22.77º (c=0.60, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.31 (m, 1H, arom); 7.64 (m, 1H, arom); 7.48-7.12 (m, 22H, arom); 4.94 (d, ^{3}J=9.6Hz, 1H, CH); 4.47 (d, ^{3}J=10 Hz, 1H, CH); 2.85-2.68 (m, 2H, CH_2); 1.31-1.14 (m, 2H, CH_2); 0.59 (t, ^{3}J=7.2Hz, CH_3). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 162.2 (C=N), 144.4-126.9 (arom); 79.1 (CH); 74.4 (CH); 47.8 (CH_2); 21.1 (CH_2); 11.3 (CH_3). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm):-12.7 (s). **HRMS** (ESI-TOF): *m/z* = 525.2464, calcd for $[M]^+$: 525.2460. Anal. Calcd for $C_{36}H_{33}N_2P$: C, 82.42; H, 6.34; N, 5.34; P, 5.90. Found: C, 82.37; H, 6.41; N, 7.95.

(4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-1-tosyl-4,5-dihydro-1*H*-imidazole (326)



To a solution of compound (4*R*,5*R*)-2-(2-fluoro-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazole (**314**) (300 mg, 0.54 mmol) and 4-dimethylaminopyridine (120.5 mg, 0.98 mmol) in CH_2Cl_2 (2 mL) at 273K, a solution of *p*-toluenesulphonylchloride (125.1 mg, 0.65 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 5h. Evaporation of the mixture gave a yellow oil that was purified by column chromatography (hexane/ethyl acetate 6:4 (5% NEt_3)) to obtain **326** as a white foam (290 mg, 65%). **[α]$_D^{20}$=** -59.66º (c=1.02, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.60 (m, 1H, arom); 7.47-6.81

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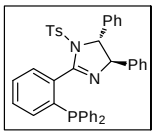
(m, 17H, arom); 5.02 (d, ^{3}J=4.9Hz, 1H, CH); 4.99 (d, ^{3}J=4.9 Hz, 1H, CH); 2.31 (s, 3H, CH_3); **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 162.2 (C=N), 144.6-116.1 (arom); 78.2 (CH); 72.5 (CH); 21.3 (CH_3). **^{19}F NMR** ($CDCl_3$, 332.5 MHz): -114.7 (m). **HRMS** (ESI-TOF): *m/z* = 471.1545, calcd for $[M]^+$: 471.1543. Anal. Calcd for $C_{28}H_{23}FN_2O_2S$: C, 71.47; H, 4.93; F, 4.04; N, 5.95; O, 6.80; S, 6.81. Found: C, 71.43; H, 5.01; N, 5.98; S, 6.86.

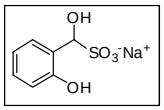
(4*R*,5*R*)-2-(2-diphenylphosphanyl-phenyl)-4,5-diphenyl-1-tosyl-4,5-dihydro-1H-imidazole (327)



Procedure a: Compound **326** (102 mg, 0.217 mmol) was added to a solution of potassium diphenylphosphide (0.48 mL, 0.238 mmol, 0.5M en THF) and the resulting mixture was stirred overnight at room temperature. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography under nitrogen (hexane/ethyl acetate 6:4 (5% NEt_3)) to give compound **327** as a white solid (104 mg, 76%).

Procedure b: Compound **316** (100 mg, 0.21 mmol) was stirred in tetrahydrofurane at 0ºC. Then, a solution of KH (13mg, 0.22 mmol) was added. The solution was stirred for 15 minutes at room temperature. The, TsF (43.6 mg, 0.25 mmol) were added at room temperature. The solution was stirred for 64 hours at room temperature. **$[\alpha]_D^{20}$=** -35.72º (c=1.01, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.43 (m, 1H, arom); 7.70-6.88 (m, 27H, arom); 5.10 (d, ^{3}J=4.8Hz, 1H, CH); 5.07 (d, ^{3}J=4.8Hz, 1H, CH); 2.40 (s, 3H, CH_3); **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 162.2 (C=N), 144.7-115.9 (arom); 78.4 (CH); 72.0 (CH); 21.8 (CH_3). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): -10.4 (s). **HRMS** (ESI-TOF): *m/z* = 637.2073, calcd for $[M]^+$: 637.2079. Anal. Calcd for $C_{40}H_{33}N_2O_2PS$: C, 75.45; H, 5.22; N, 4.40; O, 5.03; P, 4.86; S, 5.04. Found: C, 75.39; H, 5.28; N, 4.45; S, 5.07.

Sodium hydroxy(2-hydroxyphenyl)methanesulfonate (329)



0.04 mol of 2-hydroxybenzaldehyde and 0.04 mol of sodium bisulfide were dissolved in 20 mL of ethanol and water, respectively. Then the solution was stirred for 10 min at room temperature. The mixture was filtered and sodium hydroxyl (2-hydroxyphenyl)methane sulfonate salt (86%) was obtained from the crude extract and it was used without further purification.

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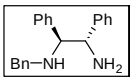
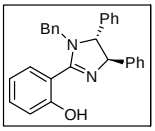
(1*R*,2*R*)-N1-benzyl-1,2-diphenylethane-1,2-diamine (331)



To a solution of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (1.26 g, 6.0 mmol) in anhydrous DMF (30 mL), activated 4A molecular sieves (1.9 g) and cesium hydroxide monohydrate (509 mg, 3.0 mmol) were added. After being stirred for 30 minutes at room temperature, BnCl (633 µL, 5.5 mmol) was added to solution at 0ºC for 15 minutes. Then, the solution was stirred at room temperature for 12 hours. The salts were filtered off and the solution was concentrated in *vacuo*. The residue was extracted with an aqueous solution of NaOH (1M) and extracted with diethyl acetate (3x15 mL) and dried over $MgSO_4$. The crude of the reaction was purified by a flash silica gel column chromatography affording compound **331** in 57% yield. **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.31-7.00 (m, 15H, arom); 4.88 (d, ^{3}J=9.6Hz, 1H, CH); 4.35 (d, ^{2}J=14.8Hz, 1H, CH_2); 4.00 (d, ^{3}J=9.6Hz, 1H, CH); 3.82 (d, ^{2}J=14.8Hz, 1H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 143.4-126.6 (arom), 80.2 (CH), 72.1 (CH), 49.6 (CH_2).

2-((4*R*,5*R*)-1-benzyl-4,5-diphenyl-4,5-dihydro-1H-imidazol-2-yl)phenol (334)



The crude of sodium hydroxyl (2-hydroxyphenyl)methanesulfonate (**329**) (2.26 g, 0.01 mol) and (1*R*,2*R*)-N1-benzyl-1,2-diphenylethane-1,2-diamine (**331**) (3.02 g, 0.01 mol) were mixed in dimethylformamide (30 mL). Then, the solution was heated at 80ºC for 12 hours. Later, the solution was cooled at room temperature and the solvent was removed under vacuum. The reaction crude was purified by silica gel column chromatography (hexane/ethyl acetate 8:2). The compound **334** was obtained in 74% yield (2.9 g). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.63 (d, J=8Hz, 1H, arom); 7.44-7.01 (m, 17H, arom), 6.86 (m, 1H, arom), 5.06 (d, ^{3}J=8.4Hz, 1H, CH); 4.97 (d, ^{2}J=16.4Hz, 1H, CH_2); 4.37 (d, ^{3}J=8.4Hz, 1H, CH); 4.24 (d, ^{2}J=16.4Hz, 1H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 165.6 (C=N), 160.7 (C, arom), 142.9-112.6 (arom), 75.9 (CH), 73.2 (CH), 51.2 (CH_2). **HRMS** (ESI-TOF): *m/z* =405.1959, calcd for $[M]^+$: 405.1967. Anal. Calcd for $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98; N, 6.93; O, 3.96. Found: C, 83.08; H, 6.02; N, 6.99.

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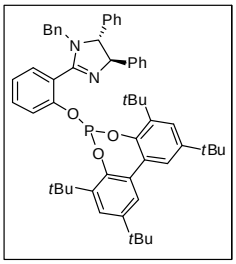
(4*R*,5*R*)-1-benzyl-4,5-diphenyl-2-(2-((2,4,8,10-tetra-tert-butyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)oxy)phenyl)-4,5-dihydro-1H-imidazole (337)

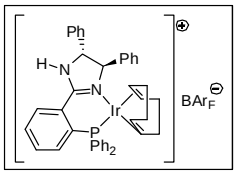


To a solution of compound **334** (250mg, 0.62 mmol), which was previously azeotropically dried with toluene (3x2mL), in dry and degassed tetrahydrofurane (2mL) was added dropwise *n*-butyl lithium (308µL, 0.77 mmol, 2.5M) followed by N,N,N',N'-tetramethylethylenediamine (206µL, 1.35 mmol) at -78ºC. The cooling bath was removed and the reaction mixture was stirred for 1 hour. Then, phosphorochlorhydrite (320mg, 0.67 mmol) was added at 0ºC during 15 minutes. The resulting solution was stirred overnight at room temperature. After that, the solvent was removed under vacuum and the residue was purified by silica gel column chromatography (hexane/ethyl acetate 4:1, and then pure ethyl acetate (7% NEt_3)). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.46 (d, J=7.2Hz, 1H, arom); 7.31-7.28 (m, 2H, arom), 7.12-6.99 (m, 6H, arom), 6.88-6.63 (m, 13H, arom), 6.57 (m, 1H, arom), 4.89 (d, ^{3}J=9.6Hz, 1H, CH); 4.20 (d, ^{2}J=15.6Hz, 1H, CH_2); 4.12 (d, ^{3}J=9.6Hz, 1H, CH), 3.39 (d, ^{2}J=15.6Hz, 1H, CH_2), 1.23 (s, 9H, CH_3), 1.22 (s, 9H, CH_3), 1.02 (s, 9H, CH_3), 1.01 (s, 9H, CH_3). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 162.8 (C=N), 149.7-119.9 (arom), 82.2 (CH), 71.5 (CH), 53.9 (CH_2), 40.35 (C), 39.38 (C), 32.1 (CH_3), 31.7 (CH_3), 31.6 (CH_3), 31.5 (CH_3). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, -90ºC, δ ppm): 151.9 (s), 138.9 (s). **HRMS** (ESI-TOF): *m/z* =843.4657, calcd for $[M]^+$: 843.4655. Anal. Calcd for $C_{56}H_{63}N_2O_3P$: C, 79.78; H, 7.53; N, 3.32; O, 5.69; P, 3.67 Found: C, 79.60; H, 7.65; N, 3.57.

Synthesis of Iridium complexes: General Procedure

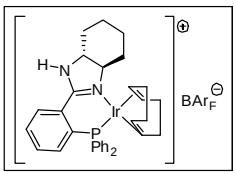
$[Ir(\mu\text{-}Cl)COD]_2$ (0.11 mmol) were added to solution of the corresponding phosphino-imidazoline ligand (0.2 mmol) in anhydrous dichloromethane (2mL). The solution was stirred for 2 hours under reflux conditions. After 5 minuts at room temperature, $NaBAr_F$ (0.26 mmol) was added to the mixture and 2mL of degassed water. The solution was vigorously stirred for 30 minutes and then, the organic phase was separated. The aquous phase was extracted with dichloromethane (3x10 mL). The organic phases were collected and filtered through celite. Later, the solution was dried over $MgSO_4$. Finally, the solvent was removed under vacuum affording the desire complexes in good yields (53-68%).

[Ir(COD)316]BAr_F (341)



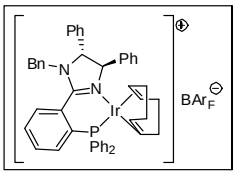
^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.01-6.47 (m, 36H, CH arom); 5.07 (d, ^{3}J=4.8Hz, 1H, CH); 4.94 (m, 1H, CH(COD)); 4.81 (m, 1H, CH(COD)); 4.54 (d, ^{3}J=4.8Hz, 1H, CH); 3.03 (m, 1H, CH(COD)); 2.87 (m, 1H, CH(COD)); 2.36 (m, 1H, CH_2(COD)); 2.15 (m, 1H, CH_2(COD)); 2.02 (m, 3H, CH_2(COD)); 1.72 (m, 1H, CH_2(COD)); 1.52 (m, 2H, CH_2(COD)). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 162.9 (q, ^{1}J=66.3Hz, arom), 162.1 (d, ^{3}J=9.9Hz, C=N), 141.5-117.6 (arom), 96.6 (d, ^{2}J=11.8Hz, CH, COD), 94.4 (d, ^{2}J=11.8Hz, CH, COD), 79.9 (CH), 68.4 (CH), 68.1 (CH, COD), 61.4 (CH, COD), 34.2 (CH_2, COD), 31.5 (CH_2, COD), 30.0 (CH_2, COD), 27.7 (CH_2, COD). **^{19}F NMR** ($CDCl_3$, 332.5 MHz): -62.12. **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 15.7 (s). **HRMS** (ESI-TOF): *m/z* =843.4657, calcd for $[M]^+$: 843.4655. Anal. Calcd for $C_{73}H_{51}BF_{24}IrN_2P$: C, 53.26; H, 3.12; B, 0.66; F, 27.70; Ir, 11.68; N, 1.70; P, 1.88 Found: C, 79.60; H, 7.65; N, 3.57.

[Ir(COD)317]BAr_F (342)



^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 8.12 (m, 1H, arom), 7.88 (m, 1H, arom), 7.63-7.32 (m, 23H, arom); 7.04 (m, 1H, arom), 5.22 (br, 1H, CH(COD), 5.04 (br, 1H, CH(COD)), 4.66 (q, J=6.8Hz, 1H, CH(COD)), 3.57 (br, 1H, CH), 3.23 (m, 1H, CH(COD)), 2.88 (br, 1H, CH), 2.51-2.30 (m, 4H, CH_2(COD), CH_2), 2.01-0.9 (m, 8H, CH_2(COD), CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 164.3 (d, ^{3}J=5.8Hz, C=N), 161.6 (q, ^{1}J=49.8Hz, arom), 137.8-117.4 (arom), 96.6 (CH, COD), 87.9 (CH, COD), 71.9 (CH), 66.9 (CH), 64.4 (CH, COD), 62.4 (CH, COD), 33.8 (CH_2, COD), 32.2 (CH_2, COD), 30.9 (CH_2), 29.7 (CH_2), 26.4 (CH_2, COD), 24.8 (CH_2, COD), 23.7 (CH_2), 23.4 (CH_2). **^{19}F NMR** ($CDCl_3$, 332.5 MHz): -62.38. **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 22.3 (s). **HRMS** (ESI-TOF): *m/z* =685.2318, calcd for $[M]^+$: 685.2319. Anal. Calcd for $C_{65}H_{49}BF_{24}IrN_2P$: C, 50.43; H, 3.19; B, 0.70; F, 29.45; Ir, 12.42; N, 1.81; P, 2.00 Found: C, 50.36; H, 3.24; N, 1.86.

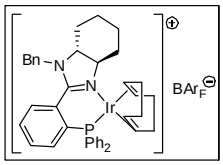
[Ir(COD)322]BAr_F (343)



^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.92 (br, 1H, arom); 7.81-7.09 (m, 34H, arom), 7.01 (br s, 2H, arom),

6.75 (br s, 2H, arom), 6.58 (br s, 2H, arom), 5.07 (br s, 1H, CH(COD)), 5.02 (d, ^{3}J=4.3Hz, 1H, CH), 4.80 (d, ^{2}J=14Hz, 1H, CH_2), 4.68 (m, 1H, CH(COD)), 4.14 (br s, 1H, CH), 3.94 (d, ^{2}J=14Hz, CH_2), 3.14 (br s, 1H, CH(COD)), 2.83 (br s, 1H, CH(COD)), 2.28 (br s, 1H, CH_2(COD)), 2.03 (br s, 2H, CH_2(COD)), 1.84 (br s, 2H, CH_2(COD)), 1.54 (br s, 3H, CH_2(COD)). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 165.0 (br s, C=N), 161.9 (q, ^{1}J=50.0Hz, arom), 142.1-117.6 (arom), 96.3 (CH, COD), 92.9 (CH, COD), 77.39 (CH), 71.7 (CH), 61.1 (CH, COD), 52.8 (CH, COD), 48.3 (CH_2), 31.9 (CH_2, COD), 29.4 (CH_2, COD), 22.7 (CH_2, COD), 19.8 (CH_2, COD). **^{19}F NMR** ($CDCl_3$, 332.5 MHz): –62.7 ppm. **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 16.2 (s). **HRMS** (ESI-TOF): *m/z* =843.4657, calcd for $[M]^+$: 843.4655. Anal. Calcd for $C_{80}H_{57}BF_{24}IrN_2P$: C, 55.34; H, 3.31; B, 0.62; F, 26.26; Ir, 11.07; N, 1.61; P, 1.78. Found: C, 55.01; H, 3.43; N, 1.67.

[Ir(COD)323]BAr$_F$ (344)[111]



^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.75 (br s, 8 H, arom), 7.63-7.45 (m, 15 H, arom), 7.31 (dd, ^{3}J = 7.5 Hz, ^{3}J = 3.4 Hz, 1 H, arom), 7.31-7.26 (m, 3 H, arom), 7.14 (m, 2 H, arom), 7.02 (m, 2 H, arom), 5.30 (br s, 1 H, CH(COD)), 4.48 (m, 1 H, CH(COD)), 4.41 (d, ^{2}J= 16.8 Hz, 1 H, CH_2), 3.91 (br s, 1 H, CH(COD)), 3.54 (d, ^{2}J = 16.8 Hz, 1 H, CH_2), 3.35 (m, 1 H, CH), 3.11 (m, 1 H, CH(COD)), 2.54 (d, ^{3}J = 8.1 Hz, 1 H, CH_2), 2.40 (m, 1 H, CH_2(COD)), 2.20-2.36 (m, 3 H, CH_2(COD)), 2.01-1.87 (m, 3 H, CH_2(COD)), 1.80 (m, 1 H, CH_2), 1.72-1.61 (m, 2H, CH_2), 1.52 (m, 1H, CH_2(COD)), 1.39 (m, 1H, CH_2(COD)), 1.32-1.09 (m, 3H, CH_2), 0.93 (m, 1H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 166.1 (d, ^{3}J=6Hz, C=N), 161.7 (q, ^{1}J=50 Hz, arom), 135.7-117.6 (arom), 95.0 (d, ^{2}J=10 Hz, CH(COD)), 85.6 (d, ^{2}J= 16 Hz, CH(COD)), 73.5 (CH), 69.8 (CH), 65.0 (CH(COD)), 62.1 (CH(COD)), 53.4 (CH_2), 36.9 (d, ^{3}J=5 Hz, CH_2(COD)), 34.6 (CH_2(COD)), 33.7 (CH_2), 29.7 (CH_2), 28.2 (CH_2(COD)), 25.8 (d, ^{3}J=2 Hz, CH_2(COD)), 25.1 (CH_2), 24.1 (CH_2). **^{19}F NMR** ($CDCl_3$, 332.5 MHz): –62.8 ppm. **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 24.0 (s). **HRMS** (ESI-TOF): *m/z*=775.2784, calcd for $[M]^+$: 775.2788. Anal. Calcd for $C_{72}H_{55}BF_{24}IrN_2P$: C, 52.79; H, 3.38; B, 0.66; F, 27.83; Ir, 11.73; N, 1.71; P, 1.89. Found: C, 52.68; H, 3.42; N, 1.76.

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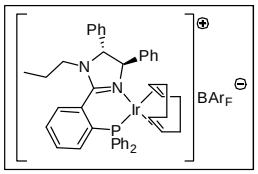
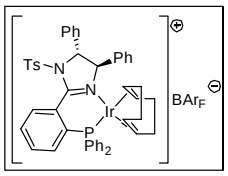
[Ir(COD)325]BAr_F (345)



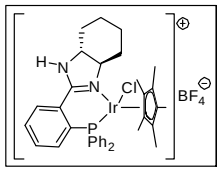
^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.77-6.81 (m, 36 H, arom), 4.96 (br s, 1H, CH), 4.61 (br s, 1 H, CH(COD)), 4.42 (br s, 1H, CH), 4.33 (br s, 1H, CH(COD)), 3.16 (br s, 1H, CH(COD)), 2.80 (br s, 1H, CH(COD)), 2.29-1.61 (m, 5H, CH_2, CH_2(COD)), 1.25-0.5 (m, 10H, CH_2, CH_2(COD), CH_3). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 165.2 (br, C=N), 161.7 (q, ^{1}J=25 Hz, arom), 142.3-117.5 (arom), 95.6 (br s, CH(COD)), 92.2 (br s, CH(COD)), 77.2 (CH), 73.4 (CH), 60.8 (CH(COD)), 53.5 (CH(COD)), 37.9 (CH_2), 31.7 (CH_2(COD)), 39.9 (CH_2(COD)), 29.7 (CH_2), 22.7(CH_2(COD)), 21.1 (CH_2(COD)), 14.1 (CH_3). **^{19}F NMR** ($CDCl_3$, 332.5 MHz): –62.9 ppm. **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 15.8 (s). **HRMS** (ESI-TOF): *m/z*=825.2954, calcd for $[M]^+$: 825.2950. Anal. Calcd for $C_{76}H_{57}BF_{24}IrN_2P$: C, 54.07; H, 3.40; B, 0.64; F, 27.01; Ir, 11.39; N, 1.66; P, 1.83. Found: C, 53.98; H, 3.48; N, 1.69.

[Ir(COD)327]BAr_F (346)



^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.97 (m, 1H, arom), 7.70-6.96 (m, 38 H, arom), 6.77 (d, ^{3}J=7.2Hz, 1H, arom), 5.06 (d, ^{3}J=5.2Hz, 1H, CH), 4.94 (br s, 1 H, CH(COD)), 4.80 (br s, 1H, CH(COD)), 4.54 (d, ^{3}J=5.2Hz, 1H, CH), 4.23 (br s, 1H, CH(COD)), 3.84 (br s, 1H, CH(COD)), 3.03 (br s, 1H, CH_2(COD)), 2.87 (br s, 1H, CH_2(COD)), 2.04 (s, 3H, CH_3), 1.71-1.07 (m, 4H, CH_2(COD)). **^{19}F NMR** ($CDCl_3$, 332.5 MHz): –62.3 ppm. **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 15.6 (s). **HRMS** (ESI-TOF): *m/z*=936.2561, calcd for $[M]^+$: 937.2564.

[Cp*IrCl(317)]BF_4 (347)



To a solution of $[Cp^*IrCl_2]_2$ (81.34 mg, 0.11 mmol) in dichloromethane (2 mL) was added a solution of ligand 317 (86 mg, 0.224 mmol) in 1 mL of dichloromethane. The resulting solution was stirred for 30 minutes. Then, $AgBF_4$ (43.4 mg, 0.22 mmol) was added at room temperature and stirred for 2 hours. The solution was then filtered through Celite and then concentrated under vacuum. 0.5mL of dichloromethane was added to the crude and 3 mL of hexane were added. The complex **347** precipitated immediately as a yellow-brown solid (87mg,

47%). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.46 (m, 1H, arom), 8.08 (m, 1H, arom), 7.72-6.92 (m, 12H, arom); 3.39 (m, 1H, CH), 3.23 (m, 1H, CH), 2.60-2.40 (m, 2H, CH_2), 2.25-1.90 (m, 4H, CH_2), 1.30 (d, ^{2}J=2Hz, 15H, CH_3), 1.22-0.89 (m, 2H, CH_2).

General Procedure for Asymmetric Hydrogenation of Unfunctionalised Olefins

To a multiautoclave with a glass insert and a magnetic stir was added the corresponding olefin (1 mmol), the metal complex (0.01 mmol) and 5 mL of dichloromethane. After purging with hydrogen, the autoclave was pressurized with 50 bar of hydrogen and sealed. After stirring at room temperature for 24 hours the pressure was released. The resulting solution was filtered off though celite and the resulting filtrate was directly analysed by NMR to determine the conversion and by HPLC to determine the enantioselectivity. The ee was determined with OJ-H for alkane **237a** and with OD-H for alkane **266h**.[114]

General Procedure for Asymmetric Hydrogenation of Imines

To a solution of $[Ir(\mu\text{-}Cl)COD]_2$ (3.4 mg, 0.005 mmol) in toluene (1.5mL) was added a solution of the ligand (0.011 mmol) in the same solvent (1.5mL). After 30 min, the mixture was transferred under argon into a schlenk tube containing the substrate (1 mmol) and iodine (12.6 mg, 0.05 mmol). The resulting solution was stirred for 30 min and transferred into a stainless steel autoclave (10 mL) equipped with a glass inlet. The autoclave was pressurised with hydrogen (40 bar) and stirred for 16h. After releasing the hydrogen pressure, the reaction mixture was diluted with CH_2Cl_2 (5mL) and extracted with saturated $NaHCO_3$ solution (10mL). The aqueous phase was washed with CH_2Cl_2 (3x5 mL) and the organic phase dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was analysed by NMR and chiral GC or chiral HPLC. GC Chirasil-dex (*S*)-18.47 min, (*R*)-18.60 min for product **291a**. GC Chirasil-dex (*S*)-21.62 min, (*R*)-22.16 min for amine **350a**. HPLC Chiralcel OD-H, Heptan/*i*PrOH 90:10, 0.5 mL/min, (*S*)-19.1 min, (*R*)-23.9 min for amine **350b**. Chiralcel OD-H, Heptan/*i*PrOH 98:2, 0.5 mL/min, (*R*)-12.3 min, (*S*)-14.2 min for amine **350c**. For amine **354a** HPLC OD-H (hexane/*i*-PrOH 60:40%).

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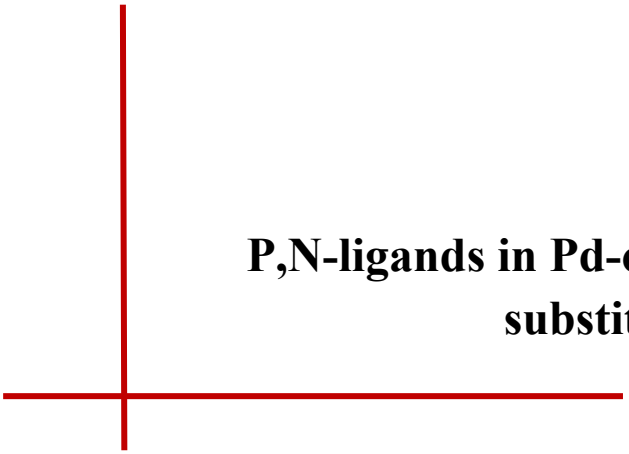

Chapter 5
P,N-ligands in Pd-catalysed allylic substitution reactions

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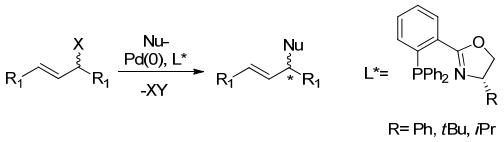
5. 1 Introduction to Pd-catalysed allylic substitution reactions

The stereoselective formation of C-C and C-N bonds is an important challenge in organic synthesis. In this context, the Pd-catalysed asymmetric allylic substitution reaction has shown to be an efficient and versatile procedure for the synthesis of drugs and natural products under mild conditions (Scheme 5.1).[1]

Chiral C_2- and C_1- symmetric ligands have been tested in the Pd-catalysed allylic alkylation affording in both cases high enantioselectivity for various substrates.[1] The C_1-symmetric ligands present the advantage of producing electronic discrimination between the two terminal allylic carbons in the η^3-allylpalladium intermediates because they contain a soft phosphorus donor atom associated with a π-acceptor and hard nitrogen donor atom.[1]

In particular, phosphino-oxazoline (PHOX)[2] and phosphite-oxazoline[3] ligands have afforded excellent results, showing that asymmetric allylic substitution reaction is sensitive to modification: 1) in the electronic characteristic of the structural aryl group, 2) in the environment of the stereogenic center adjacent to the nitrogen in the oxazoline moiety (C-4), 3) in the linker which separates the two coordinating heteroatoms[4] and, 4) in the substituents at C-5 of the oxazoline moiety.[5] Although this reaction has been widely studied there are still some problems for the obtention of systems more active and more regio- and enantioselective for unhindered disubstituted substrates and specially for monosubstituted ones.[1]



Scheme 5.1. Enantioselective allylic substitution of 1,3-disubstituted allyl substrates in the presence of a Pfaltz-Helmchen chiral PHOX ligand.

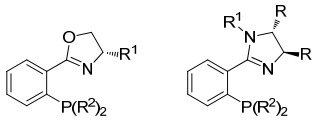
However, to the best of our knowledge phosphino-imidazoline (PHIM) ligands have never been used as chiral ligands in the Pd-catalysed asymmetric allylic substitution reactions. Although, they have shown to be very efficient in other catalytic processes.[6,7,8] PHIM ligands give new possibilities because

of the presence of a new nitrogen atom at the imidazoline ring. The additional nitrogen atom allows the introduction of different substituents (R_2), thus modifying the electronic properties of the coordinating nitrogen atom. Furthermore, the heterogenezation of the phosphino-imidazoline ligand onto insoluble organic resins which remains completely unexplored is also easier with phosphino-imidazoline ligands through the introduction of a linker at the nitrogen atom of the imidazoline ring (Figure 5.1). Recently, Pericàs *et al.* developed a new family of polymer-supported chiral phosphino-oxazoline ligands which have shown to be very active and enantioselective in Pd-catalysed asymmetric allylic amination reactions.[9]

This chapter shows the application of the phosphino-imidazoline ligands described in Chapter 4, focusing on:

a) The effect of the substituents at C-4 and C-5 on the imidazoline moiety (R).
b) The substituent at the non-coordinating nitrogen atom of the imidazoline ring (R^1).
c) The substituents of the phosphine moiety (R^2).
d) The modification of the structure of the ligand in order to anchor it into a support aiming to study the recovery and recycling of the catalyst.

This last part has been carried out in collaboration with Prof. Dr. M. A. Pericàs and is also part of the PhD Thesis of Rocío Marcos.



PHOX PHIM

Figure 5.1. Phosphino-oxazoline (PHOX) and phosphino-imidazoline ligands (PHIM).

5.1.1 Pd-catalysed allylic substitution reactions

The Pd-allylic substitution reaction consists in the reaction between an allylic racemic substrate which has a leaving group (acetate or carbonate) and a nucleophile (carbanion or amine). The allylic racemic substrates tested in this

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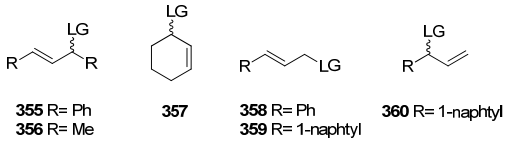
process can be linear or cyclic although *rac*-1,3-diphenylprop-2-enyl acetate is considered as the benchmark substrate for testing the new catalytic systems (Figure 5.2).



355 R= Ph
356 R= Me

357

358 R= Ph
359 R= 1-naphtyl

360 R= 1-naphtyl

Figure 5.2. Substrates tested in the Pd-catalysed allylic substitution.

Palladium is the transition metal which has been used the most extensively but there are other metals which are also applied for this C-C or C-N coupling reaction such as: nickel, ruthenium[10], rhodium[11], iridium[12], molybdenum[13] and tungsten[14]. In particular, iridium complexes are used for monosubstituted allylic substrates because they favour the formation of branched products, in contrast with palladium complexes which favour the linear ones.

The allylic substitution reactions are divided into two types depending on the substrate: a) racemic substrate (linear or cyclic) forming a symmetric allyl intermediate; b) racemic or prochiral substrates bearing two identical geminal substituents at one of the allylic terminal carbon (Scheme 5.2).

In the first type (a) of allylic substitution, the enantioselectivity is controlled by the regioselectivity of nucleophilic attack and is determined by the chiral ligand which, by electronic or steric effects, can distinguish between the two allylic terminal carbons. In the case of P,N ligands, the desymmetrization of allylic compound is due to electronic effects caused by the heterodonor atoms. The nucleophile attacks the carbon *trans* to phosphorus since the bond distance of this Pd-C bond is longer than the bond distance Pd-C *trans* to nitrogen (Figure 5.3) (Scheme 5.2a). In the second type (b) the π-allyl intermediate formed can isomerize via the π–σ–π mechanism. In this case the enantioselection can be induced in the ionization step, giving the allyl intermediate or in the nucleophilic addition step. In this context, the enantioselectivity and regioselectivity have to be controlled to avoid the formation of mixtures of isomers (Scheme 5.2b).

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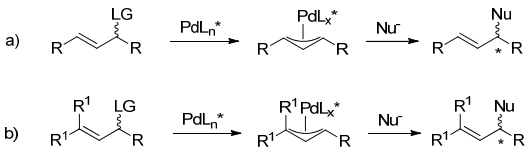


Scheme 5.2. Two types of asymmetric palladium allylic substitution reaction.

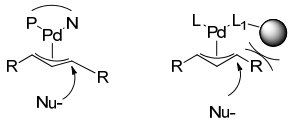
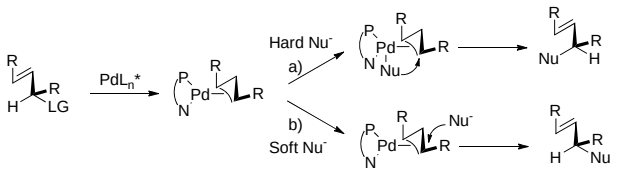


Figure 5.3. Desymmetrization of the π–allyl system with heterodonor or homodonor ligands.

Finally, the stereochemistry of the reaction depends on the type of the nucleophiles used. These can be hard nucleophile when the pka of the conjugated acids is higher than 25 or a soft nucleophile when the pka is lower than 25. Using a hard nucleophile the product obtained has the opposite configuration than that of the starting material because the nucleophile coordinates first to the metal and then the transfer of nucleophile takes place intramolecularly (Scheme 5.3a).[1b] However, employing a soft nucleophile, the configuration at the allyl carbon remains the same.[1b] (Scheme 5.3b)



Scheme 5.3. Nucleophilic attack with hard (a) or soft (b) nucleophiles.

5.1.1.1. Mechanism

The mechanism of palladium catalysed allylic substitution has been widely studied during the last twenty years.[1,15] The catalytic cycle involves four main steps. The first step consists in the coordination of the allylic substrate to the Pd(0) **361** to form the complex **362** (Scheme 5.4). Even if the starting species in the catalytic cycle is a Pd(0), Pd(II) complexes can be used as precursors because these complexes are easily reduced in the presence of a nucleophile

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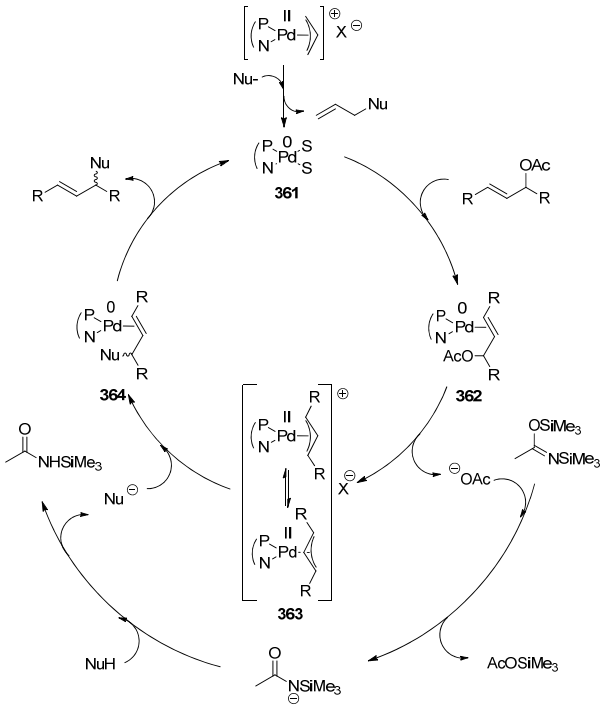
(carbanion or amine) into Pd(0). Then, the oxidative addition of **362** occurs, generating the Pd(II) intermediate **363** and the elimination of the leaving group takes place. The most common leaving group used is the acetate. The reason why racemic substrates are used in this reaction is because when the palladium allyl complex **363** is formed, the stereochemistry of the corresponding substrate is lost. The rate determining step on this catalytic cycle tends to be the oxidative addition, the complex **363** is formed. There are two possible positions for the nucleophilic attack to complex **363**. This attack will be controlled by the steric hindrance induced by the chiral homodonor ligand or by electronic discrimination when heterodonor ligands are used. The nucleophilic attack produces the intermediate **364** which consists in a Pd(0) complex stabilized by the coordination of the olefin. Finally, the decoordination of the olefin gives the desired compound and regenerates the initially species **361** (Scheme 5.4).



Scheme 5.4. Catalytic cycle of Pd-catalysed allylic substitution.

Most of the nucleophiles used are carbanions or amines. Carbanions are employed instead of their C-H counterparts because these are inactive.[1b] In

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early reports, sodium salts were used but they were not soluble in the conventional organic solvents employed. To resolve this problem, the carbanions were obtained by reaction of *N,O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate.[16] The formation of the carbanion consist in the transfer of a silyl group from the BSA to the acetate anion forming the anion of N-(trimethylsilyl)acetamide which abstracts the acidic proton of the dimethyl malonate. Once the nucleophile is formed, it attacks the allylic substrate coordinated to palladium and consequently, the desired product is formed after decoordination from palladium. When the allyl substrate is coordinated to palladium through the double bond and suffers the oxidative addition and realise the acetate anion and this is the reason why only a catalytic amount of potassium acetate is needed during the reaction (Scheme 5.4).

The enantioselectivity of the process is determined by the external nucleophilic attack on the most electrophilic allylic carbon of the π-allyl intermediate **363**.[1] Although attack on the central carbon of the allyl is possible, it is not common. This intermediate is stable in the absence of nucleophile and its behaviour can be studied by common spectroscopic techniques. Different isomers are present in solution with the *endo*-syn/syn and *exo*-syn/syn isomers being the most stables. In the palladium asymmetric allylic substitution reaction, a kinetic resolution of the substrate can take place.[17]

Generally, the configuration achieved in the product is opposite to that observed in the unreacted substrate. It suggests that one of the enantiomers of the allylic substrate forms the η^3-palladium allyl complex **363** faster than the other. This discrimination between the two enantiomers has shown to be temperature dependent.[18] Furthermore, in 1999 Amatore and co-workers reported the non-innocent role of the acetate ion in this reaction.

They suggested that the acetate ion can attack the intermediate **363** as a soft or hard nucleophile. If it attacks as soft nucleophile it will generate the initial substrate with retention of configuration while if it is as a hard nucleophile the opposite configuration of the substrate will be observed.[19] So, a competition between the acetate ion and the corresponding nucleophile could be observed (Scheme 5.5).

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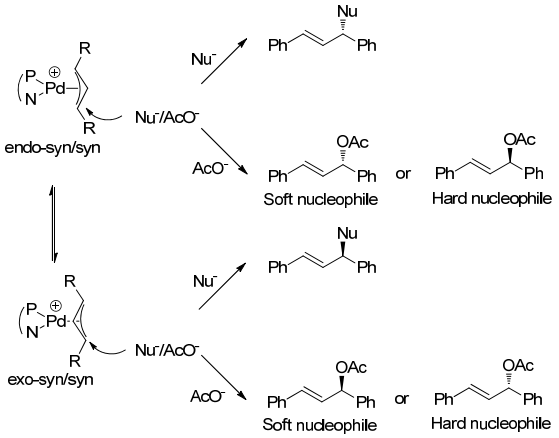

Scheme 5.5. Stereochemistry of the product and substrate in Pd-allylic substitution reactions.

Finally, Togni *et al.* published that the presence of small coordinating anions can affect the rate of interconversion between the two π-allyl palladium complexes **363**. This anion will generate a pentacoordinated intermediate which shifts the equilibrium between the two isomers *exo*-syn/syn and *endo*-syn/syn towards the major exo-syn/syn complex. This behavior has an effect on the enantioselectivity of the catalytic process.[20]

5.1.1.2. Pd-catalysed allylic alkylation reaction

In 1973, the first asymmetric allylic alkylation reaction of *rac*-1,3-diphenylprop-2-enyl acetate (**355**) with dimethyl malonate as nucleophile was reported. The ligand tested for this transformation was (+)-DIOP affording the product with 24% of enantioselectivity.[1] In 1992, Trost developed a C_2-symmetric diphosphine ligand which has been applied in this reaction obtaining excellent enantioselectivities for a wide range of substrates.[21] A year later, Pfaltz[2a], Williams[2b] and Helmchen[2c] reported the phosphino-oxazoline ligand with C_1 symmetry **211** (Scheme 5.6). This ligand has been very efficient for this transformation and due to these results a wide number of P,N derivatives ligands have been synthesised and used in this reaction.[2a-c,4e,5,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41]

Scheme 5.6 summarizes the best results obtained in the Pd-allylic alkylation of substrate **355** using phosphino-oxazoline ligands, and among then can be highlighted those providing ee's>95%, as **373**, **375-377**, **388** and **392-395**.

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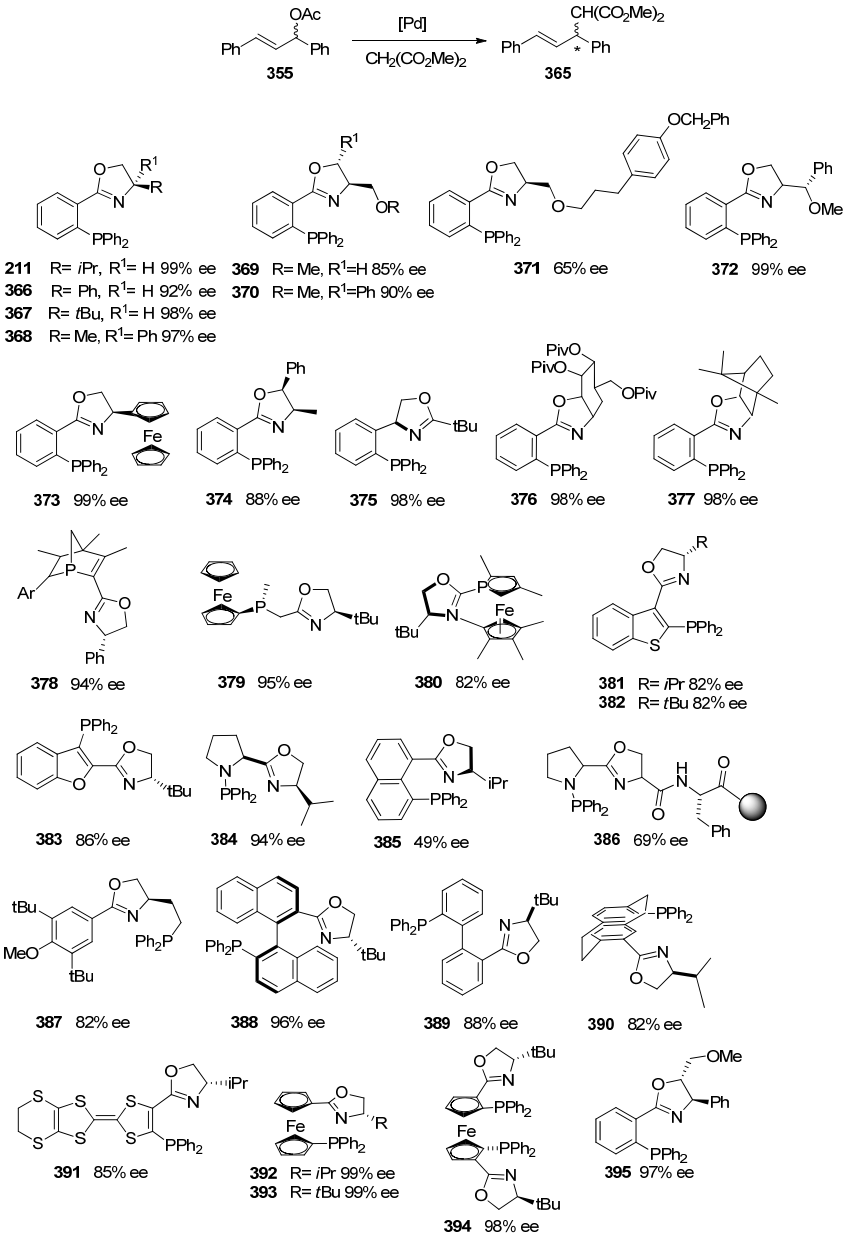

Scheme 5.6. Phosphino-oxazoline ligands used in Pd-catalysed allylic alkylation of *rac*-1,3-diphenylprop-2-enyl acetate.

Uemura reported a new family of phosphinite-oxazoline ligands derived from D-glucosamine (Scheme 5.7). All of them were successfully applied in this

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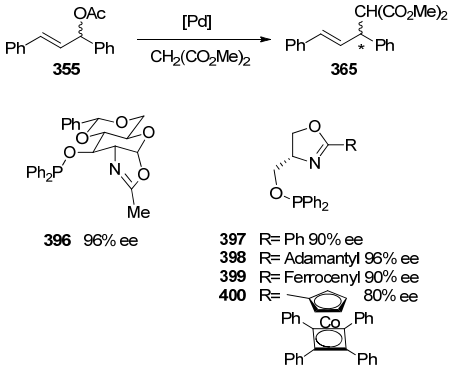
reaction achieving enantioselectivities up to 96%.[42] Richards and co-workers synthesised another type of phosphinite-oxazoline ligands bearing very bulky R groups which are analogous of the JMPhos ligands of Burgess. The enantioselectivities achieved with this benchmark substrate **355** rose up to 96% (Scheme 5.7).



Scheme 5.7. Phosphinite-oxazoline ligands used in Pd-catalysed allylic alkylation of *rac*-1,3-diphenylprop-2-enyl acetate.

Phosphite-oxazoline ligands have been reported by a number of groups. Pfaltz and co-workers reported the first use of these ligands in the Pd-catalysed allylic alkylation obtaining high regio- and enantioselectivity with monosubstituted allyl substrates (**358-359**).[43] The high regioselectivities are determined by the presence of bulky substituents around the phosphorus moiety which force the substrate to adopt an orientation with the more substituted carbon *trans* to phosphorus. The large electronic disparity between the donor atoms will also strongly favour nucleophilic attack at this position. This combination of steric and electronic effects provided the branched products in good enantiomeric excess, as is the case of ligands **402-403** containing a binol unit and **259** derived from TADDOL (Scheme 5.8).

To find more versatile phosphite-oxazoline ligands, Claver and co-workers replaced the phosphino group in the phosphino-oxazoline ligand (PHOX) by a bulky diphenyl phosphite moiety (**404a**) (Scheme 5.9).[3]

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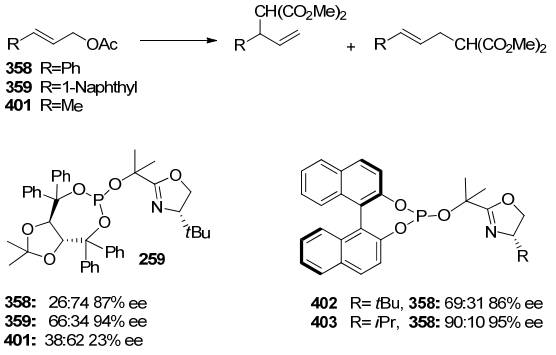
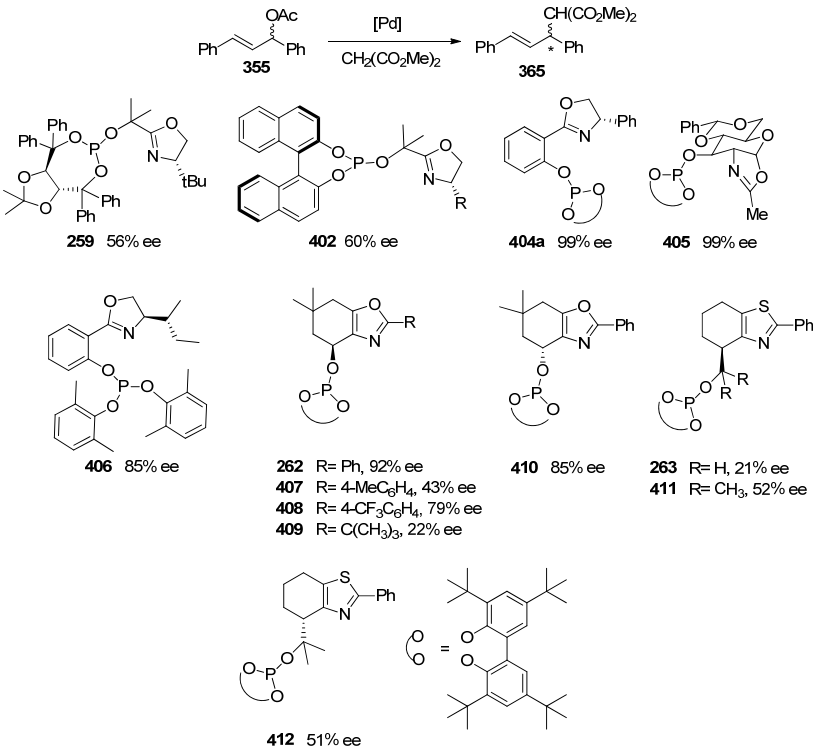


Scheme 5.8. Phosphite-oxazoline ligands tested in the allylic alkylation of monosubstituted allyl substrates.



Scheme 5.9. Phosphite-oxazoline ligands tested in the allylic alkylation of *rac*-1,3-diphenylprop-2-enyl acetate.

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Excellent activities and enantioselectivities were obtained in the palladium allylic alkylation of hindered and unhindered disubstituted and monosubstituted substrates.

Gladiali and co-workers also synthesised a new family of phosphite-oxazoline ligands bearing chiral (*S*)-binaphthalene-core. The results obtained were moderate ee's up to 43%.[44] Diéguez and Andersson have recently published a new class of modular P,N-ligand library (**407-412**).[45] These ligands can be easily tuned modifying the substituents at the heterocyclic ring and in the alkyl backbone, the configuration of the ligand backbone, and the substituents/configurations in the biaryl phosphite moiety. High regio- and enantioselectivities were achieved for a wide range of substrates (Scheme 5.9).

Scheme 5.10 summarizes the best results obtained in the palladium allylic alkylation of hindered, cyclic and monosubstituted substrates.

As a summary, catalytic systems bearing P,N ligands containing an oxazoline ring have shown to provide excellent ee's in the Pd-allylic alkylation reaction. Usually, all the catalytic systems have been tested with the standard substrate *rac*-1,3-diphenylprop-2-enyl acetate and using dimethyl malonate as nucleophile. The best results are reported with phosphite-oxazoline ligands bearing bulky substituents at the phosphorus atom. However, there are only a few examples of Pd/P,N ligands systems which are active and enantioselective in the alkylation of cyclic substrates.

In the case of monosubstituted substrates, iridium catalysts were shown to be efficient as they favour the formation of the branched product. However, when palladium complexes bearing phosphite-oxazoline ligands were used, good regioselectivities to the branched product were also achieved.

5.1.1.3. Pd-catalysed allylic amination reaction

The allylic amination reaction leads to the formation of allylamines, which are important intermediates in organic synthesis.[1e] Furthermore, they can be the starting material for the synthesis of α- and β-aminoacids,[46] alkaloids[47] and aza-carbohydrates. Scheme 5.11 summerizes some of the best results obtained with palladium complexes bearing P,N ligands.

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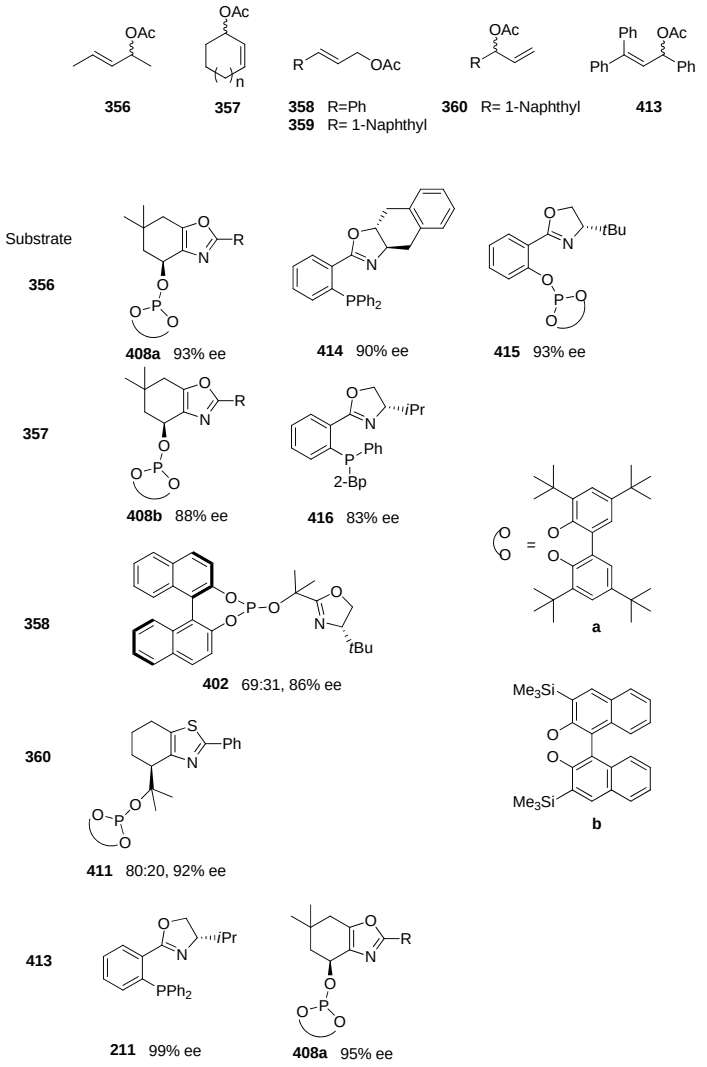

Scheme 5.10. Selected reported results in the Pd-allylic alkylation of hindered, cyclic and monosubstituted substrates.

As in Pd-catalysed allylic alkylation where the standard nucleophile is dimethyl malonate in this reaction, all the new catalytic systems are tested in the allylic amination of *rac*-1,3-diphenylprop-2-enyl acetate with benzylamine as nucleophile. Regarding phosphino-oxazoline ligands the best results published in this reaction were reported by Pericàs and co-workers who developed an efficient and modular family of phosphino-oxazoline ligands (**395**) which gave ee's up to 97%,[5] and due to the presence of an hydroxyl

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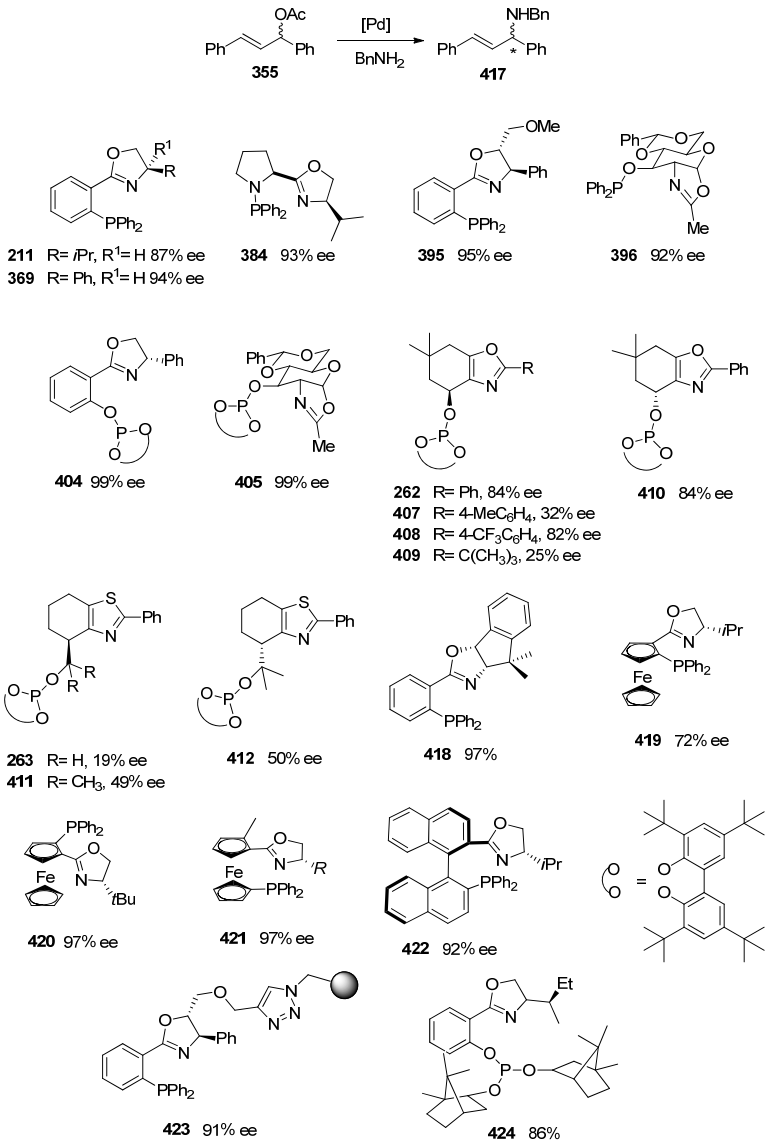
group at C-5 they can be anchored onto a polymer resin by click chemistry giving ligand **423**, achieving excellent activities and enantioselectivities under microwave conditions, and even in a continuous flow (Scheme 5.11).[9]



Scheme 5.11. P,N oxazoline derived ligands used in Pd-catalysed allylic amination of *rac*-1,3-diphenylprop-2-enyl acetate with benzylamine.

Phosphinite-oxazoline ligands have been less explored in this reaction although excellent enantioselectivities were achieved (92% ee). The best results were reported by our group using a phosphite-oxazoline ligand **404** analogue to the conventional phosphino-oxazoline ligand of Pfaltz.[3] This ligand gave 99% of enantioselectivity in the Pd-catalysed allylic amination using benzylamine. Other family of phosphite-oxazoline ligands (**262-263** and **407-412**) have been recently published by Diéguez and co-workers but the enantioselectivities were lower.[45] Gavrilov and co-workers reported a phosphite-oxazoline ligand containing an acyclic phosphorus centre with a [(1*S*)-endo]-(-)-borneol fragment and a chiral oxazoline substituent (**424**). This ligand was applied in the amination of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene acetate affording enantioselectivities up to 86% (Scheme 5.11).[48]

Finally, various substrates and several primary and secondary amines were tested in this reaction. Substrates are the same used for the allylic alkylation (**355-360**). Excellent enantioselectivities can be achieved for the hindered substrates, although when unhindered substrates are tested only moderate ee's are reported up to date with P,N-oxazoline derivatives ligands (57% ee's with Pd/**372**[49] or 69% ee's with Pd/**395**[5]) Excellent enantioselectivities are reported with a wide range of nucleophiles with the catalytic systems reported by Pericàs *et al*. In both catalytic systems, monomer phosphino-oxazoline or polymer phosphino-oxazoline analogues ligands **395**.[5,9]

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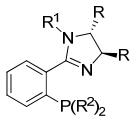
5. 2 Results and discussion

As mentioned in the introduction, phosphino-oxazoline ligands have been extensively studied in Pd-allylic substitution reactions with excellent results in terms of activity and enantioselectivity. The family of phosphino-imidazoline ligands described in Chapter 4 (Figure 5.4) of this thesis have a structure closely related with those ligands, and as indicated in section 4.2.1, they are highly modular allowing easy modifications at different positions, and making possible their anchoring onto a polymer resin.



316 R=Ph, R^1=H, R^2=Ph
317 R=-$(CH_2)_4$-, R^1=H, R^2=Ph
319 R=Ph, R^1=H, R^2=Cy
322 R=Ph, R^1=Bn, R^2=Ph
323 R=-$(CH_2)_4$-, R^1=Bn, R^2=Ph
325 R=Ph, R^1=C_3H_7, R^2=Ph
327 R=Ts, R^1=Ts, R^2=Ph

Figure 5.4. Phosphino-imidazoline ligands applied in Pd-allylic substitution reaction.

5.2.1. Pd-catalysed Asymmetric Allylic Substitution Reaction

5.2.1.1 Pd-Allylic alkylation reactions with first generation of PHIM ligands.

The alkylation of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene acetate (**355**) with dimethyl malonate in the presence of Pd/**316**[5] was studied as model reaction, and the conditions were optimised. Results are collected in Table 5.1. First, the reaction was carried out at room temperature in the presence of 0.01mmol of KOAc and 66% of conversion was obtained (entry 1, Table 5.1). The addition of 0.02 mmol of KOAc provided total conversion (entry 2, Table 5.1). Low enantioselectivity was obtained in both cases. When the reaction was performed at reflux in dichloromethane, total conversion was achieved in 24h and the ee raised up to 81% (entries 3-5, Table 5.1). This effect of temperature on the enantioselectivity was previously observed by Helmchem *et al.* in the iridium catalysed allylic alkylation.[50] Under microwave irradiation, conversion was complete in 3 h without affecting significantly the enantioselectivity (entries 6-8, Table 5.1). The use of toluene as solvent produced a slight decrease in enantioselectivity (entry 10), while using THF (entry 9), conversion and enantioselectivity were similar to those obtained in dichloromethane.

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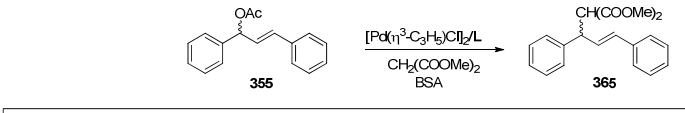
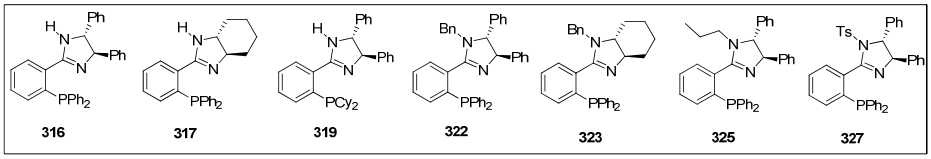
Table 5.1. Pd-allylic alkylation of **355**. Optimization of the reaction conditions and selection of the appropriate substituents R, R^1 and R^2.[a]





Entry	Ligand	Temperature (ºC)	Time (h)	Conversion [b] (%)	ee [c] (%)
1[d]	**316**	r.t.	12	66	49
2	**316**	r.t.	12	99	44
3	**316**	Reflux	4	73	87
4	**316**	Reflux	8	87	86
5	**316**	Reflux	24	100	81
6	**316**	45, MW irradiation	3	100	81
7	**316**	65, MW irradiation	3	100	83
8	**316**	85, MW irradiation	3	100	80
9[e]	**316**	65, MW irradiation	3	100	85
10[f]	**316**	65, MW irradiation	3	100	77
11	**317**	65, MW irradiation	3	91	53
12	**319**	65, MW irradiation	3	74	78
13	**322**	65, MW irradiation	3	71	85
14	**323**	65, MW irradiation	3	88	87
15	**325**	65, MW irradiation	3	99	71
16	**327**	65, MW irradiation	3	100	73

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). 65ºC, MW irradiation. [b] Conversion determined by NMR. [c] Product has (*R*) configuration. Ee was determined by HPLC. [d] 0.01 mmol of KOAc. [e] Reaction was carried out in tetrahydrofurane. [f] Reaction was carried out in toluene.

To study the influence of the substituents (R and R^2, Figure 5.4), the reaction was carried out under the conditions previously optimised (entry 7, Table 5.1). Using the PHIM ligand **317** which contains a cyclohexyl moiety, the enantioselectivity decreased dramatically, suggesting that the phenyl groups at C-4 and C-5 play a role in the enantiodiscrimination (entry 11, Table 5.1). Introducing cyclohexyl groups on the phosphorus atom (ligand **319**), produced a small decrease of the enantioselectivity (entry 12, Table 5.1).

Concerning the effect of groups R^2 of the imidazoline ring, the use of ligands **322**, **323** led to a decrease in conversion while with ligand **325** the conversion was maintained. No increase of enantioselectivity was observed in any case (entries 13-15 *versus* 7, Table 5.1). In contrast, the introduction of electron-withdrawing groups (ligand **327**) produced full conversion but the enantioselectivity decreased (entry 16 *versus* 13, Table 5.1). To summarize, R^1=R^3=Ph,-$(CH_2)_4$-, and R^2=alkyl are the more appropriate substituents to achieve high enantioselectivity in this reaction.

Table 5.2 summarizes the results obtained in the optimization of reaction conditions for the Pd-catalysed allylic alkylation of substrate **358**, using ligand **316**. The highest enantioselectivity was achieved under microwave irradiation at 65 ºC for 3 hours (entry 4, Table 5.2). As previously reported, high linear to branched ratios were obtained using palladium as a metal catalyst.[43] In the literature, the use of iridium based catalysts in the asymmetric alkylation reaction of substrate **358** is reported to give the opposite tendency.[16,17] However, when the Ir-allylic alkylation of substrate **358** was probed with PHIM ligands, the percentage of branched product increased but the enantioselectivity was dramatically affected (ee's up to 10%).

Later, the effect of the substituents (R and R^1) was examined. The results obtained with ligands **322** and **323** showed that the substituent R at the imidazoline ring has an important role in the enantiodescrimination. The introduction of bulky groups at the C-4 of the imidazoline ring increased the enantioselectivity (entries 5-6, Table 5.2). The introduction of substituents at the nitrogen atom of the imidazoline ring in the basic backbone **316** has a positive effect on the catalysis (entry 5, 7 and 8, Table 5.2). High conversions are obtained with practically all ligands. A branched to linear ratio up to 30:70 was achieved, in agreement with the results obtained with other palladium

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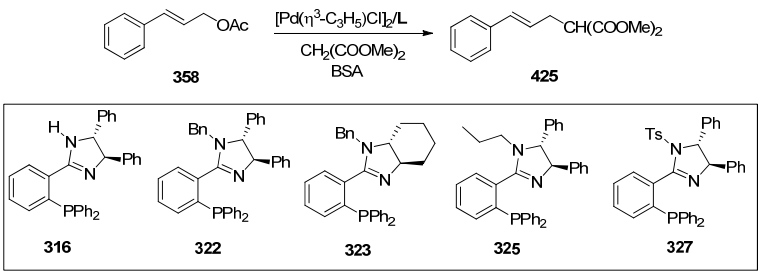
catalysts.[5] Concerning the enantioselectivity, the best results (78% ee) were obtained with ligand **327**.

Table 5.2. Optimization of the reaction conditions and effect of R and R^1 substituents in phosphino-imidazoline ligands for the Pd-allylic alkylation of **358**[a].



Entry	Ligand	T[a] (ºC)	Time (h)	Conv.[b] (%)	Ratio b:l	ee[c] (%)
1	**316**	r.t.	12	51	nd	48
2	**316**	35	12	100	23:77	42
3	**316**	reflux	12	100	17:83	35
4	**316**	65, MW irradiation	3	100	24:76	53
5	**322**	65, MW irradiation	3	100	18:82	65
6	**323**	65, MW irradiation	3	89	15:85	8
7	**325**	65, MW irradiation	3	100	24:76	67
8	**327**	65, MW irradiation	1	100	22:78	78

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). 65ºC, MW irradiation. [b] Conversion determined by NMR. [c] Product has (*R*) configuration. Ee was determined by HPLC.

Cyclic substrates such as cyclohex-2-enyl acetate (**357**) are particularly challenging in the Pd-allylic alkylation. For instance, classical phosphino-oxazoline ligands do not afford any enantioselectivity with this substrate. Recently, a new family of phosphino-oxazoline ligands with substituents at C-5 of the oxazoline ring provided enantioselectivities up to 56%.[5]

In this case, we examined the influence of the substituent at the nitrogen atom (R^1) of the phosphino-imidazoline ligands on the catalytic results. The catalytic system Pd/**316** afforded full conversion but moderate

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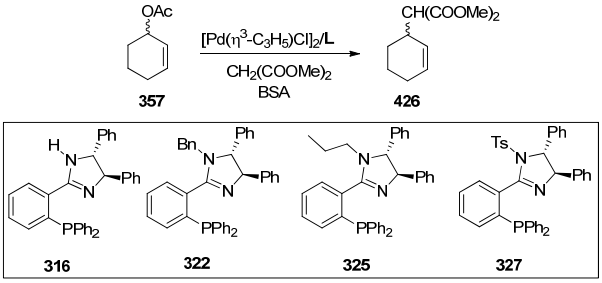
enantioselectivity (entry 1, Table 5.3). Ee's up to 53% were achieved with ligands **325** and **327** but in both cases, conversions were moderate (entry 4, Table 5.3).

Table 5.3. Effect of the R_2 substituent in phosphino-imidazoline ligands in Pd-allylic alkylation of **357**.[a]



Entry	Ligand	Conversion[b] (%)	ee[c] (%)
1	**316**	99	44
2	**322**	58	25
3	**325**	66	53
4	**327**	70	53

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). 65ºC, MW irradiation. [b] Conversion determined by NMR. [c] Product has (*S*) configuration. Ee determined by GC.

In Table 5.4, the results obtained in the Pd-allylic alkylation of substrate **356** using catalytic sytems bearing ligands **316**, **322**, **325** and **327** are described. Lower conversions and enantioselectivities were achieved with this substrate (conversions up to 56% and ee's up to 53%), when compared to those obtained with substrate **355**.

The results obtained in the alkylation of substrate **413** which contains three phenyl rings in its structure (Table 5.5), are similar to those obtained with **355**. Thus, in this case, the best ee (99%) was again obtained with ligand **322** (R^2=benzyl). The presence of a fused cyclohexyl in the imidazoline ring (**317** and **323**) has a strong negative effect in the enantioselectivity (entries 2 and 4, Table 5.5).

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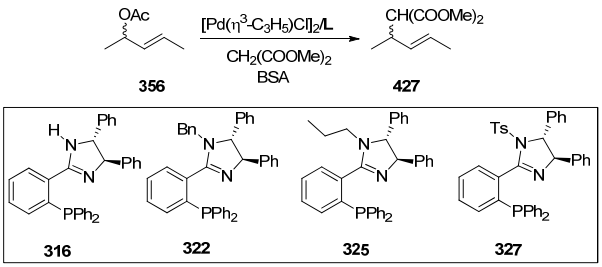
Table 5.4. Effect of the R^1 substituent in phosphino-imidazoline ligands in Pd-allylic alkylation of **356**.[a]



Entry	Ligand	Conversion[b] (%)	ee[c] (%)
1	**316**	44	50
2	**322**	44	51
3	**325**	39	53
4	**327**	56	53

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). [b] Conversion determined by NMR. [c] Product has a (*S*) configuration. Ee determined by GC.

To conclude, high enantioselectivities were obtained for substrates **355** and **413** while lower conversions and enantioselectivities were achieved with **356**. This suggests that the presence of phenyl groups within the substrate plays an important role for the chiral induction.

5.2.1.2 Pd-Allylic amination reactions with first generation of PHIM ligands.

Initially, the palladium catalysed-allylic amination of substrate **355** with benzylamine as the nucleophile was performed using ligands **316**, **317**, **322** and **323**. Table 5.6 summarizes the results of the optimization of the reaction conditions using Pd/**316** as catalytic system. No reaction was observed in the absence of N,O-bis(trimethylsilyl)acetamide (BSA) and potassium acetate[49] (entry 1, Table 5.6). When the reaction was performed in the presence of BSA but in the absence of KOAc,[51,52] low conversions and enantioselectivities were obtained (entries 2-3, Table 5.6). The use of both BSA and KOAc was required to achieve full conversion and increased the enantioselectivity of the

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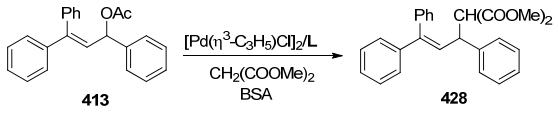
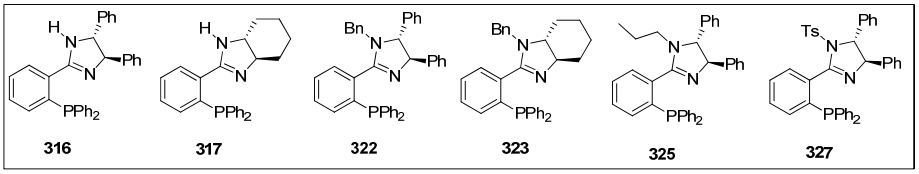
reaction (enty 4, Table 5.6).[22,53b-c, 54] The best results, (99% conversion and 92% ee), were obtained using these additives at reflux in dichloromethane.

Table 5.5. Effect of R and R^1 substituent in phosphino-imidazoline ligands in Pd-allylic alkylation of **413**[a].



413 **428**



316 **317** **322** **323** **325** **327**

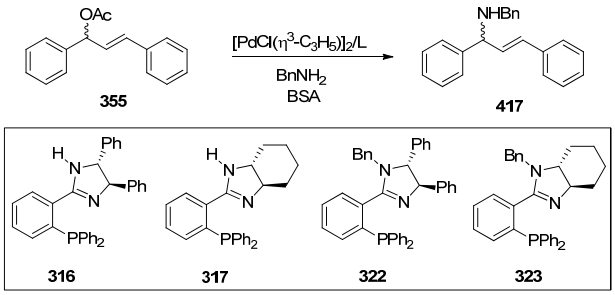
Entry	Ligand	Conversion[b] (%)	ee[c] (%)
1	**316**	39	83
2	**317**	21	44
3	**322**	48	99
4	**323**	29	28
5	**325**	27	83
6	**327**	65	92

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). [b] Conversion determined by NMR. [c] Product has (*R*) configuration. Ee was determined by HPLC.

The reaction was carried out, under these optimised conditions using ligands **322** and **323**, which contain phenyl and cyclohexyl substituents on the imidazole ring respectively.

Both ligands afforded complete lower conversions and enantioselectivities (entries 5-6, Table 5.6) than those obtained with ligand **316** (entry 4 *vs* 5-6, Table 5.6). The presence of phenyl substituents at C-4 and C-5 on the imidazoline ring is thus beneficial for achieving high enantioselectivity in this process.

Table 5.6. Amination of **355** using Pd/**316**, **317**, **322** and **323** as catalyst with benzylamine as nucleophile.[a]



Entry	Ligand	Additive	Salt	Temp. (ºC)	Conv.[b] (%)	ee[c] (%)
1[d]	**316**	-	-	Reflux	-	-
2	**316**	BSA	.	Reflux	19	28
3	**316**	BSA	-	3W, 35ºC MW	15	28
4	**316**	BSA	KOAc	Reflux	>99	92
5	**317**	BSA	KOAc	reflux	95	79
6	**322**	BSA	KOAc	Reflux	>99	74
7	**323**	BSA	KOAc	Reflux	>99	82

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). [b] Conversion determined by NMR. [c] Ee determined by HPLC. (*S*) configuration. [d] Without BSA.

5.2.1.3. Synthesis of the second generation of phosphino-imidazoline ligands

The anchoring of homogeneous catalysts onto a solid support is often the method of choice to recover the catalyst without altering their properties. For this purpose, the anchoring of the P,N ligands synthesised during this work onto a polymer was planned. The ligand **316** offered the possibility of introducing a linker at the sp^3 imidazolic nitrogen. The use of azide modified polymers and of ligands containing a propargilic group was considered as the most appropriate method. The group of Prof. M. Pericàs (ICIQ) study the anchoring of ligands onto resins by cycloaddition of azides and terminal acetylenes, also called "click chemistry"-type reactions.[55,56,57] Such systems were successfully applied for the immobilization of closely related ligands

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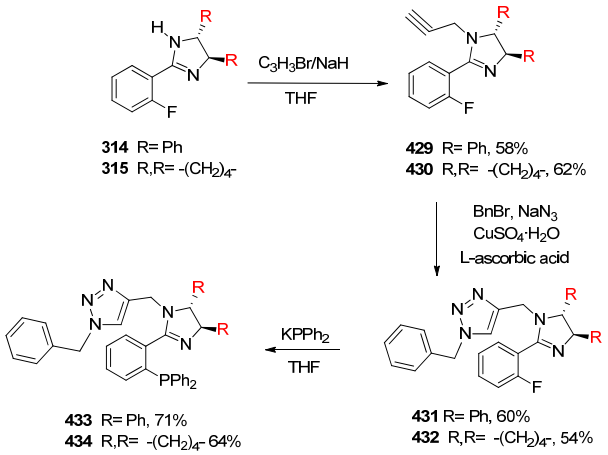
(phosphino-oxazoline).[9] Consequently, the immobilization of the catalysts was carried out in collaboration with the group of M. Pericàs.

The ligands containing imidazolines with phenyl or cyclohexyl fused groups were the most efficient ligands in the previously described catalytic tests. For this reason and for comparative purposes, the ligands **433** and **434** were initially prepared for homogeneous catalysis. Since the phosphorus moiety should be preferably introduced in the last step of the ligand synthesis, we initially prepared the propargyl derivatives **429** and **430**. Thus, compounds **314** and **315** (Scheme 5.12) were treated with propargyl bromide to afford **429**, and **430**, which were then reacted with benzyl bromide, sodium azide and L-ascorbic acid in the presence of catalytic amounts of copper sulfate to yield the compounds **431** and **432** in 60 and 54% yield, respectively. Finally, the phosphine moiety was introduced by nucleophilic substitution of fluoride with $KPPh_2$, affording the desired phosphino-imidazoline ligands **433** and **434** (Scheme 5.12).



Scheme 5.12. Synthesis of the phosphino-imidazoline ligands **433** and **434**.

5.2.1.4 Pd-catalysed allylic alkylation reactions with second generation of PHIM ligands.

The activity of the catalysts bearing ligands **433** and **434** was examined under the previously optimised conditions. Outstandingly, the ligands containing a triazole substituent in the imidazoline ring provided a remarkable increase in enantioselectivity compared to the previously studied ligands (entry 1 *vs* entry

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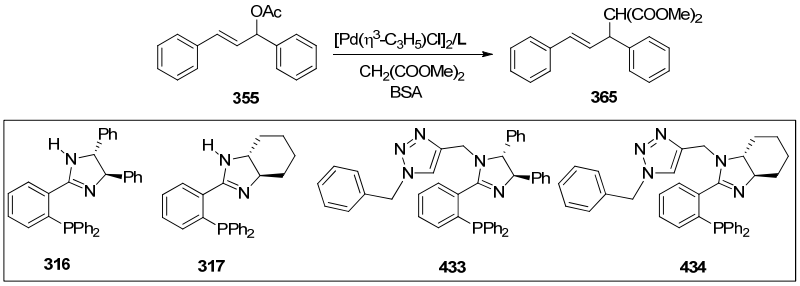
2, Table 5.7). The best result (94 % yield and 96 % ee, entry 2, Table 5.7) was obtained using Pd/**433** as catalytic system. It is noteworthy the high ee value (86%) obtained with the cyclohexyl containing ligand **434** (entry 4, Table 5.7).

Table 5.7. Effect of the triazole substituent at the nitrogen atom of the imidazoline ring in the Pd-allylic alkylation of **355**.[a]



Entry	Ligand	Conversion[b] (%)	ee[c] (%)
1	**316**	>99	83
2	**433**	94	96
3	**317**	91	53
4	**434**	85	86

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). [b] Conversion determined by NMR. [c] Product has (*R*) configuration. Ee was determined by HPLC.

Due to these promising results, the ligands **433** and **434** were also tested in the asymmetric alkylation reaction of the substrates **356-358** and **413**. The results are summarized in Table 5.8. The alkylation of **413** with dimethyl malonate using the Pd/**433** catalytic system under the optimised reaction conditions afforded high conversion and excellent enantioselectivity (99%). In contrast, when this system was used in the allylic alkylation of the substrate **358**, the results were similar to that observed in the homogeneous catalytic reactions with the other PHIM ligands, while the alkylation of **357** and **356** provided lower ee (Table 5.8).

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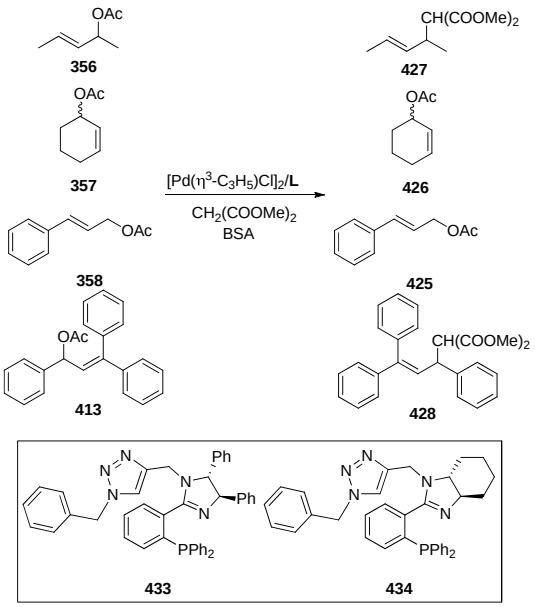
Table 5.8. Effect of the triazole substituent at the nitrogen atom of the imidazoline ring in the Pd-allylic alkylation of **356-358** and **413**.[a]



Entry	Substrate	Ligand 433			Ligand 434		
		Conv. (%)	Ratio b:l	Ee. (%)	Conv. (%)	Ratio b:l	ee (%)
1	**355**	94	-	96	85	-	86
4	**356**	70	-	47	65	-	35
3	**357**	97	-	32	91	-	29
2	**358**	92	10:90	72	97	12:88	74
5	**413**	63	-	99	32	-	75

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). [b] Conversion determined by NMR. [c] Ee was determined by HPLC or GC.

In this section, the Pd-catalysed asymmetric allylic alkylation of various substrates was investigated.

Several factors were found to influence the enantioselectivity of the reaction:

- Structure of the ligand: the highest enantioselectivities were achieved when phenyl rings were present in the imidazoline backbone of the

ligand, with phenyl rings at the phosphorus moiety and an electron-donating group at the nitrogen atom of the imidazoline ring. Such as a triazolyl group at the nitrogen atom (ligand **433**) observing an important increase on the enantioselectivity (ee's up to 99 % for various substrates).

- Substituents at the substrate: symmetric substrates bearing phenyl rings and non-symmetrical substrates containing phenyl rings as germinal substituents afforded the best results in terms of activity and enantioselectivity.

5.2.1.5. Pd-catalysed allylic amination reactions with second generation of PHIM ligands.

The ligands **433** and **434** were also tested in the palladium catalysed-allylic amination of substrate **355** using the amines **440**-**445** as nucleophile (Table 5.9).

Complete conversion and high enantioselectivities were obtained using **440** as nucleophile (entries 1 and 7, Table 5.9). The excellent enantiomeric excess obtained in the reaction with ligand **433** is among the highest reported for this reaction.[49,58]

Using the ligand **433** (entries 1-6, Table 5.9), excellent conversion and enantioselectivity were obtained except in the case of phthalimide (entry 6, Table 5.9), which is the less basic and the more hindered amine, and which provided lower yield, although the enantioselectivity remained excellent. For the ligand **434** containing the fused cyclohexyl moiety (entries 7-9, Table 5.9), high conversion and enantioselectivity were only obtained in the case of benzylamine.

In the Pd-catalysed asymmetric allylic amination of the benchmark substrate **355**, the same trends than in the allylic alkylation were observed:

- The catalytic system bearing the ligand **433** afforded the highest enantioselectivity (ee's up to 98%).

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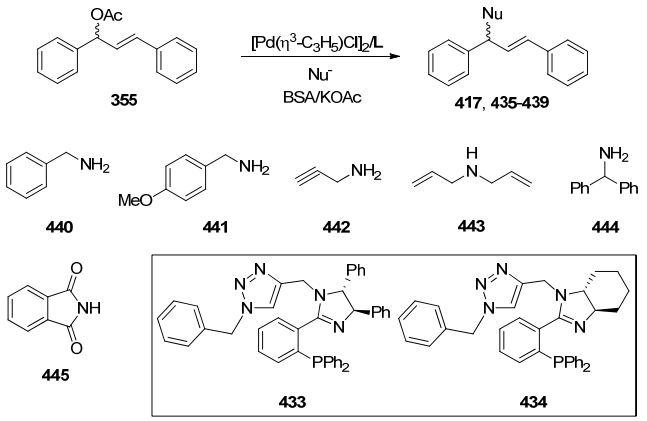
Table 5.9. Pd-allylic amination reaction of **355** using amines **440-445** as nucleophiles and Pd/**433**, **434** as catalysts.[a]



Entry	Ligand	Nucleophile	Conversion (%)[b]	ee (%)[d]
1	**433**	**440**	99	98
2	**433**	**441**	99	96
3	**433**	**442**	99	96
4	**433**	**443**	99	99
5	**433**	**444**	99	97
6	**433**	**445**[d]	47	99
7	**434**	**440**	99	84
8	**434**	**443**	49	67
9	**434**	**445**	0	-

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). [b] Conversion determined by NMR. [c] Ee determined by HPLC. Configuration (*S*). [d] Reaction time: 48h.

- The addition of BSA to the catalytic solution was required in order to form an active system.
- The addition of a catalytic amount of potassium acetate is required to achieve high level of enantioselectivity.
- Various primary and secondary amines were used, giving excellent yields and enantioselectivities (ee's up to 99%).

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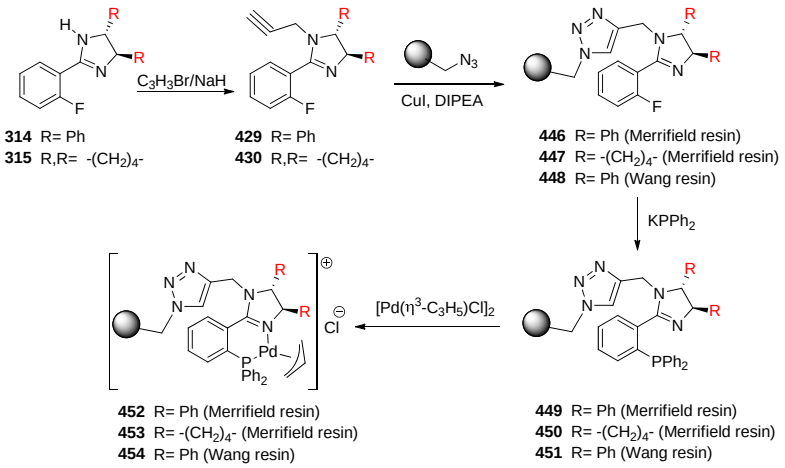
5.2.2 Anchoring the second generation ligands onto polystyrene-type resins

The synthesis of the polymer-supported phosphino-imidazoline ligands was carried out in collaboration of M. A. Pericàs group. The synthesis of the anchored ligands takes part of the PhD thesis of Rocío Marcos and as such, in this thesis, only the most relevant results will be presented.

The second generation of phosphino-imidazoline ligands was anchored according to the strategy previously reported by Pericàs.[9] The starting compounds were the fluoro-imidazoline derivatives **429** and **430**. Later, a "click chemistry"-type reaction was carried between **429** and **430** with the azido group, which were previously introduced onto commercial Merrifield and Wang resins by reaction with sodium azide affording the 2-fluorophenyl imidazoline-functionalized resins **446-447** (Merrifield resin) and **448** (Wang resin).[46a] The reaction was carried out in a mixture 1:1 of DMF/THF at 45ºC for 16 hours. These resins were treated with potassium diphenylphosphide in THF at room temperature for Merrifield resin affording the polymer-supported phosphino-imidazoline ligand **449-450** or at 65ºC for Wang resin, giving in that case ligand **451** (Scheme 5.13).



Scheme 5.13. Synthesis of polymer-supported PHIM (**449-451**) and their π-allyl Pd-complexes (**452-454**).

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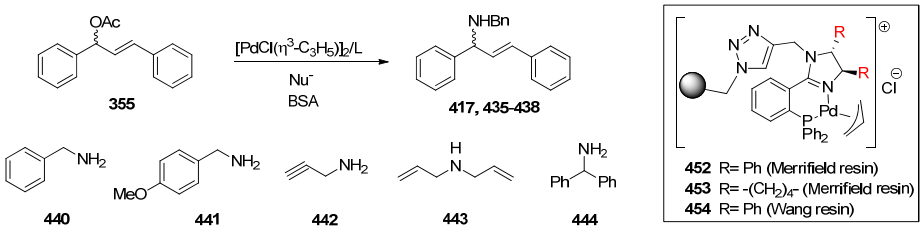
Finally, the π-allylpalladium complexes **452-454** were synthesised by reaction of π-allylpalladium chloride dimer $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$ and the corresponding resins **449-451**, previously swollen in toluene (Scheme 5.13).

The polymer-supported palladium complexes **452-454** were tested in the palladium catalysed amination of substrate **355** with benzylamine (entries 1-3, Table 5.10).

Table 5.10. Asymmetric allylic amination of **355** with different *N*-nucleophiles catalysed by Pd/supported PHIM complexes **452-454** [a]



Entry	Cat.	Nucleophile	Product	Time (h)	Yield [d] (%)	ee [e] (%)
1	**452**	**440** [b]	5.91	2	80	91
2	**453**	**440** [c]	5.91	3	82	76
3	**454**	**440**	5.91	3	99	92
4	**454**	**441**	5.98	3	99	83
5	**454**	**442**	5.99	3	98	96
6	**454**	**443**	5.100	4	99	90
7	**454**	**444**	5.101	4	99	91

[a] *Reaction conditions*: all reactions were run under microwave irradiation at 8W power (40 ºC) with 12 mol% catalyst, 3 equiv of amine nucleophile and 3 equiv of BSA, 7 equiv of CH_2Cl_2. [b] Reaction at 3 W microwave power (31 ºC). [c] Reaction at 5 W microwave power (38 ºC). [d] Yield of isolated product after purification by flash chromatography. [e] Enantiomeric excesses were measured by chiral HPLC.

The reactions were carried out according to a previously optimised methodology.[59] When polymer-supported palladium complexes with phosphino-imidazoline ligands anchored onto Merrifield resins (**452-453**)

were tested, significant precipitation of Pd black was observed at 8 W, 40 ºC.[60]

However, using the palladium complex **454**, which contains second generation PHIM ligands **433** onto a Wang-type resin, excellent conversion and enantioselectivity were obtained without any precipitation of palladium black (entry 3, Table 5.10). This indicated that a longer distance between the π-allylpalladium complex and the polymer backbone favours the thermal stability of the catalysts (Comparison of Merrifield resin with Wang resin). The resin **454** was tested in the allylic amination of substrate **355** with different primary and secondary amines (Table 5.10). The reactions were carried out under microwave conditions during 3 or 4 hours achieving excellent enantioselectivities and quantitative yields. It is important to mention that all the enantioselectivities obtained with the catalytic systems bearing the polymer-supported phosphino-imidazoline ligand were higher than the polymer-supported phosphino-oxazoline ligands except for the *p*-methoxybenzylamine. In contrast to the monomeric palladium systems where the addition of potassium acetate was required to achieve high enantioselectivities, in the case of polymer supported systems, this additive was not required.

Finally, the recycling of the catalytic system **454** was tested. The catalytic system could be recovered by filtration at the end of the reaction. Table 5.11, shows how the catalytic system **454** can be recovered and reused in the allylic amination of **355** with benzylamine.

After each run, the reaction mixture was separated by decantation, and the resin was rinsed with deoxygenated dichloromethane. The catalyst was then dried under argon and pre-swollen with dichloromethane prior to the next run. During all the cycles, the enantioselectivity remains excellent although the catalytic activity decreased (entries 1-4, Table 5.11). For the fourth run, the reaction time was increased to 6 hours to obtain complete conversion (entry 4, Table 5.11). As the colour of the resin darkened in each run we interpreted that some thermally-induced precipitation of palladium black occurred during the reaction.

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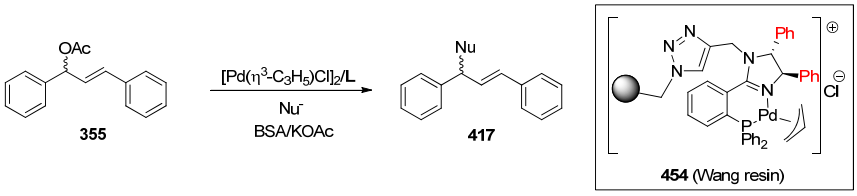
Table 5.11. Asymmetric allylic amination of **355** with benzylamine catalysed by polymer-supported Pd/PHIM complexes **454**.[a]



Entry	Cycle	Catalyst	Temp. (ºC)	Time (h)	Yield[b] (%) Conv.[c] (%)	ee[d] (%)
1	1	**454**	40	3	99 (100)	92
2	2	**454**	40	3	96 (97)	92
3	3	**454**	40	4	97 (98)	93
4	4	**454**	40	6	98 (99)	93

[a] *Reaction conditions*: Reactions were run under microwave in power control mode (8W) with 12 mol% catalyst, 3 equiv of benzylamine and 3 equiv of BSA in 7 equiv of CH_2Cl_2 (resin swelling). [b] Yield of isolated product after purification by flash chromatography. [c] Conversion determined by ^{1}HNMR of a crude sample. [d] Enantiomeric excesses were measured by chiral HPLC.

From the results obtained in the Pd-catalysed asymmetric allylic amination using polymer-supported phosphino-imidazoline ligands, the following conclusions can be drawn:

- The introduction of a spacer between the chiral palladium complex and the corresponding resin avoids the deactivation of the catalytic system.
- The palladium complex anchored to Wang resin afforded from high to excellent enantioselectivities for a wide range of amines (ee's up to 96%).
- The catalytic system anchored to Wang resin was successfully recycled in the allylic amination of substrate **355** with benzylamine: the enantioselectivity remains excellent during all runs although a decrease of the conversion was observed after 2 runs and was attributed to some deactivation of the catalytic species.

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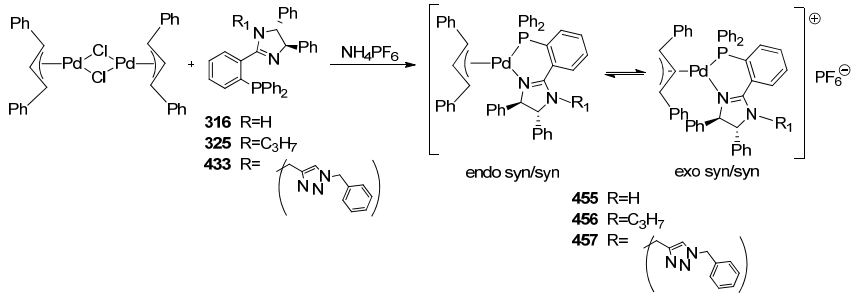
5.2.3 Origin of Enantioselectiviy-Study of the Pd-π Allyl Intermediates

As shown above, the introduction of a triazole moiety at the nitrogen atom of the imidazoline ring has a major effect on the enantioselectivity of the palladium catalysed-allylic substitution reactions. To obtain further insights into this unexpected result, the palladium-π allyl compounds **455**, **456** and **457**, [Pd(ŋ^3-allyl)(L)]PF_6 (L= **316**, **325** and **433**), which are key intermediates in the catalytic cycle, were synthesised from the corresponding palladium-allyl dimer and the appropriate ligand in the presence of NH_4PF_6, as shown in Scheme 5.14.[61]



Scheme 5.14. Synthesis of [Pd(ŋ^3-1,3-allyl)(PHIM)]PF_6 complexes

A VT-NMR (30ºC, -80ºC) study in CD_2Cl_2 of the palladium-allyl intermediate **455** showed a mixture of two isomers in equilibrium in a 3:1 ratio.[61] The structure of both isomers was unambiguously assigned by multinuclear NMR spectroscopy (^{1}H, ^{13}C, ^{31}P, ^{1}H-^{1}H, ^{31}P-^{1}H and ^{13}C-^{1}H correlation and ^{1}H-^{1}H NOESY experiments) to the two complexes endo-syn/syn **455a** and exo-syn/syn **455b** (Scheme 5.15). In both isomers, the NOESY experiment showed interactions between the terminal protons of the allyl group (Ht-Ht'), and between the central allyl proton (Hc) with the ortho hydrogens of both phenyl groups of the allyl fragment, which clearly indicates a *syn/syn* disposition for the substrate. A NOE interaction between the terminal allyl proton Ht of the major isomer **455a** with the ortho hydrogen of the phenyl-imidazoline substituent was also observed. Significantly, in the minor isomer **455b** Ht gave a NOE interaction with the proton at C-4 of the imidazoline backbone (Scheme 5.15).

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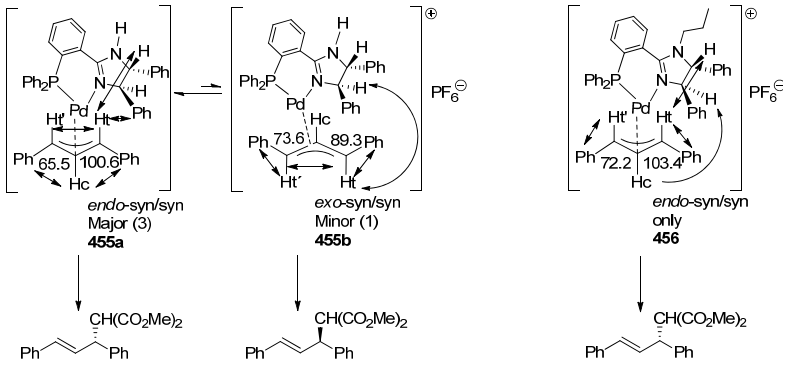
For both isomers **455a,b**, the ^{13}C NMR chemical shifts indicated that the more electrophilic allyl carbon terminus is *trans* to the phosphine moiety. Assuming that the nucleophilic attack takes place at the more electrophilic allyl carbon terminus and that the expected diastereomeric excess of the palladium intermediates is 50% (See Scheme 5.15a,b, ratio **455a**/**455b**=3:1), and knowing that the stereochemical outcome of the reaction is 83% in Pd-catalysed allylic alkylation reaction, it can be concluded that the major isomer **455a** reacts faster than the minor isomer **455b**.



Scheme 5.15. Isomer ratio (in brackets), relevant NOE contacts, selected ^{13}C NMR data of [Pd(η^3-1,3-diphenylallyl)(**316**, **325**)]PF_6 (**455**, **456**) isomers, and the relation with the configuration of the final products.

The VT-NMR study of the Pd-allyl intermediate **456**, which contains the ligand **325**, revealed the presence of only the syn/syn endo isomer **456**. The NOE study showed the following significant through space interactions: a) the central allyl proton (Hc) with the proton at C-4 of the imidazoline ring, b) between both terminal allyl protons (Ht, Ht') with aromatic protons and, b) between one of the terminal allyl protons (Ht) with the proton at the C-5 of the imidazoline ring. These data are in agreement with those expected for a *syn/syn*-endo isomer. The more electrophilic allyl carbon terminus was again *trans* to the phosphine moiety (Scheme 5.15). In spite of the presence of only one isomer the enantioselectivity was 85% in allylic alkylation, which indicates that the attack in the less electrophilic carbon takes also place or the minor isomer cannot be detected by NMR due to its low concentration.

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The VT-NMR study of the Pd-allyl intermediate **457**, bearing the triazole containing ligand **433**, showed the presence of a mixture of two *syn/syn*-endo (**457a**) and *syn/syn*-exo (**457b**) isomers in a ratio of 6:1. The NMR study in CD_2Cl_2 focused on the major isomer since the minor isomer was present at very low concentration. In contrast with what was previously observed for the complexes **455** and **456**, no NOE interactions were detected between the allyl terminal protons with the protons at the C-4 or C-5 of the imidazoline ring in **457**. However, surprisingly, interactions between: a) Ht/Hd,d' (strong), b) Ht/Ha (strong), and c) Ht/He,e' (weak), were detected (Figure 5.5). gHMBC experiments allowed to unambigously assign the Hd,d' and He,e' signals to the two methylene groups that bond triazole-imidazoline and triazole-phenyl units, respectively.

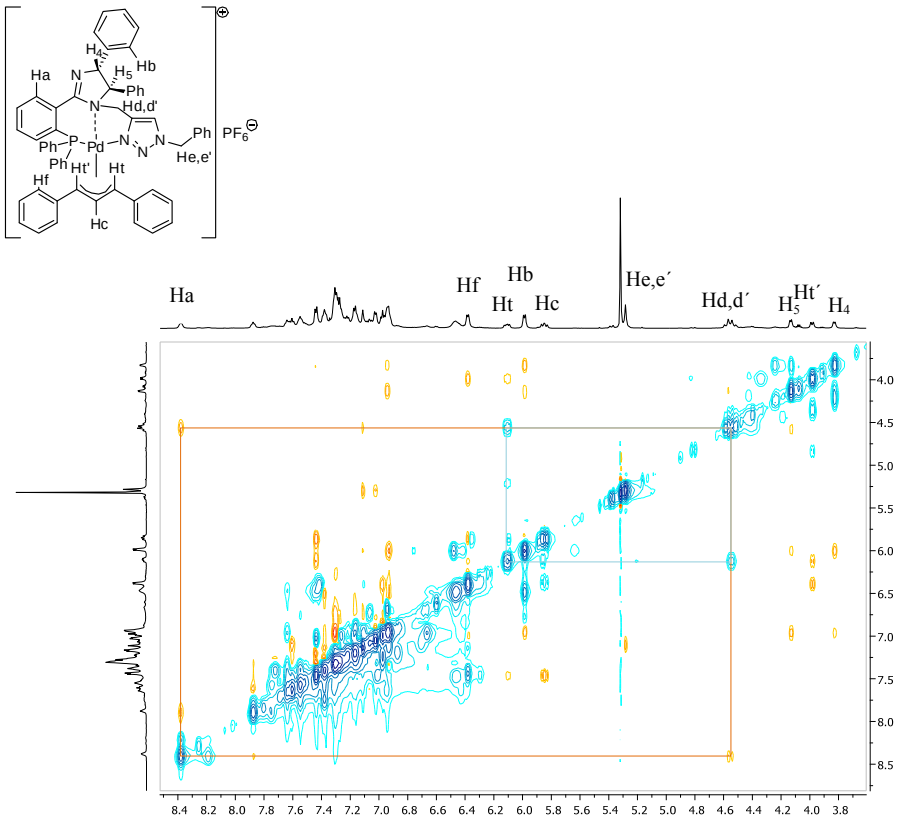

Figure 5.5. Relevant NOE contacts from NOESY experiment of [Pd(η^3-1,3-diphenylallyl)(**433**)]PF_6 (**457**) isomers.

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Due to these unexpected correlations, a similar study using more coordinating solvents such as acetonitrile and pyridine was carried out. In both solvents, the NOESY experiments revealed the same interactions than in dichloromethane. However, in acetonitrile Hd,d' appeared as two doublets and it was possible to distinguish that Ht interacts with Hd only, while Hd,d' interacted with Ha (Figure 5.6). When the temperature was decreased to -40ºC, the previous interactions were not detected in the NOESY spectrum.

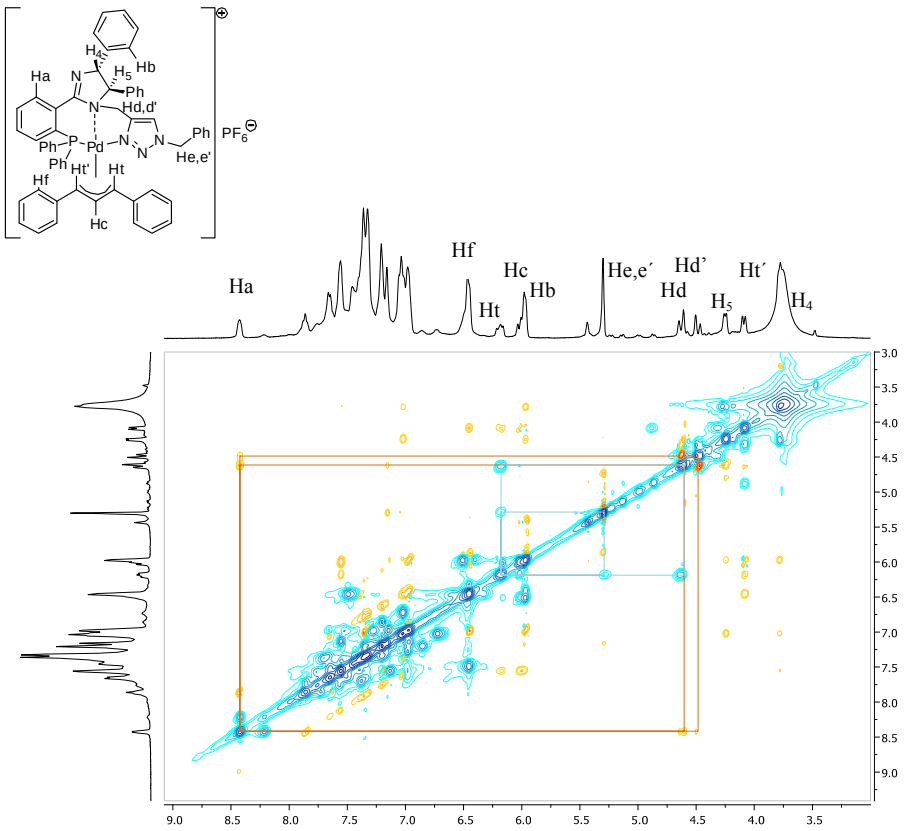

Figure 5.6. Relevant NOE contacts from NOESY experiment of [Pd(ŋ^3-1,3-diphenylallyl)(**433**)]PF_6 (**457**) isomers in acetonitrile at room temperature.

Interestingly, a 1D selective NOE in CD_2Cl_2 showed that while the selective irradiation of Ha afforded a positive NOE in Hd,d', the selective irradiation of Ht produced a negative NOE in Hd. Similarly, the irradiation of Hd, Hd' produced a positive NOE in Ha and negative in Ht (Figure 5.7).

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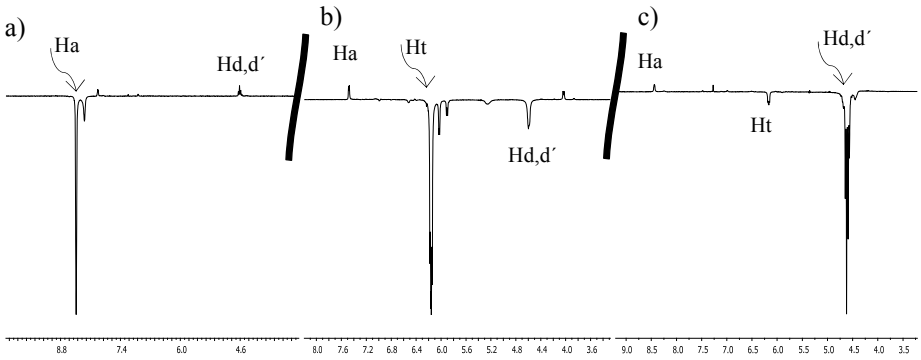


Figure 5.7. Selective 1D NOE irradiation of complex [Pd(η^3-1,3-diphenylallyl)(**433**)]PF_6 (**457**).

A negative NOE is produced when two protons exchange via chemical exchange or when a dynamic process exists between two fragments of a molecule (segmental motion).[62,63] The intensity of the negative peak (NOE) was found to vary as a function of temperature and mixing time.[62,33] Thus, a set of selective NOE experiments was carried out varying the temperature and the mixing time (Figure 5.8).

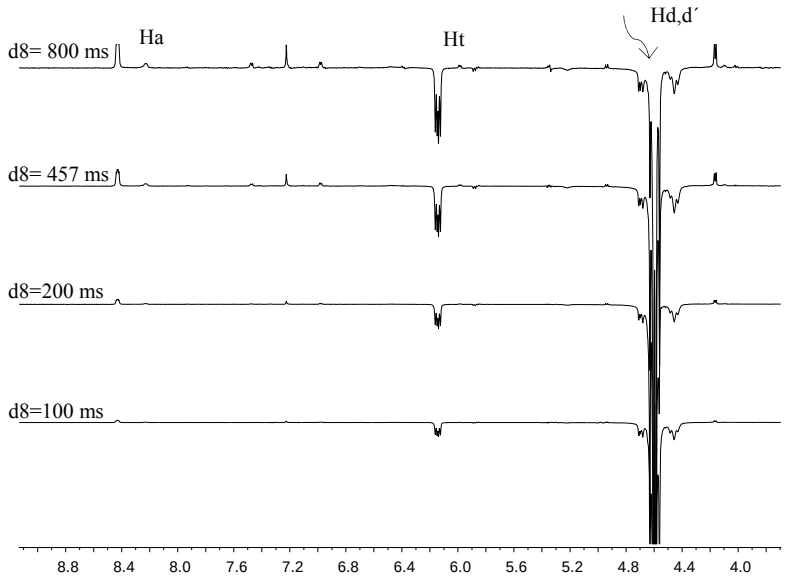


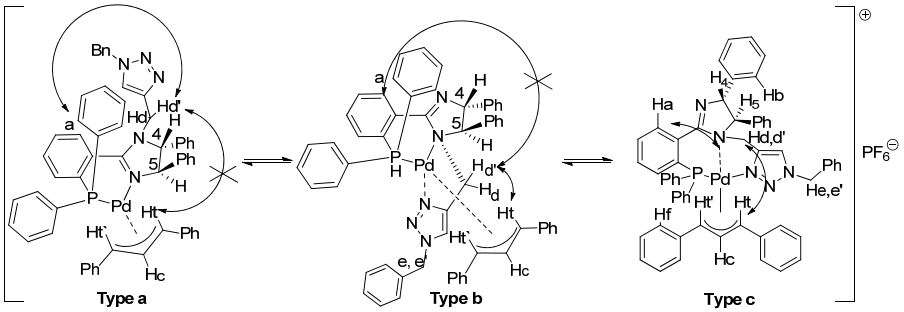
Figure 5.8. Selective NOE irradiation of complex **457** at 285 K and different mixing time (d8=100, 200, 457 and 800).

An increase of the negative signal was observed when the temperature was decreased and the mixing time increased, which is agreement to the described for NOE contacts between two fragments of a molecule in a "segmental motion" (Figure 5.8 shows the 1D selective NOE irradiation at 275K, Table 5.12 shows the 1D selective irradiation at different temperatures). [62, 63]

Table 5.12. Summary of integration on 1D selective NOE irradiation for [Pd(η^3-1,3-diphenylallyl)(**433**)]PF_6 (**457**).

Entry	Temperature	Mixing time	Negative NOE interaction
1	275K	d8=100	-3%
2	275K	d8=200	-5%
3	275K	d8=457	-9%
4	275K	d8=800	-15%
5	285K	d8=100	-4%
6	285K	d8=200	-6%
7	285K	d8=457	-10%
8	285K	d8=800	-15%
9	298K	d8=100	-3%
10	298K	d8=200	-4%
11	298K	d8=457	-6%
12	298K	d8=800	-8%
13	308K	d8=100	-1%
14	308K	d8=200	-1%
15	308K	d8=457	-2%
16	308K	d8=800	-2%

The NOE interaction Ht/Hd and Ht/He,e' can be explained if the coordination mode of the imidazoline to palladium is distinct from that of the other species studied, in such a way that the sp^3 nitrogen and/or the triazole ring are now coordinated to palladium (Scheme 5.16b) (Type b) or by coordination through the sp^2 nitrogen of the triazole ring as depicted in Scheme 5.16c (Type c).



Scheme 5.16. Possible isomers in complex **457**.

The observed negative NOE could be then justified by a 1) coordination-decoordination process of triazole to palladium; 2) chemical exchange between the two different coordination modes of the imidazoline ring to the palladium centre metal, through the sp^2 nitrogen or through the sp^3 nitrogen atom or 3) chemical exchange of the allyl moiety between *exo* and *endo* isomers.

As in NOESY experiments, the peaks corresponding to a chemical exchange can be confused with negative NOEs, a ROESY experiment was carried out to investigate the nature of this process. The presence of cross peaks between the resonances corresponding to Ht and Hd,d' clearly indicated that a chemical exchange is taking place under these conditions (Figure 5.9).

Looking for additional information about the of coordination mode of the ligand in this complex and about the chemical exchange reflected in the NOE study, the synthesis of the complex **460**, which is ^{15}N enriched in the triazolyl fragment, was carried out. Thus, compound **429** was treated with (1-^{15}N)NaN_3 and BnBr in the presence of Cu_2SO_4, to afford the compound **458**. The splitting of the triazolic proton signals into two doublets confirmed the presence of ^{15}N enriched (50%) in the 1,3-nitrogens of the triazole ring. Compound **458** was treated with $KPPh_2$ to give the phosphine **459**, which was then reacted with $[Pd(\eta^3\text{-allyl})Cl]_2$ to afford **460** (Scheme 5.17). When the $^{31}P\{^1H\}$ NMR spectra of the resulting complex **460** was acquired at temperatures between 0 and -90ºC, the signal corresponding to this species appeared as a broad singlet at 19.68-19.29 ppm (Figure 5.10). The absence of ^{31}P-^{15}N coupling indicated that the triazole ring is not permanently coordinated to the palladium centre. However, as the ligand was only enriched

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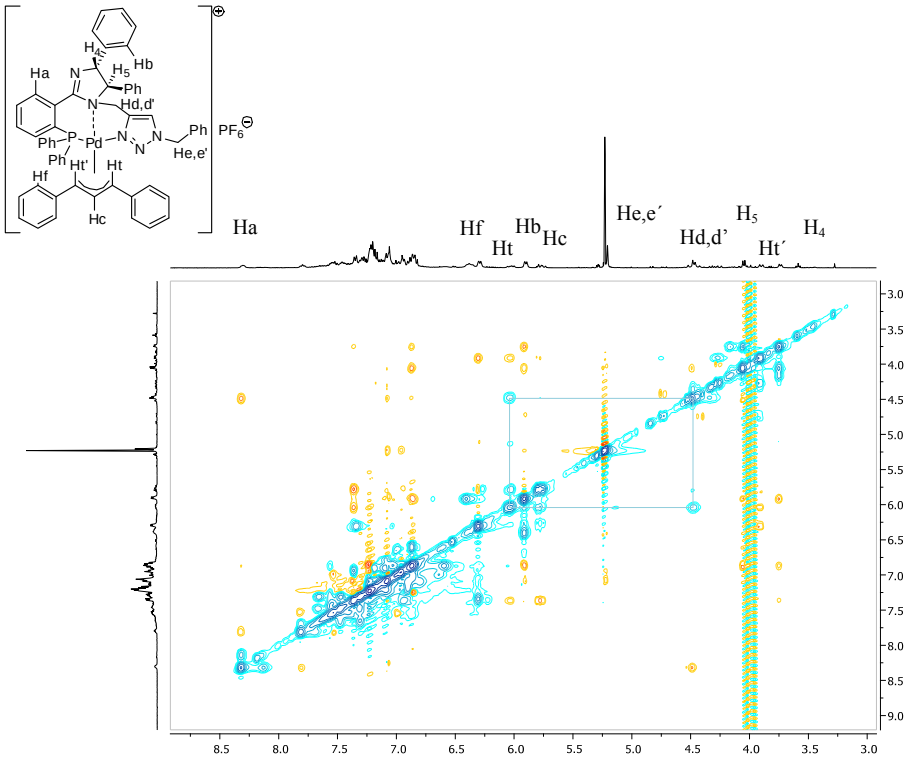
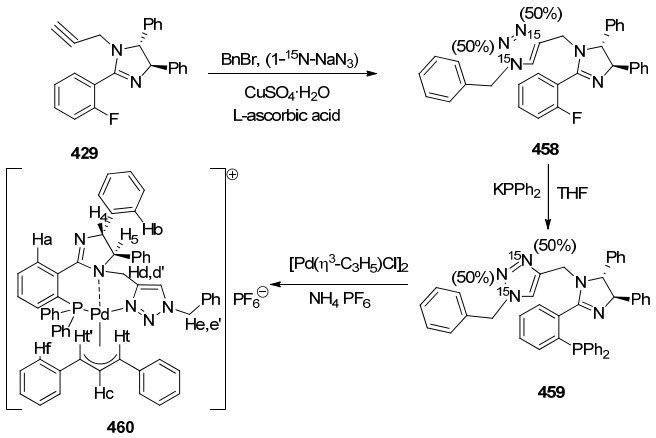


Figure 5.9. Relevant ROE contacts from ROESY experiment of [Pd(η^3-1,3-diphenylallyl)(**433**)]PF_6 (**457**) isomers.



Scheme 5.17. Synthesis of ^{15}N enriched ligand **459** and complex **460**.

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at 50% and in view of the broadness of the signal, no clear conclusion could be drawn from this experiment.

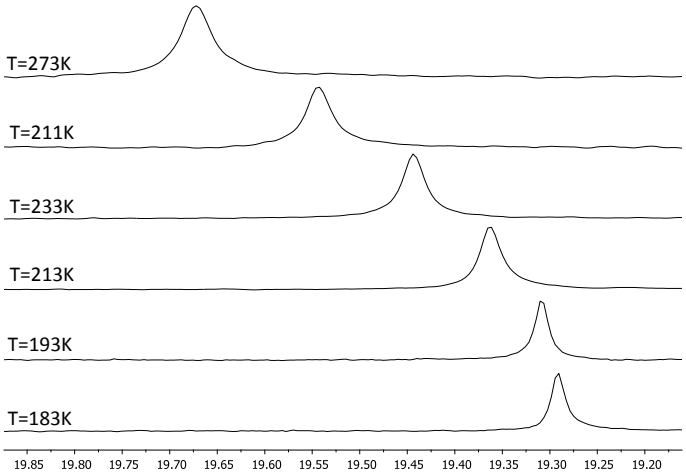
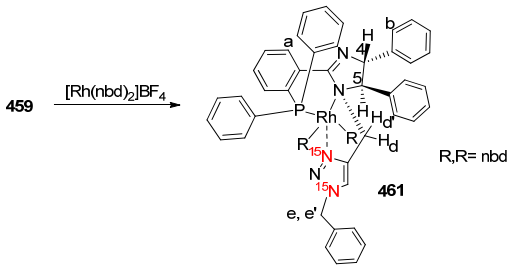


Figure 5.10. ^{31}P-$\{^{1}H\}$ VT experiments of complex **460** in CD_2Cl_2.

To favour the coordination of this ligand in a tridentate manner, the cationic rhodium complex **461** was prepared by reaction of ligand **459** with $[Rh(nbd)_2]BF_4$ (Scheme 5.18). Comparing the $^{31}P\{^{1}H\}$ spectra of the ^{15}N labeled species with that of the not labeled complex (**462**), several additional couplings can be observed (Figure 5.11), indicating that the triazole ring is coordinated to the rhodium centre. It can be concluded that the sp^2 nitrogen of the triazole ring is coordinated to the rhodium metal centre, which supposes that the imidazoline ring is coordinated through its sp^3 nitrogen atom. It is noteworthy that this is the first example of such a coordination of an imidazoline ligand to a metal centre.



Scheme 5.18. Synthesis of [Rh(nbd)(**459**)]BF_4.

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Similar interactions of a remote hydroxyl substituent contained in a P,N ligand were shown to lower the symmetry of an allylic moiety and as such, yielded increased enantioselectivity in asymmetric Pd-catalysed allylic alkylation reactions.[34,35]

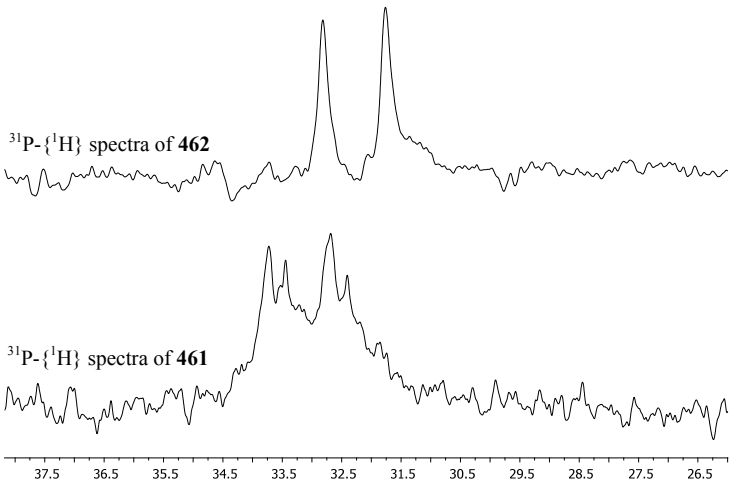
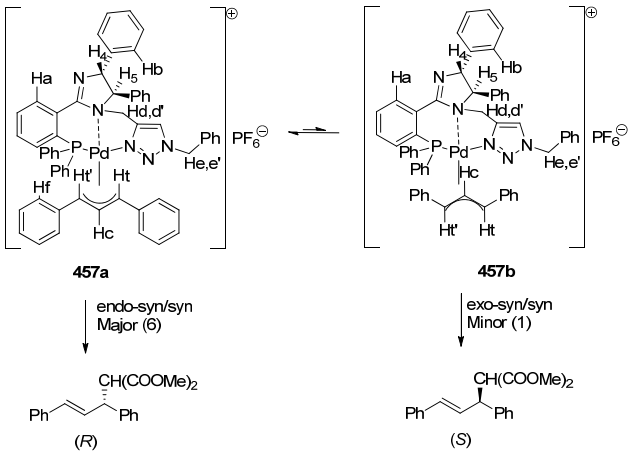


Figure 5.11. ^{31}P-{^{1}H} spectra of complexes **461** and **462** at 213K.

Once again, the more electrophilic allyl terminal carbon was *trans* to the phosphine moiety (Scheme 5.19).



Scheme 5.19. Diastereoisomer Pd-allyl intermediates for substrate **355** with ligand **433**. The relative amounts of each isomer are drawn in parenthesis.

On the basis of the stereochemical outcome of the reaction, which gave 96% ee of the *R* isomer product using Pd/**433**, it can be concluded that the *endo* isomer **457a** reacts faster than the *exo* isomer **457b**. To demonstrate this, the complex **457** was reacted with the corresponding nucleophile and the reaction was monitored by NMR spectroscopy. The signal corresponding to the isomer **457a** was observed to disappear faster than the signal of isomer **457b**. The high enantioselectivity achieved with ligand **433**, much higher than the obtained with other ligands, can be attributed to the distinct coordination mode of the imidazoline moiety to palladium.

In view of these experimental results, we decided to study by theoretical means (DFT) the π-(1,3-diphenylallyl)palladium intermediates arising from the three proposed coordination modes of the PHIM ligand to palladium. For each coordination mode, *exo* and *endo* isomers of *syn-syn* type were considered. The calculations were performed with the Minnesota 06 (M06) functional,[64] as implemented in Gaussian09.[65] The triple zeta Stuttgart-Dresden (SDD) basis set and effective core potentials[66] were used for palladium and the split-valence double-zeta 6-31G basis set with additional d polarization functions[67] for all the other atoms.

To start with, a simplified model was studied in which all the exocyclic substituents with respect to the chelate ring had been removed. After an exhaustive conformational analysis, six absolute minima for the *endo* and *exo* isomers of the three coordination modes were determined (Figure 5.12, see also Scheme 5.16). Interestingly, although the most stable structures were predicted to be those with the classical imidazoline sp^2 coordination, the energy gap with the triazole-coordinated structures was small (1.8 to 2.6 kcal·mol^{-1}). The sp^3 N-coordinated structures, on the other hand, laid significantly higher in energy respect to the other two types (8.5 to 9.6 kcal·mol^{-1}). This result clearly suggests that the triazole can coordinate to palladium, and as such, can incite the deccordination of the imidazoline, although this latter can form a very stable six-membered chelate ring with the metal centre. To gain further information, we performed optimizations of these basic structures with real model systems using the M06 functional and SDD/6-31G(d) basis sets as described above. In order to obtain as accurate energies as possible, single point frequencies calculations were run on the optimized structures with scrf solvent model[68] for dichloromethane.

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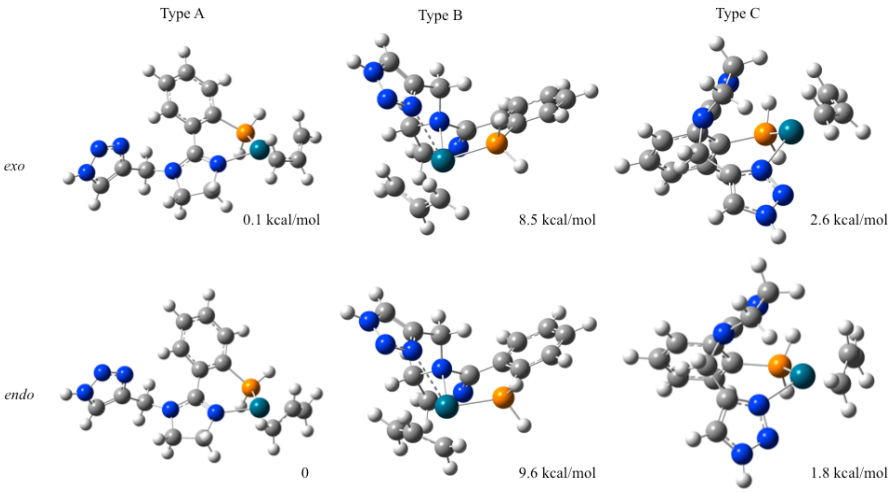

Figure 5.12. Optimised structures for the three possible coordination modes in simplified models of $[Pd(\eta^3\text{-}C_3H_5)(PHIM)]^+$ cationic complex.

The results, summarized in Figure 5.13, surprisingly revealed an extremely strong stabilization of the type C structures with respect to the *classical* type A (> 11 kcal/mol) and to the type B (> 6 kcal/mol).

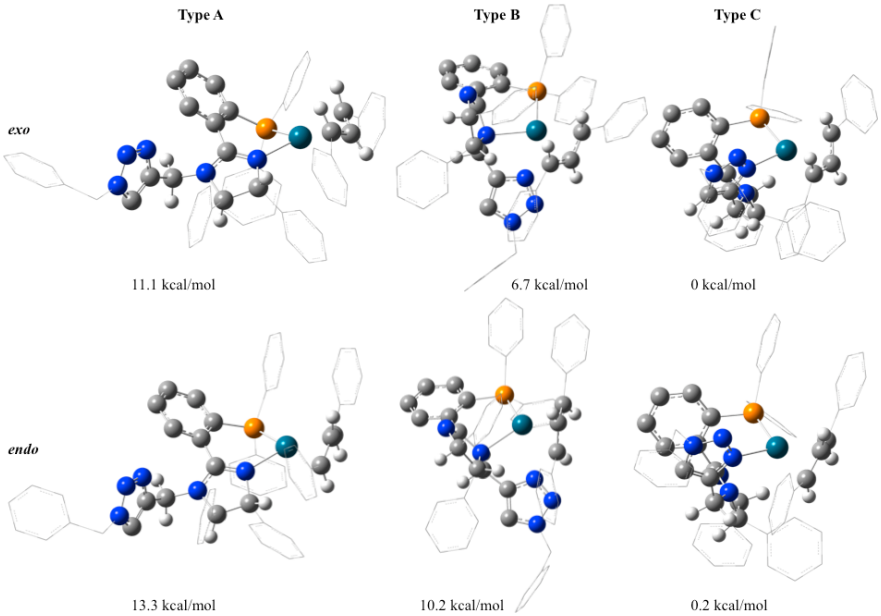

Figure 5.13. DFT-optimised structures of the $[Pd(\eta^3\text{-diphenylallyl})(\mathbf{433})]^+$ cationic complex.

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A careful comparison of these observations with the structures predicted by computational means (Table 5.13) makes apparent that the most consistent structures with the experimental data are of the type C, in which the triazole unit is coordinated to palladium instead of the imidazoline.

Table 5.13. NOE-relevant H-H distances in the computed optimised structures of [Pd(η^3-1,3-diphenylallyl)(**433**)]$^+$ cationic complex.[a]

H	H	NOE observed	Distance (Å)					
			A	A'	B	B'	C	C'
H_a	H_d	Yes	2.36	2.43	3.67	3.53	3.15	3.17
H_a	$H_{d'}$	Yes	3.77	3.82	4.05	3.59	4.66	4.68
H_d	H_t	Yes	**7.23**	**7.59**	4.55	**5.59**	3.61	4.89
H_t	H_{C4}	No	**2.97**	**3.77**	6.28	**4.81**	5.03	7.21
H_t	H_{C5}	No	5.52	6.38	**3.51**	**2.88**	5.24	7.05
H_c	H_{C4}	No	**4.78**	**4.83**	5.70	6.96	7.07	5.36
H_c	H_{C5}	No	7.45	6.73	**3.79**	**4.37**	7.74	5.80

[a]Highlighted in boldface are the distances considered not to be consistent with the experimental data. For this simplification we have assumed a cut between observable or not observable NOE in 5.00 Å, which is in fact a somewhat extreme distance. However, the computational techniques used are known to frequently overestimate to some extent the length of Pd-C and Pd-heteroatom bonds, so it is not wrong to assume the real distances can be slightly shorter.

Therefore, it was concluded that the triazole linker is coordinated to palladium and force a twist of the imidazoline unit in such a way that the sp^3 nitrogen points towards the palladium atom while the sp^2 nitrogen that is classically involved in coordination, points away from the Pd centre. This coordination mode of the ligand is proposed to explain the increase in the enantioselectivity observed with the second generation of PHIM ligands and their polymer-supported version.

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5.2.4. Pd-allylic alkylation in ionic liquids

Over the last decade, the importance of ionic liquids has increased in the field of organic synthesis due to their unique features such as: low vapor pressure, low toxicity, immiscibility with some organic solvents, along with the fact that they readily dissolve metal catalysts and organic compounds. These characteristics, combined with the possibility of catalyst recycling and ease of products separation, make them very attractive alternatives to usual organic solvents.[69,70,71]

The earliest example of the use of an ionic liquid in Pd-catalysed allylic alkylation reactions was reported by Xiao et al. in 1999 with the utilization of the IL 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) (**463**).[72a] Since then, only a few works concerning the use of ionic liquids in this reaction have been reported.[72] To the best of our knowledge, there are only two precedents in the literature concerning the asymmetric version of this reaction. In 2000 and 2002, Toma *et al.* described the alkylation of 1,3-diphenyl-3-acetoxy propene (**355**) with dimethyl malonate in [bmim][PF_6] (**464**) using chiral ferrocene-based ligands, achieving 86 % ee but low conversions. No efficient recycling of the catalyst was possible under these conditions, and the ee decreased with each run (Table 5.14).[72g,h]

Due to the excellent results achieved with palladium complexes bearing phosphino-imidazoline ligands and the success in recycling the catalyst, we decided to test our family of ligands in the Pd-catalysed allylic alkylation using ionic liquids as solvent and in a second stage, to recycle the catalytic system.

Initially the reaction of *rac*-1,3-diphenylprop-2-en-1-yl acetate with dimethyl malonate catalyzed by Pd/**316** was investigated in the previously reported IL [bmim][BF_4] (**463**) and [bmim][PF_6] (**464**). In both cases the conversions and enantioselectivities were low, and not reproducible. Thus, when the ionic liquid **463** ([bmim][BF_4])[72c] was used, a conversion range between 54-64% with an enantiomeric excess range of 25-64% were obtained (entry 1, Table 5.15). The same behaviour was observed when the counter anion was PF_6^- (**464**), with a conversion range of 22-52% and enantioselectivities between 56 and 61% (entry 2).

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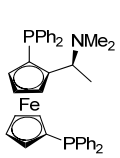
Table 5.14. Chiral ferrocene-based ligands tested in allylic alkylation



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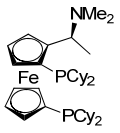

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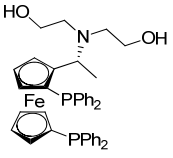

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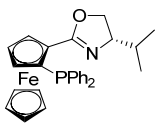

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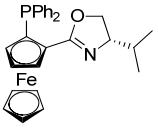

469

Ligand	Base	Cycle	Yield (%)	Ee (%)
466	BSA/KOAc	1	69	56
466	BSA/KOAc	2	25	46
467	K_2CO_3	1	81	74
468	K_2CO_3	1	34	86
468	K_2CO_3	2	27	84
468	BSA/KOAc	1	55	68
468	BSA/KOAc	2	47	66

When the reaction was performed in 2,3-dimethyl-1-butylimidazolium hexafluorophosphate ([2,3-dmbim][PF_6], (**470**) complete conversion was obtained but the enantioselectivity was low (entry 3). The use of ionic liquid **471** led to full conversion with an excellent enantioselectivity up to 90% (entry 4). Interestingly, in both cases, the results were reproducible.

Various palladium precursors and reaction temperatures were screened in **471**. Using [Pd(η^3-C_3H_5)Cl]$_2$ as precursor, the reaction was carrying out at room temperature and 120ºC. Under these conditions, the conversions were similar but the ee decreased significantly at 120ºC (entries 5 and 6). As described earlier in this thesis (see Section 5.2.1.1), some heating was required in order to obtain good enantioselectivity, probably for facilitating the isomerization between allylpalladium intermediates.[50] However, the experiments obtained in IL (entry 6) show that heating at 120°C is detrimental to the enantioselectivity of the reaction. It was therefore concluded that a temperature somewhat intermediate between room temperature and 120ºC is the most appropriate. The use of a Pd(0) source did not improve the catalytic results (entry 7 and 8).

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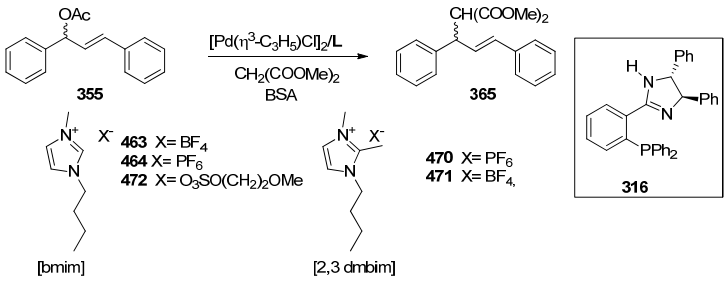
Table 5.15. Screening of Ionic Liquid in the Pd-Allylic Alkylation of *rac*-1,3-diphenylprop-2-en-1-yl acetate.[a]



([bmim]= 1-butyl-3-methylimidazolium, [2, 3- dmbim]= 2,3-dimethylbutylimidazolium)

Entry	Precursor	Ionic Liquid	Temp. (ºC)	Conv.[b] (%)	Ee.[c] (%)
1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	**463**	45	54-64[d]	25-64[d]
2	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	**464**	45	22-52[d]	56-61[d]
3	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	**470**	45	>95	55
4	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	**471**	45	>95	90
5	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	**471**	rt	>95	61
6	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	**471**	120	93	41
7	$Pd_2(dba)_3$	**471**	rt	54	48
8	$Pd_2(dba)_3$	**471**	45	>95	68
9	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	**472**	45	44	94

[a] *Reaction conditions*: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol); substrate (1 mmol); dimethyl malonate (3 mmol); BSA (3 mmol), KOAc (0.02 mmol) in CH_2Cl_2 (2 ml). [b] Conversion determined by NMR. [c] Product has R configuration. Enantiomeric excess determined by HPLC on a Chiracel-OD-H column. [d] Range of results obtained in 5 different essays.

The difference between ionic liquids **463**, **464** and **470**, **471** is the presence in the formers of an acidic proton in position 2, which in presence of base can lead to the formation of carbene species that could react with the catalytic species.[73] In order to gain information about such behaviour, we studied the reactivity of the Pd precursors and Pd/**316** phosphine ligand with the ionic liquids under the basic conditions used in the alkylation

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reaction by in situ ^{31}P and ^{1}H NMR and mass spectrometry. In the experiment with the palladium precursor the formation of the carbene complex **473** was observed (Figure 5.14).

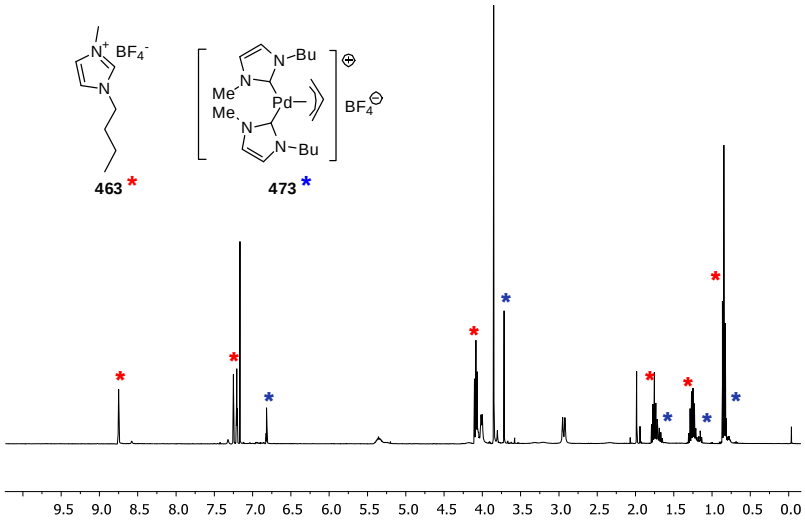

Figure 5.14. ^{1}H NMR spectra of reaction of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ with IL **463** and KOAc.

The species was identified by comparison with reported related complexes, and by NMR spectroscopy and HRMS analysis.[74] While when Pd/**316** was used, the formation of carbene complexes **473**, **474** together with the expected catalyts **475** were detected (Figure 5.15 and 5.16).[75] Although a similar acid-base process could be expected when the IL **472** was used, the study carried out under similar conditions revealed the only presence of complex **475**. Furthermore, the catalytic experiments were reproducible obtaining moderate conversion and excellent enantioselectivity (up to 94%) (entry 9, Table 5.15). This behaviour is attributed to the steric hindrance of the anions in the ionic liquid which makes unaccesible the acidic proton of the imidazole ring.[73c]

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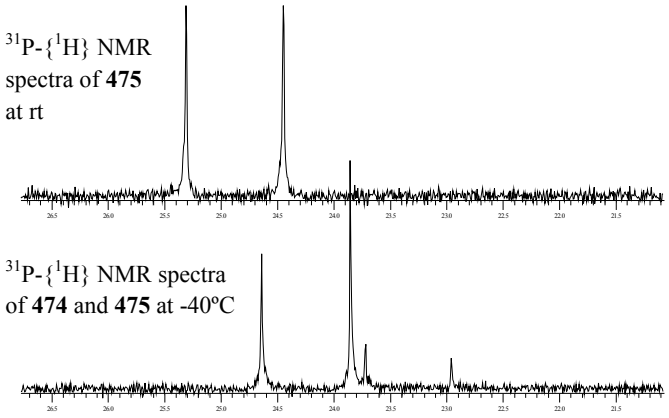


Figure 5.15. ^{31}P-{^{1}H} NMR spectra of complexes **474** and **475**.

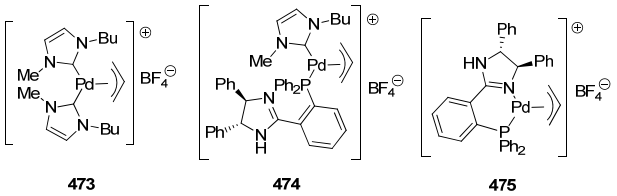
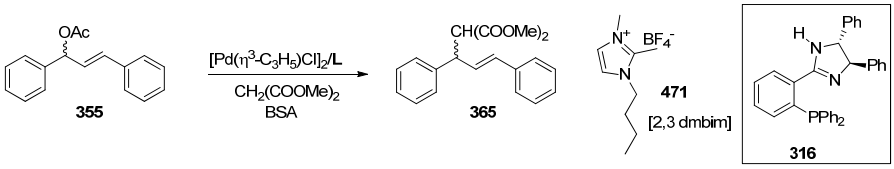


Figure 5.16. Complexes formed in the presence of palladium precursor, ligand **316**, ionic liquid **463** and KOAc.

Recycling experiments were first performed under microwaves irradiation in order to optimize the reaction time. Complete conversion and 87% enantioselectivity was achieved in only 3 hours under microwave irradiations (P=8 watts, entry 1, Table 5.16) and in 1 hour over 90% conversion was already achieved with the same ee (entry 2, Table 5.16).

After each run, the ionic liquid was extracted with dry degassed toluene (3 times) and kept under vacuum for at least 3 hrs. The next run was then initiated by simply adding the *rac*-1,3-diphenylprop-2-en-1-yl acetate (**355**), dimethyl malonate, BSA and potassium acetate. After the second run, the conversion and the enantioselectivity remained unchanged with 93% conversion and the same enantioselectivity (89%). After 4 cycles using the same ionic liquid solution, the conversion was still around 70% and the enantioselectivity was 77%.[76]

Table 5.16. Recycling and Microwave in the Pd-allylic alkylation of *rac*-1,3-diphenylprop-2-en-1-yl acetate (**316**) in ionic liquid **471**.



Entry	Cycle	Time (h)	Conv.[a] (%)	Ee[b] (%)
1	1	3	>95%	87%
2	1	1	94%	90%
3	2	1	93%	89%
4	3	1	90%	88%
5	4	1	68%	77%

[a] Conversion determined by ^{1}H NMR analysis. [b] Enantiomeric excess determined by HPLC on a Chiracel-OD-H column.

Next, the ligands **316**, **317**, **433** and **434** were tested in the palladium catalysed allylic alkylation reaction (Table 5.17). The results can be summarized as: a) the incorporation of a cyclohexyl group at the imidazoline ring produces a negative effect on the enantioselectivity as previously observed (entry 1 *vs.* 2, Table 5.17); b) the introduction of a triazolyl substituent at the nitrogen atom of the imidazoline ring has a beneficial effect on the enantioselectivity (entry 1 and 2 *vs.* 3 and 4, Table 5.17).

From these results, it can be concluded that the choice of the ionic liquid is critical to obtain high activity and enantioselectivity and that the use ionic liquids which have a blocked C-2 position of the ring is required. The optimised catalytic system is very stable and allows efficient recycling as well as the use of microwave conditions providing high level of conversion and enantioselectivity (up to 95%).

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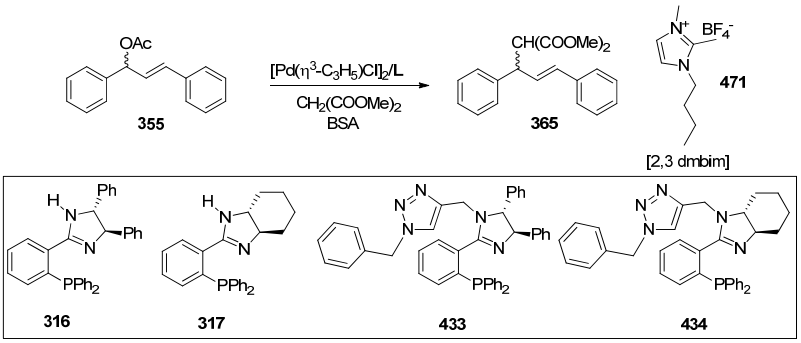
Table 5.17 Recycling and Microwave in the Pd-allylic alkylation of rac-1,3-diphenylprop-2-en-1-yl acetate (**355**) in ionic liquid (**471**).



Entry	Ligand	Conv.[a] (%)	Ee.[b] (%)
1	**316**	99	90
2	**317**	99	53
3	**433**	99	95
4	**434**	87	73

[a] *Reaction conditions*: 0.02 mmol $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$; 1 mmol substrate; 3 mmol dimethyl malonate; 3 mmol BSA; 0.02 mmol KOAc in the corresponding ionic liquid, at 45ºC. [b] Conversion determined by NMR. [C] Product has R configuration. Enantiomeric excess determined by HPLC on a Chiracel-OD-H column.

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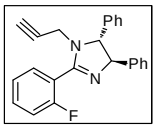
5. 3. Experimental section

General Methods

All reactions were carried out under an argon atmosphere using Standard Schlenk techniques. Solvents were distilled and degassed prior to use. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini spectrometer at 300 and 357 MHz. Chemical shifts were reported relative to tetramethylsilane for ^{1}H and $^{13}C\{^{1}H\}$ as internal reference, H_3PO_4 85% for $^{31}P\{^{1}H\}$, and trichlorofluoromethane for $^{19}F\{^{1}H\}$ as external references. Elemental analyses were carried out on a Carlo Erba Microanalyser EA 1108. VG-Autospect equipment was used for FAB mass spectral analyses with 3-nitrobenzylalcohol as matrix. EI mass spectra were obtained on an HP 5989 A spectrometer at an ionizing voltage of 70eV. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Melting points were determined in an open capillary tube with a Tottoli-Büchi 473 melting point apparatus and are uncorrected. Conversion was measured by NMR spectrometry. The enantiomeric excesses were measured by HPLC (OJ-H, OD-H and AD-H columns)

(4*R*,5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-1-(prop-2-yn-1-yl)-4,5-dihydro-1H-imidazole (429).



A solution of (4*R*,5*R*)-2-(2-fluoro-phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazole (**314**) (500 mg, 1.59 mmol) in 1mL of anhydrous tetrahydrofurane was added to a cooled solution (0ºC) of NaH (60% in oil suspension, 142.85 mg, 3.57 mmol) in 0,5 mL of anhydrous tetrahydrofurane. The mixture was stirred for 30 min and then propargyl bromide (247.52 µl, 2.78 mmol) was added drop wise. The reaction mixture was stirred for 48 hours at room temperature. Then, the reaction mixture was filtered through celite and purified by column chromatography (hexane/ethyl acetate 3:1(5% NEt_3)) to give compound **429** as a yellow oil (327 mg, 58%). $[\alpha]_D^{20}$= -90.73º (c=1.00, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.75 (m, 1H, arom); 7.59-7.18 (m, 13H, arom); 4.60 (d, ^{3}J=9.2 Hz, 1H, CH); 4.73 (d, ^{3}J=9.2 Hz, 1H, CH); 3.95 (dd, ^{2}J=18.4 Hz, ^{3}J=2.0 Hz, 1H, CH_2); 3.50 (dd, ^{2}J=18.4 Hz, ^{3}J=2.0 Hz, 1H, CH_2); 2.55 (s, 1H, CH). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 161.9 (d, ^{1}J=65.7 Hz, C, arom), 159.1 (C=N); 143.6-116.8 (C, arom); 78.7 (C); 78.3 (CH); 74.1 (CH); 73.6 (CH); 36.2 (CH_3). **^{19}F NMR** ($CDCl_3$,

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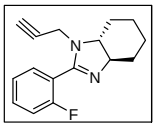
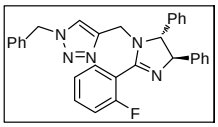
376.5 MHz): -114.1 (m). **HRMS** (ESI-TOF): *m/z* = 355.1613, calcd for $[M]^+$: 355.1611. Anal. Calcd for $C_{24}H_{19}FN_2$: C, 81.33; H, 5.40; F, 5.36; N, 7.90. Found: C, 81.28; H, 5.42; N, 7.96.

2-(2-fluorophenyl)-1-(prop-2-yn-1-yl)-3a,4,5,6,7,7a-hexahydro-1H-benzo[d]imidazole (430).



A solution of **315** (425 mg, 1.95 mmol) in 1mL of anhydrous tetrahydrofurane was added to a cooled solution (0ºC) of NaH (60% in oil suspension, 175.2 mg, 4.38 mmol) in 0,5 mL of anhydrous tetrahydrofurane. The mixture was stirred for 30 min and then propargyl bromide (304.08 µl, 3.4 mmol) was added dropwise. The reaction mixture was stirred for 48hours at room temperature. Then, the reaction mixture was filtered through celite and purified by column chromatography (hexane/ethyl acetate 6:4 and pure ethyl acetate (5% NEt_3)) to give compound **430** as yellow oil (309 mg, 62%). $[\alpha]_D^{20}$= +23.72º (c=0.71, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.49 (m, 1H, arom); 7.40 (m, 1H, arom); 7.20-7.08 (m, 2H, arom); 3.84 (dd, ^{2}J= 18.4Hz, ^{4}J= 2.4Hz 1H, CH_2); 3.73 (dd, ^{2}J= 18.4Hz, ^{4}J= 2.4Hz, 1H, CH_2); 3.17 (m, 1H, CH); 2.97 (m, 1H, CH); 2.39 (br, 1H, CH); 2.14 (m, 2H, CH_2); 1.87 (m, 2H, CH_2); 1,59-1.23 (m, 4H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 164.4 (C=N); 160.8 (C, arom); 158.1 (C, arom); 131.7 (d, ^{3}J=8.15 Hz, C arom), 131. 1 (C, arom); 124. 6 (C, arom); 116.0 (d, ^{3}J=8.15 Hz, C arom); 78.0 (C); 73.2 (CH); 71.4 (CH); 68.9 (CH); 36.1 (CH_2); 31.2 (CH_2); 29.0 (CH_2); 25.8 (CH_2); 24.7 (CH_2). **^{19}F NMR** ($CDCl_3$, 376.5 MHz): -113.5 (m). **HRMS** (ESI-TOF): *m/z* = 257.1459, calcd for $[M]^+$: 257.1454. Anal. Calcd for $C_{16}H_{17}FN_2$: C, 74.97; H, 6.69; F, 7.41; N, 10.93. Found: C, 74.95; H, 6.75; N, 10.99.

1-benzyl-5-((2-(2-fluorophenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazole (431).



Compound **429** (400 mg, 1.15 mmol) was dissolved in a mixture of water and *tert*-butanol (1:1). Then, benzyl bromide (128 µL, 1.15 mmol), sodium azide (156.8 mg, 2.45 mmol), copper sulphate pentahydrate (5.6mg, µ23mol) and L-ascorbic acid (46.56mg, 0.24 mmol) were added. The reaction mixture was heated at 40ºC for 12 hours. The compound was extrated into dichloromethane (3x15 mL) and the residue after the evaporation was purified

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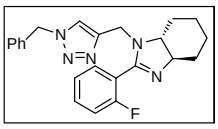
by column chromatography (hexane:ethyl acetate 6:4, and then pure ethyl acetate (5% NEt_3)) to give compound **429** as a yellow foam (206 mg, 60%). **$[\alpha]_D^{20}$=** -28.11º (c=0.53, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.69 (m, 1H, arom); 7.48-7.11 (m, 18H, arom); 6.87 (s, CH); 5.40 (d, ^{2}J=16Hz, 1H, CH_2); 5.34 (d, ^{2}J=16Hz, 1H, CH_2); 5.00 (d, ^{3}J=8Hz, 1H, CH); 4.47 (d, ^{3}J=8Hz, 1H, CH); 4.38 (d, ^{2}J=16Hz, 1H, CH_2); 4.14 (d, ^{2}J=16Hz, 1H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 161.5 (d, ^{1}J=57.7Hz, C arom); 158.7 (C=N); 143.8-116.1 (C, arom); 78.3 (s, CH); 73.71 (s, CH); 54.2 (s, CH_2); 41.3 (s, CH_2). **^{19}F NMR** ($CDCl_3$, 376.5 MHz): -113.28 (m). **HRMS** (ESI-TOF): *m/z* =488.2256, calcd for $[M]^+$: 488.2250. Anal. Calcd for $C_{31}H_{26}FN_5$: C, 76.36; H, 5.37; F, 3.90; N, 14.36. Found: C, 76.29; H, 5.43; N, 14.42.

(3a*R*,7a*R*)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-2-(2-fluorophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzo[d]imidazole (432).



Compound **430** (250 mg, 0.71 mmol) was dissolved in a mixture of water and *tert*-butanol (1:1). Then, benzyl bromide (116μL, 0.71 mmol), sodium azide (135 mg, 1.17 mmol), copper sulphate pentahydrate (4.86mg, 19μmol) and L-ascorbic acid (40.3mg, 0.20 mmol) were added. The reaction mixture was heated at 40ºC for 12 hours. The compound was extrated into dichloromethane (3x15 mL) and the residue after the evaporation was purified by column chromatography (hexane:ethyl acetate 6:4, and then pure ethyl acetate (5% NEt_3)) to give compound **432** as a yellow foam (281 mg, 59%). **$[\alpha]_D^{20}$=** +37.15º (c=0.81, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.36-6.9 (m, 9H, arom); 5.44 (br, 2H, CH_2); 4.4 (d, ^{2}J=16Hz, 1H, CH_2); 4.07 (d, ^{2}J=16Hz, 1H, CH_2); 3.12 (m, 1H, CH); 2.78 (m, 1H, CH); 2.32 (m ,1H, CH_2); 2-1.2 (m, 7H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 164.1 (C,arom.); 160.5 (C=N); 159-115 (C, arom); 71.1 (s, CH); 54.2 (s, CH_2); 42.9 (s, CH); 32.1 (s, CH_2); 29.9 (s, CH_2); 29.8 (s, CH_2); 25.6 (s, CH_2); 24.6 (s, CH_2);. **^{19}F NMR** ($CDCl_3$, 376.5 MHz): -113.28 (m). **HRMS** (ESI-TOF): *m/z* =390.2094, calcd for $[M]^+$: 390.2084. Anal. Calcd for $C_{31}H_{26}FN_5$: C, 70.93; H, 6.21; F, 4.88; N, 17.98. Found: C, 70.89; H, 6.35; N, 17.65.

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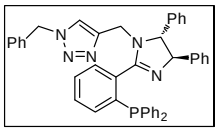
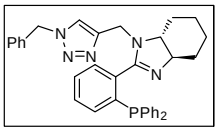
1-benzyl-5-((2-(2-(diphenyl-phosphino)phenyl)-4,5-diphenyl-4,5-dihydro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazole (433).



Compound **431** (150 mg, 0.31 mmol) was added to a solution of potassium diphenylphosphide (0.48 mL, 0.38 mmol, 0.5M en THF) and the resulting mixture was stirred overnight at room temperature. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column chromatography under nitrogen (hexane/ethyl acetate 6:4 (5% NEt_3)) to give compound **433** as a white solid (141 mg, 70%). $[\alpha]_D^{20}$= -23.41º (c=0.34, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.63-7.59 (m, 1H, arom); 7.33-7.00 (m, 32H, arom); 6.79 (s, 1H, CH); 5.26 (d, ^{2}J=19Hz, 1H, CH_2); 5.21 (d, ^{2}J=19Hz, 1H, CH_2); 4.83 (d, ^{3}J=12Hz, 1H, CH); 4.25 (d, ^{3}J=12Hz, 1H, CH); 4.14 (d, ^{2}J=16Hz, 1H, CH_2); 3.85 (d, ^{2}J=16Hz, 1H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 165.2 (s, C=N); 143.8-122.3 (C, arom); 78.6 (s, CH); 73.9 (s, CH); 53.9 (s, CH_2); 41.5 (s, CH_2). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): -11.4 (s). **HRMS** (ESI-TOF): *m/z* =654.2793, calcd for $[M]^+$: 654.2787. Anal. Calcd for $C_{43}H_{36}N_5P$: C, 79.00; H, 5.55; N, 10.71; P, 4.74. Found: C, 79.02; H, 5.67; N, 10.76.

(3a*R*,7a*R*)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-2-(2-(diphenylphosphino)phenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzo[d]-imidazole (434).



Compound **432** (150 mg, 0.31 mmol) was added to a solution of potassium diphenylphosphide (0.48 mL, 0.38 mmol, 0.5M en THF) and the resulting mixture was stirred overnight at room temperature. The reaction crude was then poured into water and extracted twice with dichloromethane. The organic layer was dried with anhydrous $MgSO_4$ and purified by column cromatography under nitrogen (hexane/ethyl acetate 6:4 (5% NEt_3)) to give compound **434** as a white solid (83 mg, 68%). $[\alpha]_D^{20}$= +32.47º (c=0.30, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.39-6.92 (m, 19H, arom,1H CH); 5.36 (br, 2H, CH_2); 4.18 (d, ^{2}J=15.6Hz, 1H, CH_2); 3.83 (d, ^{2}J=15.6Hz, 1H, CH_2); 2.70 (m, 1H, CH); 2.46 (m, 1H, CH); 2.13 (m, 1H, CH_2); 1.66-1.5 (m, 3H, CH_2); 1.2-1 (m, 4H, CH_2). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 167.5 (C=N); 134.9-122.3 (C, arom); 74.2 (s, CH); 54.2 (s, CH); 43.6 (s, CH_2); 31.1 (s, CH_2); 30.2 (s, CH_2); 25.7 (s, CH_2); 24.7 (s, CH_2); 21.2 (s,

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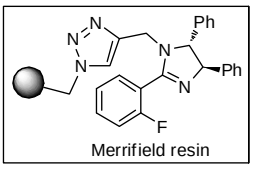
CH_2). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): -11.4 (s). **HRMS** (ESI-TOF): *m/z* =556.2643, calcd for $[M]^+$: 556.2630. Anal. Calcd for $C_{43}H_{36}N_5P$: C, 77.65; H, 6.17; N, 12.60; P, 5.57. Found: C, 77.60; H, 6.29; N, 12.64.

Synthesis of the click-resins 446-448.

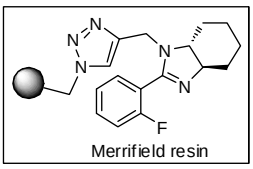
The N_3-functionalized resin[VI] (0.75 g, f = 0.53 mmol g^{-1}) was reacted with the corresponding alkynyloxymethyl imidazoline **429-430** (0.59 mmol), CuI (2 mg, 0.01mmol) and DIPEA (0.08 mL, 0.47 mmol) in a 1:1 mixture of DMF and THF (5 mL) at 45 ºC. The progression of the reaction was monitored by IR spectroscopy. After disappearance of the azide signal (16 h) the resin was collected by filtration and sequentially washed with water (250 mL), DMF (250 mL), THF (250 mL), THF-MeOH 1:1 (250 mL), MeOH (250 mL) and THF (250 mL). The solid was dried *in vacuo* overnight at 40 ºC.

Resin 446:



^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.25-6.77 (m, polymer), 6.75-6.05 (m, polymer), 5.33-5.24 (m, 1H), 5.20 (m, 2H), 4.60-4.25 (m, 1H), 3.65 (m, 2H), 2.13-1.72 (m, polymer); 1.70-1.20 (m, polymer); **^{13}C NMR** (HRMAS, CD_2Cl_2): δ = 161.8 (m, CF), 159.0 (C=N), 146.5-145.5 (m, polymer), 129.3-128.0 (CH), 127.8-126.8 (CH), 126.4 (CH), 124.1 (CH), 113.4-108.5 (m, polymer), 105.2 (CH), 85.4 (CH), 78.2 (CH), 67.9 (CH_2), 41.8-40.7 (m, polymer), 40.6-39.6 (m, polymer), 25.7 (CH_2); **^{19}F NMR** (CD_2Cl_2): δ = –111.6 (s, F); **IR** (ATR): ν = 3058, 3025, 2922, 2850, 1665, 1598, 1449, 1452, 1385, 1255, 1215, 1092, 1049, 1028, 758, 698, 659 cm^{-1}. A 100 % yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd (%): N, 3.17; found: C 86.91, H 7.25, N 2.86; f = 0.41 mmol g^{-1}.

Resin 447:



^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.40-6.89 (m, polymer), 6.75-6.22 (m, polymer), 5.44-5.20 (m, 2H), 5.16 (m, 1H), 4.55-3.93 (m, 1H), 3.65 (m, 2H), 2.34-1.68 (m, polymer); 1.63-1.18 (m, polymer); **^{13}C NMR** (HRMAS, CD_2Cl_2): δ = 161.8 (m, CF), 159.8 (C=N), 147.2-145.8 (m, polymer), 134.7-130.8 (CH), 129.3-126.9 (CH), 126.3-125.5 (CH), 122.3-119.2 (CH), 116.0-106.9 (m,

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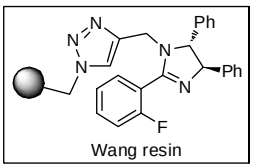
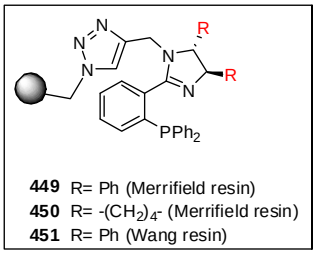
polymer), 105.2 (CH), 85.3 (CH), 77.6 (CH), 67.9 (CH_2), 53.7 (CH_2), 47.0-42.3 (m, polymer), 40.5-39.6 (m, polymer), 29.6 (CH_2), 25.7 (CH_2); **^{19}F NMR** (CD_2Cl_2): δ = -112.8 (s, F); **IR** (ATR): ν = 3058, 3024, 2920, 2849, 1600, 1448, 1450, 1330, 1218, 1154, 1067, 1027, 906, 754, 696 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd (%): N, 3.32; found: C 85.02, H 7.65, N 2.79; f = 0.40 mmol g^{-1}.

Resin 448:



^{1}H NMR (HRMAS, CD_2Cl_2): δ = 8.50-6.13 (m, polymer), 5.62-5.49 (m, polymer), 5.48-5.25 (m, 1H), 5.24-4.96 (m, 2H), 4.89-4.46 (m, 1H), 4.07-3.74 (m, 2H), 2.76-1.22 (m, polymer); **^{13}C NMR** (HRMAS, CD_2Cl_2): δ = 161.8 (m, CF), 158.9 (C=N), 148.3-142.6 (m, polymer), 141.3 (CH), 135.6 (CH), 133.3-123.1 (m, polymer), 119.4 (CH), 112.3-109.5 (m, polymer), 105.9 (CH), 85.2 (CH), 78.1 (CH), 67.9 (CH_2), 53.7 (CH_2), 42.5-36.2 (m, polymer), 25.8 (CH_2); **^{19}F NMR** (CD_2Cl_2): δ = -113.2 (s, F); **IR** (ATR): ν = 3057, 3025, 2920, 2848, 1626, 1600, 1449, 1452, 1328, 1216, 1154, 1065, 1028, 906, 755, 696 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd (%): N, 7.31; found: C 79.59, H 6.41, N 6.36; f = 0.91 mmol g^{-1}.

Synthesis of the polymer-supported phosphinooxazolines 449-451.



A solution of $KPPh_2$ (0.41 mmol, 0.82 mL of 0.5 M solution in THF) was added dropwise under argon at 0 ºC to an oven-dried Schlenk flask which contained the corresponding resin **446-448** (0.29 mmol) previously swollen with anhydrous and degassed THF (5 mL). The reaction mixture was shaken at 0 ºC for 2 h, allowed then to reach room temperature and further shaken for 12 h at this temperature. The solution was removed under argon *via cannula* and the resin was washed with anhydrous and degassed CH_2Cl_2 (7 x 10 mL) and dried *in vacuo* for 10 h. Resins **449-451** were not fully characterized (only ^{31}P NMR in gel-phase was recorded) and were immediately transformed into the corresponding palladium complexes **452-454**. Resin **449**: **^{31}P NMR** (CD_2Cl_2): δ = –9.5 (s, PPh_2). Resin **450**: **^{31}P**

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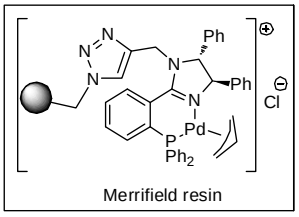
NMR (CD_2Cl_2): δ = –7.6 (s, PPh_2). Resin **451**: **^{31}P NMR** (CD_2Cl_2): δ = *–10.2* (s, PPh_2).

Synthesis of the polymer-supported phosphinooxazoline allylpalladium complexes 452-454.

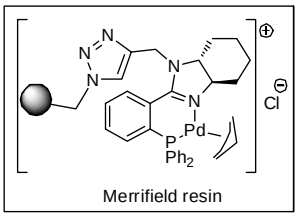
A solution of $[Pd(C_3H_5)Cl]_2$ (0.014 mmol, 50 mg) in anhydrous and deoxygenated toluene (1 mL) was added to an oven-dried Schlenk flask which contained the corresponding resin **449-451** (0.26 mmol) previously swollen with anhydrous and degassed toluene (4 mL). The reaction mixture was shaken for 1 h. The resin was filtered, rinsed with toluene (10 mL) and CH_2Cl_2 (200 mL) and dried *in vacuo* for 12 h.

Resin 452:



^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.87-6.73 (m, polymer), 6.70-5.85 (m, polymer), 5.24 (m, 1H), 5.13 (m, 2H), 4.84-3.88 (m, 2H), 2.24 (m, 2H), 1.99 (m, 2H), 1.95-0.86 (m, polymer); **^{13}C NMR** (HRMAS, CD_2Cl_2): δ = 146.5-144.3 (m, polymer), 141.3 (CH), 138.1 (CH), 135.5-131.1 (m, CH), 130.2-126.6 (m, CH), 126.5-124.1 (m, CH), 119.8 (m, CH), 116.0-105.8 (m, polymer), 85.2 (CH), 76.4 (CH), 73.2 (CH_2), 53.6 (m, CH_2), 47.2-42.7 (m, polymer), 41.5-39.4 (m, polymer), 29.8 (CH_2), 25.6 (CH_2); **^{31}P NMR** (CD_2Cl_2): δ = 28.24 (s, PPh_2); **IR** (ATR): ν = 3024, 2920, 1630, 1591, 1542, 1449, 1451, 1435, 1341, 1277, 1181, 1122, 1100, 1041, 1020, 998, 910, 749, 695 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd (%): N, 2.48; found: C 76.86, H 6.47, N 2.28; f = 0.33 mmol g^{-1}.

Resin 453:



^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.63-7.28 (m, polymer), 7.25-6.82 (m, polymer), 6.73-6.17 (m, polymer), 5.29 (m, 1H), 5.17 (m, 2H), 4.77-4.16 (m, 2H), 2.28 (m, 2H), 2.05 (m, 2H), 2.25-1.68 (m, polymer) 1.66-0.87 (m, polymer); **^{13}C NMR** (HRMAS, CD_2Cl_2):δ= 146.6-144.8 (m, polymer), 138.1 (CH), 135.5-131.4 (m, CH), 129.1-128.0 (m, CH), 127.9-126.8 (m, CH), 126.6-126.1 (m, CH), 126.0-125.5 (m, CH), 125.5-124.6 (m, CH), 114.5-

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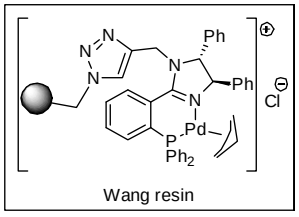
106.0 (m, polymer), 85.4 (CH), 79.6 (CH), 73.5 (CH_2), 53.7 (m, CH_2), 47.8-42.4 (m, polymer), 41.9-40.8 (m, polymer), 40.7-39.8 (m, polymer), 29.8 (CH_2), 24.7 (CH_2); **^{31}P NMR** (CD_2Cl_2): δ = 31.2 (s, PPh_2); **IR** (ATR): ν = 3055, 3024, 2921, 1633, 1598, 1449, 1451, 1354, 1169, 1125, 1035, 1008, 831, 755, 725, 696 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd (%): N, 2.43; found: C 75.85, H 6.55, N 2.19; f = 0.31 mmol g^{-1}.

Resin 454:



^{1}H NMR (HRMAS, CD_2Cl_2): δ = 7.97-5.90 (m, polymer), 5.27-5.20 (m, 2H), 5.17-4.28 (m, 2H), 3.64-3.56 (m, polymer), 3.55-3.41 (m, polymer), 2.24 (m, 2H), 2.17 (m, 2H), 1.80-1.68 (m, polymer), 1.68-1.50 (m, polymer); **^{13}C NMR** (HRMAS, CD_2Cl_2): δ = 145.0-140.0 (m, polymer), 134.6-123.6 (m, CH), 119.9 (CH), 114.9-107.6 (m, polymer), 67.7 (CH_2), 53.9 (CH_2), 53.6 (CH_2), 25.6 (CH_2), 25.5 (CH_2); **^{31}P NMR** (CD_2Cl_2): δ = 27.5 (s, PPh_2, *exo*), 17.3 (s, PPh_2, *endo*); **IR** (ATR): ν = 3025, 2920, 1625, 1598, 1448, 1452, 1339, 1214, 1180, 1122, 1047, 1028, 999, 909, 755, 695 cm^{-1}. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd (%): N, 4.77; found: C 67.73, H 6.03, N 4.83; f = 0.69 mmol g^{-1}.

Synthesis of di-μ-chloro-bis-(η^3-1,3-diphenylallyl)palladium (II)

0.450 g (2.56 mmol) of palladium dichloride was placed in a schlenk under nitrogen atmosphere. Then, 0.450 g (10.72 mmol) LiCl in 30 mL of deoxygenated water was added. The solution was stirred for 30 minutes. Then, 5mL of deoxygenated ethanol was added with the *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (1.7 g, 6.74 mmol) in 15 mL of THF. The solution was cooled down at 0ºC and HCl conc was added (1mL). This solution was stirred and carbon monoxide was bubbled into this solution for 5 minutes. After that, an additional millilitre of HCl conc. was added to the solution. The reaction mixture was stirred for 30 minutes. An orange precipitate appeared at this moment. Finally, the solution was stirred overnight under 1 atmosphere of carbon monoxide. The water solution was extracted with dichloromethane (3x15 mL). The organic layer was washed with water and brine solution. The organic phase was dried with $MgSO_4$ and concentrated under vacuum to

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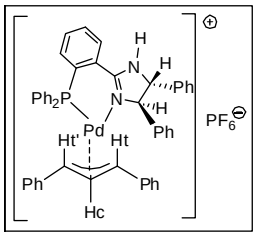
dryness. The complex was purified by recrystallization with a mixture of dichloromethane and hexane giving the formation of a yellow powder.

General procedure for the preparation of [Pd(ŋ^3-allyl)(L)]PF_6 complexes 455-457.

The corresponding ligand (0.05 mmol) and the complex [Pd(μ-Cl)(ŋ^3-1,3-allyl)]$_2$ (0.025 mmol) were dissolved in CD_2Cl_2 (1.5 mL) at room temperature under nitrogen. NH_4PF_6 (0.5 mmol) was added after 30 minutes and the mixture was stirred for 30 minutes. The mixture was then filtered over Celite under nitrogen and the resulting solutions were analyzed by NMR. After the NMR analysis, the complexes were precipitated adding hexane as pale yellow solids.

Complex 455:



Major diastereoisomer: **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.75 (m, 1H, arom); 7.79-6.11 (m, 34H, arom); 6.09 (m, 1H, H allyl central); 5.77 (m, 1H, H allyl terminal trans to phosphorus); 4.46 (d, ^{3}J=6.4 Hz, 1H, CH); 3.80 (d, ^{3}J=6.4 Hz, 1H, CH); 3.78 (br, 1H, H allyl terminal cis to phosphorus). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 165.1 (C=N); 140.2-126.3 (C, arom); 111.3 (C allyl central); 102.3 (d, J=25.1 Hz, C allyl terminal trans to P); 77.8 (CH); 66.4 (CH); 66.2 (br, C allyl terminal cis to P). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 21.46 (s) Minor diastereoisomer: **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.65 (m, 1H, arom); 7.78-6.29 (m, 34H, arom); 6.21 (m, 1H, H allyl central); 4.47 (br, 1H, CH); 4.40 (br, 1H, H allyl terminal trans to phosphorus); 4.28 (d, ^{3}J=6.8 Hz, 1H, H allyl terminal cis to phosphorus); 3.81 (br, 1H, CH). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 165.2 (C=N); 140.2-126.3 (C, arom); 108.1 (C allyl central); 88.1 (d, J=25.1 Hz, C allyl terminal trans to P); 78.3 (CH); 74.2 (br, C allyl terminal cis to P); 76.3 (CH). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 26.17 (s). **HRMS** (ESI-TOF): *m/z* = 781.1969, calcd for $[M]^+$: 781.1964. Anal. Calcd for $C_{48}H_{40}F_6N_2P_2Pd$: C, 62.18; H, 4.35; F, 12.29; N, 3.02; P, 6.68; Pd, 11.48. Found: C, 61.97; H, 4.42; N, 3.07.

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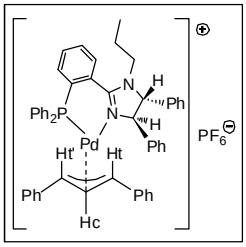
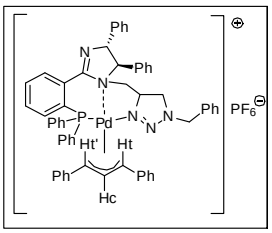
Complex 456:



Major diastereoisomer: **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 7.93-6.51 (m, 33H, arom); 6.37 (d, J=7.6Hz, 1H, arom); 6.11 (d, ^{2}J=6.8 Hz, 1H, H terminal trans to phosphorus); 5.85 (dd, J=13.6 Hz, J=10 Hz, 1H, H allyl central); 4.15 (d, J=6.4 Hz, 1H, H allyl terminal cis to phosphorus); 4.01 (d, ^{3}J=10 Hz, 1H, CH); 3.83 (d, ^{3}J=10 Hz, 1H, CH); 3.0-3.11 (m, 2H, CH_2); 1.28 (m, 2H, CH_2); 0.57 (m, 3H, CH_3). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 165.3 (C=N); 140.9-126.0 (C, arom); 111.1 (C allyl central); 103.4 (d, J=21.03 Hz, C allyl terminal trans to P); 75.2 (CH); 72.2 (br, C allyl terminal cis to P); 66.7 (CH); 50.5 (CH_2); 21.3 (CH_2); 10.7 (CH_3). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 17.74 (s). **HRMS** (ESI-TOF): *m/z* =823.2442, calcd for $[M]^+$: 823.2433. Anal. Calcd for $C_{51}H_{46}F_6N_2P_2Pd$: C, 63.20; H, 4.78; F, 11.76; N, 2.89; P, 6.39; Pd, 10.98. Found: C, 63.14; H, 4.87; N, 2.97.

Complex 457:



Major diastereoisomer: **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.38 (m, 1H, arom); 7.93-6.86 (m, 33H, arom); 6.47 (m, 1H, arom); 6.39 (br, 2H, arom); 6.14 (m, 1H, H terminal trans to phosphorus); 6.00 (d, J=7.2Hz, 2H, arom); 5.87 (m, 1H, H allyl central); 5.34 (br, CH_2); 4.59 (br, CH_2); 4.08 (m, 1H, CH); 3.92 (d, J=9.6 Hz, 1H, H allyl terminal cis to phosphorus); 3.75 (d, ^{3}J=6.2 Hz, 1H, CH). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100.6 MHz, δ ppm): 163.3 (C=N); 140.4-122.7 (C, arom); 110.5 (br, C allyl central); 102.5 (d, J=24.11 Hz, C allyl terminal trans to P); 74.6 (CH); 71.9 (CH); 65.8 (br, C allyl terminal cis to P); 53.1 (CH_2); 43.2 (CH_2). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 20.4 (s) **HRMS** (ESI-TOF): *m/z* =952.2745, calcd for $[M]^+$: 952.2755. Anal. Calcd for $C_{58}H_{49}F_6N_5P_2Pd$: C, 63.42; H, 4.50; F, 10.38; N, 6.38; P, 5.64; Pd, 9.69. Found: C, 63.36; H, 4.63; N, 6.42.

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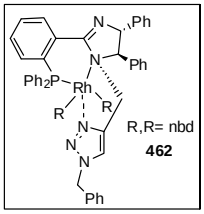
[Rh(nbd)(433)]BF_4



To a solution of ligand **433** (15 mg, 0.023 mmol) in dichloromethane (2 mL) was added $[Rh(nbd)_2]BF_4$ (8.6 mg, 0.023 mmol). The solution was stirred for 2 hours. Then, the solution was filtered through Celite. The solution was concentrated and 3 mL of hexane were added. The complex **462** precipitated and was washed with hexane (3x 3mL). Then, the solution was concentrated under vacuum affording 11 mg of **462** (52% yield). **^{1}H NMR** ($CDCl_3$, 400 MHz, δ ppm): 8.34 (br, 1H, CH, arom), 7.84-7.01 (m, 28H, arom), 6.74 (br, 1H, CH), 5.33-5.31 (br, 4H, CH_2, CH nbd), 5.09 (br, 1H, CH nbd), 4.70 (d, ^{3}J=6Hz, 1H, CH), 4.57 (d, ^{2}J=17.2Hz, 1H, CH_2), 4.27 (br, 1H, CH), 4.24 (br, 1H, CH nbd), 3.82 (br, 1H, CH nbd), 3.60-3.56 (br, 2H, CH nbd), 1.58 (br, 2H, CH_2 nbd). **^{31}P NMR** ($CDCl_3$, 161.9 MHz, δ ppm): 32.3 (d, ^{1}J=169Hz).

General Procedure for Palladium-Catalysed Allylic Alkylation; Thermal Conditions Allylic alkylation of 355[5]

In an inerted Schlenk tube was introduced $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (7.32 mg, 0.02 mmol, 2%) and the phosphine-imidazoline ligand (0.044 mmol) in CH_2Cl_2 (2 mL). The resulting solution was stirred for 20 minutes. Then, 3-acetoxy-1,3-diphenylpropene (250 mg, 1 mmol), dimethyl malonate (350 µL, 3 mmol), BSA (740 µL, 3 mmol) and 0.02 mmol KOAc were successively introduced. The mixture was stirred under reflux for 24h. The reaction mixture was then diluted with diethyl ether, filtered over Celite, and washed with water (3x5 mL). The organic phase was dried over anhydrous Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure. The crude mixture was filtered through a short SiO_2 pad eluting with ethyl acetate. The conversion of the reaction was measured after removing the solvent by ^{1}H NMR of the crude mixture. Enantiomeric excesses were determined from the residue by HPLC[5] on a OD-H column (0.5 mL/min, n-hexane/isopropyl alcohol, 99:1): (*R*)-**365** Rt=23 min, (*S*)-**365** Rt=25 min.

Allylic alkylation of 413[5]**:**

The procedure was analogous to the one described for **355**. The enantiomeric excesses were determined by HPLC on an AD-H column (0.3 mL/min, n-hexane/isopropyl alcohol, 97:3): (*R*)-**428** Rt=49.4 min, (*S*)-**428** Rt=51.6 min.

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General Procedure for Palladium-Catalysed Allylic Alkylation; Microwave-Assisted Conditions

In an inerted Schlenk tube was introduced $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (7.32 mg, 0.02 mmol, 2%) and the phosphine-imidazoline ligand (0.044 mmol) in CH_2Cl_2 (2 mL). The resulting solution was stirred for 20 minutes. Then, 3-acetoxy-1,3-diphenylpropene (250 mg, 1 mmol), dimethyl malonate (350 µL, 3 mmol), BSA (740 µL, 3 mmol) and 0.02 mmol KOAc were successively introduced. The resulting solution was then put under microwave (P=8watts) for 3 hours. The reaction mixture was then diluted with diethyl ether, filtered over Celite, and washed with water (3x5 mL). The organic phase was dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The conversion of the reaction was measured after removing the solvent by ^1H NMR of the crude mixture. Enantiomeric excesses were determined from the residue by HPLC[5].

General Procedure for the Palladium-Catalysed Allylic Amination of 355 with different N-Nucleophiles (440-445).

To an inerted Schlenk tube are introduced $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.84 mg, 5 µmol, 2%) and the phosphine-imidazoline ligand (0.011 mmol) in CH_2Cl_2 (2 mL). The resulting solution was stirred for 20 minutes. Then, 3-acetoxy-1,3-diphenylpropene (62.5 mg, 250µmol), the N-nucleophile (750 µmol), BSA (185 µL, 750 µmol) and 5 µmol KOAc were successively introduced. The mixture was stirred under reflux conditions for 24-48h. The reaction mixture was then diluted with diethyl ether, filtered over Celite, and washed with water (3x5 mL). The organic phase was dried over anhydrous $MgSO_4$. The residue was purified through a short SiO_2 pad eluting with (hexanes/EtOAc from 100:0 to 80:20). The conversion of the reaction was measured after removing the solvent by ^1H NMR of the crude mixture.

General Procedure for the Palladium-Catalysed Allylic Amination with different Nitrogen Nucleophiles using Polymer Complexes

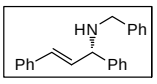
To an oven-dried vial for microwave reactor containing the corresponding polymer complexes (22 mg, 0.015 mmol), previously swollen with anhydrous and degassed CH_2Cl_2 (0.05 mL) under argon, were successfully added (*E*)-3-acetoxy-1,3-diphenyl-1-propene **355** (35 mg, 0.158 mmol, 1 eq), the

corresponding nitrogen nucleophile **440-444** (3 eq) and BSA (0.103 mL, 0.416 mmol, 3 eq). The reaction mixture was heated in a microwave reactor in power control mode (8 W) for 3h. Then the resin was filtered off and rinsed with anhydrous CH_2Cl_2 (3x0.5 mL). The combined filtrates were concentrated under reduced pressure and the residue was purified by flash chromatography (hexanes/EtOAc from 100:0 to 80:20). The enantiomeric excess was determined by HPLC on the corresponding column and method.

General Procedure for the Recycling Experiments

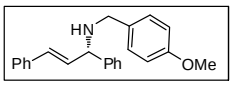
(*E*)-3-acetoxy-1,3-diphenyl-1-propene **355** (35 mg, 0.138 mmol), benzylamine **440** (0.045 mL, 0.416 mmol) and BSA (0.103 mL, 0.416 mmol) were added via syringe to an oven-dried vial for microwave reactor containing the polymer complex **454** (22 mg, 0.0153 mmol), previously swollen with anhydrous and degassed CH_2Cl_2 (0.05 mL) under argon. The reaction mixture was heated in a microwave reactor in power control mode (8 W) for 3h. The temperature of the reaction mixture, measure with an internal, Teflon-coated Pt-100 probe, was 40ºC. Then, the solution was removed under argon via cannula and the resin was rinsed with dichloromethane (3x0.5 mL) and dried under argon for 10 min. The resin was pre-swollen again with CH_2Cl_2 (0.05 mL), the reactants were added and the mixture was reacted as indicated before. The same resin was used for each cycle and no further Pd source was added.

(+)-(S,E)-N-Benzyl-(1,3-diphenyl-2-propenyl)amine (417)[9]:



The enantiomeric excess was determined by HPLC on an OD-H column (0.6 mL/min, n-hexane/isopropyl alcohol 99:1,254 nm): (*R*)-**417** Rt=19.5 min, (*S*)-**417** Rt=20.8 min.

(+)-(S,E)-N-(*p*-Methoxybenzyl)-(1,3-diphenyl-2-propenyl)-amine (435)[9]:



The enantiomeric excess was determined by HPLC on a AD-H column (0.7 mL/min, n-hexane/isopropyl alcohol 94:6, 254 nm): (*S*)-**435** Rt=18.0 min, (*R*)-**435** Rt=20.9 min.

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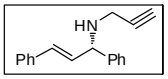
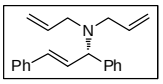
(+)-(S,E)-N-Propargyl-(1,3-diphenyl-2-propenyl)amine (436)[9]:



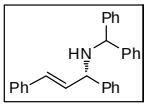
The enantiomeric excess was determined by HPLC on a AD-H column (0.5 mL/min, hexane/isopropyl alcohol 90:10, 254 nm): (*R*)-**436** Rt=17.0 min, (*S*)-**436** Rt=18.4 min;

(+)-(S,E)-N,N-Diallyl-(1,3-diphenyl-2-propenyl)amine (437):



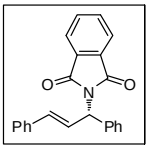
The enantiomeric excess was determined by HPLC on a AD-H column (0.4 mL/min, n-hexane from 0 to 5 min, 0.2 mLmin_1 n-hexane from 5 to 40 min, 254 nm): (*R*)-**437** Rt=19.0 min, (*S*)-**437** Rt=20.0 min.

(+)-(S,E)-N-Benzhydryl-(1,3-diphenyl-2-propenyl)amine (438) [9]:



The enantiomeric excess was determined by HPLC on a AD-H column (0.6 mL/min, n-hexane/isopropyl alcohol 98:2, 254 nm): (*S*)-**438** Rt=8.0, (*R*)-**438** Rt=9.2 min.

(+)-(S,E)-N-(1,3-Diphenyl-2-propenyl)phthalimide (439)[9]:



The enantiomeric excess was determined by HPLC on an OD-H column (0.5 mL/min, n-hexane/isopropyl alcohol 98:2, 254 nm): (*S*)-**439** Rt=25.6 min, (*R*)-**439** Rt=31.6 min.

General Procedure for Palladium-Catalysed Allylic Alkylation in Ionic Liquid; Thermal Conditions Allylic alkylation of 355[5]

Typical reaction procedure: in an inerted Schlenk tube are introduced $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.84 mg, 5 μmol, 2%) and the phosphine-imidazoline ligand (0.011 mmol) in [2,3-dmbim][BF_4] (2 mL). The resulting mixture is heated at 85°C for 20 min. Under nitrogen to preform the Pd complex. After cooling to rt, 3-acetoxy-1,3-diphenylpropene (62.5 mg, 250μmol), dimethyl malonate (750 μmol), BSA (185 μL, 750 μmol) and a pinch of KOAc are successively introduced. The resulting solution is then put under microwave (P=8watts) for 1 hour. After cooling to rt, the products are extracted from the ionic liquid

using dry degassed toluene (3x 5mL), filtered over celite and the solvent removed. The ionic liquid is kept under vacuum for 3 hrs under stirring to removes the traces of organic solvent and reused for another bacth reaction by simply adding 3-acetoxy-1,3-diphenylpropene (31 µL, 250 µmol, 1 eq.), dimethyl malonate (86 µL, 3 eq), BSA (152 µL, 3 eq.) and a pinch of KOAc.

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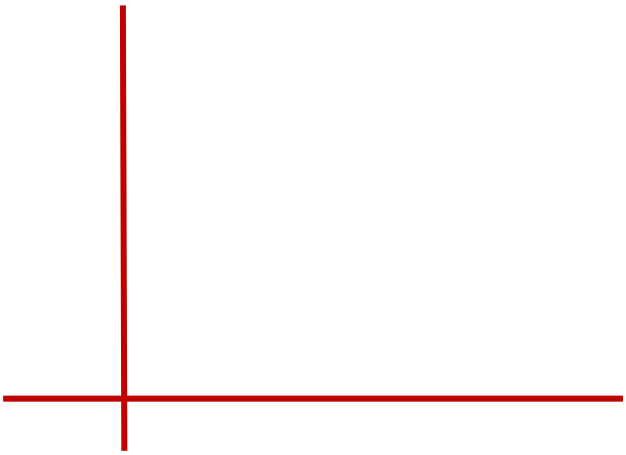

Chapter ***6***
Conclusions

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a) Part I: Carbonylation reactions

a.1) From the study of the Pd-catalysed methoxycarbonylation of ethene, the following conclusions can be drawn:

- Four new bidentate bis-*tert*-butylphosphine ligands (**26-29**) containing saturated cycloalkyl rings of different size were synthesised in high yields.

- The synthesis of the corresponding palladium(II) phosphine complexes was carried out. Their characterization through X-ray crystallography analysis allowed the determination of their geometries and of the bite angles of the ligands.

- The best catalytic results were obtained with ligands having an intermediate flexibility in the backbone (**27** and **29**). However, catalytic systems containing ligands with high conformational mobility (**28**) or with a rigid backbone (**26**) afforded lower performances.

- The basicity of the ligand and the strength of the acid used in the catalytic medium play an important role to achieve high activity.

- The catalytic cycle using ligands **26-29** was investigated by NMR spectroscopy and indicated that the process takes place *via* a hydride pathway. In this case, the palladium hydride complexes could not be isolated as the equilibria between the trifluoroacetate (**55-58**) and hydride (**64-67**) complexes were strongly shifted in favour of the trifluoroacetate complexes.

- The Pd-ethyl complexes **70-73** were only stable in the presence of an overpressure of ethene. *In situ* NMR studies confirmed the presence of the ethyl complexes in the absence of CO.

- The resting state of the *operando* catalysts were the trifluoroacetate **55-58** complexes.

a.2) On the basis of the study of the Pd-catalysed carbonylation of aryl iodides, the following conclusions were drawn:

- The catalytic system Pd/**29** is highly active in the Pd-catalysed aminocarbonylation reaction for a wide scope of substrates and nucleophiles under mild conditions.

- The catalytic systems Pd/**26**-**29** were very efficient in the Pd-catalysed double-carbonylation reaction under mild conditions (1 bar CO) in the presence of a large excess of DBU; however, the mechanistic study performed on these systems strongly indicated that the real catalysts do not contain the phosphine ligands **26**-**29**.

- From the mechanistic study, it can be concluded that the rate determining step is the oxidative addition and the resting state is the complex [Pd(**29**)$(CO)_n$] **182**.

- When the Pd/PPh_3 catalytic system was used in the presence of DBU but in the absence of amine nucleophile, the corresponding amide bearing DBU was formed, demonstrating that DBU also acts as a nucleophile under these conditions.

- The phosphine free Pd-catalysed double-carbonylation reaction of aryl iodides was successfully carried out using DBU as a base. The complex $PdCl_2(DBU)_2$ was isolated and revealed to be an excellent precursor to form an active and selective catalyst for this reaction. This demonstrated that DBU also acts as a ligand in this process.

- This is the first example of phosphine free Pd-catalysed double-carbonylation reaction and excellent results were achieved with a wide range of substrates and nucleophiles.

- The X-ray structure of the complex *trans*-$PdI_2(DBU)_2$ reveals that DBU is coordinated to the metal centre in a *trans* disposition and the complex exhibits a square planar geometry.

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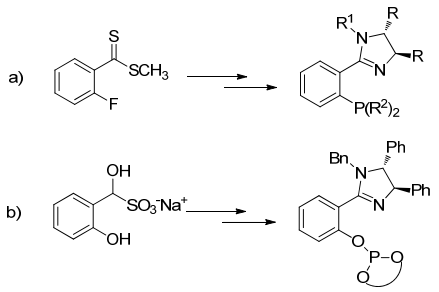
b) Part II: Asymmetric reactions:

- A new family of phosphino- or phosphite-imidazoline ligands was successfully synthesised starting from the readily accessible dithioester **311** for the phosphine functionality or from the sodium sulfonate salt **329** for the introduction of a phosphite group.
  Fine tuning of the ligands can be achieved varying:
  a) The substituents of the imidazoline ring changing the chiral diamine used in the condensation reaction (R).
  b) The steric and electronic properties of the group at the sp^3 nitrogen atom of the imidazoline ring (R^1).
  c) The substituents at the phosphorus moiety (R^2).



b.1) From the study of the Ir-catalysed asymmetric hydrogenation of unfunctionalised olefins and imines with phosphino-imidazoline ligands, the following conclusions can be extracted:

- The phosphino-imidazoline ligands **316**, **317**, **319**, **322**, **323**, **325**, **327** and **337** were applied in the asymmetric hydrogenation of C=X bonds, where X is a CH group or a N atom. Excellent conversion was obtained with complex **345** in the asymmetric hydrogenation of 1,3-diphenyl-1-propene with moderate enantioselectivity (up to 57%). The Ir-catalysed asymmetric hydrogenation of 1,1-disubstituted olefins was carried out even under 1 bar of hydrogen pressure, achieving good conversions but very poor enantioselectivities with all the catalytic systems tested.

- The cationic complexes [Ir(COD)**L**]BAr_F and the Ir/**L** catalytic systems bearing the phosphino-imidazoline ligands **316**, **317**, **319**,

322, **323**, **325** and **337** were very active in the hydrogenation of N-(β-phenylethylidene)aniline but the enantioselectivity was very low. Varying the substituent at the sp^3 nitrogen atom of the imidazoline ring did not produce any improvement.

- The asymmetric hydrogenation of 2-methylquinoline and its derivatives requires the addition of additives to the iridium precursors to form an active system. Introduction of a bulky and electron-rich substituent at the phosphorus atom of the phosphino-imidazoline ligands improved significantly the enantioselectivity of the reaction (Ir/**319**) (up to 60%). The replacement of the phosphine function by a phosphite group (Ir/**337**) produced an increase of the ee up to 40% but had a negative effect on the activity.

b.2) The phosphino-imidazoline ligands were also used in Pd-catalysed allylic substitution reactions and the following conclusions can be drawn:

- Phosphino-imidazoline ligands bearing a triazole moiety and the corresponding polymer-supported phosphino-imidazoline ligands were successfully synthesised.

- The best results were achieved with ligand **433** which contains a triazolyl substituent at the nitrogen atom, observing an important increase in enantioselectivity with various substrates (ee's up to 99%).

- Excellent enantioselectivities were also obtained using ligand **433** in Pd-catalysed asymmetric allylic amination reactions using various nucleophiles (ee's up to 99%). The addition of BSA to the catalytic solution was required to form an active system. Furthermore, the addition of a catalytic amount of potassium acetate is required to produce the corresponding amines with excellent enantioselectivities.

- The recycling of the catalytic system formed by the palladium complex **454**, which was anchored to the Wang resin, was successfully carried out in the Pd-catalysed asymmetric allylic amination of substrate **355** with benzylamine. Furthermore, using this

supported complex enantioselectivities up to 96% were obtained for a wide range of nucleophiles.

- The introduction of a triazole moiety linked by a methylene at the nitrogen atom of the imidazoline ring of the ligand led to improve the enantioselectivity up to 99% ee. From the results obtained by NMR studies and theoretical calculations, this unexpected result was attributed to a modification of the coordination mode of the phosphino-imidazoline ligand to the palladium centre.

- The use of Pd/phosphino-imidazoline catalytic system in ionic liquids also resulted in high enantioselectivities, although the use of ionic liquids with a blocked C-2 position at the ring was required. The catalytic system is very stable and allows the efficient recycling of the catalyst and the use of microwave conditions with high level of conversion and enantioselectivity (ee's up to 95%).

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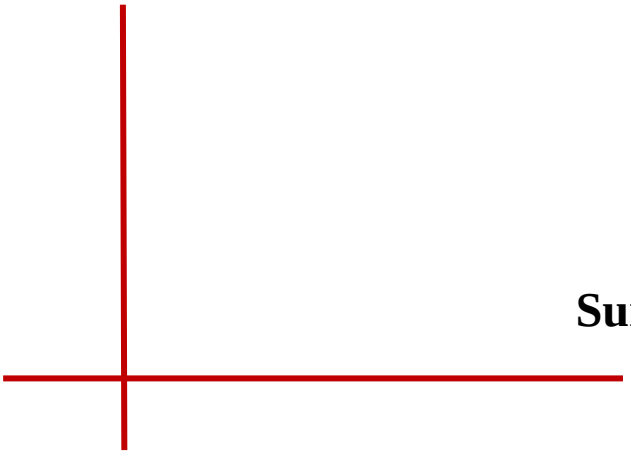

Chapter 7
Summary/ Resum

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7.1. Summary of this thesis

The presence of homogeneous catalysis in industrial processes has increased in the recent years. This is due to the high activity and selectivity observed for a wide range of catalytic systems in several industrial processes. However, the fact that the catalytic system cannot be recovered from the solution limits the application of the homogeneous catalysis in industrial processes. For this reason, academic and industrial research groups are working in the design of biphasic systems, in the immobilization of the catalytic system in polymers, SiO_2 or in nanoparticles for catalyst recovering and reusing.

The compounds obtained using a homogeneous catalyst are produced a large scale for the case of polymers, oligomers, alcohols for the production of plastics and surfactants, etc... However, products obtained in fine chemistry are synthesised in a small scale with a high added value.

In this context this thesis focuses on two sets of industrial processes. One of them, involved in an industrial process applied in a large scale and the other set in the formation of intermediates with high added value. The first reaction studied in this thesis is the Pd-catalysed methoxycarbonylation of ethene. This reaction has been extensively studied by different companies and finally, Lucite International has applied this methodology in the formation of methyl methacrylate in industrial scale in a plant in Singapur.[1,2] Thus, our first objective was the study of new catalytic systems in the Pd-catalysed methoxycarbonylation of ethene and the mechanism involved in the reaction.

The carbonylation reaction of aryl halides is having a great importance in fine chemistry. Specially, Pd-catalysed double carbonylation reaction allows the formation of α-ketoamides which are privileged scaffold in medicinal chemistry and this structural motif can be found in natural products such as the immunosuppressant drugs FK-506 and rapamycin. These compounds are used as serine or cysteine protease inhibitors.[3] Therefore, our second objective was the study of the catalytic systems previously described in Chapter 2 in the Pd-catalysed aminocarbonylation and double-carbonylation reaction.

In pharmaceutical companies, most products obtained are with high added value because they are enantiomerically pure compounds. There are three strategies for obtaining these compounds: a) the use of natural molecules

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which are optically actives as building blocks, b) the optical resolution by resolution agents or c) the asymmetric synthesis, which is the procedure most extensively used. This methodology allows obtaining chiral compounds from pro-chiral substrates o racemic by catalytic amounts of compounds which transfer their chirality. Particularly, in homogenous catalysis the chirality becomes from the organometallic complex which bears chiral ligands. In general, the ligands can be easily modified and the optimization of them produces an improvement on the activity and selectivity of the corresponding process. In this field, the asymmetric hydrogenation of olefins and imines for obtaining chiral alkanes of amines represent some of the most important enantioselective industrial processes. The asymmetric hydrogenation of olefins by a homogeneous catalyst is used in the synthesis of L-Dopa,[4] which is a drug uses for the Parkinson disease. Related asymmetric hydrogenation of imines allows the synthesis of an herbicide (S)-Metolachlor which is the enantioselective process produced in the biggest scale actually.[5] In this context, our third objective was the design iridium complexes bearing chiral P,N ligands in their application in the Ir-catalysed asymmetric hydrogenation of uncfuntionalised olefins and imines.

Finally, the stereoselective formation of C-C and C-N bonds is an important challenge in organic synthesis. In this context, the Pd-catalyzed asymmetric allylic substitution reaction has shown to be an efficient and versatile procedure in the synthesis of drugs and natural products under mild conditions.[6] As a consequence, our last objective was the use of P,N ligands described for the asymmetric reaction in the Pd-catalysed allylic alkylation and amination reaction. Furthermore, as the recovery of the catalyst and its recycling is an important tool, the anchoring of the P,N ligands into a polymer support and the use of ionic liquids as reaction media will be discussed.

After revising the antecedents in the Pd-catalysed methoxycarbonylation reaction, in Chapter 2 "*P,P-ligands in Pd-catalysed methoxycarbonylation reaction"* is shown the synthesis of a novel family of bidentate phosphine ligands bearing bulky substituent at the phosphorous atom. These ligands are related to ligand **6**, which is being used by Lucite International. These ligands are modified in the backbone because they contain cycloalkyl rings of different sizes (Figure 7.1).

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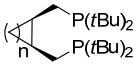

26 n=1
27 n=2
28 n=3
29 n=4

Figure 7.1. Ligands synthesed for the Pd-catalyzed methoxycarbonylation reaction.

The synthesis and characterization of the corresponding palladium complexes bearing ligands **26**-**29** is described in this chapter. These catalytic systems are applied in the methoxycabonylation of ethene, observing that is necessary a flexibility on the backbone of the ligand for obtaining high activities and selectivities in this reaction. The best results are obtained with the catalytic system Pd/**29** and the TON numbers obtained are the highest reported up to date. Furthermore, mechanistic studies with these catalytic systems are presented. The mechanism involved in the catalytic reaction follows the Pd-hydride. Even though, the Pd-hydride formed in the reaction is not stable and isolable, shows that it is not a requisite for achieving high activities in this reaction. Finally, the Pd-olefin complexes were only stable under the presence of an overpressure of ethene.

In Chapter 3, *"P,P-ligands in Pd-catalysed aminocarbonylation and double-carbonylation reaction"* describes the utilization of the catalytic systems descirbed in Chapter 2 in the Pd-catalysed aminocarbonylation and double-carbonylation reaction. The catalytic system Pd/**29** is very active and chemoselective in the aminocarbonylation reaction of different aryl iodides and using different nucleophiles. The use of DBU as a base in the catalytic system modifies the chemoselectivity of the reaction *versus* the formation of α-ketoamide instead of the amide as it is observed with all the other bases used. Ligands **6** and **26-29** are used in this reaction observing how the catalytic system formed by Pd/**29**/DBU affors the doblecarbonylated product when the substrates contain electron-donating groups at the *para*- position of the aromatic ring or when primary amines are used as nucleophiles. Some mechanistic aspects with Pd/**29** are discussed observing in the absence of DBU some intermediates of the catalytic cycle. However, when DBU is added to the solution, no palladium species are detected by NMR spectroscopy, because the signal corresponding to the free phosphine ligand is observed during all the reaction. As a consequence of the results obtained, the double-carbonylation reaction was carried out in absence of a phosphine

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ligand, observing that DBU acts as a ligand controlling the chemoselectivity of the process to the double-carbonylation reaction instead of the aminocarbonylation. A wide range of substrates and nucleophiles have been tested observing in both cases excellent results in terms of conversion and chemoselectivity. Finally, trying to understand the role of DBU in the catalytic reaction, different experiments are shown. It is concluded that the DBU has a dual role on the reaction because it is acting as a ligand, and as a base in the presence of amine.

Chapter 4, *"P,N-ligands in Ir-catalysed hydrogenation reactions"* describes the synthesis of a new family of phosphino-imidazoline ligands (Figure 7.2) incorporating structural modifications at: a) the substituent of the imidazoline ring, b) the substituents at the nitrogen atom of the imidazoline ring and c) modification on the substituents at the phosphorous atom. The synthesis and characterization of the iridium complexes bearing phosphino-imidazoline ligands is described in this chapter. The Ir-catalysed asymmetric hydrogenation of uncfunctionalised olefins shows that all the catalytic systems are very active in the hydrogenation of trisubstituted or 1,1-disubstituted olefins. However, from poor to moderate enantioselectivities (up to 57%) are obtained.

The acyclic imine **278a** is successfully hydrogenated by the iridium complexes, observing that the introduction of bulky substituent at the nitrogen atom of the imidazoline ring has a dramatic effect on the enantioselectivity, obtaining the highest results with the systems Ir/**317**, although the enantioselectivities achieved are moderated (ee's up to 24%).

Using the cyclic imine 2-methylquinoline, a similar tendency is observed being the ligands with a proton bonded to the nitrogen atom which affords higher enantioselectivities. The highest enantioselectivities are obtained when the phenyl rings at the phosphorous atoms are modified by bulkier groups such as cyclohexyl ring or by introducing a phosphite function instead of a phosphine (ee's up to 60%).

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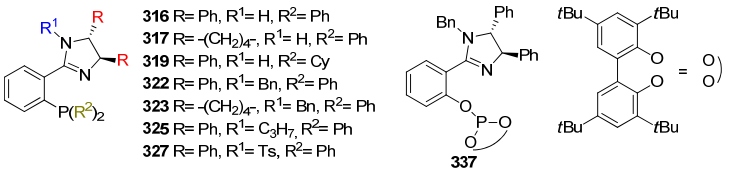

Figure 7.2. Phosphino-imidazoline ligands synthesised for the Ir-catalysed asymmetric hydrogenation of olefins and imines.

Finally, Chapter 5 *"P,N-ligands in Pd-catalysed allylic substitution reactions"* shows the application of the ligands described in Chapter 4 in the Pd-catalysed allylic alkylation and amination reactin. Curiously, the introduction of a triazole substituent at the nitrogen atom of the imidazoline ring produces a beneficial effect on the enantioselectivity of both reactions (ee's up to 99%). Due to these, the ligands bearing the triazole substituent at the nitrogen atom of the ring were anchored to a polymer resin (Figura 7.3), observing excellent enantioselectivities in the Pd-catalysed allylic amination reaction for a wide range of amines. Also, recycling experiments with these polymers are shown in this Chapter. Finally, the reaction is also studied in ionic liquid as reaction media, observing that the acidic proton of position C-2 has to be blocked for obtaining high enantioselectivites (up to 95%). Finally, as the incorporation of a triazole ring produces an increase on the enantioselectivity of the process, NMR studies and theoretical calculation are shown indicating that the coordination mode of the ligand to the palladium centre can be altered by the presence of this triazole.

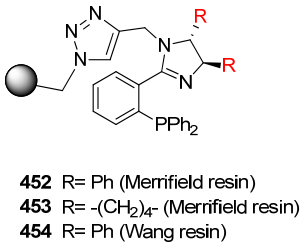

Figure 7.3. Polymer-supported phosphino-imidazoline ligands.

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7.2. Resum de la tesis

La presència de la catàlisis homogènia en els processos industrials ha augmentat en els darrers anys. Això és degut a l'elevada activitat i selectivitat que han mostrat diferents sistemes catalítics per a un ventall de reaccions d'interès industrial. Tot i així, el fet que no es pugui recuperar el sistema catalític de la solució fa que l'aplicació d'aquests sistemes encara sigui limitada. Degut en això, diferent grups de recerca tant a nivell industrial com acadèmic estant posant els seus esforços en el disseny de sistemes bifàsics, en immobilització del sistema catalític bé en resines polimèriques, en sílices o en nanopartícules.

Els productes obtinguts via catàlisis homogènia a nivell industrial són produïts a gran escala en el cas de polímers, oligòmers, alcohols per plàstics i detergents, etc…En canvi, el productes obtinguts en la química fina són sintetitzats a petita escala però tenen un alt valor afegit.

En aquest context, ens vam centrar en dos sets de processos industrials. Un d'ells aplicat a gran escala i els altres a l'obtenció d'intermedis amb alt valor afegit. La primera reacció d'estudi va ser la metoxicarbonilació d'etilè catalitzada per complexos de pal·ladi. Aquesta reacció ha sigut àmpliament estudiada per diferents empreses i finalment, Lucite International ha aplicat aquesta metodologia a escala industrial en una planta a Singapur.[1,2] Per tant, el nostre primer objectiu va ser l'estudi de nous sistemes catalítics de pal·ladi en la reacció de metoxicarbonilació d'etilè i l'estudi en profunditat del mecanisme involucrat en el cicle catalític.

Les reaccions de carbonilació d'halurs d'aril està tenint gran importància en la industria de química fina. Especialment, la reacció de doble carbonilació catalitzada per pal·ladi permet l'obtenció de dos grups carbonils adjacents els quals són un esquelet privilegiat per la química farmacèutica, ja que productes naturals incorporen aquestes funcionalitats com són les drogues FK-506 i "rapamycin". Aquests compostos s'usen com proteases inhibidores de serina o cisteïna.[3] Per tant, el nostre segon objectiu era l'estudi dels sistemes catalítics prèviament sintetitzats per la carbonilació d'etè, en la aminocarbonilació i doble carbonilació d'halurs d'aril.

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En la industria farmacèutica, la majoria de productes obtinguts són d'alt valor afegit perquè són compostos enantiomèricament purs. Existeixen tres estratègies per l'obtenció d'aquests compostos: a) la utilització de molècules naturals òpticament actives com a "building blocks", b) la resolució òptica mitjançant agents de resolució o bé, c) mitjançant la síntesi asimètrica, el qual és el mètode més utilitzat. Aquesta metodologia permet l'obtenció de compostos quirals a partir de substrats pro-quirals o racèmics a partir de quantitats catalítiques de compostos que transfereixen la seva quiralitat. Concretament, en la catàlisis homogènia la quiralitat prové del complex organometàl·lic el qual conté lligands quirals. Els lligands són en general fàcilment modificables i l'optimització d'ells permet la millora de l'activitat i selectivitat del procés. En aquest àmbit la hidrogenació asimètrica d'olefines i imines per l'obtenció d'alcans o amines quirals representen uns dels processos enantioselectius amb aplicació industrial més importants. La hidrogenació asimètrica d'olefines amb un catalitzador homogenis és utilitzada per síntesi del L-Dopa,[4] fàrmac aplicat per la malaltia del Parkinson i referent a la hidrogenació de imines permet l'obtenció de l'herbicida (*S*)-Metolachlor el qual és el procés enantioselectiu actualment produït en major escala.[5] En aquest context, el tercer objectiu d'aquesta tesis era el disseny de nou sistemes catalítics amb iridi incorporant lligands quirals P,N en la hidrogenació enantioselectiva d'olefines no funcionalitzades i imines.

Per últim, la formació estereoselectiva d'enllaços C-C i C-N són d'especial interès en la síntesis orgànica. En aquest context, la substitució al·lílica asimètrica catalitzada per pal·ladi representa in procediment eficient i versàtil en la síntesis de drogues i productes naturals en condicions suaus de reacció per a la industria farmacèutica.[6] Per tant, el nostre darrer objectiu va ser la utilització dels lligands P,N utilitzats en la reacció d'hidrogenació, provar-los en la reacció d'alquilació i aminació al·lílica. A més, com el reciclatge del sistema catalític és un dels principals objectius per a la industria, l'anclatge del lligands en resines polimèriques i la utilització de líquids iònics en aquestes reaccions per al posterior reciclatge es va plantejar com a darrer objectiu.

Després d'haver revisat els antecedents en la reacció de metoxicarbonilació d'etilè catalitzada per complexos pal·ladi, en el Capítol 2 *"P,P-ligands in Pd-catalysed methoxycarbonylation reaction"* es presenta la síntesis d'una nova família de lligands difosfina amb substituents voluminosos a l'àtom de fòsfor.

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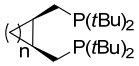
Aquests lligands són anàlegs al lligand **6**, utilitzat industrialment per Lucite International però modificant l'esquelet del lligands per anells cicloalquílics de diferent tamanys (Figura 7.4).



26 n=1
27 n=2
28 n=3
29 n=4

Figura 7.4. Lligands sintetitzats en per la reacció de metoxicarbonilació d'etè catalitzada per pal·ladi.

Els corresponents complexos de pal·ladi amb els lligands **26-29** van ser sintetitzats i caracteritzats en aquest capítol. Aquests sistemes catalítics s'apliquen en la metoxicarbonilació d'etè, mostrant que és necessària una flexibilitat intermitja en l'anell cicloalquílic del lligand per obtenir elevades activitats i selectivitats en aquesta reacció obtenint els millors resultats publicats fins les hores amb el sistema catalític Pd/**29**. A més estudis mecanístics amb aquests sistemes catalítics són discutits en aquests capítol, on el mecanisme que opera en condicions anàlegs a les catalítiques és el mecanisme Pd-hidrur. Tot i així, el Pd-hidrur format no és estable i reacciona ràpidament, mostrat que no es necassari un Pd-H estable i aïllable per tenir elevades activitats. Finalment, el complexos Pd-olefina són només estable sota elevades pressió d'etilè.

En el Capítol 3, *"P,P-ligands in Pd-catalysed aminocarbonylation and double-carbonylation reaction"* es descriu la utilització dels sistemes catalítics descrits en el capítol 2 en la reacció d'aminocarbonilació i doble carbonilació catalitzades per pal·ladi. El sistema catalític, Pd/**29** és molt actiu i quimioselectiu en la reacció d'aminocarbonilació de diferents d'halurs d'aril i amb diferents nucleòfils. La utilització de DBU com a base en el sistema catalític modifica la quimioselectivitat de la reacció per la formació del producte biscarbonilat enlloc de la amida com succeeix amb les altres bases. Els lligands **6** and **26-29** són usats en aquesta reacció observant que el sistema Pd/**29**/DBU produeixen els productes de la doble carbonilació amb substrats amb grups electrònicament dadors a la posició *para-* de l'anell aromàtic i també amb la utilització d'amines primàries. Alguns aspectes mecanístics amb el sistema Pd/**29** són discutits observant que en absència de DBU diferents

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intermedis en el cicle catalític són identificats en condicions similars a les de la reacció catalítica. En canvi, en presència de DBU, cap intermedi del cicle catalític pot ser identificat, ja que només la senyal corresponent al lligand lliure és observada.

Degut als resultats obtinguts, la reacció de doble carbonilació en absència de lligand difosfina és estudiada observant que la DBU actua com a lligand dirigint la quimioselectivitat de la reacció cap a la doble carbonilació enlloc de la aminocarbonilació. Un gran nombre de substrats i nucleòfils han estat estudiats observant en ambdós casos excel·lent resultats. Finalment, intentant entendre el paper de la DBU a la reacció diferents assajos en condicions similars a les catalítiques es descriu en aquest capítol observant el triple paper que té la DBU en la reacció catalítica com a lligand, nucleòfil i base.

El Capítol 4, *"P,N-ligands in Ir-catalysed hydrogenation reactions"* descriu la síntesi d'una nova família de lligands fosfina-imidazolina (Figura 7.5) incloent modificacions estructurals en: a) en el substituents de l'anell imidazolina, b) en els substituents a l'àtom de nitrogen de l'anell imidazolina i c) modificacions en els substituents de l'àtom de fòsfor. La síntesi i caracterització dels corresponents complexos d'iridi també es descriu en el capítol. La utilització dels complexos d'iridi amb lligands fosfina-imidazolina en la hidrogenació asimètrica d'olefines no funcionalitzades mostra com els sistemes catalítics són molt actius en la hidrogenació d'olefines tri-substituïdes o 1,1-disubstituïdes. En canvi, les enantioselectivitats obtingudes són inferiors al 57%.

Referent a la hidrogenació asimètrica de imines, la imina acíclica **278a** és hidrogenada amb els sistemes catalítics d'iridi amb fosfines-imidazolines s'observa que la introducció de substituents a l'àtom de nitrogen té un efecte negatiu en l' enantioselectivitat sent els sistemes catalítics amb el lligand **317** amb el que s'obtenen millors resultats tot i que són moderats (ee's up to 24%).

Amb el substrat cíclic 2-methylquinolina, s'observa una tendència similar sent els lligands que contenen en l'àtom de nitrogen un protó enlloc d'estar alquilat els que donen millors resultats. Les millors enantioselectivitats s'obtenen quan el substituent a l'àtom de fòsfor es modifica de fenils a ciclohexil o bé introduint una funció fosfit enlloc de fosfina (ee's up to 60%).

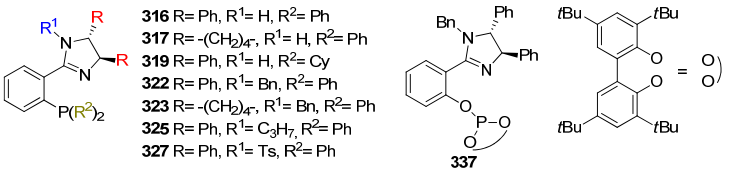

Figura 7.5. Lligands fosfina-imidazolina sintetizades per la reacció d'hidrogenació asimètrica d'olefins i imines.

Finalment, el Capítol 5 *"P,N-ligands in Pd-catalysed allylic substitution reactions"* mostra l'aplicació dels lligands descrits en el Capítol 4 en la reacció d'alquilació i aminació al·lílica. Curiosament, la introducció d'un grup triazòlic a l'àtom de nitrogen produeix un augment en la enantioselectivitat del sistema tant en la reacció d'alquilació com en aminació (ee's up to 99%). Degut, a què la introducció de l'anell triazòlic a l'àtom de nitrogen de la imidazolina els sistemes catalítics suportats sobre resines polimèriques (Figura 7.6) es va portar a terme observant que són sistemes molt enantioselectius en la reacció d'aminació al·lílica catalitzada per pal·ladi amb diferent nucleòfils. A més es van dur a terme experiments de reciclatge, observant com després de quatre cicles el sistema continua sent enantioselectiu. També la reacció és estudiada en líquids iònics observant que és necessari el bloqueig del protó àcid a la posició dos de l'anell al líquid iònic. Les enantioselectivitats obtingudes en líquid iònics arriben al 95%.

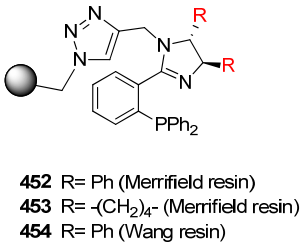

Figure 7.6. Polymer-supported phosphino-imidazoline ligands

Finalment, com la incorporació del substituent triazòlic al lligand produeix una millora molt notable en l'enantioselectivitat, estudis de RMN i de càlculs teòrics demostren el mode de coordinació del lligand al centre metàl·lic pot ser alterat degut a la presència del grup triazòlic.

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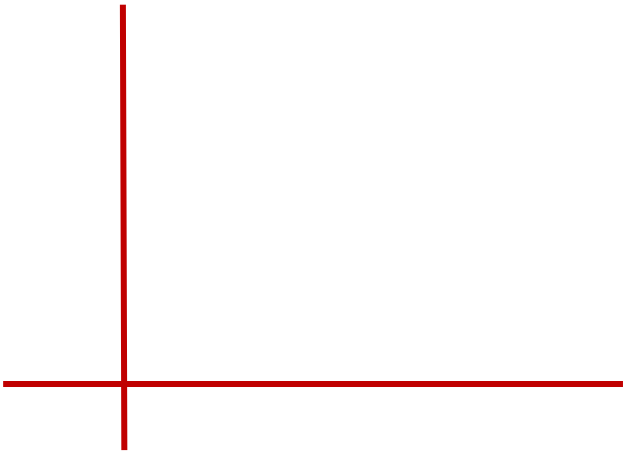

*Chapter **8***
Appendix

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8.1. Congresses and Scientific meetings

2008

a) 16th International Symposium on Homogeneous Catalysis, 6th-11th July 2008, Florence, Italy.
Poster contribution: "*Phosphino-imidazoline modified ligands. Synthesis and application in iridium catalysed hydrogenation reactions*"

2009

b) International Symposium on Organometallic Chemistry and Catalysis (RENACOM 2009), 29th-30th April 2009, Tetouan, Morocco.
Poster contribution: *"First application of phosphino-imidazoline ligands in Pd-allylic alkylation reactions"*

c) XXXII Reunión Bienal de la Real Sociedad Española de Química, 13th-18th September 2009, Oviedo, Spain.
Oral communicaton: *"Phosphino-imidazoline ligands in Asymmetric Allylic Substitution reactions catalysed by Palladium Complexes"*

d) Reunión anual del Consolider (Intecat), Octubre 2009, Teruel, Spain.
Oral communicaton: *"Phosphino-imidazoline ligands in Pd-Asymmetric Allylic Substitution reactions catalysed by Palladium Complexes"*

2010

e) 6th Flash Conference Era-Chemistry, 28th of February to 3rd of March 2010, Roscoff, France.
Poster contribution: *"Homogeneous and Polymer-Supported Phosphino-imidazoline Ligands for Asymmetric Catalysis. Is the Remote Triazole Substituent Modifying the Palladium Coordination Mode?"*

f) 17th International Symposium on Homogeneous Catalysis, 4th-9th July 2010, Poznán, Poland.
Poster contribution: *"Novel Phosphine Ligands in the Palladium Catalysed Methoxycarbonylation of Ethene. Insights into the catalytic cycle through HP-NMR study"*

8.2. Publications based on the content of the thesis

a) V. de la Fuente, M. Waugh, G. R. Eastham, J. A. Iggo; S. Castillón, C. Claver. **"Phosphine Ligands in the Palladium Catalysed Methoxycarbonylation of Ethene: Insights into the Catalytic Cycle through an HP-NMR Spectroscopic Study"** *Chem. Eur. J.* **2010**, 16(23), 6919.

b) N. Fleury-Bregeot, V. de la Fuente, S. Castillón, C. Claver. **"Highlights on Transition Metal-Catalyzed Asymmetric Hydrogenation of Imines"** *ChemCatChem,* **2010**, 2(11), 1346.

c) **"Phosphine-free catalyst in the Pd-catalysed double carbonylation of aryl iodides. DBU is more than a base!"** *Manuscript in preparation.*

d) **"Homogeneous and Polymer-Supported Phosphino-Imidazoline Ligands for Asymmetric Catalysis. Alteration of the Palladium Coordination Mode Triggered by a Remote Triazole Substituent"** *Manuscript in preparation.*

e) **"Pd-catalysed aminocarbonylation and double-carbonylation reaction of aryl iodides using diphosphine ligands"** *Manuscript in preparation.*

f) **"Ionic Liquid Assisted Recycling of Highly Efficient Allylic Alkylation Pd Catalysts Containing Phosphino-Imidazoline Ligand"** *Manuscript in preparation.*

g) **"Enantioselective Hydrogenation of Olefins and Imines using Ir catalysts containing Phosphino-Imidazoline Ligands"** *Manuscript in preparation.*