

1. Introduction and scope

1.1. Organometallic chemistry and homogeneous catalysis

The term catalysis was coined by Berzelius around 1850 after observing changes in substances when they came into contact with small amounts of species called “ferments”. Many years later in 1895 Ostwald came up with a definition “*A catalyst is a substance that changes the rate of a chemical reaction without itself appearing into the products*” according to which a catalyst could also slow down a reaction. Nowadays, the definition in use is “*A catalyst is a substance which increases the rate at which a chemical reaction approaches equilibrium without becoming itself permanently involved*”

The effect of the catalyst is purely kinetic; catalysts work by providing an alternative mechanism that involves a different transition state and lower activation energy (**Figure 1**). The effect is that more molecular collisions have the energy needed to reach the transition state. Hence, catalysts can perform reactions that, albeit thermodynamically feasible, would not take place without the presence of a catalyst, or which take place much faster, more specifically, or at lower temperatures. However, a catalyst can catalyse competitive reactions at different rates, thus affecting the distribution of the products. Catalysts do not affect the Gibbs free energy of the overall reaction. The net free energy change of a reaction is the same whether a catalyst is used or not; the catalyst just makes it easier to activate.

A very important property of the catalyst is its activity which can be express in terms of TON (turnover number) or TOF (turnover frequency). An active catalyst presents both high TON and high TOF.

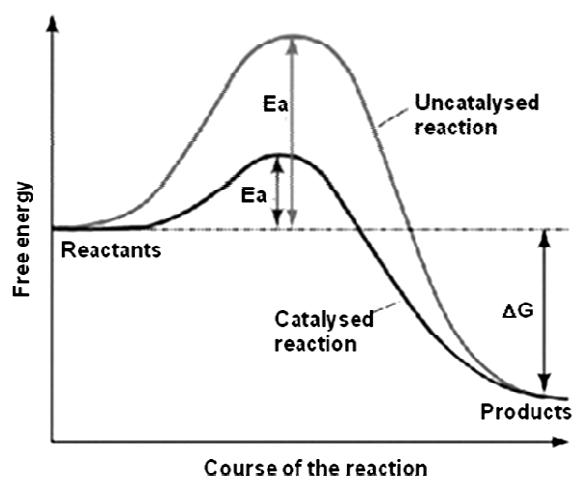


Figure 1. Effect of the catalysts in a thermodynamically favourable reaction

Catalysts can be either, homogeneous if they are in the same phase as the reactants and products, normally the liquid one¹ and heterogeneous if they are in different phases. In this latter case the catalytic reaction takes place in the interphase.

The advantages of the homogeneous catalysis over heterogeneous catalysis are its high activity, its selectivity and its mild reaction conditions. Its major problem is its industrial application regarding principally the separation of the catalyst from the products.

Catalysis plays a key role in the industrial production of liquid fuels and bulk chemicals as well as most in the processes for the production of fine chemicals. One interesting application of homogeneous catalysis is asymmetric catalysis. It focuses in the synthesis of enantiopure compounds, which are active ingredients of pharmaceuticals, agricultural products, flavours, fragrances and some advanced materials.²

Organometallic catalysts are formed by a central metal surrounded by organic and/or inorganic ligands. Organometallic complexes act in different ways within the catalytic reaction, bringing the substrates together, activating the substrates by coordinating to the metal and lowering the activation energy of the reaction. The properties of the catalyst are due to both the metal and the ligand.

The success of organometallic catalysts is due to the fact that they can be modified relatively easily by changing the ligand environment. The effect of these modifications on the catalytic reaction can then be studied by such techniques HP-NMR or HP-IR *in situ* and *operando* measurements, because organometallic catalysts are soluble in organic solvents. The information provided by these studies can help to improve the efficiency of catalytic system.

One important aspect in homogeneous catalysis is the elucidation of changes in the reactivity of a catalyst which are caused by subtle modification in the ligand environment of the metal centre. It is interesting to know how a change in the ligand environment affects the reactivity of the metal system bound to it. Ligand exchange can modify such crucial properties of the catalytic reaction as the rate of the reaction and the selectivity.

Palladium is one of the most extensively studied metals in organometallic chemistry because it is versatile and catalyses numerous organic reactions. Palladium is commonly used to catalyse reactions involving the formation of C-C bond such as oligomerisation, copolymerisation or carbonylation of alkenes, Wacker oxidation of alkenes, cross-coupling reactions, etc.³

The main steps in the mechanism reactions catalysed by palladium complexes are: oxidative addition, reductive elimination, transmetallation and migratory insertion.

In this work we shall focus on the palladium-catalysed CO/ethene copolymerisation reaction as well as the Suzuki-Miyaura cross-coupling reaction. Particular attention will be paid to the modification of diphosphine and phosphine sulfonated ligands and their effect on the activity and on the reaction mechanism.

1.2. Alternating copolymerisation of CO and ethene

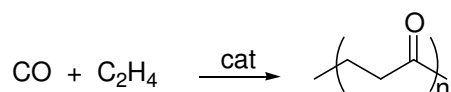
1.2.1. General aspects

Over the last decades the catalytic conversion of accessible alkenes into high molecular weight polymers using transition metal catalysts has become an interesting industrial process. Polyketones obtained by alternating copolymerisation of carbon monoxide with other unsaturated monomers such as olefins represent a class of low-cost thermoplastics whose synthesis, properties and applications are object of fundamental and applied research.

Since the discovery of the first copolymerisation of CO and ethene in 1941 by Farbenfabriken Bayer,⁴ the synthetic routes leading to polyketones have undergone constant improvement in terms of selectivity, productivity, environmental impact and economy.⁵ The catalytic systems using nickel for the CO/ethene copolymerisation which require high temperatures (around 200 °C) and high pressures (around 200 bar), were improved by replacing the nickel with palladium. Temperature and pressure were decreased to 80 °C and 20bar of CO/ethene respectively. Methanol or water have replaced environmentally incompatible solvents, such as chlorinated ones.⁶

Polyketones are featured by a unique web of chemical and physical properties, which include photo- and biodegradability, good chemical resistance to acids, bases and solvents, easy functionalisation, impermeability to hydrocarbons, and

strong rigidity and impact strength.^{5c,7} These properties can be modified and improved by changing the number or the nature of the co monomers and tuning the structure of the metal catalyst. The diversity of properties makes polyketones superior to polyolefines, polyamides and polyacetals.⁸ The simplest polyketone is the CO/ethene copolymer (**Scheme 1**).



Scheme 1. Polyketone formation by alternating CO/ethene copolymerisation

The perfectly alternating CO/ethene copolymerisation is efficiently carried out in methanol at moderate temperature (about 80 °C) in the presence of a catalyst system comprising, as essential components, a Pd(II) salt with a weakly coordinating counteranion and a chelating diphosphine (**Figure 2**).^{5b,9}

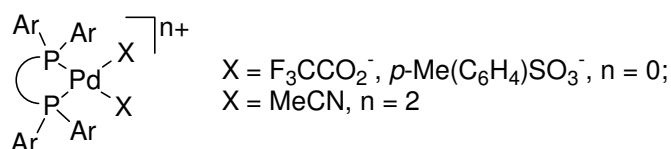


Figure 2. Pd(P-P) based precatalysts

1,3-bis(diphenylphosphino)propane (dppp) was the ligand that opened the way to the efficient synthesis of polyketones.¹⁰ The perfect alternation of CO/ethene seems to be independent of the CO pressure. Generally, pressures between 30-60 bar of CO/ethene are used but perfect alternation can also be maintained at lower CO pressure. Only when the entire CO has been consumed does the catalyst promote the dimerisation of ethene to butenes.¹¹ In methanol polyketones with different combinations of diketone, keto-ester and diester end groups can be obtained (**Figure 3**).

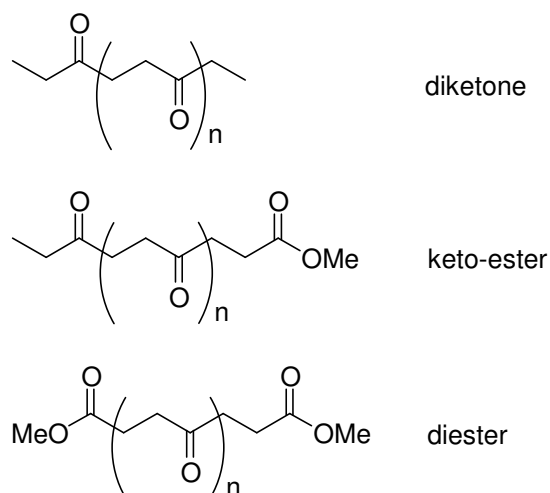
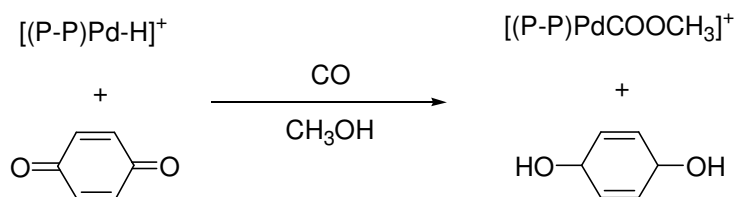


Figure 3. Polyketone structures obtained by CO/ethene copolymerisation in methanol

Optimal reaction conditions in methanol require the presence of both a strong oxidant with $E^0 \geq 0$ and a protic acid with $pK_a \leq 4$ whose conjugate base must have a low binding affinity for Pd(II). 1,4-benzoquinone (BQ, $E^0 = 0.7v$) and *p*-toluenesulfonic acid (TsOH, $pK_a = -2.7$) are two examples that amply fulfil these requirements and are indeed the stabilising compounds of the most productive catalytic systems. In these experimental conditions, productivities as high as 11 Kg polyketone/(g Pd*h) can be obtained.^{5b,9} The main role of the 1,4-benzoquinone is to oxidise the Pd(0) or Pd(I) species that have been formed in the catalytic process to Pd(II). Another important role of the oxidant is to convert Pd-H into Pd-OMe (**Scheme 2**).^{10b} While the main role of the protic acid is to prevent the deactivation of the palladium(II) catalyst into inactive (P-P)Pd(0), by protonation of the latter to yield catalytically active [(P-P)PdH]⁺ species.



Scheme 2. Role of BQ in the conversion of Pd-H into Pd-C(O)OMe

1.2.2. Ligands used in the CO/ethene Pd catalysed copolymerisation reaction

Drent et al.^{5b,10b} were the first to investigate the influence of the diphosphine ligand structure on the activity of the Pd(II) catalyst. They showed that the catalytic activity strongly depended on the chain length of the carbon backbone between the two phosphorus donor atoms (**Table 1**).

Table 1. Effect of the ligand backbone chain length on the CO/ethene copolymerisation activity^a

Ligand	$H(CH_2CH_2CO)_n-(OCH_3)_n^b$	Productivity (g polymer/g Pd*h)
$Ph_2P(CH_2)PPh_2$ (dppm)	2	1
$Ph_2P(CH_2)_2PPh_2$ (dppe)	100	1000
$Ph_2P(CH_2)_3PPh_2$ (dppp)	180	6000
$Ph_2P(CH_2)_4PPh_2$ (dppb)	45	2300
$Ph_2P(CH_2)_5PPh_2$ (dpppe)	6	1800
$Ph_2P(CH_2)_6PPh_2$ (dppph)	2	5

^aCopolymerisation carried out in 150 mL of MeOH with $Pd(NCMe)_2(TsO)_2$ (0.1 mmol), $C_2H_4/CO = 1$, temperature = 84 °C, pressure = 45 bar. ^bAverage degree of polymerisation determined by end-group analysis from $^{13}C\{^1H\}$ NMR spectra

Since the discovery of the effectiveness of palladium catalysts containing dppp ligand by Shell Research in 1984, various dppp-like ligands have been designed and successfully used to catalyse the CO/ethene copolymerisation in

combination with palladium (II) salts. Ligand variations have often involved substitutions in either phenyl groups or the carbon backbone. It has been found that the introduction of alkyl groups in the 2-position of the carbon backbone of dppp does not improve the catalytic activity of the corresponding palladium (II) precursors.¹² On the other hand a considerable increase of the productivity, more than 50%, was obtained when alkyl groups were introduced in both 1- and 3-position of the dppp backbone, to yield both the *meso* and the *rac* 2,4-bis(diphenylphosphino)pentane (bdpp)¹² (**Figure 4**).

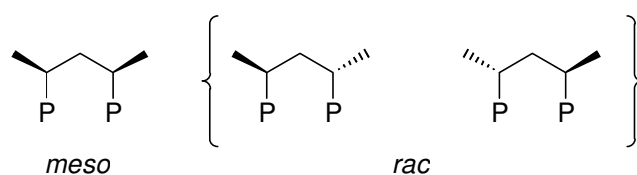


Figure 4. *Meso*- and *rac*-2,4-bis(diphenylphosphino)pentane

Under comparable experimental conditions, *meso*-bdpp has been reported to be more active in the palladium-catalysed CO/ethene copolymerisation than dppp or *rac*-bdpp. In this case, it has been suggested that both electronic and steric factors explain the remarkable activity of the *meso*-bdpp catalyst. In particular, *meso*-bdpp was found to undergo in methanol a quasireversible one-electron reduction, whereas both dppp and *rac*-dppp were irreversibly reduced. It was therefore proposed that the increased activity of Pd(*meso*-bdpp) might also be due to the more facile re-oxidation of the one-electron reduced species by both 1,4-benzoquinone or H⁺, which ultimately results in a large number of active Pd centres in the catalytic mixture.¹²

The *R,S* (*S,R*) stereochemistry of the methyl groups makes a six-membered Pd(*meso*-bdpp) ring preferentially adopting a chair conformation with equatorial methyl groups and with one equatorial and one axial phenyl group on each phosphorus atom (**Figure 5(A)**).¹³ In contrast, in solution the *rac* isomer adopts

the δ -skew conformation in which the steric hindrance due to the phenyl rings is diagonally placed with respect to the P-Pd-P plane (**Figure 5(B)**).¹³

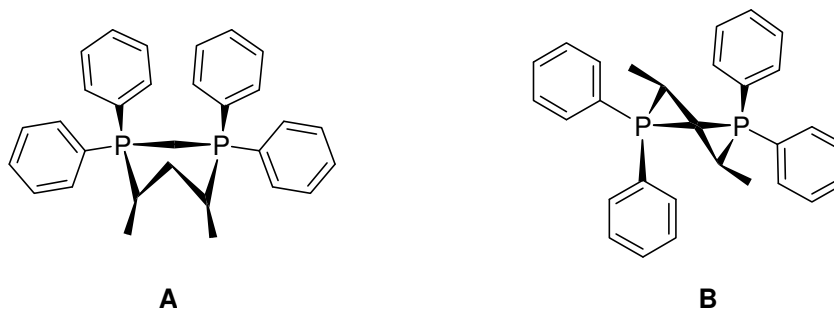


Figure 5. Preferred conformations adopted by the six-membered chelate rings with *meso*-bdpp (chair, **A**) and *rac*-bdpp (δ -skew, **B**)

It has been suggested that steric factors together with the chair conformation of the metallaring play a major role in enhancing the activity of the *meso*-bdpp precursors. This *meso effect* has also been observed by Consiglio et al. in the copolymerisation reaction of propene with CO catalysed by cationic palladium complexes.¹⁴

Excellent results in terms of productivity and catalyst stability have been obtained by introducing an *ortho*-methoxy group at each phenyl unit in dppp in order to obtain 1,3-bis(di(2-methoxyphenyl)phosphino)propane (*o*-MeO-dppp)¹⁵ (**Figure 6**).

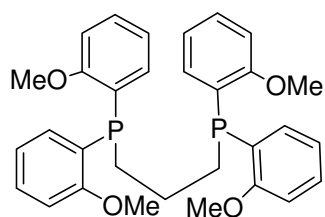


Figure 6. *o*-MeO-dppp used in both fluid and slurry CO/ethene palladium catalysed copolymerisation

A study with a water-soluble version of *o*-MeO-dppp containing *m*-sodium sulfonatophenyl groups has confirmed that the *o*-MeO moiety can exert both steric and electronic influence on the palladium centre.^{15b} Similar studies, modifying the ligand backbone of dppe-based ligands have also been performed. Indeed, the chelate ring size is not the only parameter that controls the copolymerisation activity of Pd(diphosphine) catalysts. The backbone rigidity and the overall steric crowding at the Pd centre seem to be more important than the chelate ring size in the determination of the catalytic activity.¹⁶ This is the case for the diphosphine ligands with two carbon atoms in between the phosphorous donor atoms (**Figure 7**).

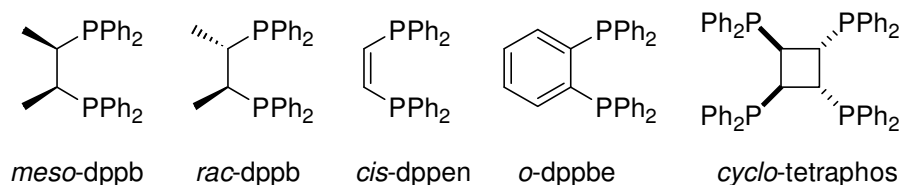


Figure 7. Rigid diphosphine ligands forming five membered metallarings

The beneficial effect of the ligand rigidity on copolymerisation reactions has also been confirmed by Doherty, in bis-phospholyl substituted carbon backbones. Some bis-phospholyl ligands are presented in **Figure 8**.¹⁷

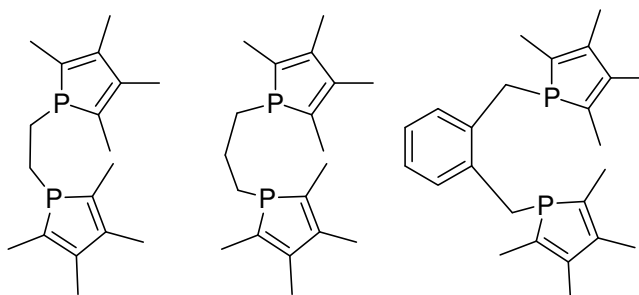
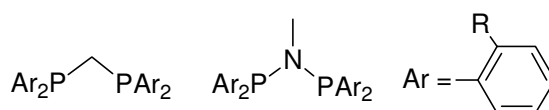


Figure 8. Bis-phospholyl ligands used in CO/ethene palladium-catalysed copolymerisation

Dossett et al. provided experimental evidence that four-membered ring systems with *i*-propyl substituted phenyl rings exhibit high catalytic activity (**Figure 9**).¹⁸



R = H, OMe, Me, Et or *i*Pr

Figure 9. Ligands which form four membered metallarings

Recently, metallocene-based ligands have been tested in the copolymerisation reaction of CO/ethene. From these studies it turned out, that both, the catalytic activity and the chemoselectivity of the copolymerisation reaction depend on the sandwiched metal centre, on the substituents of the cyclopentadienyl ring and the substituents of the phosphorous donor atoms. Since metallocene-based ligands can be considered to be both bidentate (κ^2 -P,P) and terdentate (κ^3 -P,M,P) coordinating ligands, the formation of copolymers in methanol was observed only in those cases, in which the ligand coordinated strictly in a κ^2 -P,P mode. In all other cases only low weight oxygenates or methyl propionate were obtained (**Figure 10**).¹⁹

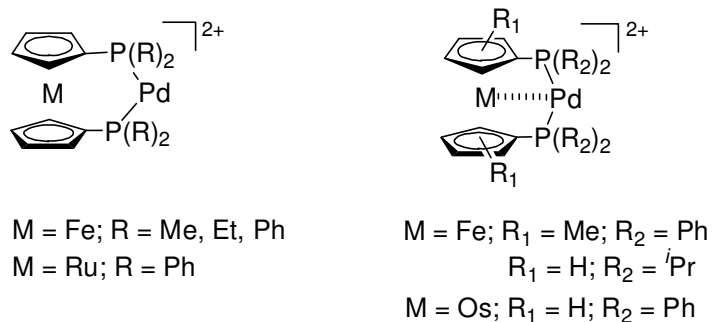


Figure 10. Bis-(diphosphino) metallocene palladium catalytic precursors

Hemilabile phosphine ligands containing oxygen, nitrogen or sulfur functions have been used in the palladium-catalysed CO/ethene copolymerisation reaction. However their catalytic activity is lower than that of dinitrogen and diphosphine ligands. Some of the P-O, P-N and P-S ligands that have been studied to obtain efficient palladium catalyst for the CO/ethene copolymerisation are presented in **Figure 11**.²⁰

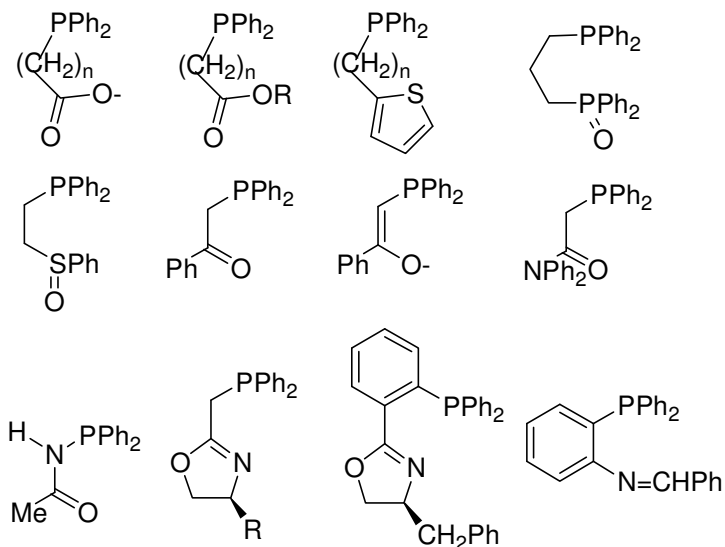


Figure 11. Hemilabile P-O, P-N and P-S ligands

Sterically rigid dinitrogen ligands such as bipyridine (bipy), phenanthroline (phen) and their alkyl-substituted derivatives are used to form efficient palladium catalysts for alternating CO/ethene copolymerisation in both homogeneous and heterogeneous conditions (**Figure 12**).²¹

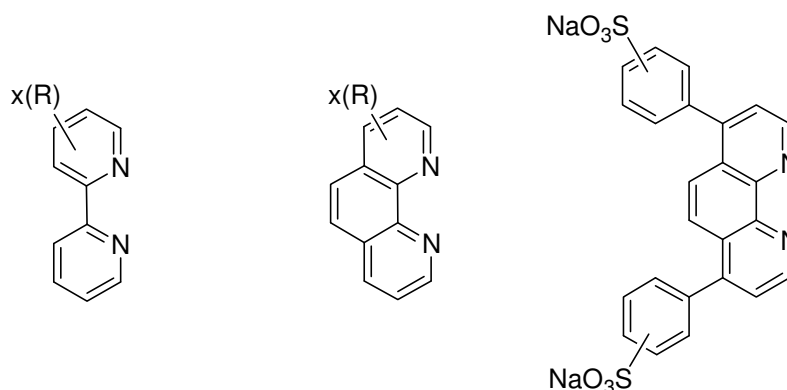


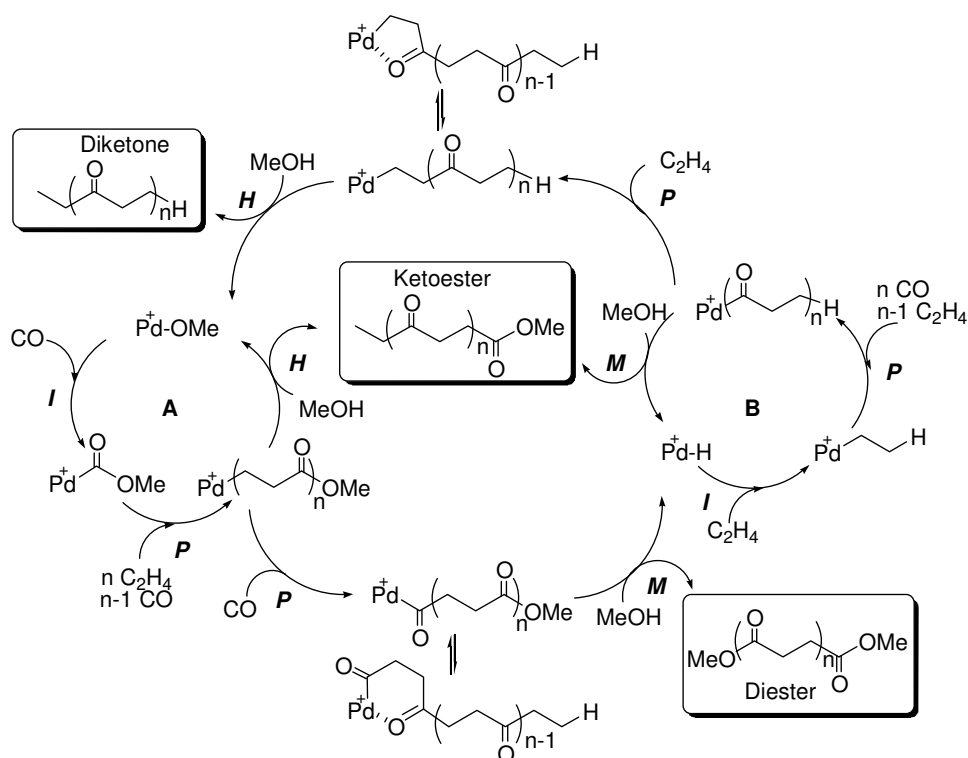
Figure 12. Dinitrogen ligands used in CO/ethene palladium-catalysed copolymerisation

1.2.3. Mechanism of the CO/ethene copolymerisation catalysed by palladium (II) catalysts with bidentate ligands

In 1991, Drent et al. reported on the basis of end-group analysis of the polyketone material, the first mechanism for the CO/ethene copolymerisation using cationic palladium complexes with chelating diphosphine ligands in alcoholic solvents.^{10b} After this first mechanism several *in situ* studies were carried out and numerous model studies have been proposed on the bases of different experimental and theoretical approaches. All these studies have contributed to a better understanding of the initiation, propagation and termination steps. Most of these studies have been reviewed by Sen in 1993^{5a} by Drent and Budzelaar in 1996^{5b} by Sommazzi and Garbassi in 1997^{5c} and by C. Bianchini et al. in 2002⁹, and 2005^{5e}

The mechanism reported in **Scheme 3** summarises all the principal steps of the alternating CO/ethene copolymerisation in MeOH catalysed by palladium(II) complexes stabilised by bidentate ligands. The catalytic process comprises two competing cycles, connected by two cross termination steps. The prevalence of both cycles depends on the experimental conditions. Cycle **B** initiates (**I**) with the insertion of ethene into a Pd-H bond that can be generated in the catalytic mixture in a variety of ways, in particular when the methanol solvent contains traces of water (Water Gas Shift reaction).²² Insertion of CO into the resulting ethyl complex is reversible and faster than ethene insertion, while CO insertion into the Pd-acyl is thermodynamically disfavoured. Since ethene insertion into the Pd-acyl is rapid and irreversible, the propagation (**P**) can occur by alternately inserting CO and ethene. The copolymer produced by this cycle shows either keto-ester or diketone end groups depending on the termination path: the keto-ester is obtained by methanolysis (**M**) of the Pd-acyl bond, while the diketone is obtained by protonolysis (**H**) of a Pd-alkyl intermediate.

A copolymer with keto-ester end groups is also produced by methanolysis of a Pd-alkyl bond formed during the propagation in the alternative cycle **A**, which starts with the insertion of CO into a Pd-OMe bond giving a palladium carbomethoxy (Pd-C(O)OMe) complex. The copolymer with diester end groups is obtained by a methanolysis reaction of the Pd-acyl species derived from cycle **A**. In the following sections, the single steps of the copolymerisation process, which comprise initiation, propagation and chain-transfer will be discussed separately.



Scheme 3. Proposed mechanism of CO/ethene copolymerisation catalysed by diposphine palladium(II) catalysts

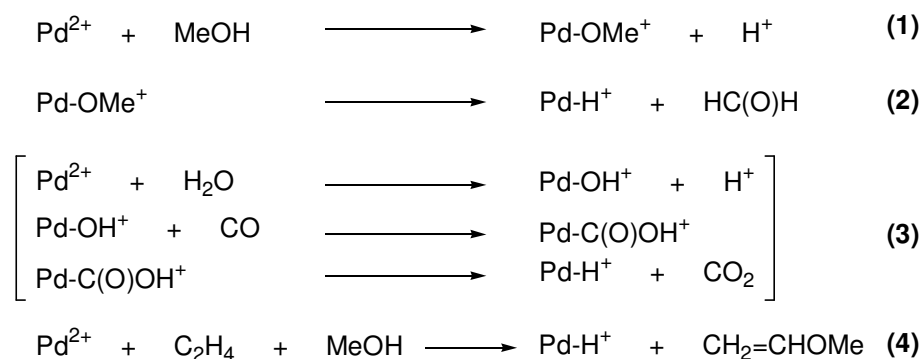
Initiation

The catalytic active species in the alternating CO/ethene copolymerisation in methanol are generally square-planar Pd(II) complexes of the general formula [Pd(II)(Pk)(S)(P-P)]X where (P-P) is a chelating diposphine, Pk is the growing polyketone chain and S may be MeOH, water, a comonomer or a keto group from the chain. X is the counteranion of weak nucleophilicity in order to avoid competition with the comonomer for coordination to palladium. These active species are formed by appropriate neutral Pd(X)₂(P-P) or cationic [Pd(S)₂(P-

P)]X₂ precursors that can also be formed *in situ* by reaction of a palladium(II) salt (commonly Pd(OAc)₂ or [Pd(NCMe)₄](BF₄)₂) with a diphosphine ligand.

In both cases, a slight excess of strong protic acid (commonly *p*-toluenesulfonic acid) must be added to the reaction mixture in order to stabilise the Pd-H species. The role of this acid is also to neutralise anionic nucleophiles (e. g., acetate ions) that can compete with methanol in the activation of the precursor and with the comonomers in the coordination on palladium(II), thus retarding the propagation step. Some studies have shown that depending on the chelating diphosphine, *in situ* preparation of the catalyst precursor may give much lower productivities as compared to reactions where a preformed palladium(II) complex is used.²³

The palladium (II) precursor needs to be activated to generate the Pd-H and Pd-OMe species that will initiate the copolymer propagation (**Scheme 4**)^{5,9,10,24} In the absence of specific reagents, the promoter is activated by the formation of a Pd(II)-OMe complex (**Scheme 4**, eq. 1) that generates a Pd(II)-H species through a β -hydride elimination (**Scheme 4**, eq. 2).²⁵ Furthermore Pd(II)-H species can also be generated by both the Water-Gas Shift reaction (**Scheme 4**, eq. 3) or a Wacker-type reaction (**Scheme 4**, eq. 4)^{5,9,10,24}

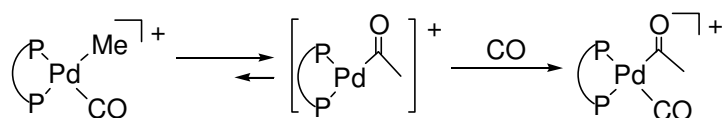


Scheme 4. Reaction path for the synthesis of Pd-OMe and Pd-H species

The spectroscopic detection of Pd-OMe as well as Pd-H species is rather seldom, as both of them constitute highly active intermediates.²⁶ However, indirect methods such as end group analysis of the polyketone, isotopic labeling and model compounds have provided experimental evidence for the proposed mechanism.^{5,9,10,24}

Chain propagation

Two alternating migratory insertion steps, involving Pd(alkyl)(CO) and Pd(acyl)(ethene) moieties comprise the chain propagation. Pd(alkyl)(ethene) insertions are virtually excluded, because the CO insertion into the Pd-alkyl bond is 10^5 faster than ethene insertion, which avoids the double ethene insertion.^{27a} Early studies under actual copolymerisation conditions have shown that the copolymerisation rate depends on the ethene pressure.^{5b} High pressure NMR experiments with model compounds in aprotic solvents (CD_2Cl_2) have provided interesting information on the energy barriers associated with the migratory insertion of CO and ethene occurring during the propagation step. It has been proved that the migratory insertion reaction of CO in $[\text{Pd}(\text{R})(\text{CO})(\text{P-P})]^+$ complexes (R = Me, Et) is reversible, following first-order kinetics and it is therefore independent of the CO concentration in solution (**Scheme 5**).²⁷

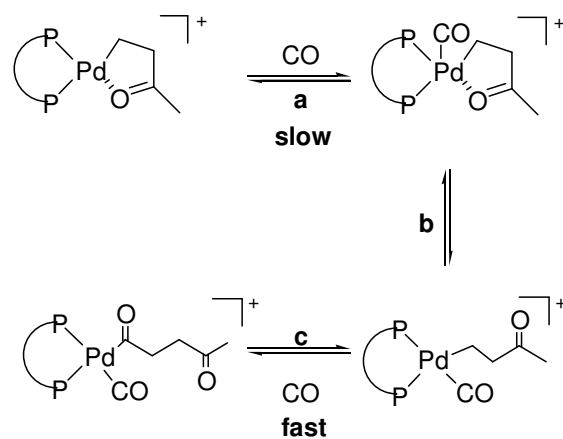


Scheme 5. Migratory insertion of CO into a Pd methyl bond

The free energies of CO insertion into a Pd-alkyl bond can be calculated from the half-life times ($t_{1/2}$) obtained by integrating the corresponding $^{31}\text{P}\{^1\text{H}\}$ NMR signals. ΔG^\ddagger values for the migratory insertions reactions of palladium(II) methyl carbonyl complexes with chelating diphosphines in range from 14 to 18 Kcal

mol^{-1} .^{27a,27b,27c} The energy barriers for the migratory insertions seem to decrease with both, the increasing P-Pd-P bite angle and the steric bulk of the diphosphine ligand.^{27e}

The displacement of the coordinating carbonyl group from palladium in β -keto chelates by ethene has never been observed. Carbon monoxide is much smaller than ethene and exhibits a greater binding affinity for palladium than ethene. In the active catalytic systems, the β -keto chelates generally react with CO to give Pd acyl(carbonyl) complexes at very low temperature (**Scheme 6**).



Scheme 6. Reaction of the Pd β -keto-chelate with CO

For the systems investigated the rates of conversion of the β -keto chelates into the corresponding Pd acyl(carbonyl) complexes were evaluated by the half-life times obtained from the decay and increase of the corresponding $^{31}\text{P}\{^1\text{H}\}$ NMR resonances at the appropriate temperatures. The results obtained show that the energy barriers for the opening of the β -keto chelates decrease by increasing the number of carbon atom spacers in between the phosphorous atoms and thus with increasing P-Pd-P bond angle.^{27b,27c}

On the basis of the CO pressure dependence of the transformation of the β -keto chelates into the Pd acyl(carbonyl) complexes, it has been proposed that the rate limiting step for this conversion is related to the opening of the metallacycle by CO (**Scheme 6**, steps **a** and **b**) rather than the following migratory insertion of CO into the Pd alkyl carbonyl compound, which follows first order kinetics (**Scheme 6**, step **c**).^{27b,27c}

A PM-RAIRS (Polarization Modulation Reflection Absorption Infrared Spectroscopy) study (**Figure 13**) clearly evidenced, that the β - and γ -keto chelates $[(dppp)Pd\{CH_2CH_2C(O)CH_3\}]^+$ and $[(dppp)Pd\{C(O)CH_2CH_2C(O)CH_3\}]^+$ complexes are resting-states in equilibrium with each other under catalytic conditions. This study also revealed that at least in solid-gas copolymerisation reactions ethene insertion into the Pd-acyl bond of the γ -keto chelate complex $[(dppp)Pd\{C(O)CH_2CH_2C(O)CH_3\}]^+$ occurs only in the presence of CO (**Scheme 7**).²⁸

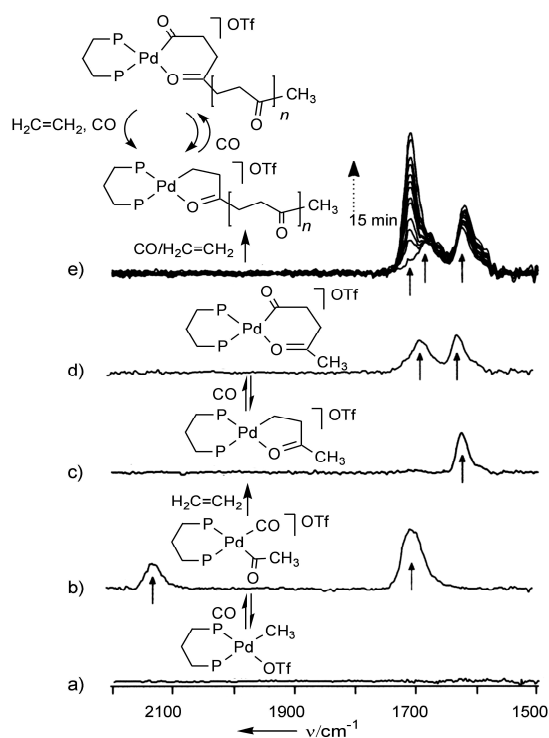
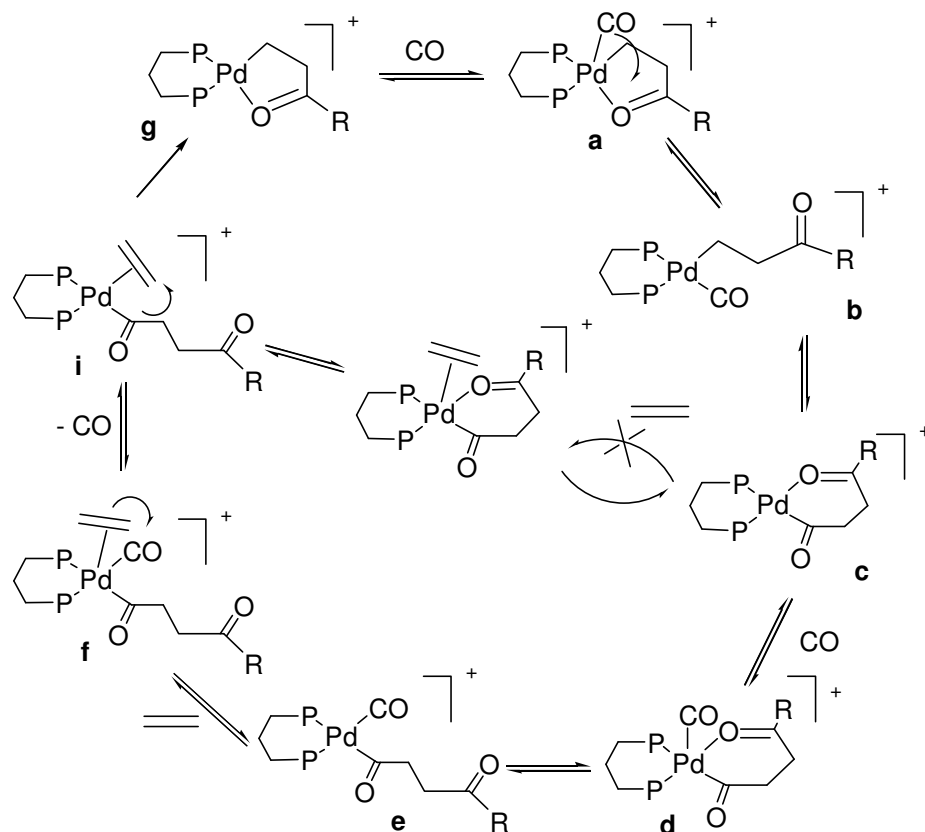


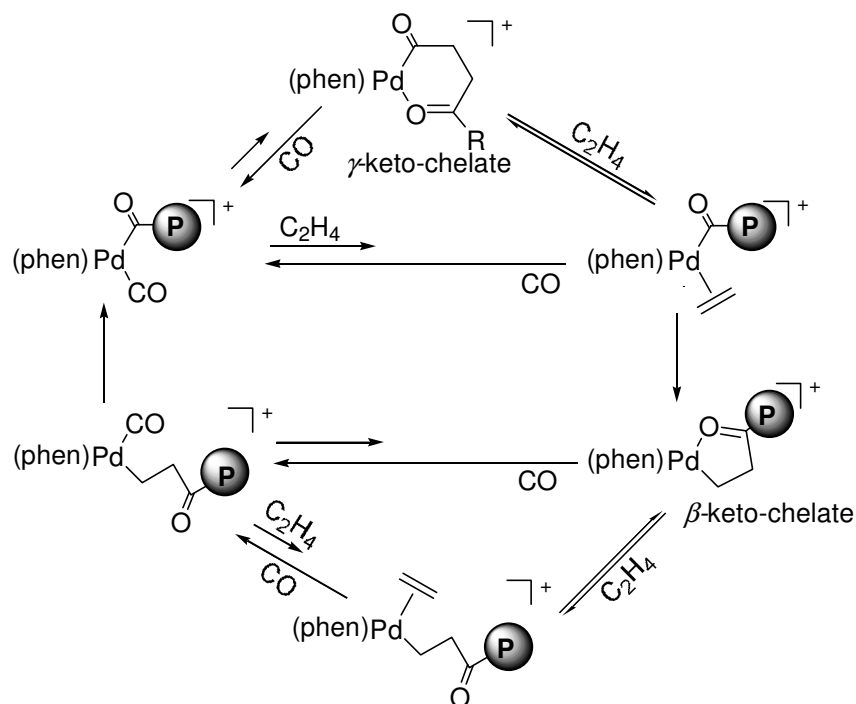
Figure 13. In situ PM-RAIRS spectra of a microcrystalline sample of $[(dppp)Pd(CH_3)(OTf)]$. (a) At room temperature, (b) under 500 mbar of CO, (c) under 2 mbar of CO and 333 mbar of ethene, (d) under subsequent exposure to 750 mbar CO, (e) during subsequent polymerisation under 666 mbar of CO/ethene (evolution of the spectrum at 15 min intervals)

The importance of β - and γ -keto chelates in controlling both the selectivity and the propagation rate of the CO/ethene copolymerisation has been confirmed by several *in situ* and model studies.^{27b,28,29}



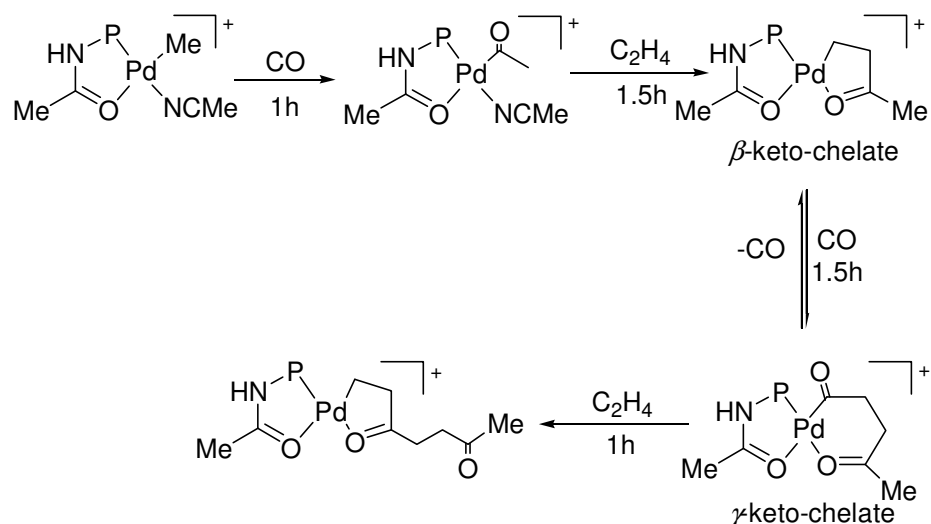
Scheme 7. Mechanism of the heterogeneous CO/ethene copolymerisation proposed on the basis of a PM-RAIRS study

Unlike diphosphine ligands, rigid dinitrogen ligands such as bipyridin (bipy), phenanthroline (phen) and bis(arylimino)acenaphthene (Ar-BIAN) also exhibit the formation of γ -keto chelates by a successive insertion of CO and ethene (**Scheme 8**).²⁹



Scheme 8. Proposed mechanistic cycle of the chain-propagation of the CO/ethene copolymerisation catalysed by the phenanthrolyne-based palladium catalysts

A similar mechanism has been observed by Braunstein et al. with a hemilabile P-O ligand $\text{Ph}_2\text{PNH}(\text{CO})\text{Me}$. The stepwise reaction of the palladium(II) precursor with CO and ethene allowed the authors to isolate the four intermediates shown in **Scheme 9** and to identify the reversible and irreversible steps.^{20a}



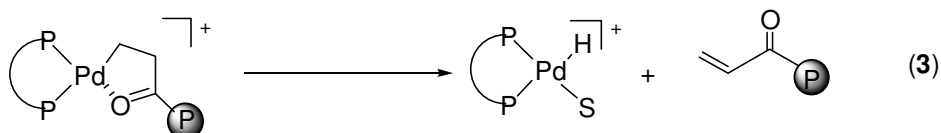
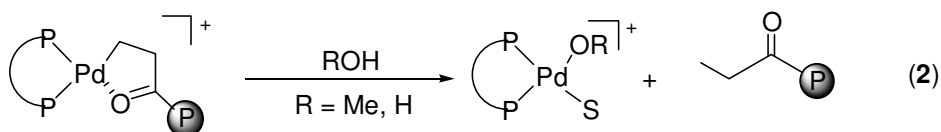
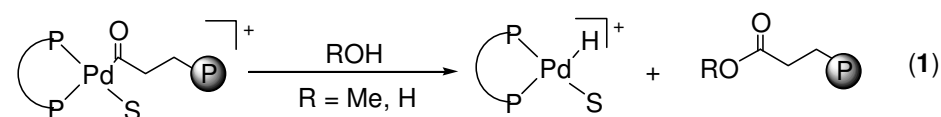
Scheme 9. Model study of the chain propagation step with a Pd(P-O)-based catalyst

In summary both the β -keto chelates and the much more favourable coordination of CO over ethene avoids a thermodynamically favourable double insertion of ethene. On the other hand the double insertion of CO is thermodynamically much less favourable than the alternating insertion of CO and ethene.

Chain-transfer

High molecular weight polyketones are obtained when the propagation rate prevails over the chain-transfer process. If both rates are similar, oligomers are obtained. If the chain-transfer is prevalent only methyl propionate is formed. The chain-transfer mechanism depends on the solvent in which the CO/ethene copolymerisation is carried out. For instance in protic solvents like MeOH, two chain-transfer mechanism occur simultaneously, namely the methanolysis reaction of Pd-acyl species (**Scheme 10**, eq. 1) and the protonolysis reaction of

Pd-alkyl species (**Scheme 10**, eq. **2**).^{5b} This is shown by NMR analysis of the polyketone end groups and the oligomeric fractions, while the mechanism of chain-transfer in aprotic solvents is accomplished by β -hydride elimination (**Scheme 10**, eq. **3**).



S = solvent, co-monomer

Scheme 10. Chain-transfer mechanism in protic and aprotic solvents

Depending on the chain-transfer mechanism, the termination metal product may contain Pd-OR, Pd-OH or Pd-H moieties, all of which can re-initiate the catalytic cycle by inserting CO or ethene, respectively. In principle, the rate of chain-transfer should not affect the overall productivity rather it influences the molecular weight of the polyketone product. When the termination processes **1** and **2** (**Scheme 10**) occur at comparable rates, the copolymers have diester, keto-ester and diketone end groups in a 1:2:1 ratio, respectively.¹⁰

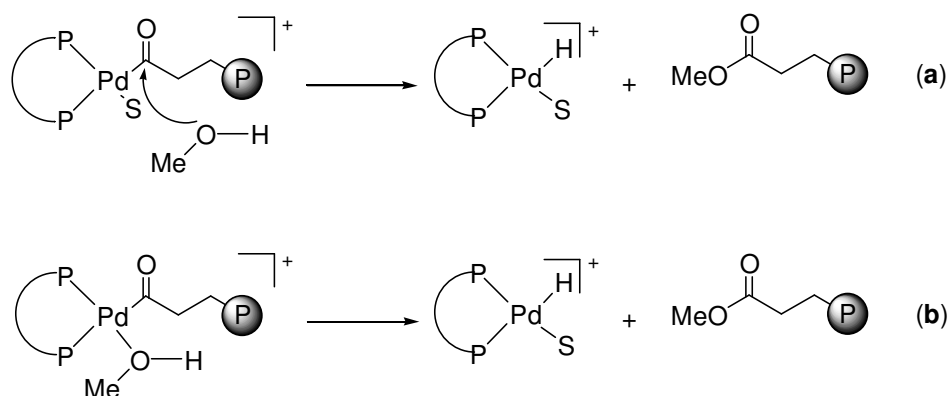
The relative occurrence of protonolysis and methanolysis depends on many factors. When the growing copolymer chain reaches a length of about 13-20 –CH₂CH₂-C(O)- units, and the copolymerisation assumes heterogeneous character, chain termination can equally proceed by protonolysis and methanolysis, while protonolysis predominates over the methanolysis in the homogeneous phase.³⁰ Furthermore the protic acids, which are commonly used to maintain a high number of catalytically centre palladium(II) species during the catalysis, can also influence the methanolysis rate.^{24a}

Chain-transfer by methanolysis

Chain-transfer by methanolysis involves the attack of a MeOH molecule on a propagating Pd-acyl species, which yields an ester-end group, and a Pd(II)-H species which re-initiates the chain growth by inserting of ethene (**Scheme 11**). The use of other alcohols as solvents in the CO/ethene copolymerisation can dramatically affect the termination rate and the molecular weight of the polyketone.³¹ Normally, the alcoholysis rate decreases by both increasing the steric bulk of the alcohol or decreasing its nucleophilicity.^{31c}

Remaining to the exclusive use of methanol, it has been found that the chain-transfer rate depends on the nature of the chelating diphosphine and on the concentration of protic acid added in the reaction media. Some studies on model palladium acyl complexes show that the methanolysis rate increases considerably with the steric bulk of the chelating diphosphine ligand.³²

Two mechanism may take part in chain-transfer through methanolysis namely, the intermolecular (**Scheme 11, a**) or intramolecular (**Scheme 11, b**) attack of Pd-acyl intermediates.



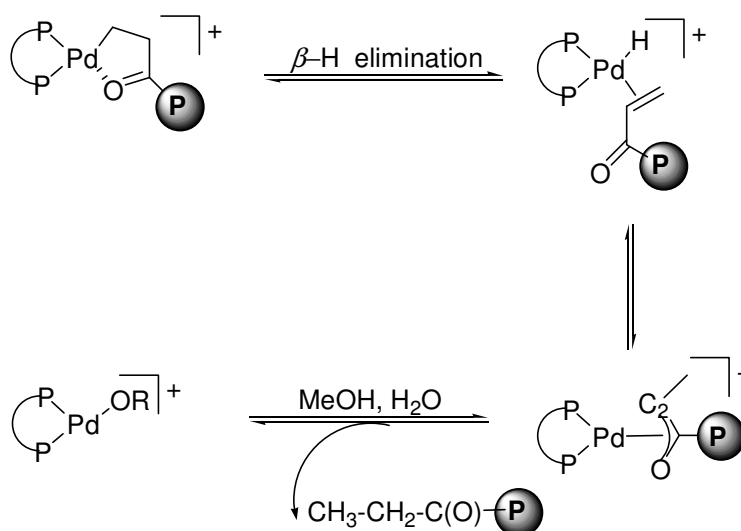
Scheme 11. Intermolecular (a) and intramolecular (b) mechanism of the methanolysis reaction

The intermolecular mechanism, which has been studied by van Leeuwen et al. seems to be less probable than the intramolecular mechanism, although it cannot be excluded.^{31c} The *cis*-coordination of the ligand is required to force the coordination of methanol *cis* to the acyl group. This intramolecular nucleophilic attack of the oxygen atom of methanol at the palladium acyl species can occur *via* a concomitant formation of Pd-H or a reductive elimination of the Pd(acyl)(methoxy) species followed by a protonation of the Pd(0) centre.³³

Chain-transfer by protonolysis

The chain-transfer by protonolysis represents the predominant termination step in homogeneous CO/ethene copolymerisation. It involves the reaction between a propagating Pd-alkyl species and MeOH or water. The propagation is terminated with the formation of a polymeric chain with a ketone end group and Pd-OMe (or Pd-OH) species. These species can re-enter the catalytic cycle by CO insertion. The protonolysis process has been elucidated by van Leeuwen et al. by means of deuterium incorporation experiments^{29c} which showed that the β -keto chelates are in equilibrium with their enolates formed by a β -hydride

elimination/hydride migration process (**Scheme 12**). The coordinated enolate is then regioselectively protonated at the C₂ carbon atom by either MeOH or H₂O. Furthermore from detailed studies of the protonolysis reaction, van Leeuwen et al. inferred a dependence of the protonolysis rate on the diphosphine bite angle. Indeed, a slight increase of the protonolysis rate with increasing bite angles of the diphosphine ligand was found.³⁴



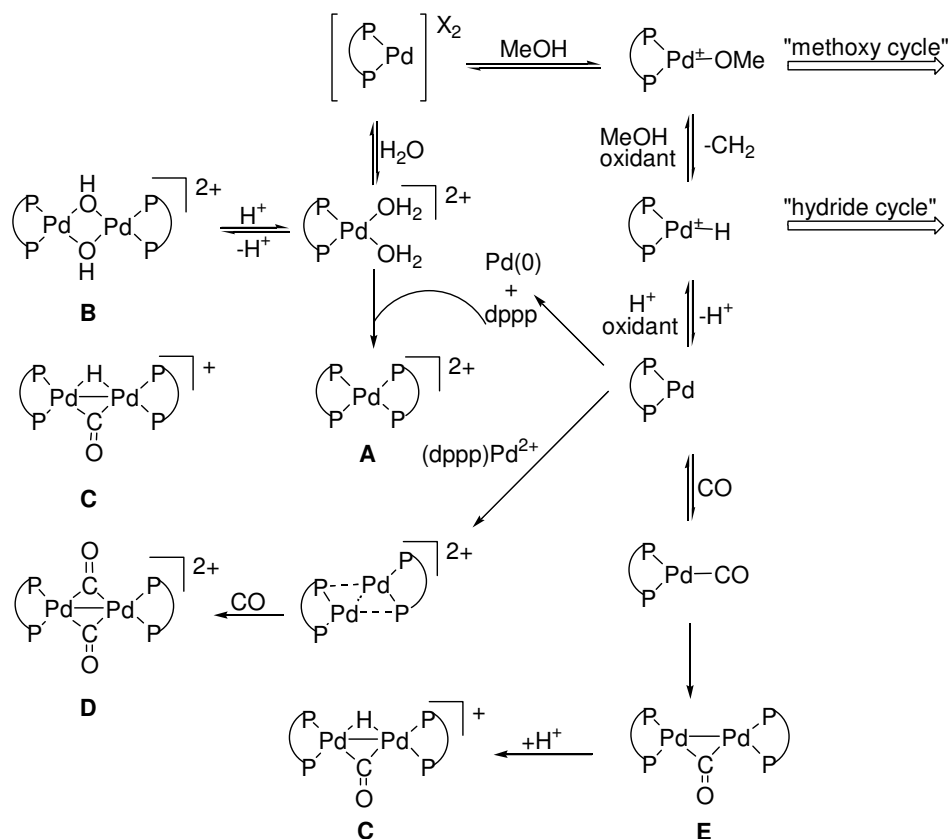
Scheme 12. Chain termination mechanism by protonolysis

When $\text{dppf}^{19\text{b}}$ was used as ligand β -keto chelate was observed in high pressure NMR experiments in $\text{MeOD-}d_4$, which contrasts with the model studies carried out by van Leeuwen et al., as dppf has a wider bite angle than dppe or dppp . In the latter cases no β -keto chelate was observed in identical high pressure NMR experiments. These evidences suggest that also other parameters in the catalytic system may also affect the protonolysis rate.

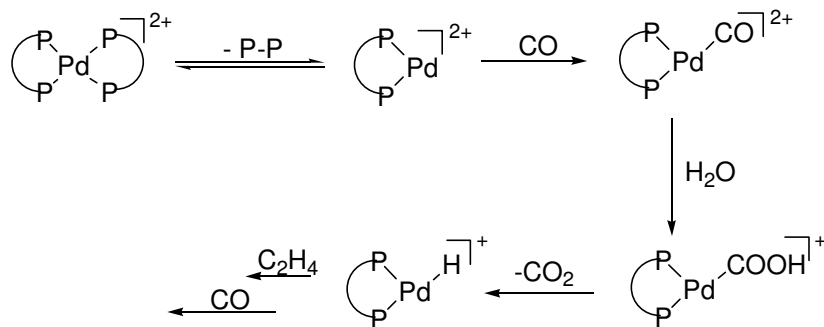
Deactivation paths in the copolymerisation process

Under the conditions, used for the CO/ethene copolymerisation, the propagation rate decreases with time, and no catalytic activity is normally observed after 8-10 hours. **Scheme 13** gives an overview of the different deactivation processes known to date involving chelating diphosphine ligands.

The deactivation process of palladium diphosphine catalysed copolymerisation reactions generally comprises five different compounds namely, the palladium bis-chelate compound **A (Scheme 13)**, the dimeric Pd μ -OH compound **B**, the dimeric Pd(I) μ -H, μ -CO compound **C** and the less common dimeric compounds **D** and **E**. Compound **A** is formed from Pd-H species, which slowly degrade under the concomitant formation of inactive Pd(0) and free ligand, which can react with active palladium (II) species to generate bis-chelate complexes. Not all species represent the dead end of the copolymerisation, rather some of them may be defined as robust resting states. Indeed, bis-chelates containing diphosphine ligands with a C₂ backbone are inactive,^{27b} but those with dppp-like ligands have an appreciable activity, due to the destabilisation of the six membered ring systems by steric interactions between the phenyl groups of each ligand **Scheme 14** shows how Pd bis-chelate complexes can re-enter the catalytic cycle.³⁵ It is important to emphasise, that they can be formed in both protic and aprotic media.

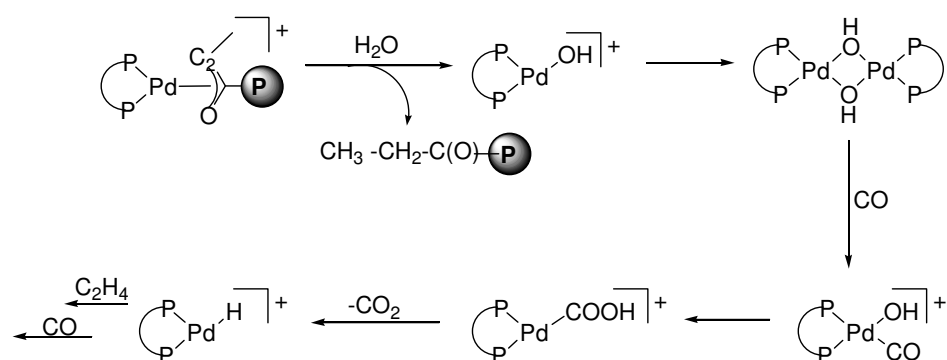


Scheme 13. Possible deactivation paths of Pd(II)(P-P) catalyst under CO/ethene copolymerisation conditions



Scheme 14. Contribution of Pd bis-chelate complexes to the catalytic process

The μ -hydroxo complexes **B** can be formed in protic systems from bis-acquo complexes as presented in **Scheme 13**. They are also formed from the protonolysis reaction, if no additional Brønsted acid is present. Under real catalytic conditions the dimeric form is in equilibrium with a monomeric species, which can insert CO into the Pd-OH bond to yield Pd-C(O)OH, which in turn inserts ethene or eliminates CO₂ to form a Pd-H species (**Scheme 15**).³⁶ The contribution of the dimeric Pd μ -hydroxo complexes to the overall productivity of the catalytic system is generally higher than that of the Pd bis-chelate compounds. In general, the steric rigidity of the ligand backbone destabilises the dimeric Pd μ -hydroxo species.^{27c}



Scheme 15. Reaction of dimeric μ -hydroxo complexes under copolymerisation conditions

The dimeric palladium(I) μ -H, μ -CO compound **C** (**Scheme 13**), which results from the formal reaction of a Pd(0)-CO complex with a Pd(II)-H intermediate has been observed during high pressure NMR experiments in MeOH as solvent.^{19b} Its formation is strongly related to the methanolysis reaction of an Pd-acyl intermediate in the presence of excess CO.^{19b} Furthermore such compounds have been obtained by independent synthesis, upon reaction of dimeric Pd μ -hydroxo compounds with CO,^{37a} or by oxidative addition of an acid at a dimeric Pd(0) monocarbonyl intermediate (**Scheme 13**).^{37b}

The dimeric compounds **D** and **E** (**Scheme 13**) have also be obtained under reductive conditions and in the presence of CO. Both of these compounds have been synthesised but never observed under real catalytic conditions.^{37c,37d}

1.3. Non-alternating CO/ethene copolymerisation

The development of novel late transition-metal catalysts for the synthesis of new copolymers containing non-polar backbone and a controlled amount of a polar monomer is of considerable interest to both academia and industry.¹¹ However, the design of metal-catalysed for such copolymerisation reactions is not a trivial task and many attempts have been made in this area. So far, however, very few new materials have been obtained.³⁸

In previous sections, we have dealt with the palladium-catalysed perfectly alternating copolymerisation reaction of carbon monoxide and ethene and its mechanism. It is well known that the double insertion of carbon monoxide in this reaction does not occur for thermodynamic reasons. However, the double insertion of ethene is kinetically disfavoured. The formation of a stable five-membered cationic palladium metallacycle (**A**) (**Figure 14**) *via* an electrostatic interaction between the oxygen of the carbonyl and the cationic palladium centre, which is called “back-biting”, kinetically favours the insertion of carbon monoxide over ethene insertion.^{29a,39,40}

In over two decades of research in the area of late transition metal catalysed polymerisation of carbon monoxide and ethene, no extra insertions of ethene or carbon monoxide have ever been reported; even high ethene/carbon monoxide ratios produce exclusively error-free polyketone until all carbon monoxide is consumed.^{10b,41} Nevertheless, the double insertion of ethene should be possible, as the same cationic palladium species that is used for the copolymerisation has been shown to efficiently dimerise ethene into butanes.¹¹

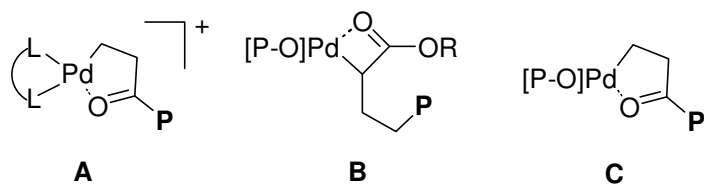


Figure 14. Chelates formed during the copolymerisation reaction

The production of non-perfectly alternating carbon monoxide and ethene copolymers is one of the aims in polyketone research in order to obtain new materials with desirable properties and that could be further functionalised.

In 2002, Drent et al. reported the first example of palladium-catalysed non-perfectly alternating copolymerisation of carbon monoxide and ethene. The palladium precursors bearing alkoxy-aryl-phosphine ligands containing sulfonic acid groups (**Figure 15**) as catalysts were formed *in situ* by mixing palladium acetate and the ligand in a near stoichiometric ratio. Double, triple and quadruple extra insertions of ethene in the growing polyketone chain were observed. These extra insertions were attributed to the destabilisation of the neutral chelate **C** (**Figure 14**) to the extent that ethene effectively competes with carbon monoxide for the next insertion.⁴²

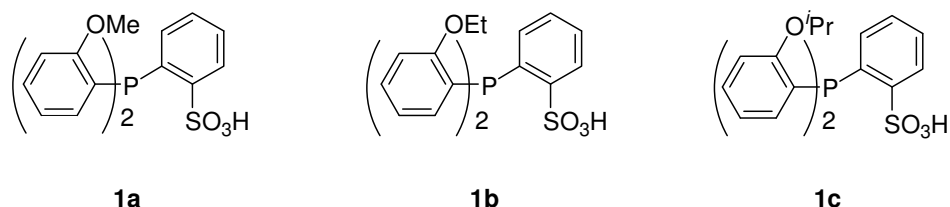


Figure 15. (P-O) ligands derivatives diphenylphosphinobenzene sulfonic acid, used in the non-alternating copolymerisation of CO and ethene

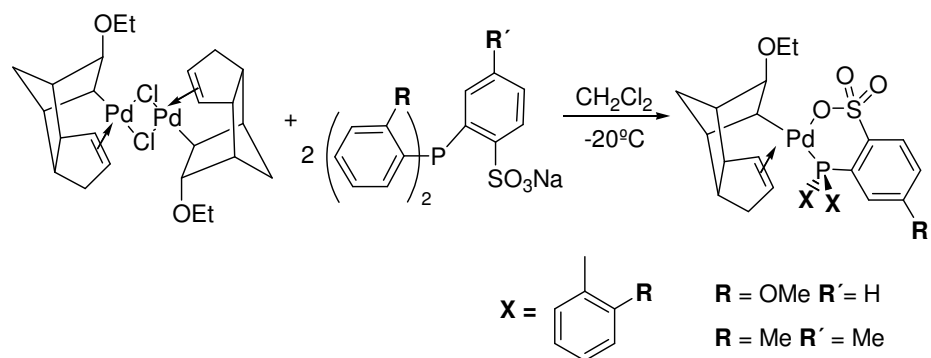
Table 2 shows the results that Drent et al. have obtained using the phosphine sulfonated ligands **1a-c** (entries 1-7). Activities were best with ligand **1a** (entry 1) while the extra insertion of ethene (up to 18%) was highest with the palladium system containing phosphine sulfonated ligand **1c** (entry 7).

Table 2. Pd catalysed non-alternating copolymerisation of CO and ethene^a

Entry	[P-O]	T (°C)	P _{ethene} (bar)	P _{CO} (bar)	Activity ^b (gmmol ⁻¹ h ⁻¹)	Extra insertion of ethene (%) ^c
1	1a	110	20	30	190	2.4
2	1a	110	30	20	123	7.3
3	1a	110	30	10	49	15.2
4	1a	100	30	20	86	4.7
5	1a	120	30	20	108	11.0
6	1b	110	30	20	103	11.9
7	1c	110	30	20	108	18.3

^aReaction conditions: catalyst, 0.04 mmol Pd(OAc)₂, solvent, MeOH. ^bBased on Pd over experiment run time (2.0-2.2 h). ^cTotal mol% ethene of copolymer involved in non-alternation, calculated from ¹³C{¹H} NMR spectra (measured in 1,1,1,3,3,3-hexafluoropropan-2-ol-C₆D₆).

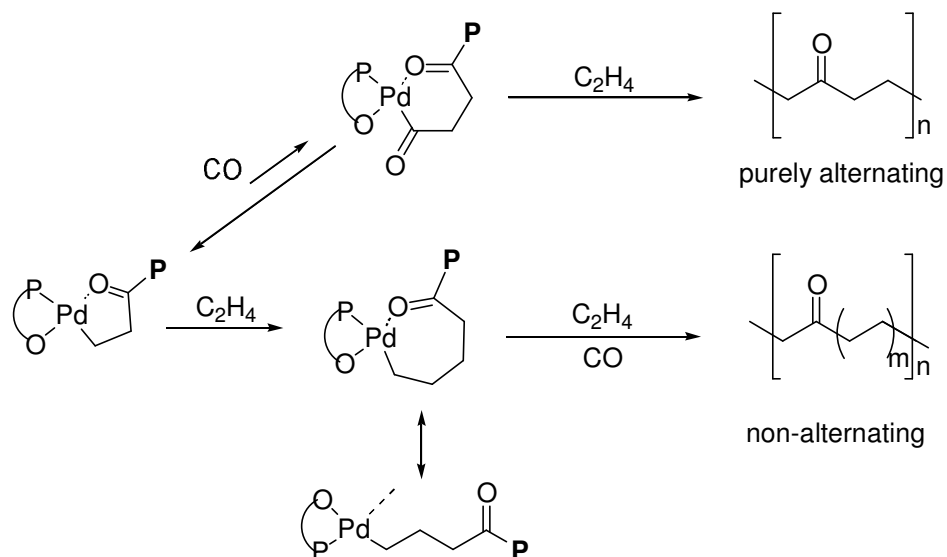
More recently, Rieger et al. reported the first examples of neutral palladium(II) complexes bearing sulfonated phosphine ligands (**Scheme 16**). Higher activities and higher insertion of extra amounts of ethene (up to 30%) into the copolymeric chain were achieved⁴³ when compared to the previously reported in *in situ* copolymerisation reactions.⁴²



Scheme 16. Neutral Pd(II) complexes bearing sulfonated phosphine ligands used as precatalyst for non alternating CO/ethene copolymerisation

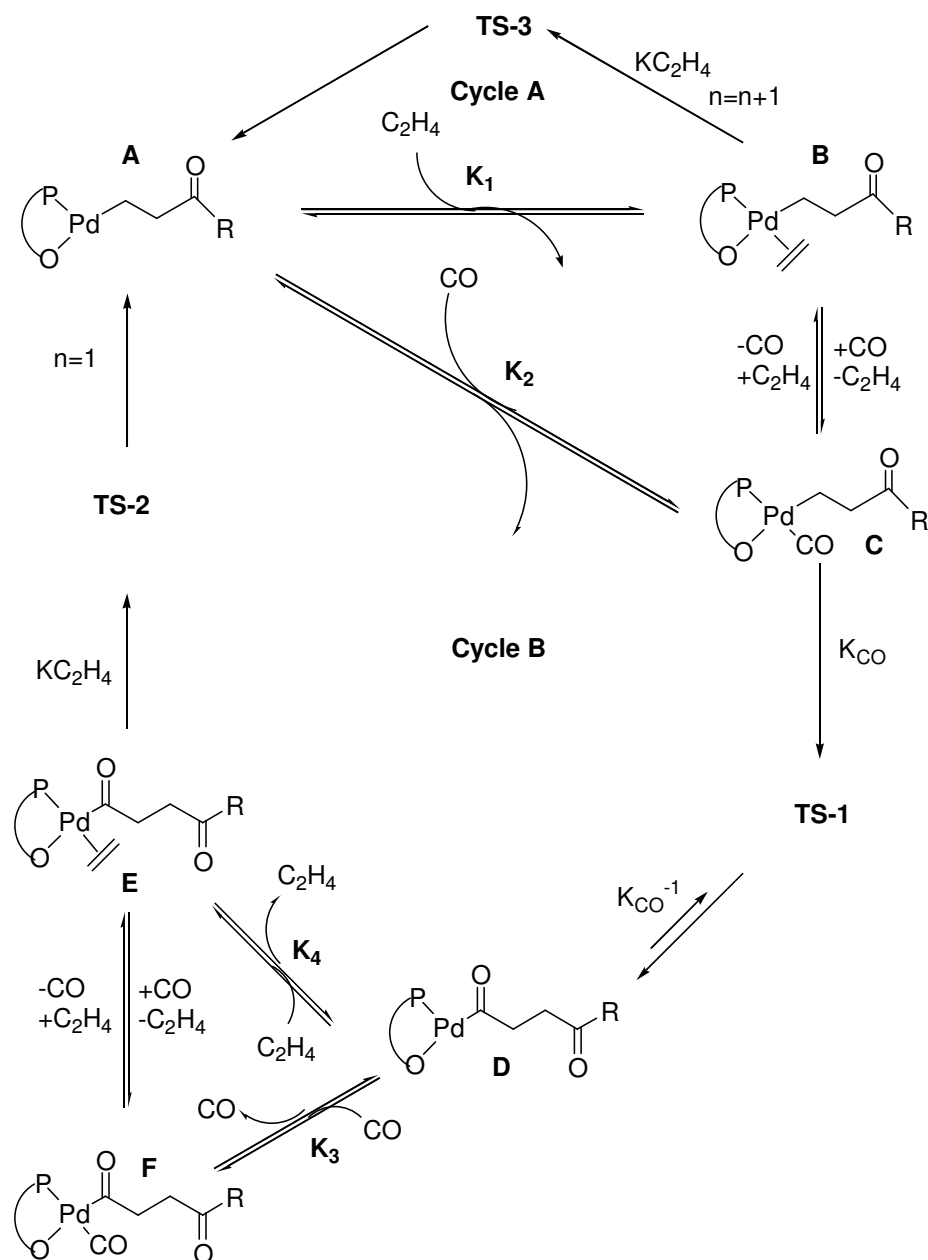
The mechanism of the perfectly alternating copolymerisation of carbon monoxide and ethene by palladium(II) catalysts based on diphosphine ligands has been extensively studied and is now well known^{5a,5b,5c,5e,9} However, few studies have reported the mechanism for the non-alternating copolymerisation of carbon monoxide and ethene.^{42,43,44}

Rieger et al. proposed that this new polymerisation proceeds *via* two intertwined pathways (**Scheme 17**), where the same active species may switch between the production of alternating and non-alternating blocks in the same polymer chain.⁴³ This mechanism is based on a stereoelectronic destabilisation of the neutral chelate, which enables ethene to compete with carbon monoxide and to open the five-membered metallacycle, as previously proposed by Drent et al.⁴² On the bases of Drent's report, it was assumed that the neutral nature of the CO-inserted 6-membered chelate could lead to a decarbonylation reaction yielding the five-membered ring complex that could therefore react with ethene to form a seven-membered chelate, which is proposed to open more easily and therefore facilitates the incorporation of further ethene units. Furthermore, increasing of the pressure of ethene at high CO/ethene ratios (1:20) provides higher probability of ethene insertion over carbon monoxide insertion.



Scheme 17. Mechanism for non-perfectly alternating carbon monoxide and ethene copolymerisation

Ziegler et al. have proposed a mechanism in which they compared catalytic systems containing ligands **1a** and **1c**, previously described by Drent et al., with the catalytic systems containing dppp ligand which produces always perfectly alternating polyketones. They explained the formation of a non-perfectly alternating copolymer in terms of the decarbonylation of the palladium-acyl complexes formed during the catalytic process.⁴⁴ The mechanism proposed by Ziegler et al. for the carbon monoxide and ethene non alternating copolymerisation is shown in **Scheme 18**.



Scheme 18. Chain propagation mechanism for the CO/ethene copolymerisation reaction

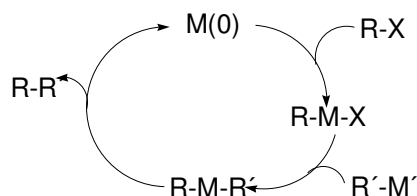
The mechanism involves two main competing cycles: cycle **A** ($A \rightarrow B \rightarrow \text{TS-3}$) corresponds to the non alternating and cycle **B** ($A \rightarrow C \rightarrow \text{TS-1} \rightarrow D \rightarrow E \rightarrow \text{TS-2}$) to the strictly alternating. Both cycles **A** and **B** start with the formation of carbon monoxide and ethene species with the Pd-alkyl complexes in a pre-equilibrium step ($A \leftrightarrow B$) for cycle **A** and ($A \leftrightarrow C$) for cycle **B**. The next step is that the complexes generated undergo migratory insertion into the Pd-alkyl bond, which leads to the formation of Pd-alkyl species ($B \rightarrow \text{TS-3} \rightarrow A$) for cycle **A** or Pd-acyl complexes ($C \rightarrow \text{TS-1} \rightarrow D$) for cycle **B**. On the basis of theoretical and experimental studies, the ethene insertion is assumed to be irreversible.^{45,46} The CO insertion into the Pd-alkyl bond ($C \rightarrow \text{TS-1} \rightarrow D$) was thought to be irreversible. However, recent studies⁴⁷ have shown that decarbonylation is also important. The decarbonylation process is shown in **Scheme 18** ($D \rightarrow \text{TS-1} \rightarrow C$). To complete the alternating cycle **B**, the Pd-acyl complex interacts with both carbon monoxide and ethene, which leads to the formation of Pd acyl carbonyl ($D \rightarrow F$) or Pd-acyl-ethene ($D \rightarrow E$) species. The Pd-acyl-ethene complex is a precursor specie for the migratory insertion of the ethene molecule into the Pd-acyl bond ($E \rightarrow \text{TS-2} \rightarrow A$), which yields strictly alternating polyketone.⁴⁷

1.4. Suzuki-Miyaura cross-coupling reaction

1.4.1. General aspects

Homogeneous palladium catalysts have acquired enormous importance in such coupling reactions as Heck,⁴⁸ Suzuki,⁴⁹ Sonogashira⁵⁰ and Stille.⁵¹ Many products can be synthesised by this methodology for the first time or in much more efficiently way than before. Palladium catalysts have emerged as extremely powerful tools for the construction of carbon-carbon and carbon-heteroatom bonds.⁵² The properties of the palladium catalysts can be modified by changing the ligands. For instance, phosphines, amines, carbenes, dibenzylideneacetone (dba), etc are used to tune the catalysts. Furthermore, subtle modifications in the substitute groups can provide fine tuning of the catalysts.

Ligand design provides catalysts that tolerate weak leaving groups, have high TON and reaction rates and improve lifetimes. Appropriate ligands make it possible to carry out reactions in water and at room temperature. **Scheme 19** shows a general catalytic cycle for cross-coupling of organic halides and organometallics.

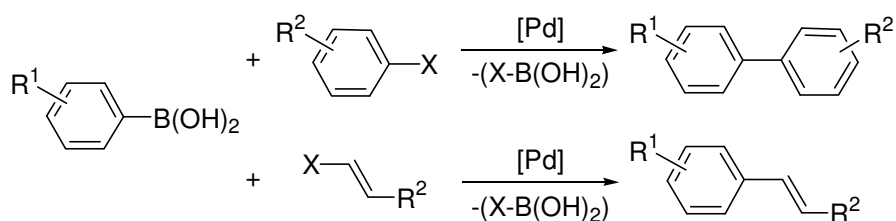


Scheme 19. Catalytic cycle for cross-coupling of organic halides and organometallics

Of the palladium-catalysed cross-coupling reactions, the Suzuki-Miyaura cross-coupling reaction is one of the most versatile and widely used reactions for the

selective construction of C-C bonds, and in particular for the formation of unsymmetrical biaryls. Since this reaction has been used in numerous synthetic processes⁵³ and it has been applied industrially to the production of compounds such as losartan, a Merck antihypertensive drug,⁵⁴ developments to improve the conditions for the Suzuki-Miyaura reaction have received much attention. Indeed, in the last 10 years, over 700 publications have been published in the area of aryl-aryl bond formation. This reaction has gained prominence in the last few years because the conditions developed for the Suzuki reaction have many desirable features for large-scale synthesis and are amenable to industrial synthesis of pharmaceuticals and fine chemicals.

Suzuki-Miyaura cross-coupling reactions generally use organic solvents such as THF and diethyl ether in the presence of Pd(II) or Pd(0) catalyst which are soluble in these solvents. This reaction comprises the coupling of aryl- or vinyl-halides with arylboronic acids (**Scheme 20**).

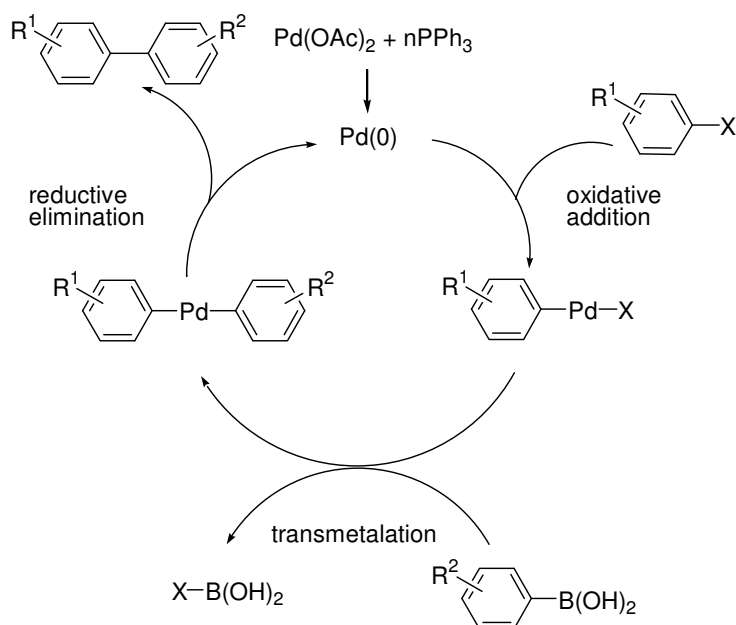


Scheme 20. Suzuki-Miyaura reaction of aryl- or vinyl-halides with arylboronic acids

This reaction is popular because of a variety of factors: a large number of boronic acids are commercially available, they are non toxic, they are stable to heat, air, and moisture. Furthermore, the boron-containing by-product of the Suzuki-Miyaura cross-coupling reaction can be easily separated from the desired product of the reaction.

1.4.2. Mechanism of the S-M cross-coupling reaction

The classical catalytic cycle described for both Heck and Suzuki reactions in most organic chemistry textbooks involves an homogeneous palladium catalyst that cycles between the Pd(0) and Pd(II) oxidation states during the course of the catalytic reaction. Normally, a Pd(II) precatalyst is used for this reaction, the catalytic cycle starts with the *in situ* reduction of the Pd(II) precatalyst to Pd(0), followed by the oxidative addition of the aryl halide to form a palladium(II) intermediate as shown in **Scheme 21**. Then the transmetalation from the arylboronic acid takes place. The last step is the reductive elimination to yield the biaryl product and the Pd(0) specie, which starts the cycle again.



Scheme 21. Typical mechanism for S-M cross-coupling reaction

Unlike other cross-coupling reactions involving the transmetalation step, the Suzuki-Miyaura reaction requires the use of a base for this transmetalation

step. The role of the base is to form a more electron-rich intermediate with the boronic acid resulting more reactive than the original boronic acid towards attack of the palladium(II) complexes making easier the transmetallation step. Normally, mineral bases such as alkali metal carbonates are used. The use of water either as a solvent or additive helps with the solvation of these organic-insoluble materials.

The possibility that palladium(IV) species were involved as intermediates was considered⁵⁵ but seems to be unlikely in the light of later results.⁵⁶ Each of the steps in the catalytic cycle can be rate-determining, depending on the type of substrate and catalyst.

Mechanistic studies published by Fu and co-workers in 2002 showed that the Pd:P ratio played a major role in the catalytic performance of the complexes formed *in situ*.⁵⁷ Whereas activity was high at a Pd:P ratio of 1:1 or 1:1.5, a ratio of 1:2, gave only lethargic reactions. In NMR studies, the only identified species observed at a Pd:P ratio of 2:1 to 1: 1.5 was the species containing two phosphines, Pd[P(*t*-Bu)₃]₂. In a further NMR studies of the reaction between an aryl chloride and a boronic acid at a Pd:P ratio of 1:1, the only species observed was Pd[P(*t*-Bu)₃]₂. Since the Pd:P ratio was 1:1, this suggested that half of the Pd contained two ligands and the other half contained no phosphine ligand. As the complex containing two phosphine ligands did not seem to be active under the condition used, the authors concluded that small amounts of the palladium-monophosphine adduct may represent the true catalytic species.⁵⁷

Recently, a mechanistic study on Suzuki cross-coupling reaction has been reported by J. M. Brown et al. In their report they compared aryl bromides with aryl triflates as substrates for the Suzuki reaction, and observe a different behavior in the catalytic cycle. Their observations showed that the Suzuki

coupling reaction was out of line with all other common cross-coupling reactions when aryl triflates derivatives are used.⁵⁸

1.4.3. Palladium catalytic systems in Suzuki-Miyaura cross-coupling reaction

Palladium catalysts containing phosphorous ligands

The triphenylphosphine ligand was one of the first ligands to be used for the earliest catalytic precursors in Suzuki and Heck cross-coupling reactions.⁵⁹ Indeed, this pre-catalyst with triphenylphosphine as the ligand was used in most coupling protocols until the mid 1990's despite the fact that other ligands such as tri(*o*-tolyl)phosphine gave better results.⁶⁰ Nowadays these well-known pre-catalysts are still being studied and basic trends such as the effect of the solvent or the palladium:phosphorous ratio are being tested.⁶¹

In 1997 Shen showed that aryl chlorides could be activated in Suzuki reaction by using P(Cy)₃, (tricyclohexylphosphine) and dppb, (diphenylphosphinobutane) as phosphorous ligands.⁶² Interestingly, the activity of phosphorous ligands that are sterically and electronically similar to P(Cy)₃, namely tricyclopentylphosphine and triisopropylphosphine were found to be poor in the Suzuki-Miyaura reaction of alkyl chlorides.⁶³

Although, it had been shown that bulky ligands facilitate cross-coupling reactions,⁶⁴ the use of bulky diphosphine ligand in the Suzuki reaction was not widespread until the late 1990's when numerous authors including van Leeuwen, Beller, Buchwald, Fu and others published accounts of bulky, monodentate phosphine ligands as effective components for palladium Suzuki-Miyaura and Heck coupling catalysts.⁶⁵ The use of a bulky trialkylphosphine P(*t*-

Bu)₃ as ligand in the Pd-catalysed Suzuki coupling reaction of a great number of aryl halides was described by Fu and co-workers.⁶⁶

In 1990 Buchwald reported a very important class of monodentate, bulky phosphines based on functionalised biphenyls (ligands **1-4**) (**Figure 16**).⁶⁷ These ligands combined *in situ* with a palladium source proved to be effective catalysts for a variety of cross-coupling reactions. The outstanding catalytic performance of these ligands in conjunction with a palladium source has been attributed to a combination of both electronic properties, which facilitates the oxidative addition, and steric hindrance, which favours the reductive elimination steps in the catalytic cycle.⁶⁸ Other authors have suggested that biphenyl-based phosphines can contribute to the stabilization of the Pd(0) intermediates through the formation of π interactions with the aryl ring.^{17,69} Detailed proof of this was given in a later study with ligand **6**, SPhos by Buchwald et al..⁷⁰

The bulky monodentate phosphine ligand **7**, diadamantyl-*n*-butyl phosphine was used in 2000 by Beller et al. for the Suzuki-Miyaura coupling of aryl chlorides.⁷¹ Later they describe monophosphine-Pd(0) complexes based on other bulky ligands and they used them as pre-catalysts in Suzuki-Miyaura coupling reactions.⁷²

Beller et al. also described N-arylpyrroles (ligand **8**) and N-aryl-2-(dialkylphosphino)imidazoles (ligand **9**) as effective ligands for activating aryl chlorides in the Suzuki coupling reaction.⁷³

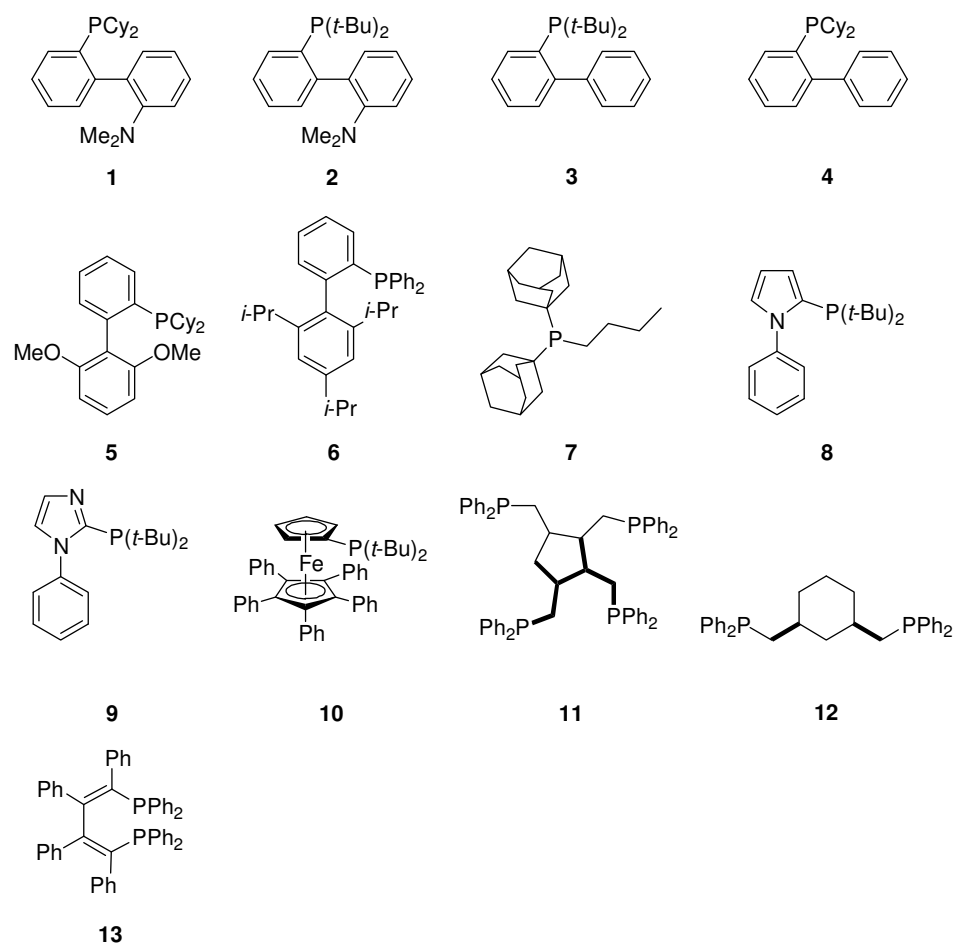


Figure 16. A variety of monodentate, bidentate, and tetradentate phosphine ligands used in palladium-catalysed Heck and Suzuki coupling reactions

Several groups have reported the use of ferrocene-based ligands for instance, Fu et al. reported a bulky, ferrocene-based triarylphosphine, ligand **10** that proved to be active in Suzuki coupling of aryl chlorides.⁷⁴

A variety of ligands containing P-O bonds have been successfully tested in Heck and Suzuki coupling reactions. Indeed, palladium(II)-phosphate

complexes and phosphates were found to be excellent complexes and ligands for the Suzuki coupling of aryl chlorides and bromides.⁷⁵

Doucet and Santelli showed that tetradentate phosphine ligand, **11** was able to activate aryl chlorides or bromides in the Suzuki coupling reaction.⁷⁶ Diphosphine ligand, **12** was reported by Anderson et al. and seemed to give stable palladium catalysts for Suzuki couplings.⁷⁷ Bidentate ligand NUPHOS, **13** was also shown to be useful in Suzuki couplings of bromoarenes with phenylboronic acid.⁷⁸

Palladium catalytic systems containing non-phosphorous or mixed phosphorous ligands

Although the most commonly studied ligands are phosphorous-based, recently interest in the use of ligands with other donor atoms has increased (**Figure 17**). Dupont et al. have reported that palladium complexes with thioether donor ligands, **14** lead effective palladium precursors in Suzuki coupling reaction.⁷⁹

Nolan et al. reported excellent results for the coupling reaction of various aryl bromides and activated aryl chlorides with arylboronic acids using palladium (II) complexes of bidentate diazabutadiene (DAB) ligands, **15**.⁸⁰ Liang et al. showed that for amido-phosphine P-N ligand, **16** the palladium complexes of which were extremely stables in the Suzuki coupling reactions, palladium black did no form during the catalytic process.⁸¹ A wide variety of amino-phosphine ligands, **17** and **18**, also proved to be highly effective in Suzuki reactions under mild conditions.⁸²

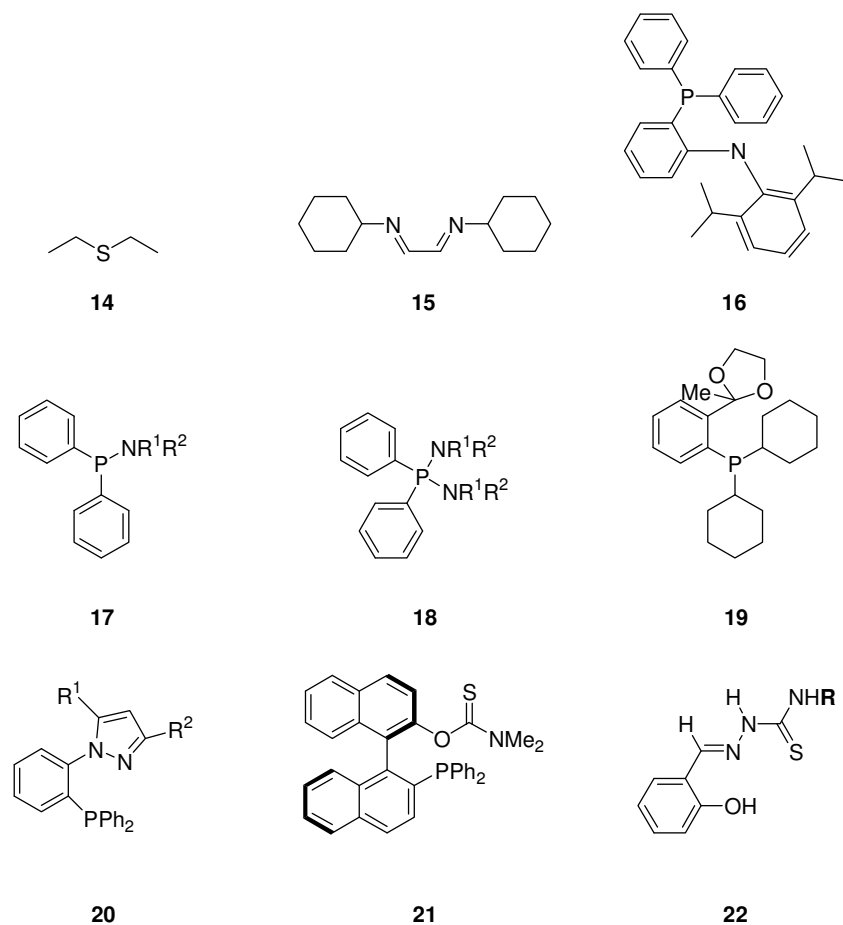


Figure 17. A variety of monodentate, bidentate, and tridentate with non-phosphorous or mixed phosphorous ligands used in conjunction with palladium source in Suzuki coupling reactions

Chelating P-O ligand, **19** has also been used in the Suzuki reaction of both aryl chlorides and bromides. The reason for the excellent catalytic properties of the palladium complexes containing ligand **19** can be ascribed to both the overall structure ligand and the presence of the “PCy₂” unit. The rigid backbone favours the generation and stability of the chelating (P-O)-Pd intermediates which

appear to be most suitable for catalysis,⁸³ while the “PCy₂” unit makes the Pd center sufficiently electron-rich to promote oxidative addition of the usually unreactive aryl chlorides.⁸⁴

Welton et al. reported the use of some commercially available imidazoles ligands for the Suzuki reaction, although in almost all cases catalyst decomposition was observed.⁸⁵ Sarkar et al. described the use of pyrazole-tethered arylphosphine, **20** as ligands for the Suzuki coupling of aryl chlorides, suggesting that palladium chelation could play an important role in stabilizing the catalyst. It has been suggested that the steric crowding in the metal complex would increase the catalytic activity of such complexes.⁸⁶

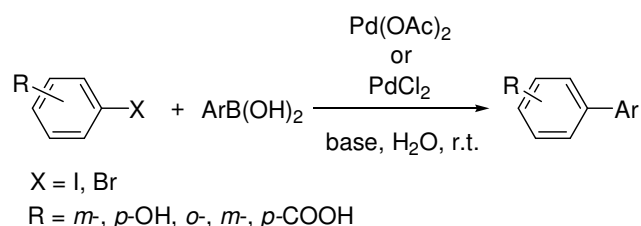
Binaphthyl-based P-S bidentate ligand, **21** was used by Shi et al. as an effective promoter in the palladium(0)-catalysed Suzuki cross-coupling of aryl bromides and iodides.⁸⁷ Kostas et al. used palladium complexes with thiosemicarbazone ligands, **22** for the first time as precatalysts in the Suzuki coupling reaction of aryl bromides and chlorides.⁸⁸

1.4.4. Suzuki-Miyaura cross-coupling reaction in aqueous media

Due to the high solubility of arylboronic acids in water and the low toxicity of both reagents and by-products compared to other reactions.^{89,90} It is particularly interesting to perform the Suzuki coupling reaction in water. The fact that organoboron compounds are quite stable to protolytic decomposition by water means that methodologies using water or aqueous media as solvents have considerable potential. When neat water is used as a solvent, the reactions can be performed using simple palladium salts such as PdCl₂ or Pd(OAc)₂ in air.

Several reports have appeared in recent years on water soluble Pd-systems.^{91,92} Beletskaya et al. proved that the reaction of arylboronic acids with

water-soluble aryl halides can be performed at room temperature in the presence of a palladium salt and an inorganic base (**Scheme 22**).⁹³



Scheme 22. Suzuki-Miyaura cross-coupling reaction performed in water

Water soluble phosphines have been used as ligands for Suzuki-Miyaura reactions in aqueous media (**Figure 18**).⁹⁴ One of the best known phosphine for its application in water is tri-(3-sulfonatophenyl)phosphine, **23** (TPPTS). The Suzuki coupling of unactivated aryl bromides has been reported using high catalyst loadings of Pd/TPPTS in the aqueous phase but modest activity was achieved.^{91a}

The related tri(4,6-dimethyl-3-sulfonatophenyl) phosphine trisodium **24** (TXPTS) and tri(4-methoxy-6-methyl-3-sulfonatophenyl) phosphine trisodium salt **25** (TMAPTS) provide active catalysts for Suzuki couplings in aqueous media of aryl bromides at 50 °C.^{91b} Water-soluble phosphines TPPTS (**23**) and TXPTS (**24**) in combination with Pd(OAc)₂ have also been applied for the efficient synthesis of aryl-modified nucleosides, which can be obtained in a single step and without protecting the halogenated nucleoside.^{91c}

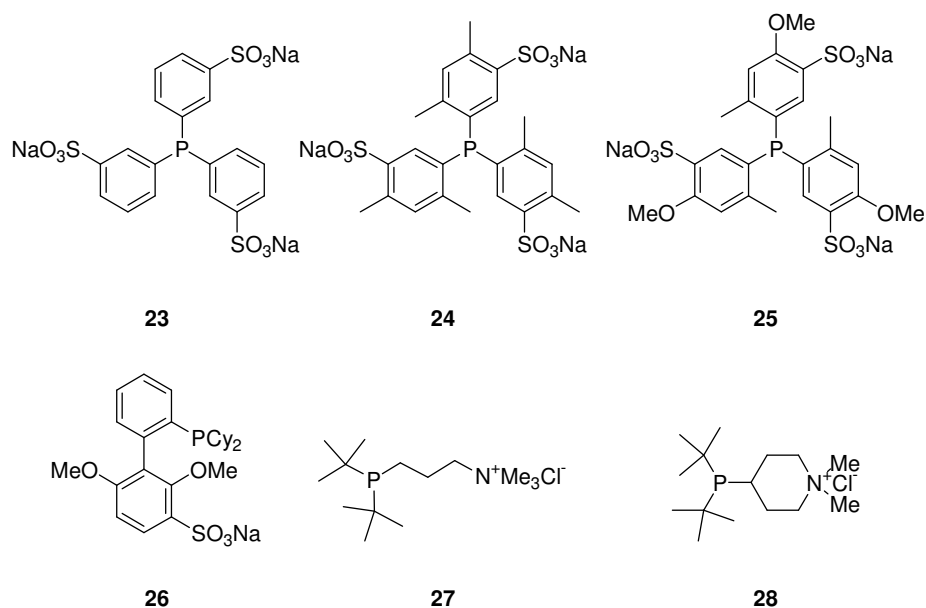


Figure 18. Some phosphine water-soluble ligands used recently in the Suzuki-Miyaura reaction performed in aqueous or neat water media

Buchwald et al. have recently reported the application of an electron-rich sulfonate ligand **26** with excellent yields and wide scope for the Suzuki coupling of highly functionalised aryl chlorides or heterocyclic chlorides/bromides and aryl or alkyl boronic acids in aqueous media.^{91d}

Shaughnessy and Booth⁹⁵ prepared two sterically demanding, water-soluble alkylphosphines **27** and **28**, which produce highly active palladium catalysts for Suzuki-Miyaura couplings of aryl bromides or chlorides with arylboronic acids in aqueous solvents. They also found that the more sterically demanding ligand **28** lead catalysts with higher activity toward aryl chlorides than the catalysts obtained with ligand **27**.

Other systems containing water-soluble Pd ligand-free systems or ligands other than sulfonated phosphines ones:⁹² for instance, the catalytic system formed by

Pd(OAc)₂/DABCO with PEG-400 as the phase-transfer catalyst,^{92c} Pd(OAc)₂/PEG-2000/H₂O under ligand-free conditions^{92d} or amphiphilic water-soluble diblock copolymers based on 2-oxazoline derivatives with pendant N-heterocyclic carbene/palladium catalysts.^{92b}

Recently, SanMartín et al. reported a palladium catalyst with a CNC pincer ligand **29** (Figure 19) that is soluble in water due to the *p*-carboxy group of the ligand. This system provides high turnover frequencies combined with effective catalyst reuse.^{92d}

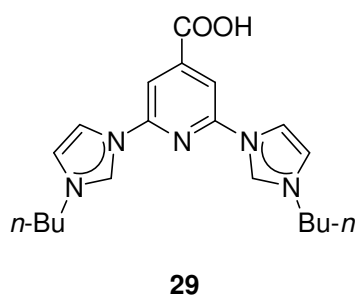


Figure 19. CNC pincer water-soluble ligand prepared by R. SanMartín et al.

1.4.5. Microwave techniques as a tool for synthetic chemistry

Microwave-promoted synthesis is an area of increasing interest in both academic and industrial laboratories; it provides a very efficient way of heating reaction mixtures. In 1986 the first reports of microwave-heating in organic synthesis appeared in the literature.⁹⁶

Microwave-promoted chemistry is founded on the fact that materials can absorb microwave energy and convert it to heat.⁹⁷ It is possible to control the temperature, the microwave power and the reaction time very easily and perform reactions reproducibly. The concept of efficient and selective synthesis in water has been exemplified as the rates, yields and selectivity observed for

may reactions in water have begun to match or in many cases, surpass those in organic solvents.⁹⁸

The effect of microwave irradiation has not yet been fully elucidated; however, it is significant that many metal-catalysed reactions are completed within a few minutes. Since polar solvents efficiently absorb microwaves, reactions have been carried out in water, ethylene glycol or DMF. The use of microwaves was first reported in 1996 for both homogeneous⁹⁹ and solid-phase coupling reactions of arylboronic acids.¹⁰⁰ Microwave irradiation significantly increases the efficiency of ligandless palladium acetate.

Water as solvent offers practical advantages over organic solvents, it is readily available, cheap, non-toxic and non-flammable. It also provides a medium for solution chemistry but also often takes part in elementary chemical events on a molecular scale. As well as water is used for chemistry at ambient pressure there has been increasing interest in high-temperature water,¹⁰¹ superheated water¹⁰² and supercritical water.¹⁰³

Because of its properties, water is an excellent solvent for microwave-promoted synthesis. For the Suzuki reaction, the solubility in water of arylboronic acids provides an interesting possibility to perform this coupling reaction in aqueous media under microwave conditions.

1.5. Scope and objectives of the thesis

The interest in the palladium(II)-catalysed copolymerisation reaction of carbon monoxide and ethene as well as other reactions involving the formation of the C-C bond is increasing because of the possibilities of application in synthesis of new products and materials. This interest is reflected in the large number of reports published in recent years

Since catalyst degradation to inactive species, is the major cause of the low productivity, considerable research effort is being made to design diphosphine ligands that can prevent them from degrading. Many papers have shown that the introduction of an *o*-methoxy substituent on the P-aryl rings of the diphosphine enhances the productivity in comparison with the unsubstituted ligands. It has been suggested that both steric and electronic factors are responsible for the positive effect of the *o*-methoxy groups on catalyst activity.

This thesis focuses on elucidating the effect of the *o*-methoxy group introduced on the P-aryl rings of the diphosphine ligands in the copolymerization reaction of carbon monoxide and ethene from a catalytic and a mechanistic point of view.

In the second part, the thesis focuses on the synthesis of new phosphine sulfonated ligands for the less well known reaction of non-alternating copolymerisation of CO and ethene and the applications of the later ligands in the Suzuki-Miyaura cross-coupling reaction in aqueous media.

To achieve these objectives, new ligands and neutral, cationic as well as anionic palladium complexes have been synthesised. New alternative synthetic protocols have been developed to: 1) introduce the -OMe group on the P-aryl

rings of known and new diphosphine ligands, 2) synthesise new phosphine sulfonated ligands.

Catalytic reactions are carried out in different media as well as high pressure NMR experiments in an attempt to better understand the beneficial effect of *o*-methoxy groups and the less well known mechanism of the non-alternating copolymerisation of CO and ethene.

Chapter 1 covers the basic literature and most recent development in the alternating copolymerisation of carbon monoxide and ethene, non-alternating copolymerisation of carbon monoxide and ethene and Suzuki-Miyaura cross-coupling reaction.

Chapter 2 discusses the effect of the *o*-methoxy group on the alternating copolymerisation reaction of carbon monoxide and ethene. Diphosphine ligands 1,2-bis(di(2-methoxyphenyl)phosphino)ethane, 1,3-bis(di(2-methoxyphenyl)phosphino)propane are synthesised by an alternative synthetic protocol. Both ligands and their phenyl counterparts for comparative purpose, are used to synthesise neutral and cationic palladium(II) complexes. The complexes are used to catalyse the CO-ethene copolymerisation reaction in either protic or aprotic solvents. *In situ* and *operando* high-pressure NMR experiments provide valuable information on catalysis resting states and intermediates. In addition, important steps in the CO/ethene copolymerisation reaction are studied by *in situ* high-pressure NMR spectroscopy, which helps rationalise the effect of the *o*-methoxy group.

In *Chapter 3*, the new diphosphine (*o*-MeO-bdpp) *rac*-2,4-bis(di(2-methoxyphenyl)phosphino)pentane is synthesised. This ligand is used to synthesise new neutral palladium(II) complexes. The ligand and complexes are fully characterised in solution by multinuclear NMR spectroscopy. This C₂-

bridged ligand is compared with the C₃-bridged ligand and the more rigid ligand bis-cationic diphosphonium-diphosphine 6,7-di(di-2-methoxyphenyl)phosphinyl-2,2,4,4-tetra(di-2-methoxyphenyl)-2λ⁴,4λ⁴-diphosphoniumbicyclo[3.1.1]heptane-bis(PF₆) (o-MeO-PCP)(PF₆)₂ in the copolymerisation of CO with ethene in different reaction media in order to compare the effect of backbone rigidity.

Chaper 4 deals with the synthesis of new phosphine sulfonated ligands. The ligands are prepared through a new and sustainable synthetic route and used to synthesise new palladium(II) anionic complexes. The later anionic complexes are used in the less well known non-alternating copolymerisation reaction of carbon monoxide and ethene and compared with other phosphine sulfonate ligands that have been applied in this kind of catalysis. In addition, high pressure NMR experiments are carried out in order to go further into the mechanism of this polymerisation reaction.

Furthermore, taking advantage of the fact that the new phosphine sulfonated ligands are both water-soluble and air stable, they are successfully applied in palladium-catalysed Suzuki-Miyaura cross-coupling reactions in neat water in conjunction with microwave heating.

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