UNIVERSITY OF PÉCS

Doctoral School of Chemistry

TRANSITION METAL-CATALYSED (HYDRO)ARYLOXYCARBONYLATION REACTIONS

PhD thesis

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List of abbreviations

acac: acetylacetonate anion

BDPP: 2,4-bis(diphenylphosphino)pentane

BDPPTS: 2,4-bis[di(*m*-sodiumsulfonatophenyl)phosphino]pentane

BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene

bmim: 1-butyl-3-methylimidazolium cation

BNPPA: 1,1′-binaphthyl-2,2′-diyl-hydrogenphosphate

CBDTS: 1,2-bis[di(*m*-sodiumsulfonatophenyl)phosphinomethyl]cyclobutane

COD: 1,5-cyclooctadiene

dba: *trans*,*trans*-dibenzylideneacetone

DBP: 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(dibenzophospholyl)butane

DBU: 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine

de: diastereomeric excess

diglyme: bis(2-methoxyethyl) ether

DIOP: 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

DIPAMP: 1,2-bis[(2-methoxyphenyl)(phenylphosphino)]ethane

DIPEA: diisopropylethylamine

dippp: 1,3-bis(diisopropylphosphino)propane

DMC: dimethyl carbonate

DMF: dimethylformamide

DM-SEGPHOS: 5,5′−bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole

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

dppb 1,4-bis(diphenylphosphino)butane

dppbts: 1,4-bis[di(*m*-sodiumsulfonatophenyl)phosphino]butane

dppf: 1,1′-bis(diphenylphosphino)ferrocene

dppp: 1,3-bis(diphenylphosphino)propane

dpppts: 1,3-bis[di(*m*-sodiumsulfonatophenyl)phosphino]propane

DTBM-SEGPHOS: 5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole

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

ee.: enantiomeric excess

H_2BCOS: *trans*-2,3-bis(mercaptomethyl)-bicyclo[2.2.2]-octane

ILs: ionic liquids

MeO-BIPHEP: -2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl

MMA: methyl methacrylate

nbd: norbornadiene

NMDPP: neomenthyldiphenylphosphine

NSAIDs: nonsteroidal anti-inflammatory drugs

NTf_2^-: bis(trifluoromethanesulfonyl)imide anion

OAc^-: acetate anion

PAMAM: polyaminoamido.dendrimer

PCy_3: tricyclohexylphosphine

Phanephos: 4,12-bis(diphenylphosphino)-[2.2]-paracyclophane

Ph-BPE: 1,2-bis[2,5-diphenylphospholano]ethane

PTSA (TsOH): *para*-toluenesulfonic acid

SEGPHOS: 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole

THF: tetrahydrofuran

TOF: turnover frequency

TPP: triphenylphosphine

TPPTS: triphenylphosphine trisulfonate (tris(*m*-sodiumsulfonatophenyl)phosphine)

T_{rev}: reversal temperature

XANTPHOS: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

σ_{para}: Hammett constants

1. Introduction

1.1. General consideration

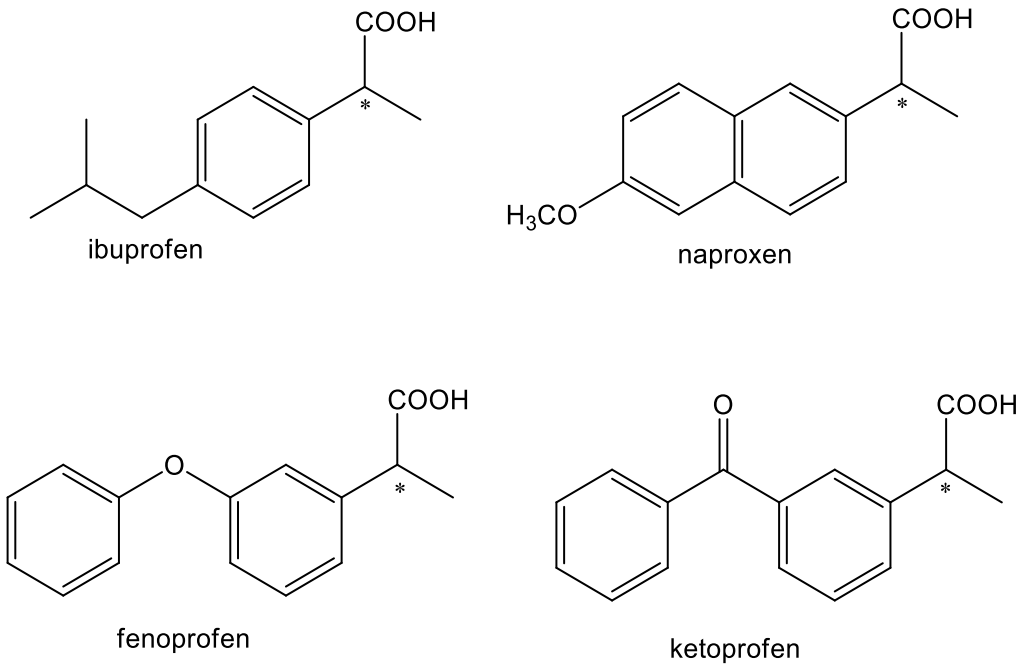
Catalysis introduces a fundamental and crucial basis for both academic and industrial sectors. Fine and bulk chemicals productions are enriched by the involvement of both homogeneous and heterogeneous catalysis. Starting from eighties, the number of homogeneously catalysed reactions has been growing steadily.

When the catalyst systems, the substrates and the required components to perform a chemical reaction are brought together into one phase, most often the liquid phase, then the expression "homogeneous catalysis" is applied. Transition metal-containing compounds which are applicable for homogeneously catalysed reactions could be either organometallic or non-organometallic compounds. An advantage for using transition metal-containing compounds as catalysts is that they can be tuned by changing the ligand environment. Accordingly, several catalytic systems can be obtained.

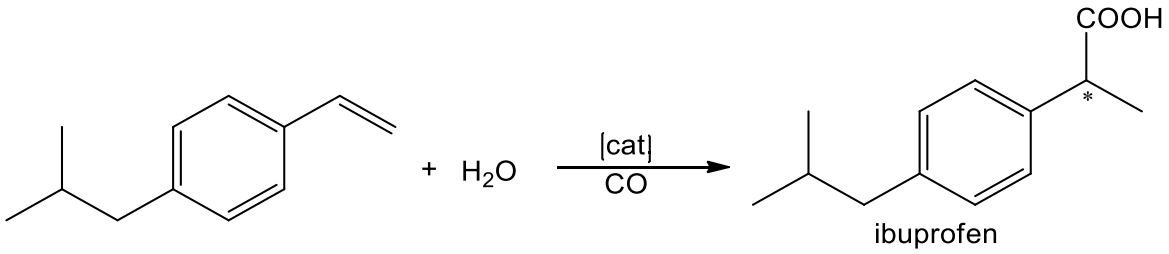
A very important class of compounds in organic chemistry is that the one which contains carbonyl groups in their structures such as aldehydes, ketones, carboxylic acids and their corresponding derivatives like esters, amides, acid anhydrides and acid chlorides. Fortunately, the aforementioned compound classes can be prepared according to homogeneous catalysis approach, specifically, by conducting carbonylation reactions which incorporated in the introduction of at least one CO group to the structure of reacted substrates [1]. Hence the carbonylation reactions are of great importance due to their utilization in the synthesis of carbonyl moiety-containing organic compounds [2-4]. The preparation of various compounds containing CO moiety under carbonylation reaction conditions makes this reaction to be considered as an elegant synthetic pathway.

The production of fine chemicals from olefins using carbonylation reaction approach is of great importance [5]. Additionally, the preparation of optically active compounds that can serve as intermediates or building blocks in pharmaceutical industry can be afforded and introduced by carbonylation reaction of unsaturated olefins [1]. For example, when the substrate 4-isobutylstyrene is treated with carbon monoxide and water, the product that is achieved under carbonylation process is 2-(4-isobutylphenyl)propanoic acid (commonly named ibuprofen), a very important nonsteroidal anti-inflammatory drug (NSAID). Related drugs such as naproxen, ketoprofen and fenoprofen can be prepared by the same synthetic approach [6]. The structure of these drugs and the general equation for the formation of one of these derivatives, ibuprofen, can be seen in *Scheme 1* and *2*, respectively.

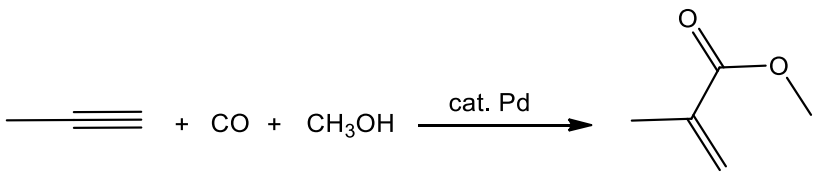
Esterification is a very important and fundamental transformation as it provides the formation of esters which can be found widely in fragrances, flavours, natural products, polymers as well as fine chemicals [7]. Methyl methacrylate (MMA) is a fundamental precursor in homopolymerization process. This monomer can be afforded by carbonylation reaction of propyne and a palladium-containing catalyst system [8] as shown in *Scheme 3*.



Scheme 1. Examples of biologically important drugs



Scheme 2. Formation of ibuprofen by carbonylation reaction



Scheme 3. Production of MMA by carbonylation reaction of propyne

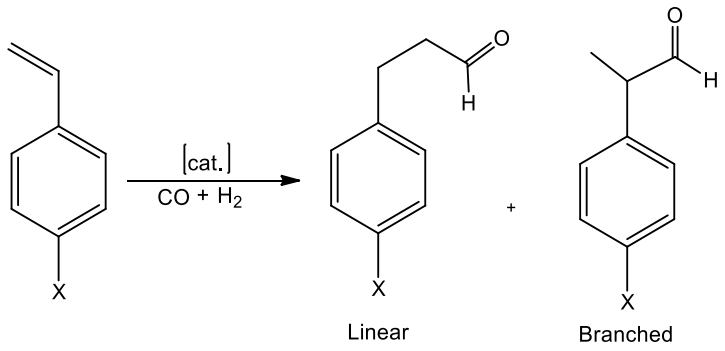
The state of the art provides several examples about the importance of carbonylated compounds formation. Hence, our interests in studying carbonylation reactions and producing carbonylated compound derivatives seems to be realistic.

1.2. Carbonylation reaction types
1.2.1. Hydroformylation reaction

A major category of carbonyl moiety-containing compounds which can be generated and produced by carbonylation reaction is that of the aldehydes. When both H_2 and CO gases are applied to a substrate such as an alkene, the result is the formal addition of H-CHO bond to that alkene. Hence, the process can be named as hydroformylation reaction and aldehydes are obtained as the target compounds.

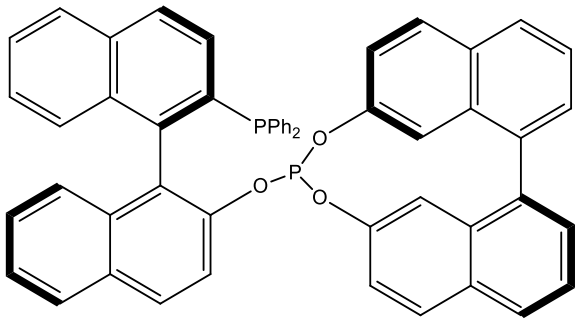
The hydroformylation reaction of alkenes (oxo synthesis) has gained much interest in two fields. The first one is the production of *n*-butyraldehyde (linear regioisomer) - considered to be very important for industry sector- which can be obtained from the hydroformylation reaction of propene by using Rh- or Co-containing catalysts [9-13].

The second field is the synthesis of optically active 2-arylpropanals from the hydroformylation reaction of vinyl aromatics by Pt- and Rh-containing catalysts. 2-Arylpropanals are important intermediates for the selective preparation of NSAIDs [14-20]. Actually, the direct route for the NSAIDs preparation is often not easy because it involves the addition of water as a reactant (generally catalytic systems are affected by water) hence, a careful selection of the catalytic systems is a demand. Besides the separation of the active catalysts from the crude mixture in these cases sometimes is difficult especially in industry sector [21]. The preparation of 2-arylpropanals is regarded as an effective and alternative solution to avoid and overcome these difficulties. It is worth noting that hydroformylation reaction of vinyl aromatics resulted in the production of both linear and branched regioisomers as can be seen in *Scheme 4*.



Scheme 4. Hydroformylation of vinyl aromatics

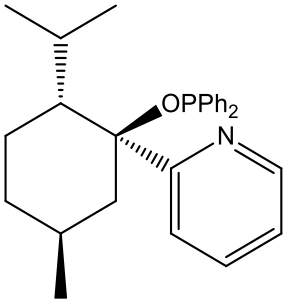
Rh-catalysed hydroformylation reactions of olefins has attracted much interest among other transition metal systems after the major breakthroughs achieved by Takaya and Union Carbide which introduced and applied diphosphorous ligands in the catalytic system such as phosphine-phosphinite (two P-C and one P-O bond) and diphosphite ligands, respectively [22, 23]. For instance, Rh-system containing an outstanding ligand (*Scheme 5*) was utilised in the hydroformylation reaction of substituted styrenes which showed to afford enantiomeric excess up to 95% for the branched isomer. Besides 99% conversion for styrene substrates were achieved and the ratio of the branched: linear aldehydes obtained from the reaction was up to 86: 14 when substrate to catalyst ratios were 300-2000: 1 [24]. This catalyst was patented widely in 1994.



Scheme 5. BINAPHOS ligand used in hydroformylation of vinyl aromatics

Soon later Union Carbide reported the hydroformylation of styrene compound using diphosphite ligand. The reaction was carried out under moderate conditions; room temperature and 35 atm *syngas* pressure [24]. Toluene was used as a solvent and 4:1 ratio of ligand to catalyst was applied. The reaction resulted in 90% ee for the branched aldehyde and 98:2 ratio of branched: linear aldehyde regioisomers.

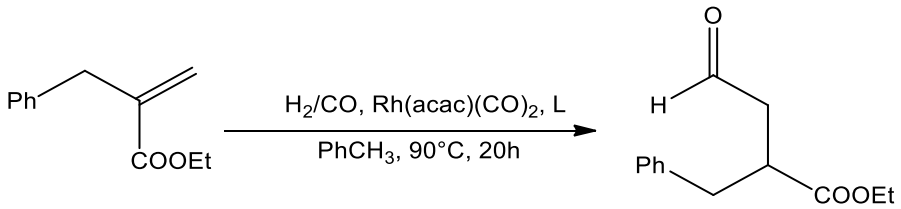
After the great results given by Rh-catalysed hydroformylation of styrenes based on phosphine-phosphite, phosphine-phosphonite and phosphine-phosphinite ligands, several modified ligands of the basic structure of the previous types of ligands were introduced. Among the various types of these ligands, chiral P-N types were studied and were very promising (*Scheme 6)*. For instance, exclusive formation of the branched aldehyde and full conversion of the substrate were noticed from the hydroformylation reaction of vinyl naphthalene substrate using Rh catalyst. Additionally, 78% ee for the formation of the (*R*) enantiomer of the branched isomer was observed.



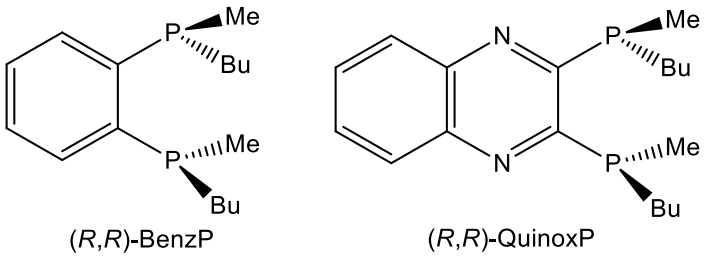
Scheme 6. P-N ligand used in the hydroformylation of vinyl naphthalene

In another report, the aforementioned ligand, (*R,S*)-BINAPHOS, was utilized to prepare the *in situ* Rh(acac)(BINAPHOS) complex by the reaction of the precursor $Rh(acac)(CO)_2$ and the chiral ligand in dichloromethane. The Rh(I) complex was used for carrying out asymmetric hydroformylation experiments for substituted styrenes in benzene solvent [25]. Several substitutions were used in this study such as methyl, isobutyl, chloro and methoxy. Actually, very high ee-s were obtained for the branched aldehyde and were in the range between 88-95%. The substrates' conversion values and the chemoselectivity towards both isomers also showed to be very high and were greater than 99%. The branched: linear isomer ratio was (86-88): (12-14) for the studied substitutions. In these experiments no formation for either hydrogenated products or polymerized compounds was observed. Besides, it was shown that the previous catalytic system prepared *in situ*, Rh(acac)(BINAPHOS), comprised a very effective species to hydroformylate not only monosubstituted alkenes such as the previously-mentioned styrenes, but rather 1,2-disubstituted alkenes such as (*E*)-2-butene and (*E*)-3-hexene [26].

Buchwald group reported Rh-catalysed hydroformylation of 1,1-disubstituted olefins. According to the report, enantioenriched aldehydes preparation by using *P*-chirogenic phosphine ligands like BenzP and QuinoxP ligands were afforded (*Scheme 7* and *8*) [27]. Using ethyl 2-benzylacrylate and corresponding derivatives will lead to the formation of the *β*-chirality of the linear aldehyde in high enantioselectivities as well as good regioselectivites.

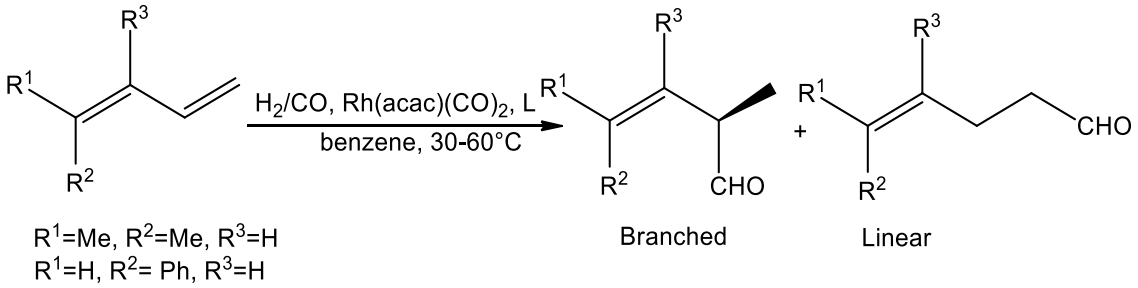


Scheme 7. Hydroformylation of a 1,1-disubstituted olefin



Scheme 8. *P*-chirogenic phosphine ligands used in hydroformylation reaction of olefins

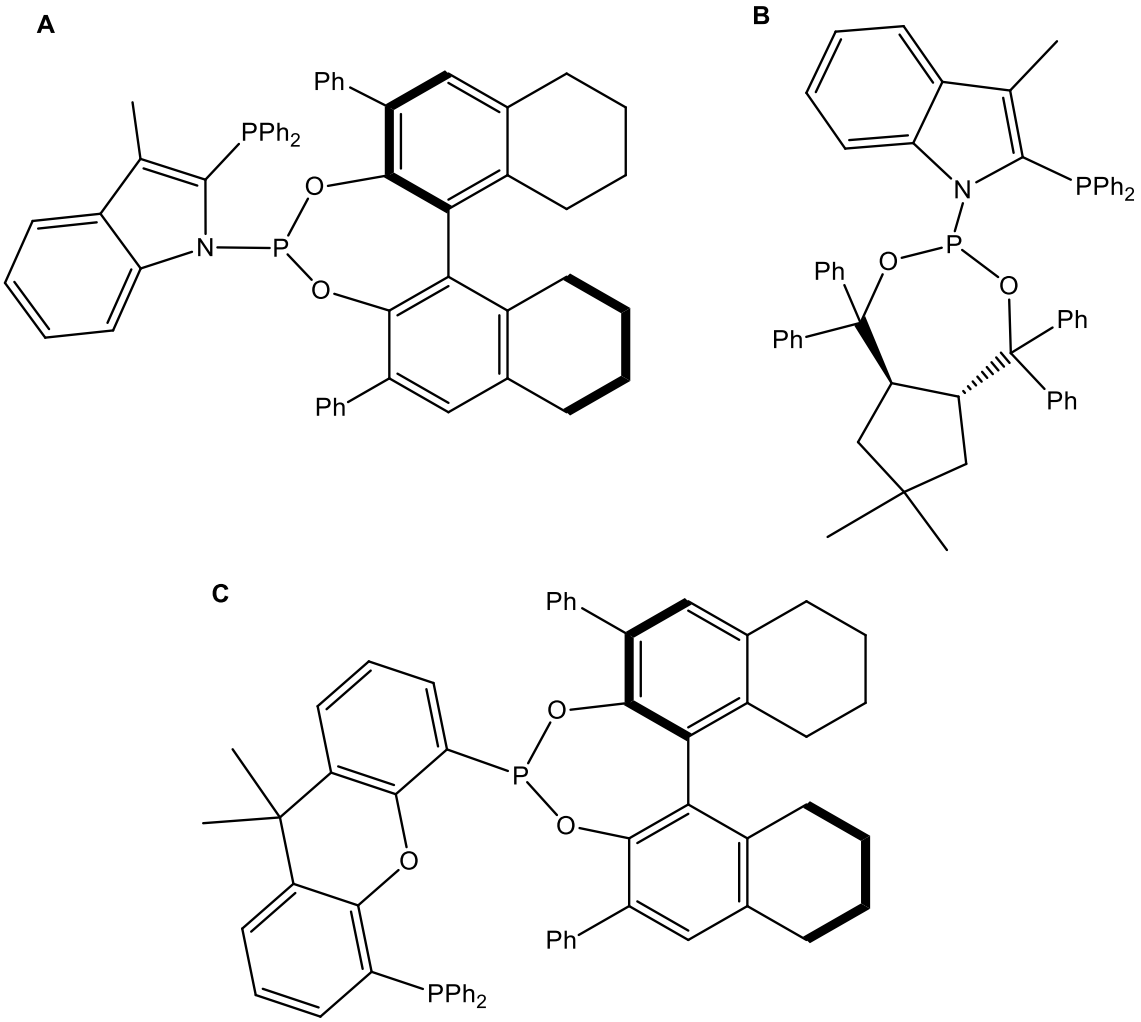
Hydroformylation of conjugated 1,3-dienes such as 1-vinylcyclohexene, 4-methyl-1,3-pentadiene and (*E*)-1-phenyl-1,3-butadiene by Rh catalyst system, more precisely the *in situ* generated Rh-BINAPHOS complex, resulted in the formation of *β,γ*-unsaturated aldehydes as the major products (*Scheme 9*). High enantio- and regioselectivities (toward branched aldehydes) of 80-97% and 78-94% were obtained, respectively [28]. It should be stated that the hydroformylated products which were formed according to this catalytic system were derived from the addition of H-CHO bond to the lowest substituted alkene moiety (terminal alkene group).



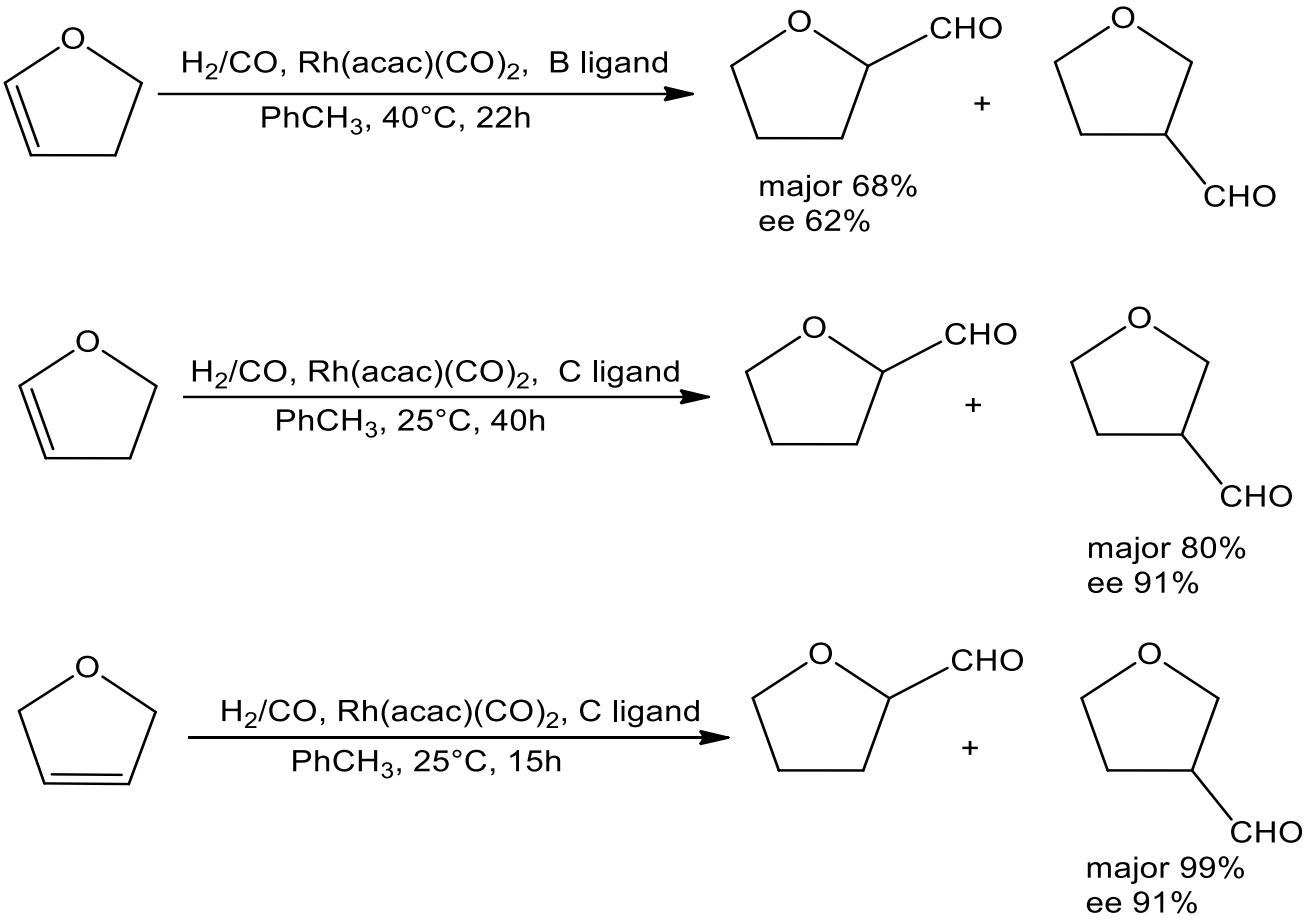
Scheme 9. Branched *β,γ*-unsaturated aldehyde and linear aldehyde formation from hydroformylation of conjugated dienes

Hybrid diphosphorus ligands and $Rh(acac)(CO)_2$ precursor were used as the catalytic systems to carry out highly selective asymmetric hydroformylation of heterocyclic olefins (*Scheme 10*) [29]. Treatment of phosphine-phosphoramidite ligands (phosphorus indole-based ligand), PP, Rh precursor and *syngas* at the selected reaction conditions will afford the *in situ* generated $Rh(CO)_2(H)(PP)$ catalyst, which in turn was reactive to catalyse the asymmetric hydroformylation of 2,3-dihydrofuran (*Scheme 11*). The 2-carbaldehyde as the major regioisomer was obtained with up to 68% yield and good ee up to 62%. In the contrary, the regioselectivity has been switched towards 3-carbaldehyde as the major isomer in the asymmetric hydroformylation upon the treatment of the same substrate with the catalytic complex prepared *in situ* from phosphine-phosphonite ligand (phosphorus xanthene-based ligand) and Rh precursor. The yield and the ee that were obtained for the 3-carbaldehyde were

80% and 91%, respectively. However, when the former ligand (phosphorus xanthene-based ligand) was applied to hydroformylate 2,5-dihydrofuran substrate under the selected reaction conditions, it was found that a complete regioselectivity for the 3-carbaldehyde isomer was achieved.



Scheme 10. Hybrid ligands used in hydroformylation of heterocyclic olefins

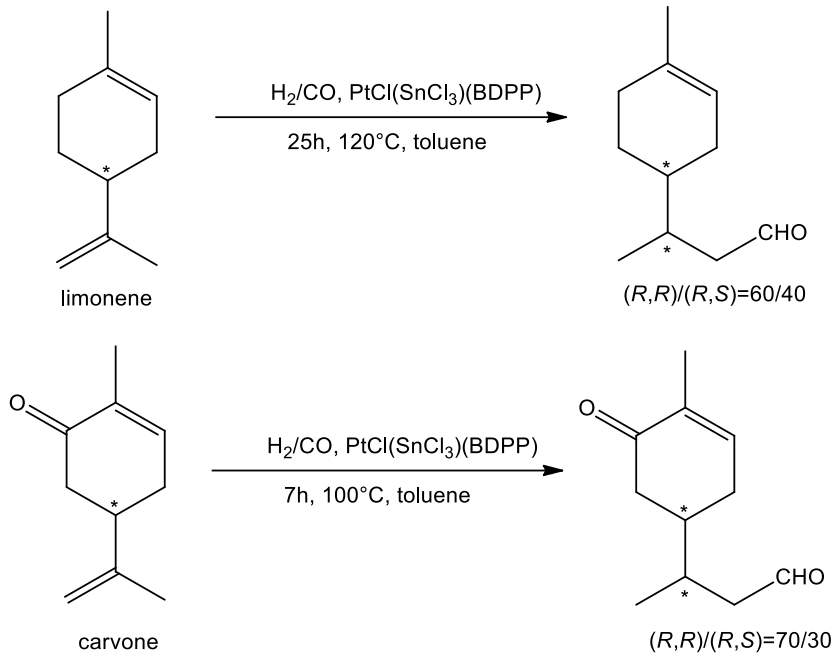


Scheme 11. Asymmetric hydroformylation of dihydrofuran isomers

(+)-*trans*-2,3-Bis(mercaptomethyl)-bicyclo[2.2.2]-octane ligand, (+)-H_2BCOS, was synthesised [30] and exploited with conjunction of Rh precursor, [Rh(μ-OMe)(COD)]$_2$ (COD= 1,5-cyclooctadiene), to prepare the complex [Rh_2(μ-BCOS)$(COD)_2]_2$. The tetranuclear complex and a chiral ligand like (+)-BDPP, (+)-(*2R,4R*)-2,4-bis(diphenylphosphino)pentane, were combined together to conduct the asymmetric hydroformylation of styrene. The catalyst system was very selective to aldehyde production with more than 99% and the branched aldehyde formed in a very high selectivity with 95%. Moreover, the reaction provided good enantioselectivity with 55% for (*S*)-2-phenylpropanal.

The well-known $PtCl_2$-diphosphine-$SnCl_2$ system was utilised to conduct the asymmetric hydroformylation of unsaturated terpenes [31]. Initially, $PtCl_2$(diphosphine) complex was prepared by the reaction of $PtCl_2(PhCN)_2$ with the corresponding diphosphine ligand, then mixing of $PtCl_2$(diphosphine) complex with $SnCl_2$ will be established to afford the *in situ* generated species, $PtCl(SnCl_3)$(diphosphine), which will be used to carry out the hydroformylation process. For instance, Kollár and his group reported the asymmetric hydroformylation of terpenes such as (+)-(*R*)-limonene and (-)-(*R*)-carvone by applying the *in*

situ generated PtCl($SnCl_3$)(BDPP) as the catalytic system (*Scheme 12)* [31]. In this report, the exclusive formation of the linear aldehyde was obtained and considered as a main feature. An additional feature can be noticed for the hydroformylation reaction of terpenes using the former system is that the internal double bond remained intact during the reaction for both substrates. In case of carvone the carbonyl moiety did not react and remained intact as well. 0.1 mmol of Pt precursor and a ratio of 1: 2000 for Pt: substrate were used to carry out the hydroformylation reaction. It is worth noting that the diastereomeric ratio for both isomers formed in each case may be reversed.



Scheme 12. Hydroformylation of unsaturated terpenes; (*R*)-limonene and (*R*)-carvone

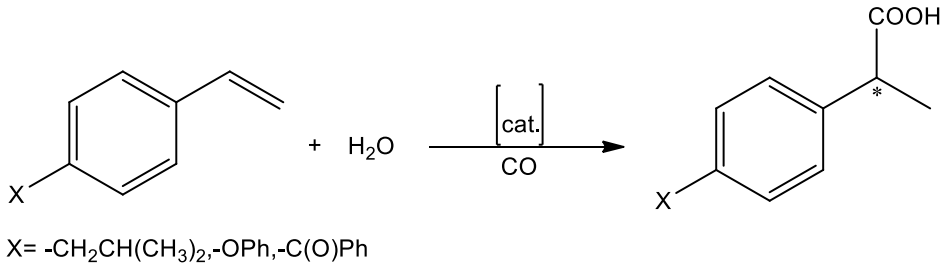
In 2014 Kégl *et al* studied the asymmetric hydroformylation of *para*-substituted styrenes by applying the *in situ* prepared catalyst [PtCl($SnCl_3$)((2*S*,4*S*)-(BDPP))] [32]. The group demonstrated that the afforded enantioselectivity of the produced chiral 2-arylpropanals was affected by the reaction temperature. In this context, it was found that preferred (*R*) enantiomers formation was noticed at high temperatures, while preferred (*S*) isomers formation was observed at low temperatures. Moreover, a correlation between the electronic property of the *para*-substituents of styrene and the reversal temperature, T_{rev} (the temperature at which a racemic mixture is existing for the branched aldehyde), was observed. It was found that the stronger the electron withdrawing group is, the higher the reversal temperature is. On the other hand, as the electron donating group properties of the substituents increased, the reversal temperature decreased. The strong dependence between the electronic properties of styrene

substituents and the corresponding reversal temperatures can be clearly derived from the observed linear correlation between Hammett constants (σ_{para}) and the practically determined reversal temperatures of the enantioselectivity of 2-arylpropanals. The study manifested that (*R*)-2-arylpropanals predominated when the temperature of the reaction was above its reversal temperature. However, (*S*)-2-arylpropanals predominated when the temperature of the reaction is below its reversal temperature. 5-21% of (*R*)-2-arylpropanals were produced in the asymmetric hydroformylation of the 4-substituted styrenes, while 32-65% of (*S*)-2-arylpropanals were produced from the same styrenes hydroformylation at $T>T_{rev}$ and $T<T_{rev}$, respectively. The substituents used in this study were: H, Me, OMe, F, Cl and CF_3.

1.2.2. Hydrocarboxylation reaction

Another useful approach of carbonylation reaction which can be established by transition metal catalysis is the process that is called hydrocarboxylation. Carboxylic acids are the target compounds of this reaction. Alkenes for example, can be hydrocarboxylated in the presence of CO source and H_2O. The use of water for carboxylic acid synthesis seems to be an elegant synthetic procedure due to the highly desired environmental and economical perspectives [33, 34].

In addition to the former advantages, hydrocarboxylation reaction has gained much more interest as it provides a direct synthetic route for the NSAIDs derivatives preparation (*Scheme 13)*.

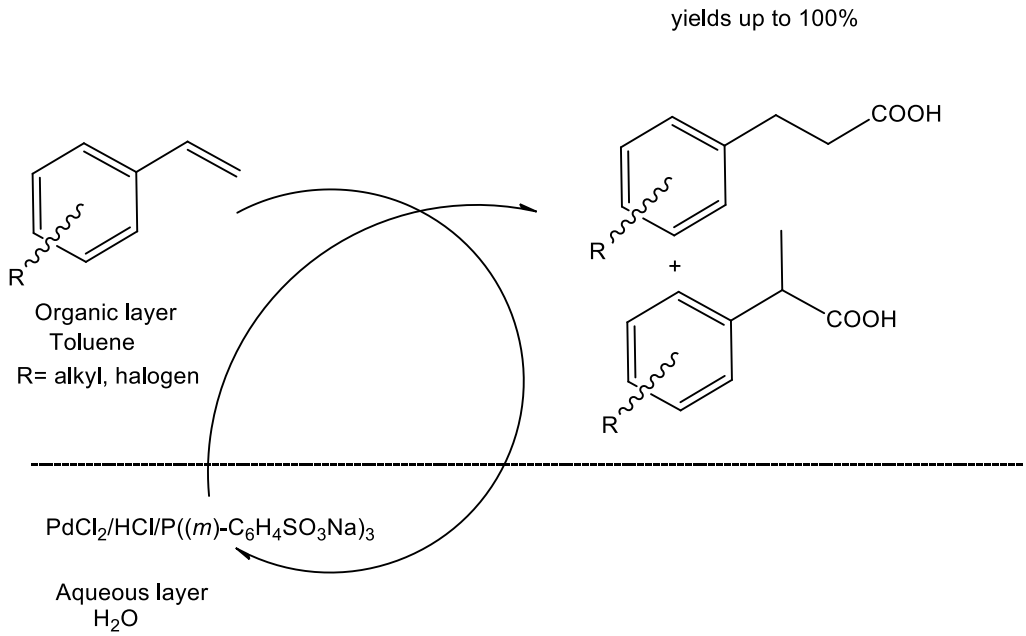


Scheme 13. Hydrocarboxylation for NSAIDs production

Different catalytic systems were described and reported concerning the hydrocarboxylation process of alkenes. The most widely used systems for hydrocarboxylation reaction of olefins can be generated from palladium precursors and phosphorous-containing ligands as well as the addition of Brønsted acids of different strengths in some cases [35-39].

A very high regioselectivity towards the branched carboxylic acid, α-(4-methylphenyl) propanoic acid was achieved via the hydrocarboxylation of 4-methylstyrene by applying $PdCl_2$-$CuCl_2$-PPh_3 system [37]. Several parameters and conditions were studied and optimised to accomplish that regioselectivity. It is important to elaborate some of these parameters and conditions to understand such kind of catalytical systems. For instance, the addition of mineral acids was investigated and it was found that HCl addition provided the best substrate conversion and branched acid regioselectivity. It was thought that it was the proton effect, however, HNO_3 and HF were tested as well and they participated in stopping the reaction progress. Hence, it might be the role of the counter anion which is responsible for observing such results. To confirm this hypothesis the catalyst system was tested in the absence of HCl and only 55% of substrate conversion was noticed. The addition of a Cl^- source like $N(C_4H_9)_4Cl$ instead of HCl provided the same 100% conversion obtained in case of HCl addition. It is believed that Cl^- anion can serve as a ligand to stabilise Pd(II) species [40]. A second factor that was studied is the addition of O_2, that is, the addition of 3 bar of oxygen decreased the conversion to 24%. In contrast to this observation, Alper and co-workers reported the use of O_2 as a promotor in hydrocarboxylation of olefins using $PdCl_2$-$CuCl_2$-HCl system [41-45]. The reduction of the conversion after applying O_2 can be explained by two views. The first one is that $PdCl_2$-$CuCl_2$ is well known for the oxidation of CO to CO_2 [46-48]. This can be confirmed by the high drop of the pressure noticed upon the addition of O_2 during the early stage of the reaction. The second view is that O_2 as an oxidizing agent can oxidise PPh_3 to form the inactive phosphine oxide ($P(O)Ph_3$) [49]. PPh_3 is one of the major components of the catalyst system as it is used to stabilise the molecular zero valent species and retard the formation of Pd particles [49]. The $CuCl_2$ as a promoter found to maintain the role of the active species in the catalytic cycle by reoxidizing Pd(0) to Pd(II) species. Various solvents were tested in this study; THF and methylethylketone gave good results, in the contrary non polar solvents like toluene, hexane and diethylether were not effective. The amount of applied water was also studied and the conversion showed a maximum as the ratio of water: substrate increased up to 10 and then decreased very rapidly as the ratio increased above 10. The study done by Fenton [50] revealed that at high water levels a two-phase system would exist, consequently, water concentration in the organic phase which contain the olefin substrate will be reduced and lowered substrate conversion would be noticed. A final condition in this report was the effect of temperature. It was noticed that increasing temperature of the reaction resulted in increasing both regioselectivity as well as the substrate conversion.

Using water as a solvent in the hydrocarboxylation reaction is of great importance [51]. For instance, the catalyst consisting the combination of $PdCl_2$ and triphenylphosphine trisulfonate (TPPTS), a water-soluble ligand, was used with Brønsted acid as a promotor to catalyse hydrocarboxylation reaction of styrene derivatives in the presence of water-toluene as a solvent mixture (*Scheme 14)* [21]. The typical experiment was to combine both aqueous and organic layers in an autoclave and conduct the hydrocarboxylation reaction at 100 °C under a pressure of 40 atm CO gas. In this experiment the organic layer composed of toluene and substrate, while the precursor and the ligand were soluble in the aqueous layer. The novelty of using biphasic system is the easy separation of carboxylic acid products because of their tendency to be solved in organic layers. After decanting the organic layer, the aqueous layer can be washed with toluene and then combined with another batch of organic layer that consists of dissolved substrate. This procedure can be repeated several times and the term recycling experiments is used to describe such a process. Regarding this study up to five recycling experiments were done without any observation of catalytic activity drop. These results suggested that Pd catalyst leaching into the organic phase under the experimental conditions was not occurring.



Scheme 14. Biphasic system for hydrocarboxylation reaction of styrenes based on TPPTS ligand

In this report a correlation between hydrocarboxylation reaction rates and substrates solubility in water was found. For example, styrene and 4-acetoxystyrene showed the highest activity while 4-trifluoromethylstyrene showed lower activity than styrene since its solubility in water

is 14 times less. To achieve higher activity for 4-trifluoromethylstyrene substrate, very long reaction time was required.

Other studies for the hydrocarboxylation reaction of vinyl arenes were conducted in the presence of Pd precursor and diphosphine chelate ligands. In particular, $Pd(OAc)_2$ precursor and water-soluble sulfonated diphosphine ligands were utilised to perform the hydrocarboxylation reaction for styrene derivatives [52, 53]. Four different chelated diphosphine ligands, dpppts (1,3-bis[di(*m*-sodiumsulfonatophenyl)phosphino]propane), dppbts (1,4-bis[di(*m*-sodiumsulfonatophenyl)phosphino]butane), (*S*,*S*)-BDPPTS (2,4-bis[di(*m*-sodiumsulfonatophenyl)phosphino]pentane) and (*R*,*R*)-CBDTS (1,2-bis[di(*m*-sodiumsulfonatophenyl)phosphinomethyl]cyclobutane), were efficient in this study without the addition of a promotor acid. In order to study the optical yield of the prepared branched carboxylic acids, chiral diphosphine ligands were investigated like (*S*,*S*)-BDPPTS and (*R*,*R*)-CBDTS. Three substrates were tested for the hydrocarboxylation process, styrene, *para*-methoxystyrene and *para*-fluorostyrene, and the formation of both linear and branched carboxylic acids were obtained in all cases. The catalytic systems were generated by the addition of the sulfonated ligand to a suspension of substrate and $Pd(OAc)_2$ in water with a ligand: Pd ratio of 2. Previous studies of hydrocarboxylation reaction of ethene [54] revealed that the use of dpppts: Pd ratio of 1 encouraged the copolymerization reaction of ethene/CO rather than the hydrocarboxylation reaction. The copolymerization reaction was inhibited by using ligand: metal ratio of 2 [54]. Hydrocarboxylation reaction of styrenes afforded total conversion to carboxylic acid isomers and gave a branched acid of 24% and 33% by using dpppts and dppbts ligands, respectively. When the chiral phosphine ligands BDPPTS and CBDTS were tested for asymmetric hydrocarboxylation reaction of vinyl arenes, it was found that the ligand CBDTS was more active than the BDPPTS and generally afforded more branched acid yields for the tested substrates. Using CBDTS/Pd system, *para*-methoxystyrene afforded the highest branched acid yield with 49%. Additionally, the highest enantioselectivity was also observed for *para*-methoxystyrene with 22% when the ligand BDPPTS was used. The range for enantioselectivity values by using CBDTS was between 10-14%. The authors of this study stated that these results explained that Pd-sulfonato diphosphine systems were active for the hydrocarboxylation reaction of styrenes in water without the addition of a Brønsted acid, as only two hours are required to carry out these experiments and very high carboxylic acid yields were obtained. Recycling experiments for the hydrocarboxylation reaction of styrene were tested by extracting the aqueous layer with diethyl ether and feed the aqueous layer with an additional amount of styrene substrate and re-establish the reaction. However, a loss of the

catalytic activity for the catalyst was noticed and only 60% conversion for styrene after 16 h was observed.

1.2.3. (Hydro)alkoxycarbonylation and (hydro)aryloxycarbonylation reaction

A third general category of hydrocarbonylation reaction is hydroalkoxycarbonylation reaction, can also be called hydroesterification, which is the process that involves the preparation of esters by carbonylation reaction strategy. Actually, the esterification process via carbonylation reaction has emerged after the outstanding work of Reppe's research group on the carbonylation of acetylene in the presence of water to synthesize acrylic acid. Replacing water with alcohols seemed realistic after this work, consequently, a lot of unsaturated substrates like alkenes and alkynes have been tested and successfully transformed to their corresponding alkyl esters via this protocol [55-57].

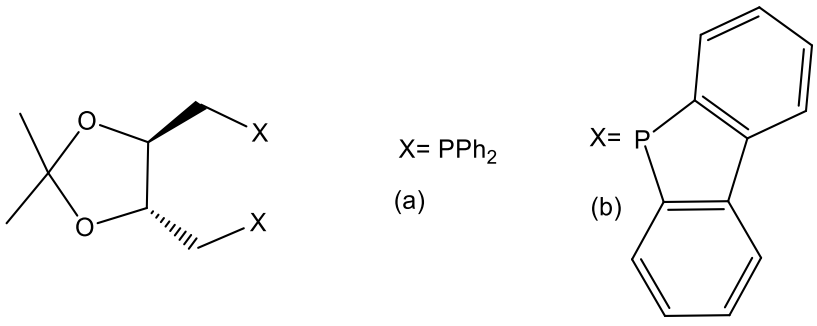
Basically, hydroalkoxycarbonylation reaction requires the presence of unsaturated substrates, alcohol nucleophiles, catalyst systems and carbonylating agents. The catalyst systems could be derived either from 'preformed' transition metal complexes as precursors, or *in situ* systems prepared from a transition metal complex and the appropriate ligand(s). Among different systems, Pd systems can be counted as the best regarding conversion, regioselectivity, chemoselectivity and stereoselectivity [55-57].

In fact, several reports are dealing with carbonylation reactions of vinyl arenes as substrates as they receive much more attention since their carbonylated products, especially the branched isomers of esters or carboxylic acids, are possessing chiral centres which can be counted as useful chiral building blocks for subsequent reactions, gained high attention [56]. The direct synthesis of 2-arylpropanoic acid derivatives which can be considered as a class of non-steroidal anti-inflammatory drugs is often not easy because it involves the addition of water as a reactant and or solvent in some cases, hence a careful selection of the catalyst systems is a demand.

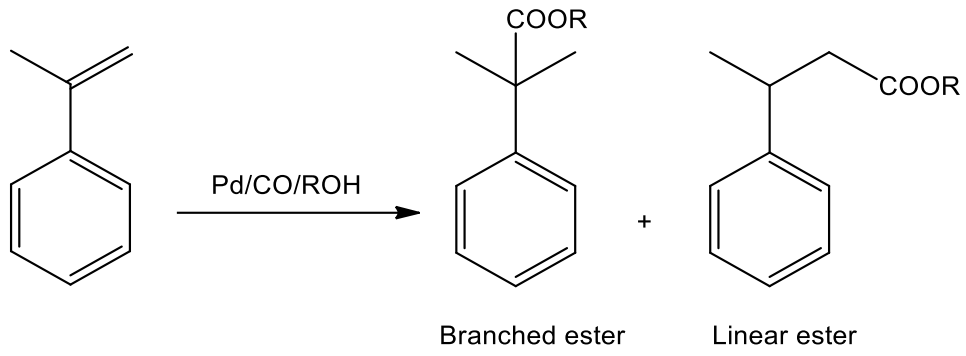
In general, for hydroalkoxycarbonylation reaction of vinyl arenes, the use of monodentate phosphine ligands with Pd precursors favours the formation of the branched alkyl 2-arylpropanoates, while the linear alkyl 3-arylpropanoates are favoured upon using the bidentate phosphine ligands.

Different factors and conditions may affect the chemo-, regio-, and stereoselectivity of hydroalkoxycarbonylation reactions. The substrate 2-phenylpropene (α-methylstyrene) can be taken as an example to study the effect of some tested parameters [58]. For instance, in this

study chiral diphosphine ligands were used to study the asymmetric induction in the formation of the chiral linear ester (alkyl 3-phenylbutanoate), however the branched ester (alkyl 2-phenyl-2-methylpropanoate) which formed in this case is achiral compound. $Pd(PhCN)_2Cl_2$ and two chiral diphosphine ligands (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) and (2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(dibenzophospholyl)butane) (DBP) (*Scheme 15* (a) and (b), respectively) were used to carry out the induction experiment of 2-phenylpropene (*Scheme 16*). One studied factor was CO pressure and it was shown that increasing CO pressure resulted in increasing substrate conversion, ester selectivity (chemoselectivity) and optical yield. In the contrary, the linearity of the afforded ester (regioselectivity) was lowered. It seemed that the coordination of CO to the active catalytic species would be favoured when CO pressure increased, therefore, both conversion and ester selectivity were encouraged and observed in high yields. Nevertheless, it seemed that at high CO pressure coordination of diphosphine ligands are less favoured leading to decrease the regioselectivity of the linear ester formation. Moreover, different solvents were tested in this study, some of these solvents like CH_2Cl_2 and acetone showed to enhance the ester yield. The addition of LiCl as an additive to the Pd catalyst system showed to increase both the substrate conversion as well as the ester selectivity. This might be explained in terms of preventing the aggregated reduced Pd species since halide anion can coordinate to the Pd centre and maintain the activity of the Pd species in the catalytic cycle. Despite increasing both conversion and ester selectivity in case of LiCl additive, the optical yield was lowered, due to the formation of chloro complex which has a lower ability of asymmetric induction formation compared to the chiral diphosphine ligand-containing complex. It was also found that the use of bulky bidendate ligands can improve the linearity of the ester formation.



Scheme 15. (*R*,*R*)-diphosphine ligands used in asymmetric hydroalkoxycarbonylation of 2-phenylpropene (a)= DIOP; (b)=DBP



Scheme 16. Asymmetric hydroalkoxycarbonylation reaction of 2-phenylpropene

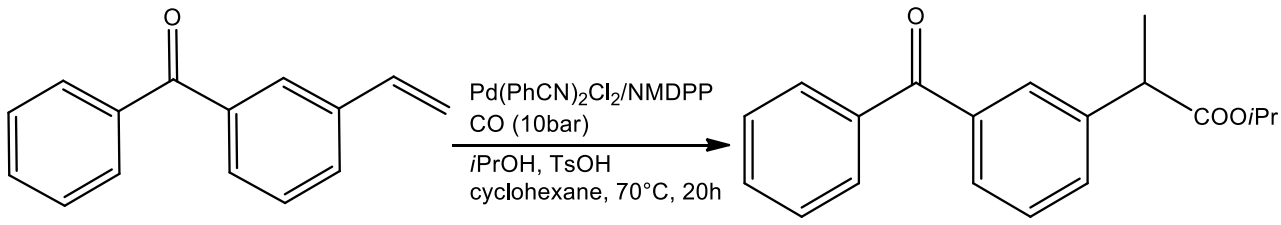
It is worth mentioning that the effect of parameters and conditions like CO pressure, solvent, ligand/metal ratio, temperature, *etc*, on chemo-, regio-, and stereoselectivity cannot be generalized for the hydroalkoxycarbonylation reactions. The study of the parameters' effect on different substrates using either different or similar catalytic systems may lead to different influence on these selectivities. In fact, literature contains numerous examples of the hydroalkoxycarbonylation reactions, so a few systems concerning olefins reaction such as vinyl arenes will be mentioned in this regard.

One system is that consisting of $PdCl_2$-$CuCl_2$-PPh_3, which provided a complete conversion of the substrate 4-methylstyrene with high regioselectivity of 97% to the branched ester under 40 bar of CO pressure when slight amount of methanol in xylene solvent was used [59]. It was found that the addition of HCl and O_2 to the catalytic system deteriorated its performance. The optimal temperature in this study was between 100-120 °C, higher temperatures increased the activity of the reaction and decreased the branched ester regioselectivity. The lowering in the branched ester selectivity was due to the favoured formation of the linear ester at elevated temperatures. Higher CO pressures afforded higher reaction activity and regioselectivity towards the branched ester. The role of $CuCl_2$ is to reoxidize Pd(0) to the active Pd(II) species thus maintaining the efficiency of the catalytic cycle. The role of PPh_3 is to coordinate Pd species and prevent the formation of the black inactive Pd(0) particles. Both $CuCl_2$ and PPh_3 addition resulted in the enhancement of the branched ester selectivity. The role of $CuCl_2$ of enhancing branched ester selectivity according to steric basis could not be understood. The addition of HCl to this system afforded an etheric product in high yields, but not any of the desired ester isomers. Generally, HCl is a beneficial promoter in the hydroalkoxycarbonylation reaction [41] since it is believed that HCl can cleave the Pd-C bond to form the final ester product and generate the active $Pd(PPh_3)_2Cl_2$ species [60], however, a harmful effect for HCl use was noticed and confirmed by report findings.

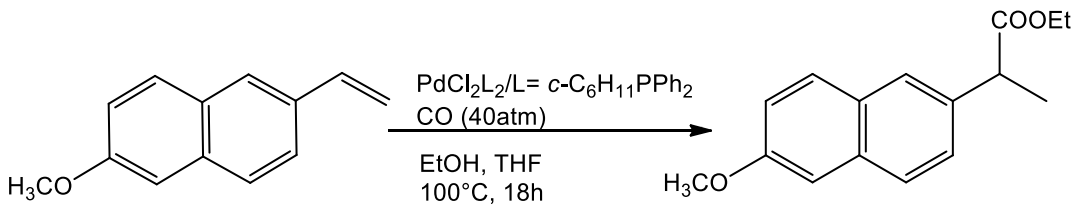
Toniolo and Cavinato employed [$PdCl_2(PPh_3)_2$] with a slight excess of PPh_3 in the hydroesterification reaction of vinyl arenes. A highly selective branched isomer formation was afforded when the reaction was performed in benzene or methyl ethyl ketone as an additional solvent at 100–110 °C and 100 bar CO [61]. The linear ester formation was afforded and dominated over the branched isomer by the addition of $SnCl_2$.

The hydromethoxycarbonylation reaction of styrene (in the presence of methanol as *O*-nucleophile) was accomplished by using the generated $Pd(PPh_3)_2$(alkene) complex (alkene= maleic anhydride, ethene or benzoquinone) at 80 °C to generate both linear and branched ester isomers. At the same temperature, the conversion of styrene was found to be 80% and a (branched: linear) ester isomers ratio of 41:59 was obtained after 90 min when Pd(maleic anhydride) complex was used. Carrying out the reaction at lower temperature, 60 °C for example, caused for the obtaining of higher selectivity towards the branched ester (63%) and lower substrate conversion [62].

Remarkable selectivity, >95%, towards the preparation of isopropyl α-arylpropanoate (ester derivative of ketoprofen) was observed by employing the catalyst system composed of $Pd(PhCN)_2Cl_2$, (+)-neomenthyldiphenylphosphine ((+)-NMDPP) and TsOH (*para*-toluenesulfonic acid) (*Scheme 17*) [63]. The hydroalkoxycarbonylation reaction was performed in cyclohexane at 70 °C and under 10 bar of CO. Interestingly, an ester derivative of naproxen was obtained in high selective preparation from 6-methoxy-2-vinylnaphthalene by using the catalyst of $PdCl_2L_2$ (L= *c*-$C_6H_{11}PPh_2$), EtOH and THF solvent (*Scheme 18*) [64]. The hydroethoxycarbonylation of the substrate was carried out at 100 °C and under 40 atm of CO.



Scheme 17. Hydroesterification of 3-vinylbenzophenone

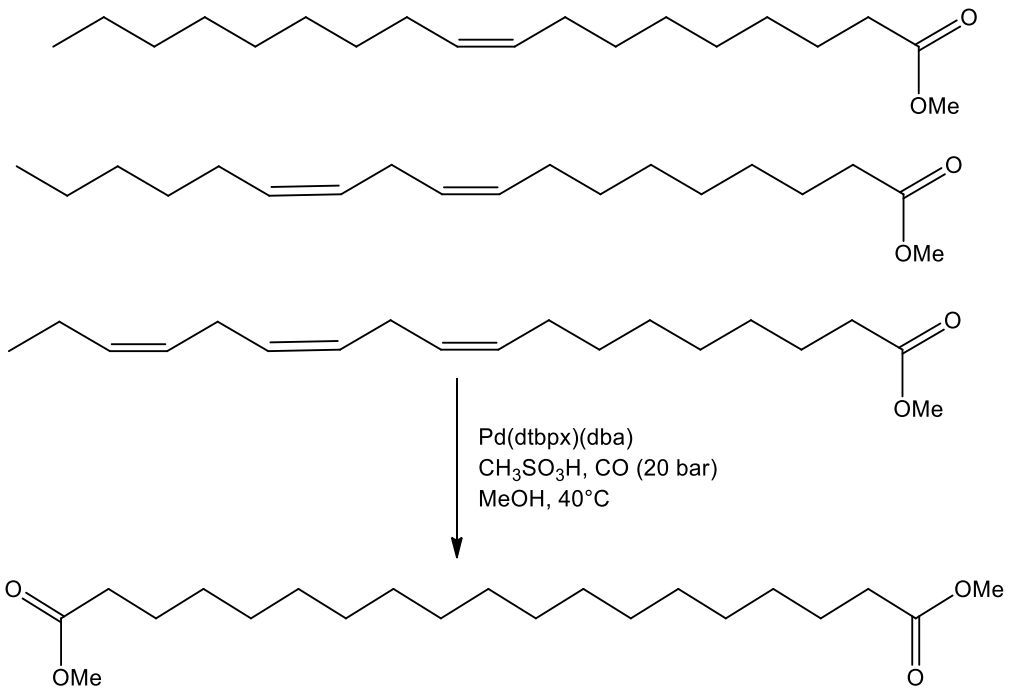


Scheme 18. Pd-catalysed hydroesterification of 6-methoxy-2-vinylnaphthalene

The branched ester formation was produced and dominated in the hydroalkoxycarbonylation reaction of styrene as van Leeuwen reported the highly selective formation of alkyl 2-phenylpropanoate from styrene carbonylation in the presence of Brønsted acid as well as the application of diphosphine-based ligand, bis[(2-diphenylphosphino)phenyl] ether (DPEphos), at 100 ℃ and under CO pressure of 70 bar [65].

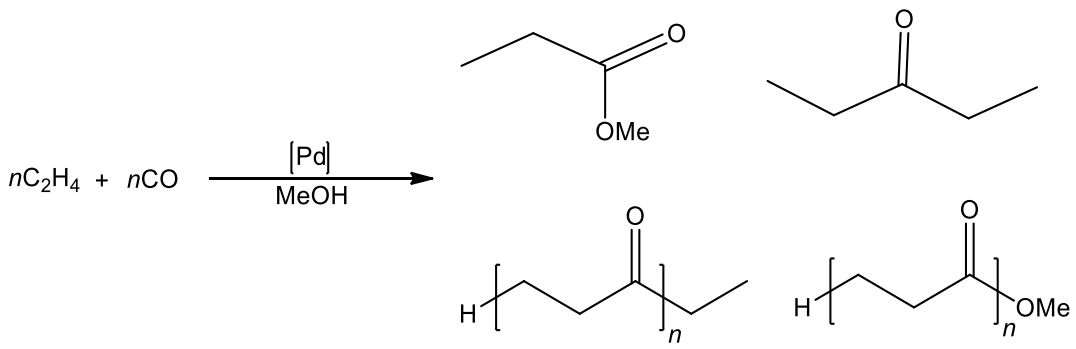
Tanaka reported the hydromethoxycarbonylation of styrenes under low CO pressure (6 bar) and room temperature by employing $Pd(OAc)_2$/dtbpx as the catalyst system, where dtbpx is 1,2-bis(di-*tert*-butylphosphinomethyl)benzene [66]. Very high chemoselectivites toward esters formation with range of 95-99% as well as high regioselectivites of 86-89% for methyl 2-phenylpropanoates were noticed when $MeSO_3H$ was used.

α,ω-Diesters with good selectivities greater than 77% were prepared by hydromethoxycarbonylation of unsaturated esters with terminal and internal double bonds by employing the catalyst system of Pd(dtbpx)(dba)/CH_3SO_3H (dba=*trans,trans*-dibenzylideneacetone) [67]. For instance, methyl linoleate, methyl linolenate and methyl oleate were transformed to dimethyl 1,19-nonadecandioate compound by hydromethoxycarbonylation reaction at 40 °C and CO pressure of 20 bar (*Scheme 19*).



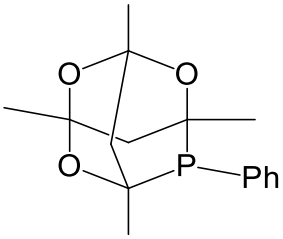
Scheme 19. Preparation of saturated α,ω-diester by hydromethoxycarbonylation of unsaturated
carboxylic acid esters

Pd-catalysed carbonylation reaction of ethene and metanol has gained much more interest in both academic and industry sector. Two pathways can be obtained for this reaction leading to the production of either methyl propanoate or the formation of oligomers and polyketones which can be generated due to the alternating copolymerization process of ethene and CO (*Scheme 20*) [68]. Methyl propanoate is very crucial compound and intermediate for the preparation of methyl methacrylate compound which in turn can be utilised to produce poly(methyl methacrylate) [69]. On the other hand, polyketones are good candidates for thermoplastics [70]. It was found that carbonylation reaction of ethene and methanol depends on the applied conditions, particularly the nature of the used phosphine ligand. For example, palladium diphosphine complexes favoured both monocarbonylation and copolymerization reaction occurrence. The application of Pd(dtbpx)(dba)/CH_3SO_3H catalyst system and very mild reaction conditions such as 10 bar of total pressure (ethene: CO= 1:1) and reaction temperature of 80 °C favoured the formation of methyl propanoate. Under these conditions methyl propanoate was prepared with >99% selectivity as well as very high production rate (TOF= 50000 h^{-1}) [71]. Very recently, the production of methyl methacrylate in large quantities has been conducted in a newly built plant via two steps. The first step involves the carbonylation reaction of ethene in methanol by applying Pd(dtbpx)(dba)/CH_3SO_3H catalyst leading to the formation of methyl propanoate compound which in turn converted to methyl methacrylate compound by the reaction with formaldehyde in the presence of a base.



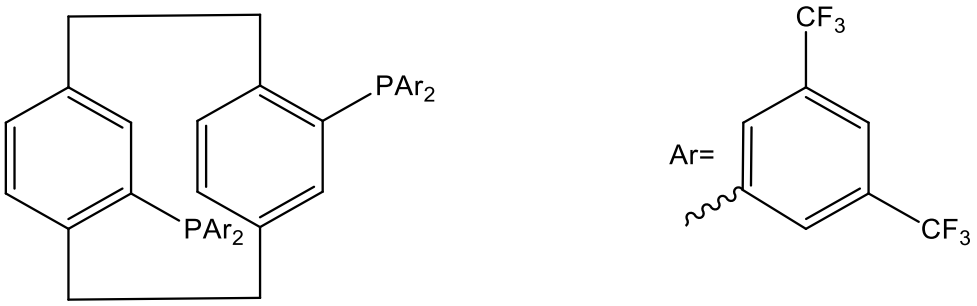
Scheme 20. Palladium-catalysed carbonylation of ethene and methanol

Styrene was hydroalkoxycarbonylated by using the catalytic species [PdCl(η^3-C_3H_5)L] complex, L= 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxo-6-phospha-adamantane (*Scheme 21*), and various alcohols such as methanol, isopropanol and *tert*-butanol in the presence of TsOH and LiCl at 80 °C and 80 bar of CO. The branched ester selectivity achieved by this system was close to 100% [72].



Scheme 21. Trioxo-adamantyl cage phosphorous-based ligand

The phanephos ligand (4,12-bis(diphenylphosphino)-[2.2]-paracyclophane) (*Scheme 22*) was used successfully in the hydromethoxycarbonylation reaction of styrene achieving very high substrate conversion (99%) at 60 °C and 22 h as well as a near complete regioselectivity towards the branched ester isomer. Besides, 79% of optical yield was also obtained for the chiral ester isomer [73, 74].



Scheme 22. Chiral phanephos bidentate ligand

Two imidazolium-based ionic liquids (ILs) were tested as solvents for the hydroalkoxycarbonylation of styrene with different alcohols at high pressure and moderate temperature (100 bar CO, 100 °C) [75]. 2-Phenylpropanoic acid esters were formed in the presence of $[PdCl_2(PPh_3)_2]$ system when the reactions were carried out in [bmim][BF_4] (1-butyl-3-methylimidazolium tetrafluoroborate). In the contrary, the use of the same catalyst system and carrying out the reaction in [bmim][PF_6] led to the formation of linear esters except for 1-propanol. Regarding this exceptional case, moderate regioselectivity towards the branched ester was detected. Indeed, the introduction of chelating diphosphines, such as DPPP, resulted in an increased amount of linear regioisomers in both ILs. The PPh_3 replacement by DPPP ligand in the aforementioned complex in [bmim][PF_6] for example was complete hence, the preference formation of the linear ester can be explained according to this basis. However, in [bmim][BF_4] only 30% of PPh_3 in the starting complex was substituted by DPPP and consequently, the branched ester was found to be as the dominant product over the linear ester.

Two-phase system composed of [bmim][BF_4] and cyclohexane was used to carry out the hydroalkoxycarbonylation reaction of styrene derivatives and isopropanol by applying $PdCl_2(PhCN)_2$/(+)-NMDPP/TsOH. Excellent regioselectivities toward the branched esters were achieved [76].

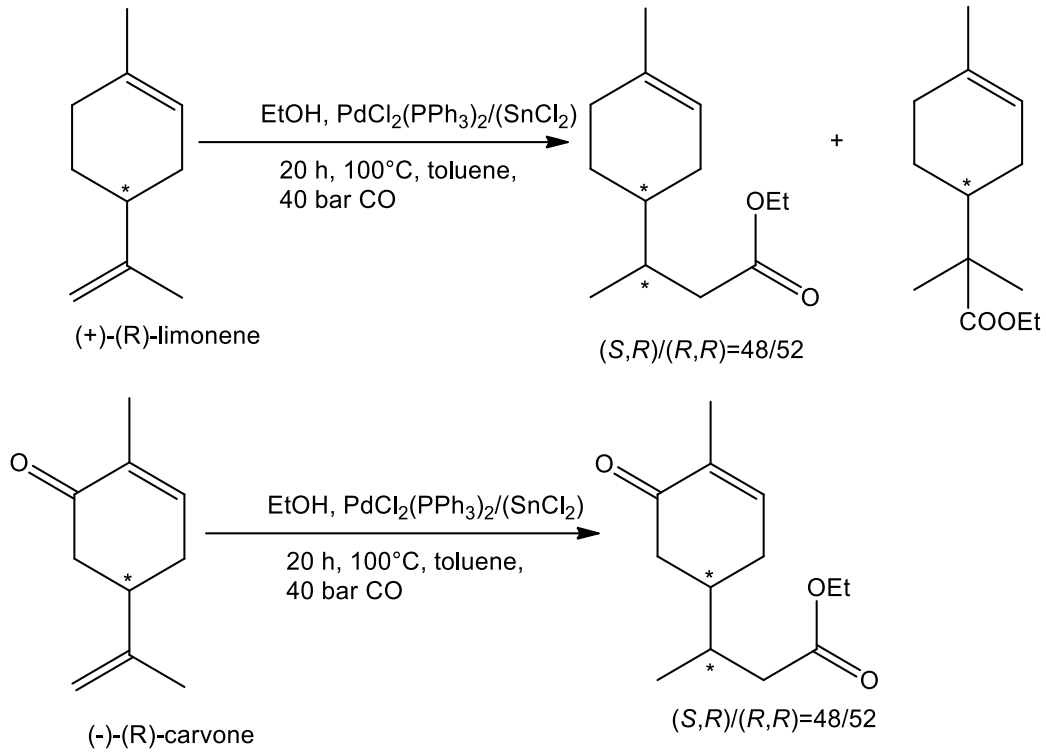
The hydromethoxycarbonylation of styrene was carried out by using [$PdCl_2(PPh_3)_2$]/PPh_3/TsOH as the catalyst system in [bmim][NTf_2] ionic liquid (NTf_2^-= bis(trifluoromethanesulfonyl)imide anion) at mild reaction conditions (14 bar of CO and 70 °C). Good yield of ester products was observed and the ratio of the linear: branched ester was found to be 81:19. Five recycle experiments on the recovered catalyst/IL were conducted and afforded an increase in the linear: branched ester ratio from 81:19 to 91:9 [77].

Moreover, the hydroethoxycarbonylation reactions of styrene were carried out by the application of $PdCl_2(PPh_3)_2$ catalyst in the presence of either [acetonyl-mim][BF_4] or [acetonyl-mim][PF_6] at 100 °C and 100 bar of CO and resulted in the exclusive production of ethyl 2-phenylpropanoate after 24 h. A reversal behaviour was obtained after the addition of dppf ligand (1,1′-bis(diphenylphosphino)ferrocene) to [acetonyl-mim][PF_6] as an exclusive formation of ethyl 3-phenylpropanoate compound was noticed [78].

Various monoterpenes such as limonene, carvone, dihydrocarvone, and pulegone were hydroalkoxycarbonylated by using achiral and chiral palladium–phosphine-$SnCl_2$ catalysts (Pd-PPh_3, Pd-DIOP, Pd-BNPPA) (BNPPA=1,1′-binaphthyl-2,2′-diyl-hydrogenphosphate) (*Scheme 23*) [79]. High chemo- and regioselectivities concerning the chiral linear ester isomers were achieved, despite this, diastereoselectivity values (*de*) were low and the use of different chiral ligands did not lead to influence these values significantly.

Two mechanisms have been suggested for the hydroalkoxycarbonylation reaction (*Scheme 24*) [57]. (**Cycle A**) represents the catalytic cycle of hydrido-palladium complex. In the 'hydride cycle', insertion of the alkene into the Pd–H bond takes place to form an alkyl complex as a first step. It is followed by the coordination and migratory insertion of CO to produce a Pd–acyl species. The alcoholic cleavage of the Pd–acyl regenerates the Pd–H complex and affords the esters in the last step.

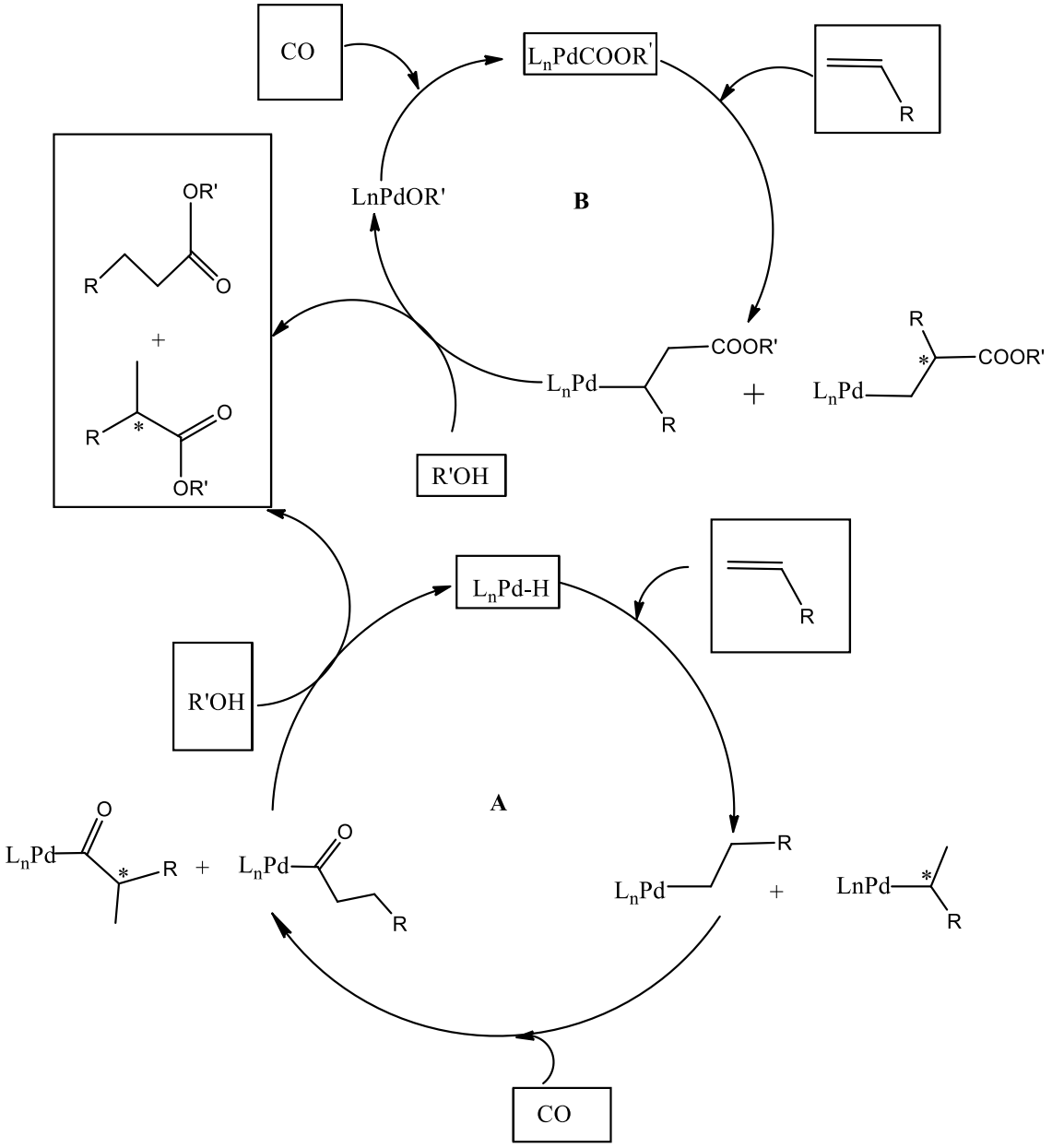
An alkoxycarbonylpalladium species can be considered as the key-intermediate in the second possible pathway of alkoxycarbonylation reaction of the olefin substrate (**cycle B**). In this cycle, alkene insertion into the Pd–carbon bond of the alkoxycarbonylpalladium complex provides the Pd-alkyl complex, which undergoes an alcoholysis yielding the alkoxo-palladium intermediate and the expected esters. CO coordination and migratory insertion into palladium-alkoxy bond is the last step, hence, regenerating the initial alkoxycarbonylpalladium complex.



Scheme 23. Hydroesterification of monoterpenes

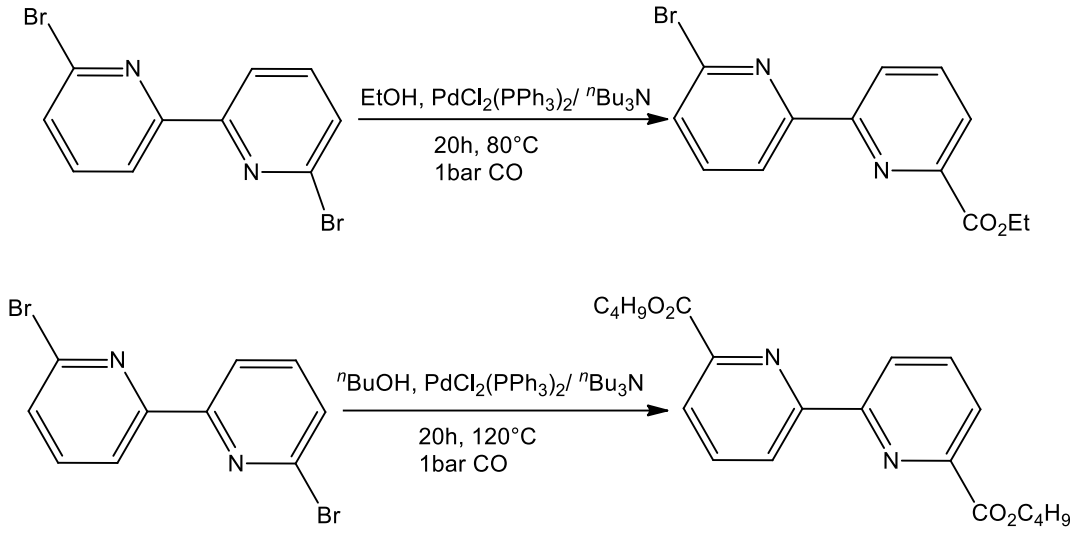
With regard to carbonylation reaction, alkyl esters can be prepared not only from olefins, but rather organic halides can provide a wide platform of substrates to generate esters, aryl-, alkenyl-, allyl- and benzyl halides (chlorides, bromides or iodides) can all participate in esters production. Typically, this category-based reaction requires the presence of the substrate and the nucleophile which in this case is the alcohol as well as the catalyst system. Alkoxycarbonylation or 'Heck-carbonylation' reaction term is used to describe this type of carbonylation process.

The mechanism of Pd-catalysed alkoxycarbonylation reaction of the above-mentioned substrates can be summarised as the following. The first step involves the oxidative addition of the organic halide compound to Pd(0), thus Pd-C bond can be generated. Pd-acyl species can be generated via CO coordination and subsequent migratory insertion into the Pd-C in the second step. Addition of the alcoholic nucleophile will regenerate the Pd(0) species and produces the desired ester compound in the last step. A base of N-type for example should be added to the initial catalyst system to assist in forming the initial Pd(0) intermediate in the last step in the catalytic cycle.



Scheme 24. Formation of esters rationalised by two catalytic cycles

The alkoxycarbonylation reaction of mono- or dihalogenated pyridines were carried out by using ethanol and *n*-butanol and resulted in the formation of mono- or diesters. For instance, 6,6′-dibromo-2,2′-bipyridine was converted to monoester at 80 °C in the presence of ethanol, while diester formation was observed at 120 °C in the presence of *n*-butanol (*Scheme 25*) [80]. Besides, mono- and diester selective formation was noticed upon the treatment of 2,6-dibromopyridine with ethanol at 80 °C and n-butanol at 120 °C, respectively [81].



Scheme 25. Pd-catalysed esterification of dihalogenated bipyridine

When 2,5-dibromopyridine was treated with alcohols in the presence of $Pd(OAc)_2$ and dppf ligand (1,1′-bis(diphenylphosphino)ferrocene) a regiospecific alkoxycarbonylation obtained at position 2 and yielded monoalkyl esters (alkyl= ethyl, methyl, benzyl) in 52-65% isolated yields [82].

Very high turnover number was achieved in the alkoxycarbonylation of 4-bromoacetophenone by applying either $Pd(PPh_3)_4$ or ($Pd(PhCN)_2Cl_2$-PPh_3) catalyst systems. At high ratio of P/Pd and long reaction times complete conversion of the substrate was obtained. Besides, it is worth mentioning that the base selection was very important in the alkoxycarbonylation of bromoacetophenone due not only to regenerate Pd(0) catalyst, but also to assist in the deprotonation of alcohols and produces alkoxide ions which might react more readily with Pd-acyl complex [83].

1,2-Dibromo-3,3,3-trifluoropropane compound can be utilised significantly in the high production of trifluoromethacrylate compound by alkoxycarbonylation pathway. An inorganic base (Li_2CO_3) was used with $Pd(PPh_3)_2Cl_2$ catalyst, and dual purposes for the addition of Li_2CO_3 might be deduced according to the report findings [84]. The first purpose is the production of 2-bromo-3,3,3-trifluoropropene compound by HBr abstraction which is considered as an intermediate for the formation of the corresponding ester compound. The beneficial production of the trifluoropropene intermediate is not only due to the production of the acrylate compound but also to the discouraging formation of the probably expected 3-alkoxy-2-trifluoromethylpropanoate by-product which can be understood as a second task of adding Li_2CO_3 base.

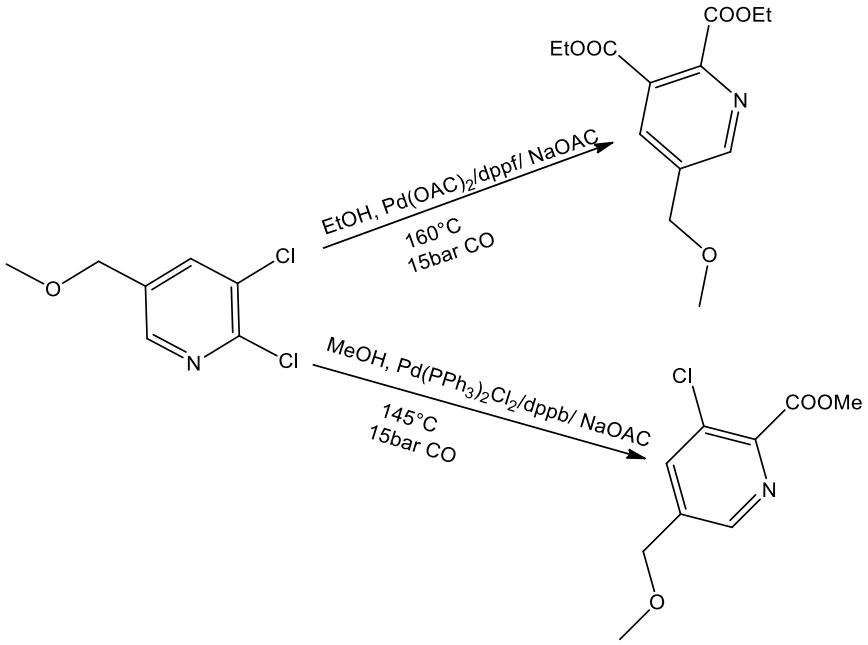
Actually because of their availability as well as their low cost, chloro-aromatics are attractive substrates for alkoxycarbonylation reactions. Despite these advantages, their carbonylation reactions assisted by Pd catalysts is a challenging process when compared to iodo- and bromo-aromatics since their oxidative addition to Pd(0) are harder because of (sp^2)C-Cl bond which showed more reluctance to be added to Pd(0) species. Consequently, the carbonylation reactions of chloro aromatics using Pd catalysts require harsh conditions (130-160 °C and 15-100 bar of CO). Additional difficulty for carbonylation reaction of aryl chlorides might be raised especially in the presence of large excess of CO ligand which might reduce the electron density of the Pd metal centre of the catalyst by its strong π-acidity character and as a result lowered the reductive ability of the catalyst [85]. To overcome this difficulty basic phosphine ligands can be added such as dippp (1,3-bis(diisopropylphosphino)propane) [86].

Beller's group converted 4-chloroacetophenone compound to its corresponding ester derivative by using $Pd(PhCN)_2Cl_2$ and PCy_3 (tricyclohexylphosphine) catalytic system. Despite this success, failed attempts to conduct alkoxycarbonylation of neutral- and electron-rich substrates like chlorobenzene and 4-chloroanisol at 145 °C and 15 bar CO (same conditions applied for 4-chloroacetophenone compound) were observed [87]. However, successful alkoxycarbonylation of chlorobenzene was achieved and *n*-butyl benzoate compound was afforded upon applying the catalytic system of $Pd(PhCN)_2Cl_2$ and 1-{2′-(dicyclohexylphosphino)ferrocenyl}-ethyldicyclohexylphosphine under 1 bar of CO [88].

Heteroaryl chlorides can be alkoxycarbonylated easier than aryl chlorides. The existence of the heteroatom in this class of compounds can activate C-Cl bond. Accordingly, alkoxycarbonylation reaction of various heteroaryl chlorides has been investigated recently [85].

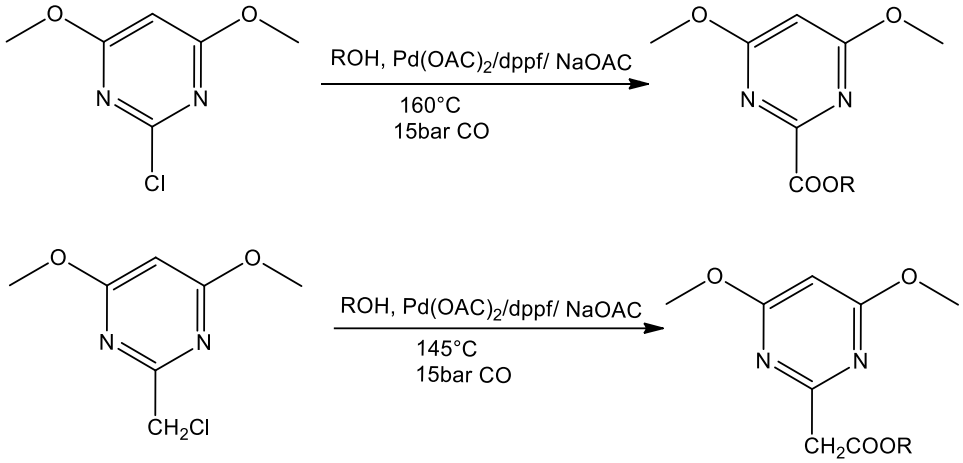
Applying $Pd(PPh_3)_4$ catalyst in the alkoxycarbonylation reaction of chloropyridine compound was leading to the formation of chloropyridinepalladium(II) dimer. To avoid the dimer formation chelating ligands should be used. After screening different ligands, it was demonstrated that applying $Pd(PhCN)_2Cl_2$ and either dppb (1,4-bis(diphenylphosphino)butane) or dppf ligand was the best catalytic system in the alkoxycarbonylation of chloropyridine and *n*-BuOH (130 °C and 25 bar CO) and afforded 94 and 95% yield, respectively [89].

Proper selection of reaction conditions such as the base, catalyst precursor and the provided alcohol resulted in the selective mono- and bisalkoxycarbonylation of 2,3-dichloro-5-(methoxymethyl)pyridine. For instance, the variation of reaction temperature and catalytic system resulted in the formation of either mono- or diester with 94 and 90% yield, respectively (*Scheme 26*) [90].



Scheme 26. Selective mono- and bisalkoxycarbonylation of dichloropyridine derivative

Treatment of 2-chloro-4,6-dimethoxypyrimidine or 2-(chloromethyl)-4,6-dimethoxypyrimidine with similar to the formerly-mentioned conditions yielded 4,6-dimethoxypyrimidine-2-carboxylic acid ester and 4,6-dimethoxypyrimidine-2-acetic acid ester derivative, respectively (*Scheme 27*) [91].



Scheme 27. Pd-catalysed esterification of chloropyrimidine derivatives

Benzyl bromide compound can be methoxycarbonylated under 1 bar CO and 40 °C by using the catalyst of the type $PdCl_2L_2$, where L is fluorinated-phosphine, fluorinated-phosphite and fluorinated-phosphinite ligand [92]. All complexes showed high activity for carbonylation reaction and it was observed that the less crowded (F,P)-based Pd catalyst, the more active the catalyst become. This can be explained based on the results obtained from non-catalytic

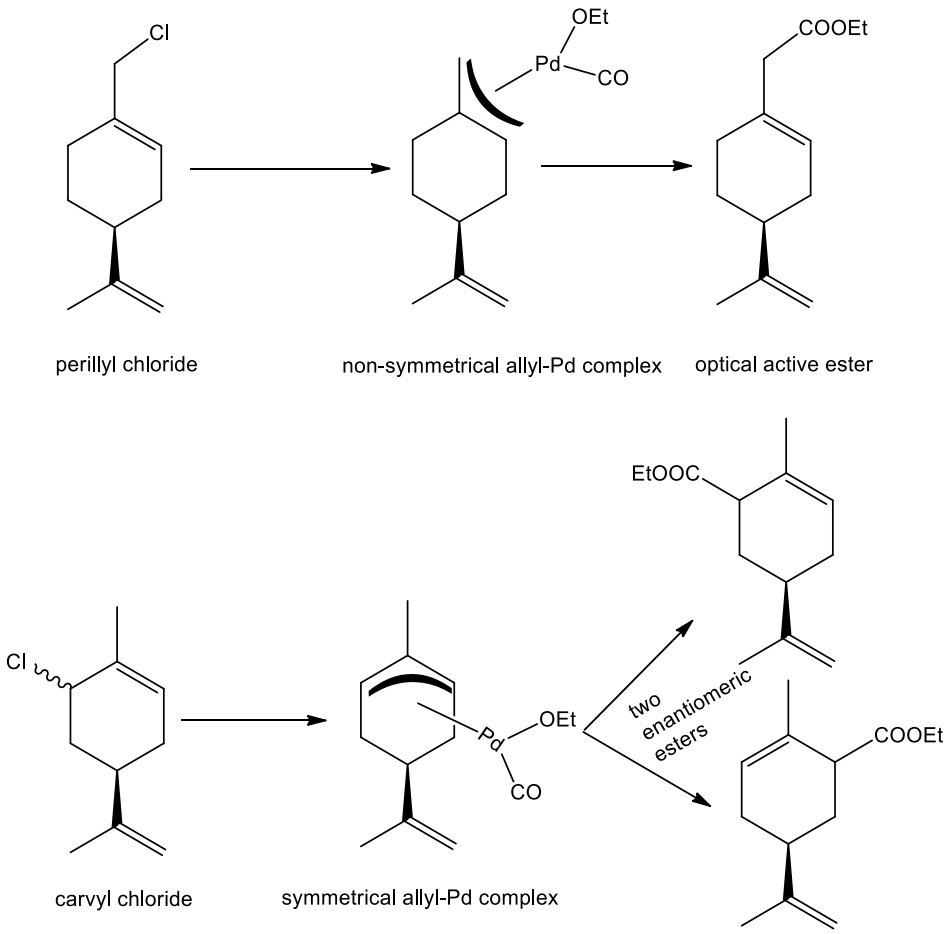
experiments that these complexes can be easier converted and reduced to Pd(0) complexes in the presence of CO.

Methoxycarbonylation reaction of benzyl chloride by using $Pd(PPh_3)_2Cl_2$ catalyst required pre-treatment of catalyst which involved the heating of the reaction medium before applying CO [93]. This step was necessary to carry out successful carbonylation. Otherwise, unsatisfactory results as well as uncompleted reaction were obtained. This might be due to the formation of Pd-carbonyl compounds which are electron-poor to favour the oxidative addition step of the benzyl chloride substrate.

Monoterpene chlorides can be transformed to ethyl esters by carbonylation reaction under atmospheric pressure of CO (*Scheme 28*). The chlorides were obtained from the corresponding alcoholic monoterpenes. Both perillyl- and carvyl chloride compounds afforded esters under such alkoxycarbonylation [94]. Interestingly, the ester obtained from the former terpene showed an optical activity while, the ester obtained from the latter one did not. This can be attributed to the formation of Pd-allylic complex, which in the first case did not have any symmetry and as a result the ethoxycarbonylation occurred exclusively on the less substituted carbon. Therefore, the ester exhibited an optical activity. In contrast, the formed Pd-allylic complex in the second case generated from carvyl chloride is symmetrical, hence the ethoxycarbonylation can occur equivalently at the two ends of the allylic moiety leading to the formation of two enantiomeric esters in equal amounts. Accordingly, the non-optical activity behaviour for the ester formed from carvyl chloride can be understood based on this interpretation.

While numerous reports regarding Pd-catalysed alkoxycarbonylation of various organic halides can be found in the literature, a few reports of alkoxycarbonylation of alkyl halides can be found. This is attributed to their low activity toward the alkoxycarbonylation reaction when compared to other halides. In this context, the order of the organic halide activity towards Pd-catalysed alkoxycarbonylation reaction is: allyl>benzyl>phenyl >vinyl>propyl>ethyl [95].

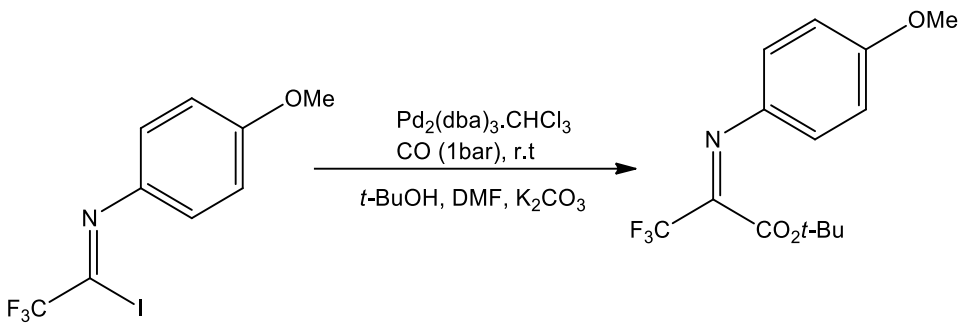
2-Chlorocyclohexanone was converted to the corresponding β-ketoester compound in very high yield in the presence of a base and under CO pressure of 100 bar and 100 ℃ by alkoxycarbonylation protocol. It was reported that the base absence and H_2O use in this reaction resulted in the hydrogen transfer from H_2O-CO system to the substrate and caused hydrogenolysis to C-Cl bond [96].



Scheme 28. Alkoxycarbonylation of monoterpene chlorides

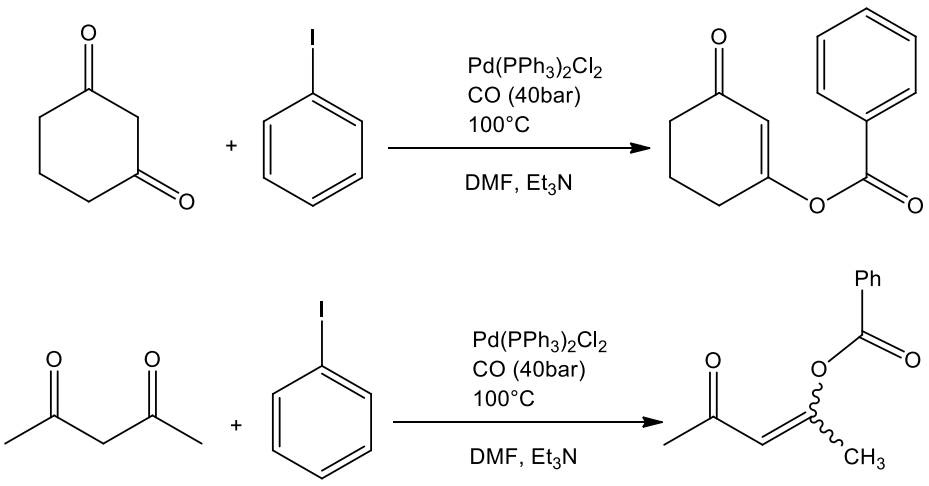
Furthermore, Maitlis and his co-workers reported the preparation of methyl acetate by methoxycarbonylation reaction of methyl iodide using $Pd(PPh_3)_2Cl_2$ or PdI_2 in the presence of excess iodide [97].

The structural restriction of tertiary alcohols renders their uses as nucleophile in the alkoxycarbonylation of organic halides as they do not work well in the alkoxycarbonylation reaction. One example for the carbonylation reaction of organic halide using *tert*-butanol is the *tert*-butoxycarbonylation of trifluoroacetimidoyl iodides under atmospheric pressure of CO. The prepared fluorinated iminoesters that contain an easily removable *O*-*t*-butyl group are very important as they can serve as precursors to the production of fluorinated amino acid compounds (*Scheme 29*) [98].



Scheme 29. Esterification of fluorinated imino-iodide derivative by *t*-BuOH

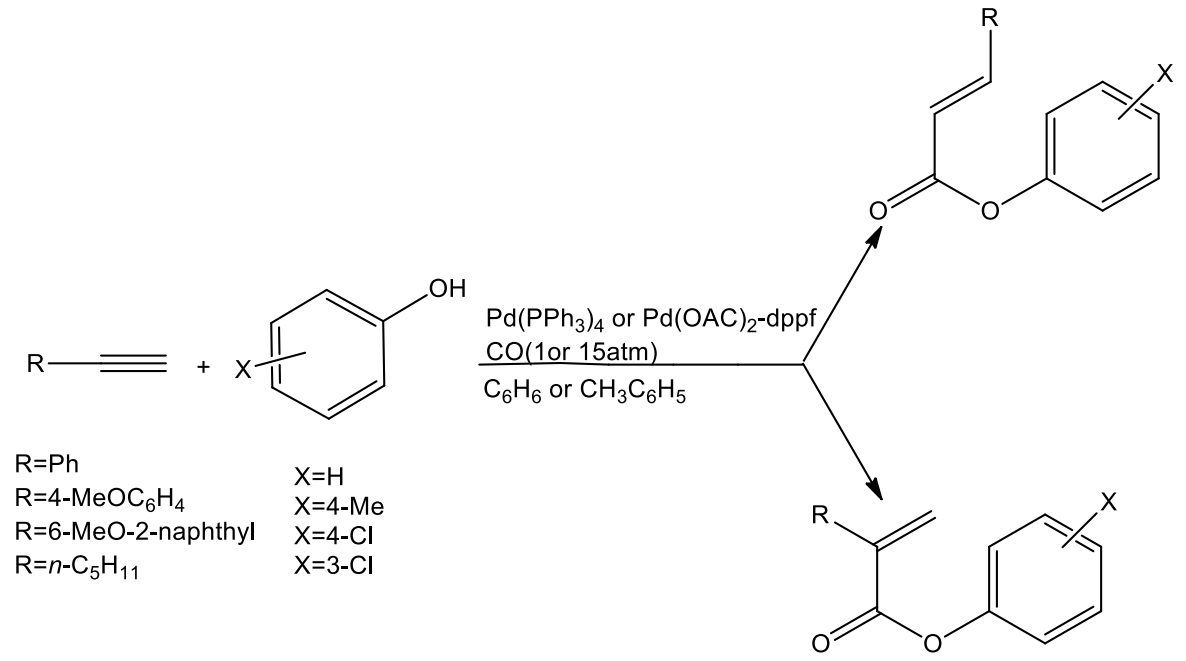
Concerning the mechanism of Pd-catalysed alkoxycarbonylation of organic halides, the formation of Pd-acyl species via the insertion of CO in to Pd-C bond in the second step of the catalytic cycle can be considered as very important step as these intermediates can be trapped with various nucleophiles such as water, amine and alcohol. For instance, Negishi and co-workers used $Pd(PPh_3)_2Cl_2$ complex and PhI compound to generate acylpalladium complex which in turn reacted with different diketone precursors [99]. Carbonylated compounds were produced in good yields when the acyl intermediate was reacted with highly acidic β-diketones such as 1,3-cyclohexandione, 1,3-cyclopentanedione and 2,4-pentanedione (*Scheme 30*). For the latter compound both *E* and *Z* isomers were produced. The use of acetophenone and cyclohexanone compounds (less acidic ketones) and the same Pd-acyl intermediate did not afford detectable yield of esters.



Scheme 30. Pd-catalysed carbonylation of phenyl iodide and enolizable diketones

The preparation of aryl esters by carbonylation reaction through applying phenol as *O*-nucleophile can be considered as a promising strategy. Hydroaryloxycarbonylation reaction term can be used to describe the reaction of unsaturated substrates such as alkenes or alkynes

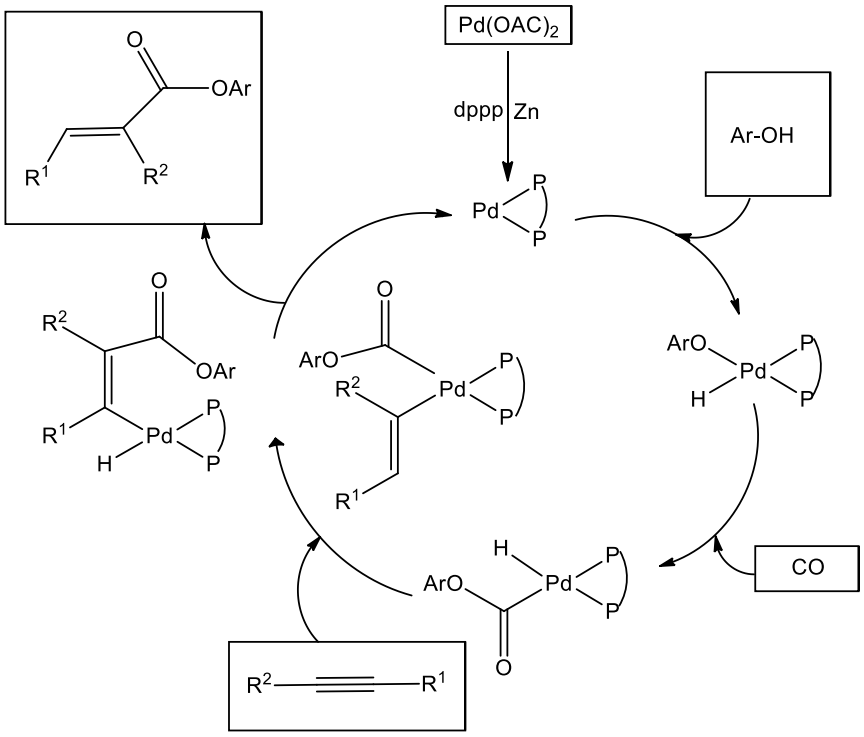
with substituted phenols. Actually, the literature contains sporadic reports regarding this protocol. Palladium-phosphine complexes for example catalysed carbonylation reaction of terminal alkynes in the presence of *meta*- or *para*-substituted phenols at low pressure and the results were reported by Miura and Nomura [100]. Based on this report alkyl and aryl acetylenes were hydroaryloxycarbonylated by applying either $Pd(PPh_3)_4$ or $Pd(OAc)_2$-dppf systems under 1 atm of CO gas in toluene, or 15 atm of CO gas in benzene. The former-mentioned substituted acetylene substrates (1 mmol) were converted to the corresponding ester derivatives by adding (2-4 mmol) of phenolic nucleophiles at 100 °C. Both linear- (aryl 3-aryl-2-propenoate) and branched ester (aryl 2-aryl-2-propenoate) derivatives were obtained from such reaction (*Scheme 31*). It was shown that higher selective formation for the branched esters over the linear ones was detected and isolated in the hydroaryloxycarbonylation of the substituted acetylenes.



Scheme 31. Pd-catalysed hydroaryloxycarbonylation of terminal alkynes

Moreover, internal alkynes showed activity towards Reppe carbonylation with phenol in the presence of Zn [101]. For example, 4-octyne was successfully converted to the ester (phenyl 2-propyl-2-hexenoate) when hydrophenoxycarbonylation reaction was carried out at 1 atm of CO gas and 100 °C in toluene using Pd-DPPP-Zn system. It seemed that the role of the added Zn dust is to reduce Pd(II) precursor to Pd(0) intermediate in the presence of DPPP ligand which can be considered as the 'starting species' in the catalytic cycle.

A possible reaction mechanism for the hydroaryloxycarbonylation of alkynes was suggested by the authors as shown in *Scheme 32* [101].



Scheme 32. Mechanism of hydroaryloxycarbonylation reaction of alkynes

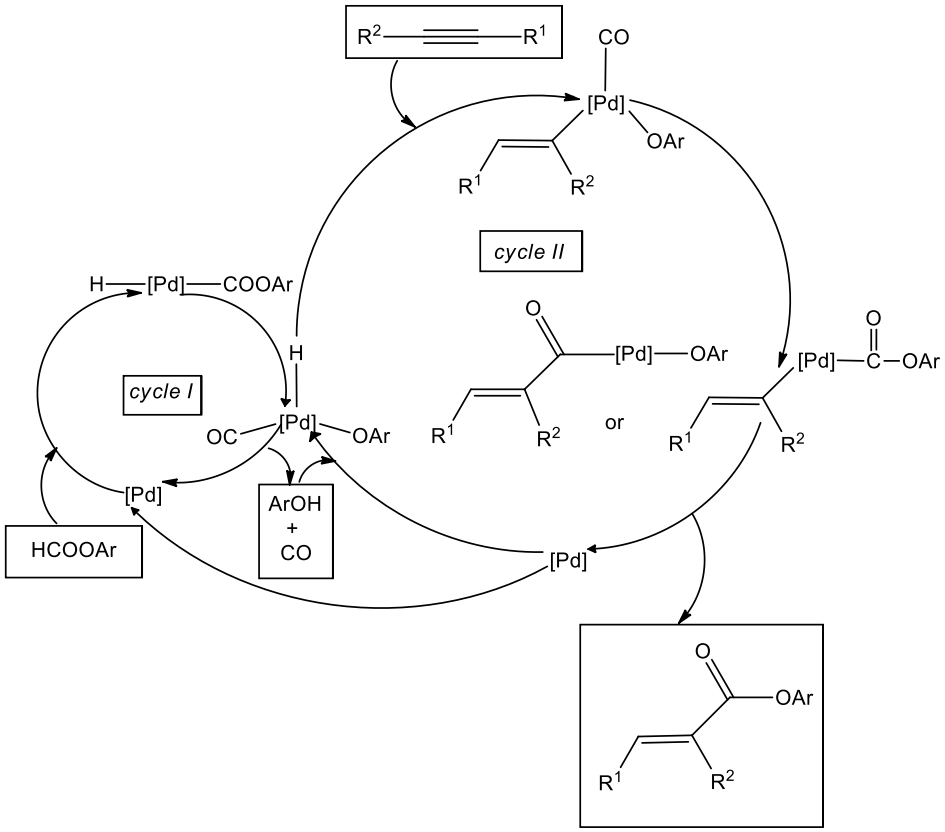
To the best of my knowledge, sporadic results and reports concerning the hydroaryloxycarbonylation reaction which involves the use of phenol derivatives as the *O*-nucleophiles and alkenes as the substrates can be found in the literature. An example for this is the hydroaryloxycarbonylation reaction of cyclohexene in toluene solvent [102] which was conducted by the catalytic system of $Pd(PPh_3)_2Cl_2$-PPh_3-TsOH and *m*-cresol as the phenolic nucleophile in order to prepare the *m*-tolyl cyclohexanecarboxylate compound.

It was also shown that the alcohol reactivity towards the carbonylation reaction of alkenes is much higher than the reactivity of phenols towards the carbonylation reaction of the same alkene substrates.

Additionally, it can be stated that alkynes exhibited higher reaction rates for carbonylation reaction than that of alkenes [103].

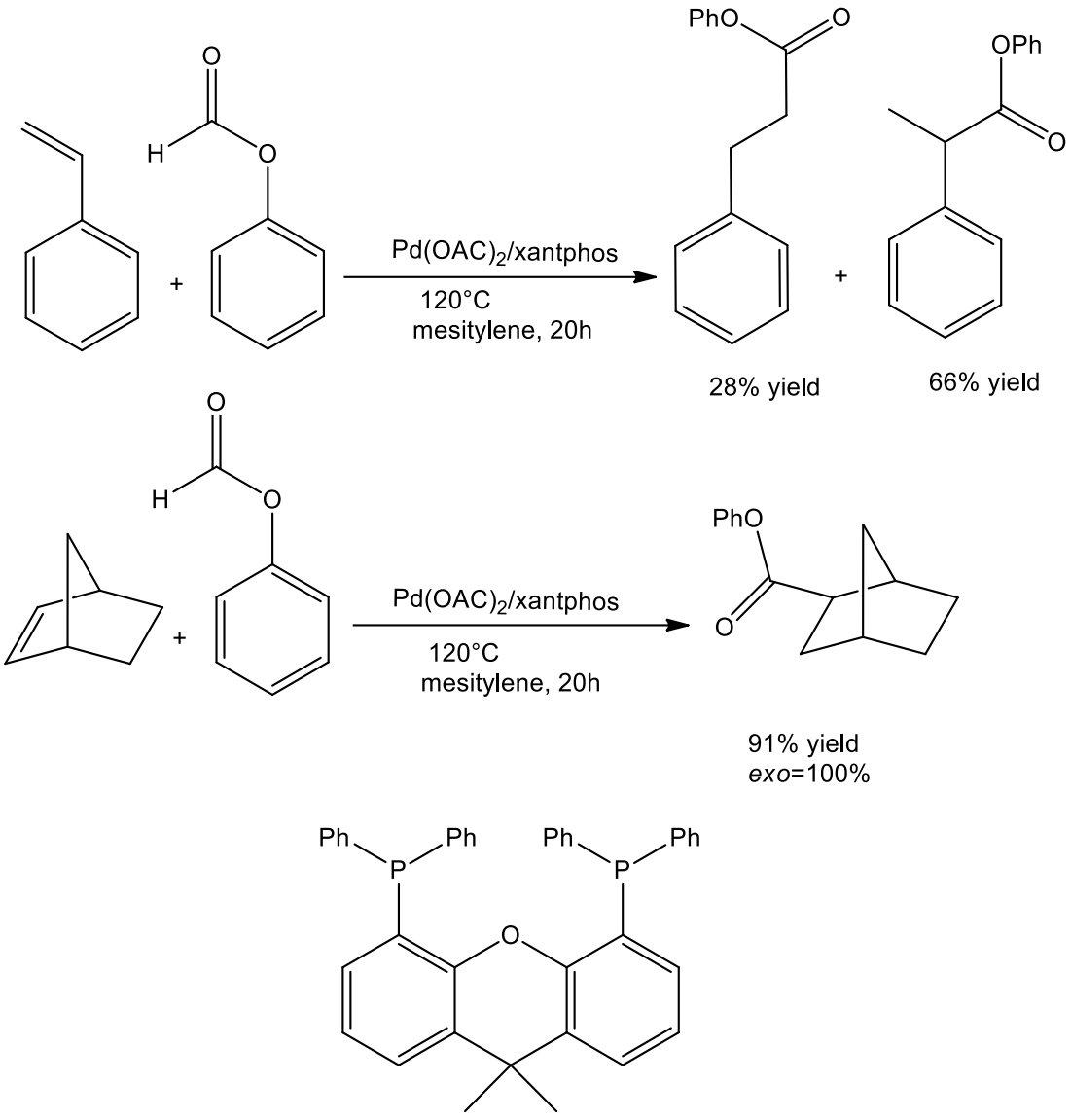
It is worth mentioning that carbonylating agents used for the carbonylation reaction are various and they could be either carbon monoxide gas or CO surrogates (paraformaldehyde, ester formates, metal carbonyl complexes, *etc*.). With respect to the CO surrogates, it was found that diverse aryl esters were produced from the reaction between aryl formates (CO surrogate) and alkenes leading to the known hydroesterification protocol [104-106]. For instance, Katafuchi

et al. [104] utilised $Pd(OAc)_2$ and xantphos ligand as catalytic system for the hydroesterification of alkynes by applying aryl formates as CO source (*Scheme 33*). For example, diphenylacetylene was transformed to the α,β-unsaturated ester product by using phenyl formate as the carbonylating agent. An exclusive *syn*-addition product was observed and consequently, (*E*) isomer was formed. Besides, the authors investigated the substrate scope for the carbonylation reaction using various aryl formates by testing several internal and terminal alkynes. The experimental conditions used to carry out the carbonylation reaction were as follows: catalyst precursor was loaded in 5%; xantphos:Pd ratio was 4:1; 2 mmol of aryl formate. These conditions were sufficient to transform 0.5 mmol of alkyne substrates in mesitylene solvent at 100 °C and 24 h to the corresponding unsaturated esters.



Scheme 33. A plausible mechanism for Pd-catalysed hydroesterification of alkynes using aryl formates as CO source

The hydroaryloxycarbonylation reaction of alkenes such as styrene and norbornene using aryl formates as CO source [104] were conducted to produce aryl esters. Applying $Pd(OAc)_2$ and xantphos ligand as well as phenyl formate as the CO source in mesitylene solvent at 120 °C and for 20 h afforded an exclusive *exo*-ester stereoisomer in case of norbornene substrate and linear and branched regioisomers in case of styrene compound (*Scheme 34*).

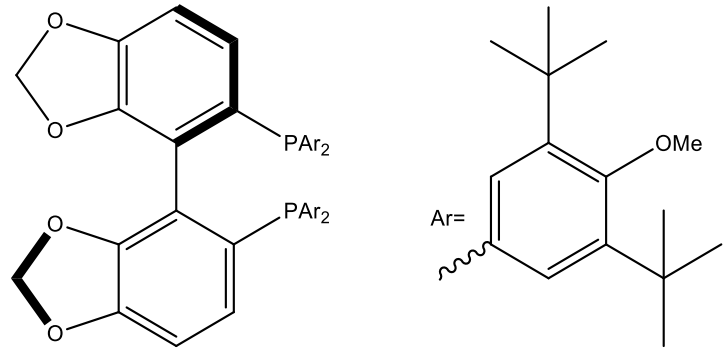


xantphos=4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Scheme 34. Hydroesterification of alkenes by phenyl formate as CO source using xantphos ligand and $Pd(OAc)_2$

It was postulated that aryl formates decomposed under catalytic conditions to gaseous CO and phenol [104]. This assumption might be supported by the notice of the increasing pressure up to 40 bar in the reaction vessel as stated by the authors.

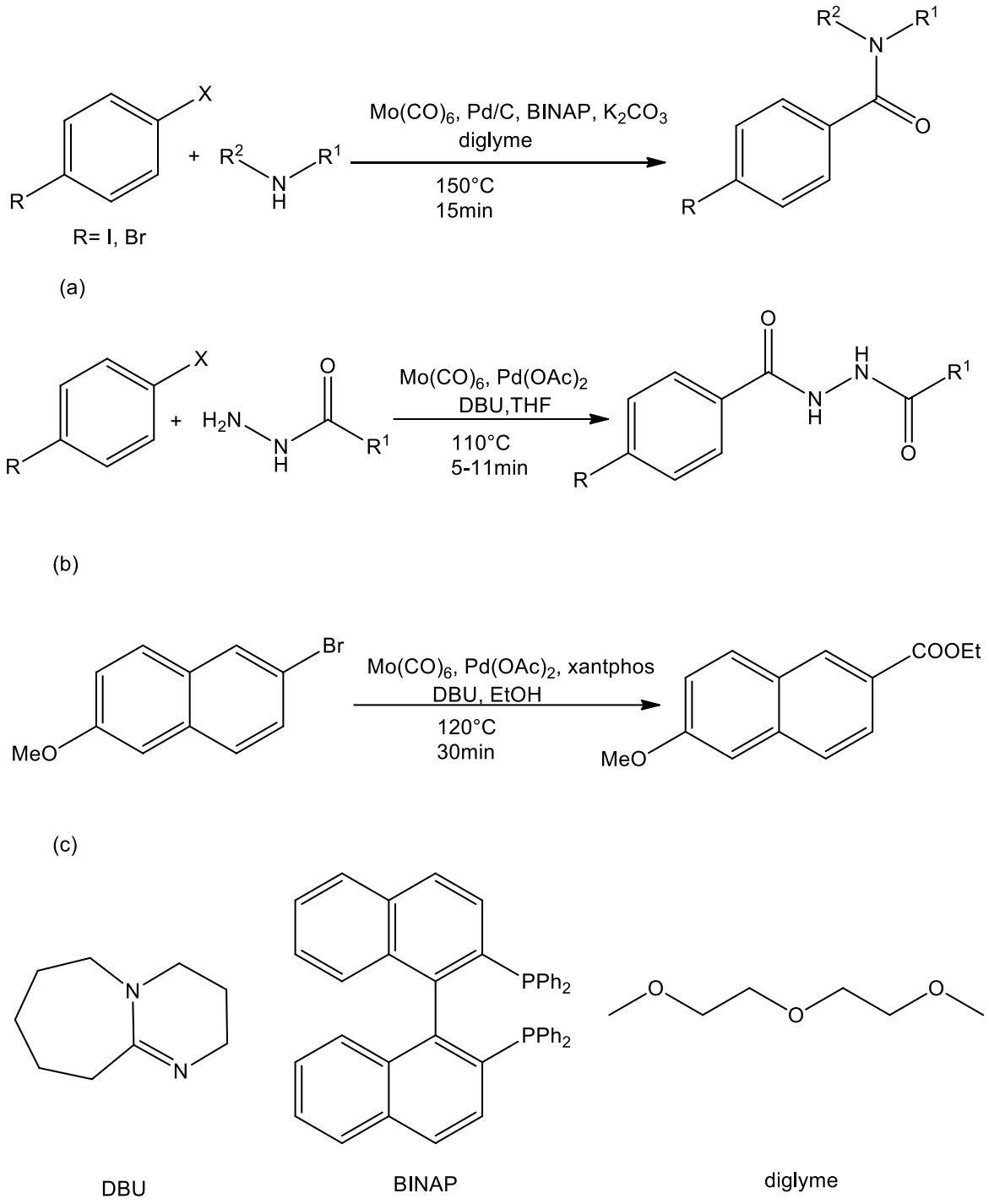
Moreover, the asymmetric induction for the chiral phenyl 2-phenylpropanoates was studied by conducting the carbonylation reaction of styrenes and phenyl formate in *n*-hexane as a solvent at 50 °C through the application of $Pd(OAc)_2$ and (*R*)-DTBM-SEGPHOS ligand (*Scheme 35*) as the catalyst system. The prepared branched esters were observed in good yields and high ratios of (branched: linear) esters were obtained as well under mild reaction conditions [6].



Scheme 35. (*R*)-(-)DTBM-SEGPHOS ligand

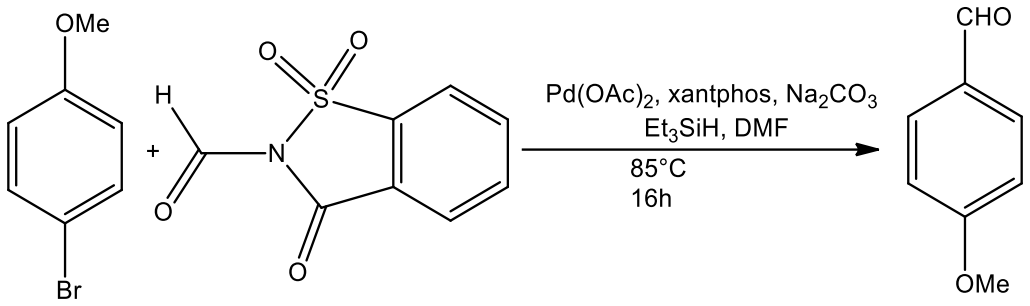
I return to spot the light on the CO surrogates because of their great importance and benefits as they can serve as CO sources. The great importance of these surrogates was stemmed from the well-accepted properties they own when compared to systems where gaseous CO was used. The highly undesired properties of free gaseous CO such as toxicity, flammability and the need of special equipment to handle carbonylation reaction can be considered as an urging and encouraging factors to seek for non-gaseous CO sources. Hence, environmentally friendly reactions and alternatives could be achieved and realised on the basis of CO surrogates' applicability.

Numerous reports were published concerning the use of CO sources in carbonylation reactions. One example is the use of $Mo(CO)_6$ as a source of CO in the report that was published by the group of Larhed which involved the use of microwave heating system to assist Pd-catalysed CO free reactions [107]. Successful alkoxy-, amino-, and amidocarbonylation reactions were carried out through the implementation of $Mo(CO)_6$ as CO source (*Scheme 36*).



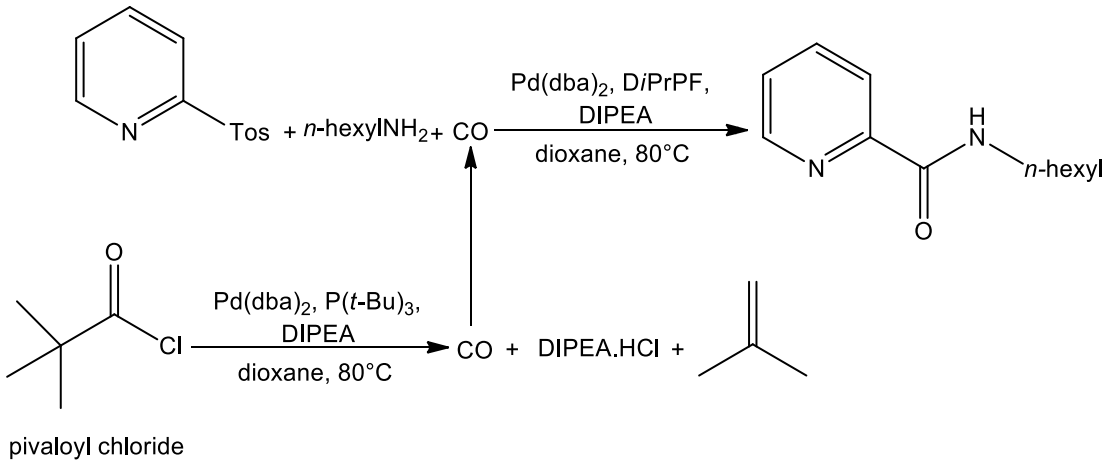
Scheme 36. Amino-, amido- and alkoxycarbonylation of aryl halides using $Mo(CO)_6$ as CO source

Different aryl bromides were carbonylated by using *N*-formylsaccharin as a CO source by the use of Pd/xantphos catalyst system and Et_3SiH as the hydride donor source and for example, 80% of 4-methoxybenzaldehyde compound was produced from 4-bromoanisol substrate using the same conditions (*Scheme 37*) [108].



Scheme 37. *N*-formylsaccharin as a CO source used for carbonylation reaction of aryl bromides

Skrydstrup group reported the aminocarbonylation reaction of various pyridyl tosylates (*Scheme 38*) by using a CO source. Two-chamber system was utilised to carry out the carbonylation reaction for the tosylate derivatives; first chamber contained $Pd(dba)_2$/(*t*-$Bu)_3P$/DIPEA (diisopropylethylamine) catalyst system to activate the CO generation from pivaloyl chloride which acted as the CO source. The generated CO can be exploited to conduct the aminocarbonylation reaction of the pyridyl tosylates or halogenated heteroaryls as it flowed to the second chamber [109].



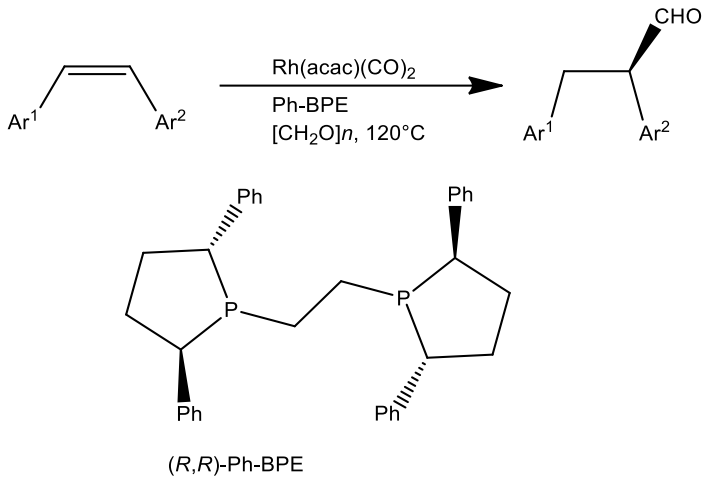
Scheme 38. Pd-catalysed aminocarbonylation of 2-pyridyl tosylates using pivaloyl chloride as CO source

Formaldehyde as well as paraformaldehyde can be considered as important CO-containing candidates and surrogates for carbonylation reactions. What make these surrogates attracting much attention in the carbonylation reaction are the easy handling of these sources, their applicability to many homogeneous carbonylation reactions [110] and the advantage beyond the perspective of atom economy.

Actually, despite the use of formaldehyde as a CO source in Rh-catalysed hydroformylation reactions since several years [111], the enriched application of this CO source in catalytic carbonylation reactions has only flourished in the last decade.

Formalin as a CO source (37% formaldehyde aqueous solution) was utilised to carry out carbonylation reaction of terminal alkenes. Formalin and $RhCl(COD)_2$/(Xantphos and BINAP) as the catalytic system were used to hydroformylate various terminal alkenes in toluene solvent at 90 ℃ for 30 minutes by microwave source assistance [112]. It is worth mentioning that the use of two ligands in this report was to exploit the Rh(I)-BINAP complex generated from BINAP ligand for the decomposition of formaldehyde to afford both CO and H_2, and to exploit the generated Rh(I)-Xantphos complex afforded from Xantphos ligand in catalysing the hydroformylation reaction.

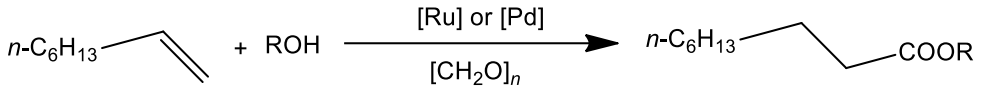
The solid paraformaldehyde compound was used to carry out the asymmetric hydroformylation of stilbene and substituted stilbenes by applying the catalytic system consisted of $Rh(acac)(CO)_2$ and the ligand 1,2-bis[(2*R*,5*R*)- 2,5-diphenylphospholano]ethane (Ph-BPE) (*Scheme 39*) [113].



Scheme 39. (*R*,*R*)-(Ph-BPE) ligand and hydroformylation of *cis*-stilbenes using paraformaldehyde as CO source

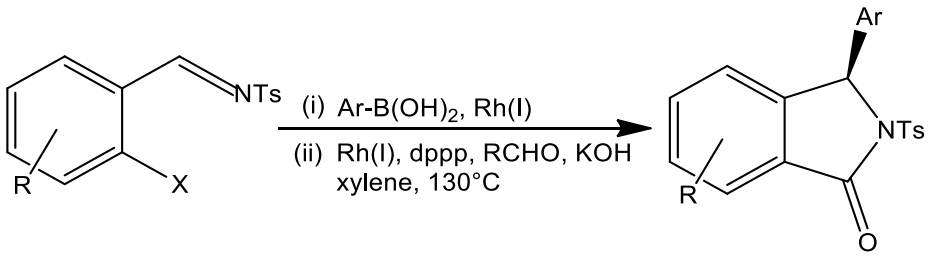
Beller's group exploited paraformaldehyde as a CO source with various alcohols to carry out the hydroalkoxycarbonylation reaction for both terminal and internal alkenes. Pd and Ru catalysts were used in these carbonylation reactions and up to 90% of different esters were produced when the catalyst system $[Ru_3(CO)_{12}]/PCy_3$ (Cy=cyclohexyl) was used to conduct the hydrocarbonylation reaction of cyclohexene, 2-octene, 1-octene and styrene. Methanol, ethanol, isopropyl alcohol and *n*-butanol were used as the *O*-nucleophiles [114]. Besides, paraformaldehyde and $Pd(OAc)_2$ were used with d^tbpx ligand (1,2-bis[di-*tert*-

butylphosphinomethyl]benzene) and TsOH to conduct the hydroalkoxycarbonylation reaction of 1-octene substrate (*Scheme 40*) [115].



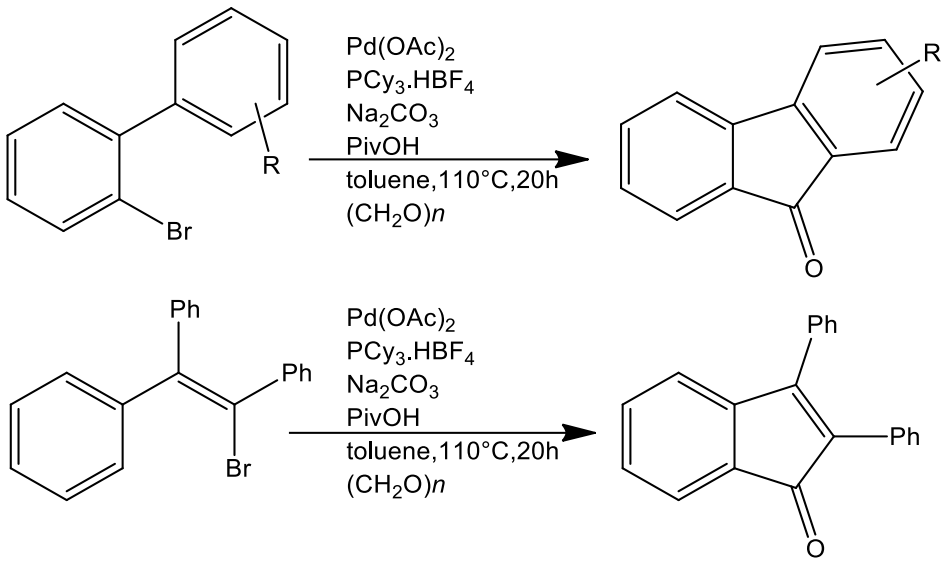
Scheme 40. Hydroalkoxycarbonylation reaction of 1-octene using paraformaldehyde as CO source

Actually, metal-catalysed carbonylation reactions of aryl halides by applying aldehydes as CO sources are common in the literature. In a study afforded by Kakiuchi, various aldehydes such as paraformaldehyde and pentafluorobenzaldehyde were used as CO sources in order to prepare isoindolinone derivatives from 2-halobenzaldimine compounds (*Scheme 41*) [116]. It was shown that the latter aldehyde afforded more product yields than the former one and showed to exhibit more activity as well. However, based on the atom economy perspective, paraformaldehyde is more preferred to introduce in the carbonylation reaction since only hydrogen by-product can be observed in these reactions.



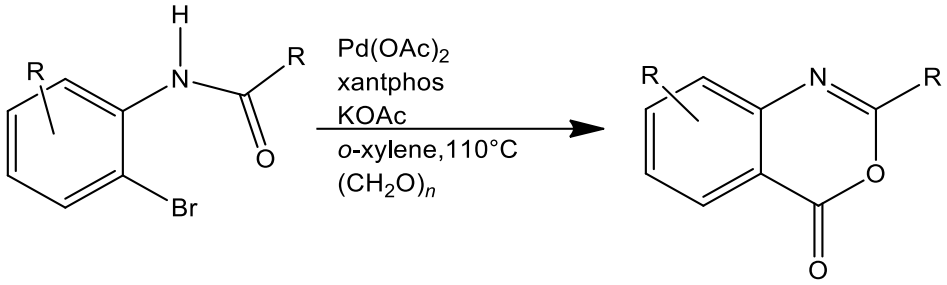
Scheme 41. Carbonylation reaction using aldehydes as CO sources

Moreover, applying paraformaldehyde to carry out the carbonylation reactions of various 2-bromobiphenyl substrates were studied [117]. Numerous fluorene-9-one derivatives were prepared according to this protocol. C-H bond activation was necessary to achieve the preparation of the fluorene-9-one compounds and was conducted through the addition of both Na_2CO_3 and PivOH. Besides, this protocol was leading to successful preparation of indenones from β-bromostyrene derivative (*Scheme 42*) [117].



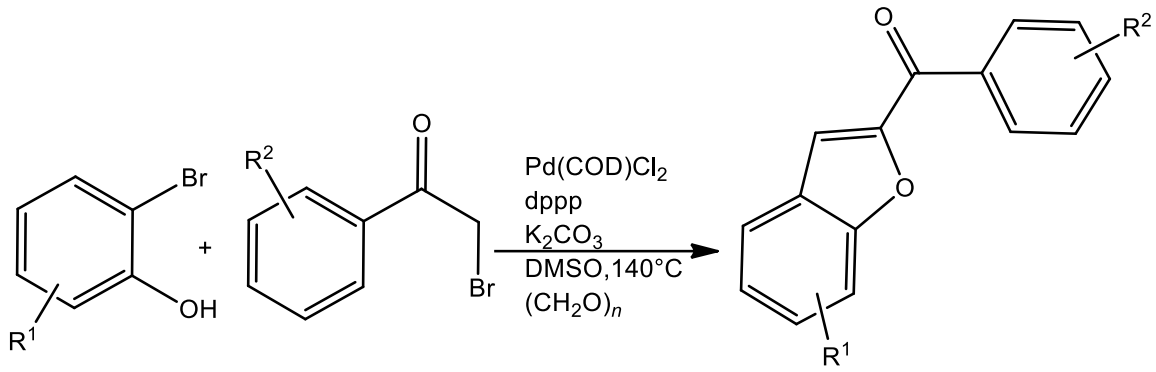
Scheme 42. Preparation of fluorene-9-ones and indenones by Pd-catalysed carbonylation reaction of aryl- and vinyl bromides enabled by paraformaldehyde as a CO source

Additionally, *N*-(*o*-bromoaryl)amide substrates were utilised to synthesize benzoxazinone derivatives via Pd-catalysed carbonylation through paraformaldehyde introduction as CO source (*Scheme 43*) [118].



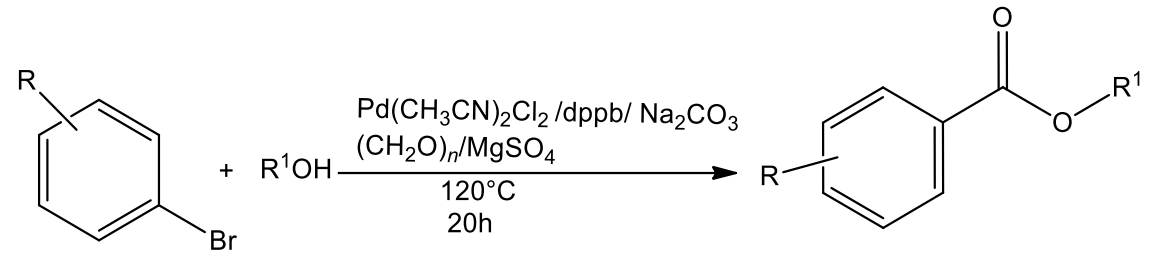
Scheme 43. Benzoxazinone derivatives preparation by Pd-catalysed carbonylation reaction assisted by paraformaldehyde as CO source

Three components-system (bromophenols, phenacyl bromides and paraformaldehyde) was used to conduct the preparation of 2-aroylbenzofuran derivatives (*Scheme 44*) [119].



Scheme 44. Pd-catalysed carbonylation reaction of bromophenols to prepare 2-aroylbenzofurans

Beller *et al* reported in 2014 Pd-catalysed alkoxycarbonylation of aryl bromide substrates using either methanol or ethanol as *O*-nucleophiles and paraformaldehyde as CO source. Various esters were prepared according to this procedure (*Scheme 45*) [120].



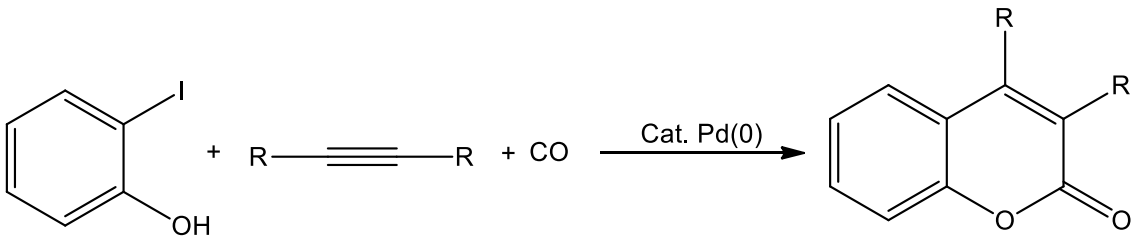
Scheme 45. Esters formation from aryl bromides by incorporation of paraformaldehyde as CO source

Recently, aryl iodides have been utilised to carry out both alkoxy- and aryloxycarbonylations using *p*-chlorobenzaldehyde as CO source. According to the published report both alkyl and aryl esters were prepared [121].

It is worth mentioning that Rh-containing systems used for the hydroformylation reactions, are well known in the literature and they are widely extended [122-125]. Despite this, their feasibility in performing alkoxy- and aminocarbonylation reactions are less studied and investigated.

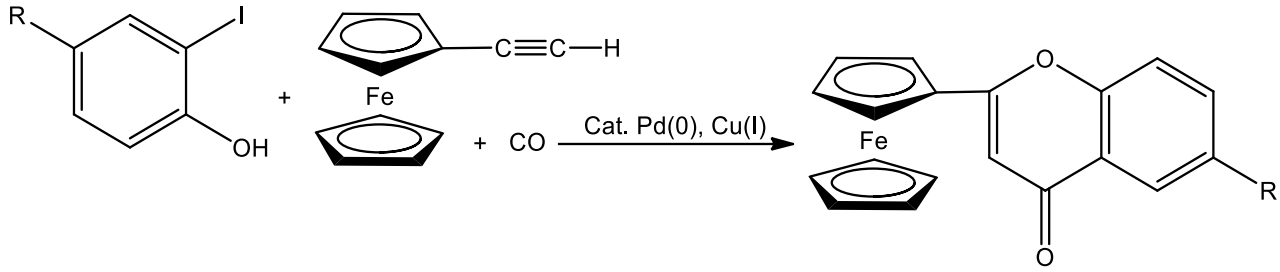
Another approach that might also be discussed is the use of alcohols and phenols which can act as *O*-nucleophilic donors [126, 127] for a special class of ester formation, more precisely lactone formation, through either the cyclohydroalkoxycarbonylation or cyclohydroaryloxycarbonylation of unsaturated alcohols and phenols respectively. Their feasibility in the biological and pharmacological disciplines [128-130] gave this class of compounds considerable interest especially in the preparation purposes. In addition to reports

found in the literature concerning *O*-heterocyclic compounds (lactone-containing compounds) preparation, two protocols for synthesising other *O*-heterocyclic compounds via transition metal-catalysed carbonylation reaction can be mentioned. The first one is the production of coumarines via Pd-catalysed carbonylation reaction of 2-iodophenol and internal alkynes (*Scheme 46*). The oxidative addition step of iodo-aryl bond to Pd(0) followed by (i) alkyne insertion in to Pd-aryl bond and (ii) CO coordination and a sequential CO insertion in to the Pd-alkenyl bond to form the palladium(acyl) complex can be considered as the crucial intermediate in this cyclisation process. The target compounds can be generated in the catalytic cycle by the *O*-nucleophilic attack of the phenolic moiety on the generated palladium-acyl intermediate [131-133].



Scheme 46. Coumarines obtained form 2-iodophenol and alkynes

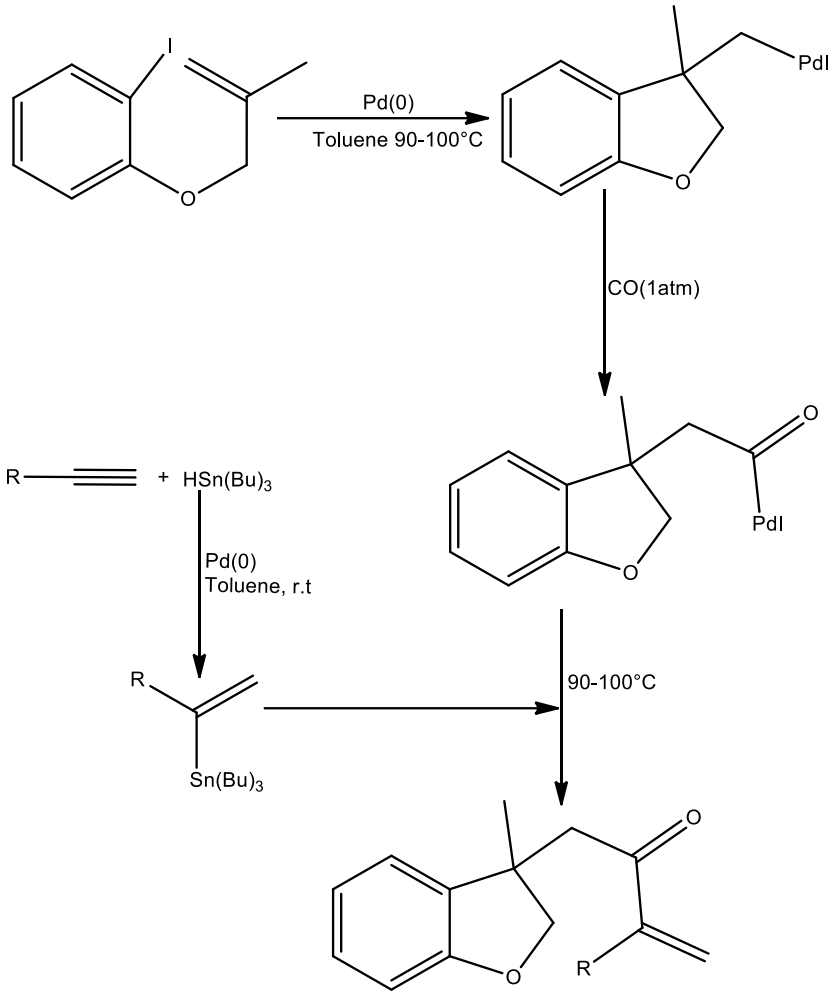
The second protocol is the formation of 4*H*-chromene-4-one derivatives (flavones) by both Pd-catalysed carbonylation reaction of a terminal alkyne-containing compound and 2-iodophenols and the assistance of Sonogashira conditions as well. The formation is believed to occur through the generation of palladium-acyl intermediate which is formed by the oxidative addition of aryl-iodide bond to Pd(0) complex which then followed by CO coordination and insertion into Pd-aryl bond. Next the terminal alkyne anion generated by the original Cu(I) might be transmetalated to the palladium-acyl complex in a second stage. Finally, the annulation process was established by the Michael addition of phenolic group to the alkynyl moiety, thus leading to the flavone compounds formation (*Scheme 47*) [134]. Additionally, similar flavones can be prepared in a similar fashion by carbonylation reaction of 2-iodophenols and acetylenes via utilising Pd(0) catalyst as well as HNRR which can act as a base to subtract hydrogen atom from acetylene moiety and iodine atom from the Pd complex, thus enable the coordination of alkynyl anion to the Pd centre. A second task for the base addition is that it acts as an added nucleophile to the triple bond forming a double bond-containing compound, which in turn behaved as a leaving group as Michael addition step established to afford the aimed flavone compounds [135].



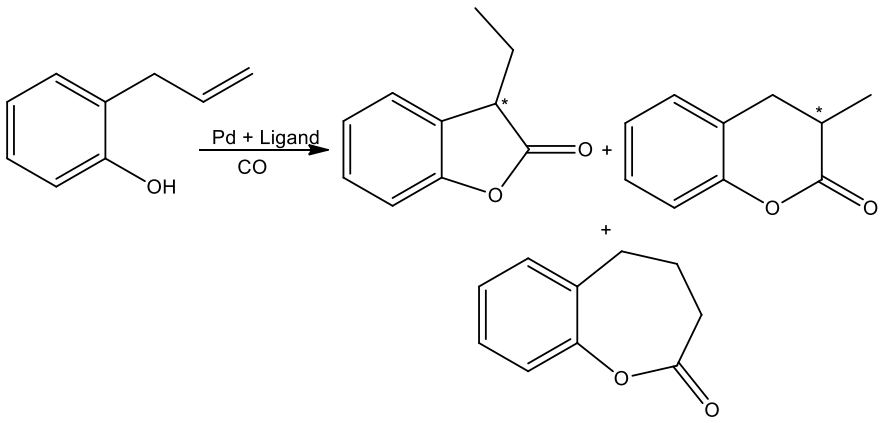
Scheme 47. Flavones formation obtained from 2-iodophenols and terminal alkynes

Vinyl stannanes generated *in situ* by Pd-catalysed hydrostannylation addition of $HSn(Bu)_3$ to different acetylenes, can be used as terminating agents for the termolecular (addition of 3 molecular components to conduct the reaction) annulation of aryl iodides in the presence of CO atmosphere [136]. For instance, methallyl 2-iodophenyl ether can be transformed to prepare *α,β*-unsaturated ketones (*Scheme 48*). It is worth noting that carrying out the reaction at high temperatures prevented the role of the capturing agents and resulted in the formation of the dihydrobenzofuran derivatives as the major compounds.

Various reports on the cyclocarbonylation reaction of unsaturated alcohols can be found in the literature [137], nevertheless, few reports concerning cyclocarbonylation reaction of unsaturated phenols are present in the literature especially for 2-allylphenols. Intramolecular aryloxycarbonylation for allylphenols was applied to synthesize cyclic esters (lactones) of different ring size; 5-, 6- and 7-membered ring lactones (*Scheme 49*) by using the catalytic system formed *in situ* from palladium acetate and 1,4-bis(diphenylphosphino)butane (dppb) in the presence of *syngas* [138]. Besides, Alper and co-workers studied the cyclocarbonylation reaction of allylphenols by applying the *syngas* and the catalytic system comprised of PdI_2 and phosphaadamantane-based ligand [139]. The same lactones (5-, 6- and 7-membered ring) were also formed in this study. It was observed that the cyclocarbonylation reaction was very sensitive to H_2 gas presence in the reaction. The use of no hydrogen gas resulted only in the formation of lactone traces.



Scheme 48. *α,β*-Unsaturated ketones preparation from methallyl 2-iodophenyl ether and hydrostannylation of terminal alkyne



Scheme 49. Pd-catalysed lactones formation from allylphenol

Polyaminoamido dendrimers supported on silica (PAMAM-SiO_2) were prepared from corresponding aminopropyl silica gel compounds and converted to the phosphonated

PAMAM-SiO_2 dendrimers by the reaction of diphenylphosphine with paraformaldehyde to afford the diphenylphosphinomethanol compound which in turn used to afford the phosphinomethylation of each terminal amine group. Complexation of the phosphino-PAMAM dendrimers were achieved by stirring the dendrimers with $Pd(PhCN)_2Cl_2$ in a degassed toluene solvent. The catalytic systems composed of the Pd-containing dendrimers and dppb ligand were used for the cyclocarbonylation process of 2-allylphenol [140]. The heterogeneous catalysts exhibited good activities and can be recycled from the reaction mixture up to 3-5 times maintain affording good conversions.

Dimethyl carbonate (DMC) is known for its low toxicity and boiling point when compared to other solvents such as toluene and CH_2Cl_2 [141]. As an eco-friendly solvent, it was also used to perform selective cyclocarbonylation reaction of allylphenol derivatives [142]. $Pd(OAc)_2$, *syngas* and dppb ligand were used to conduct lactone preparation. A dominant 7-membered lactone regioisomer formation was observed in these reaction mixtures. In some cases, and at longer reaction times methoxycarbonyl derivatives were formed in the reaction mixtures due to the ability of DMC to act as a ring-opening agent.

2. Aims of the planned research

The previous studies mentioned in the introduction part concerning esters preparation inspired our group to investigate various pathways for obtaining esters through Pd and Rh catalysts implementation and various types of substrates application such as terminal alkenes, aryl halides and allyl phenol derivatives under moderate carbonylation reaction conditions.

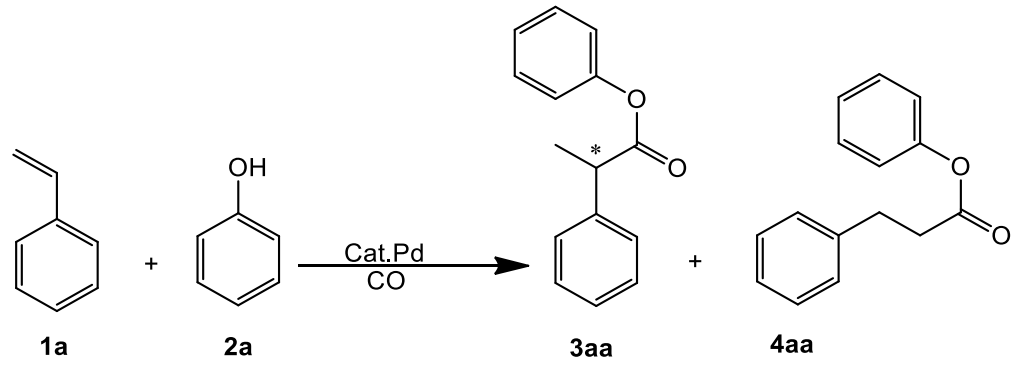
As for the details, the following points were considered.

- To get a deeper insight into the mechanism of hydroaryloxycarbonylation by systematic investigation of *para*-substituted styrenes and phenols.
- To find alternative CO sources for the carbonylation reaction.
- To carry out cyclohydroaryloxycarbonylation of 2-allylphenol derivatives leading to the preparation of different lactones and investigate the asymmetric carbonylation.

3. Results obtained in my investigations

3.1. Palladium-catalysed enantioselective hydroaryloxycarbonylation of styrenes by 4-substituted phenols

The optimisation conditions of hydroesterification reaction of styrene and phenol were scanned and the optimised experiment of this hydrophenoxycarbonylation reaction was adapted to carry out further hydroesterification reaction for 4-substituted styrenes (substrates) and 4-substituted phenols as *O*-nucleophiles under CO atmospheric pressure (*Scheme 1*) [143].



Scheme 1. Palladium-catalysed hydrophenoxycarbonylation of styrene

Basically, parent styrene (**1a**) and phenol (**2a**) were selected as models for alkenes and *O*-nucleophiles, respectively, to initiate the optimisation conditions for the hydrophenoxycarbonylation reaction leading to the production of the corresponding ester regioisomers (**3aa**) and (**4aa**). Several phosphine ligands (achiral mono- and bidentate, chiral

bidentate) were investigated in the presence of Pd precursors to afford the corresponding *in situ* generated Pd catalysts.

Firstly, we examined the catalytic system composed of $Pd(OAc)_2$ precursor and PPh_3 ligand under carbon monoxide atmosphere (100 bar) at 100 °C. Based on several reports [56, 57, 100] which confirm that the addition of excess amount of acids can contribute in enhancing the activity of hydroalkoxycarbonylation reaction, we initiated our investigation by adding *para*-toluenesulfonic acid. Only 17% of the ester regioisomers was obtained, while the major compound formed in this experiment was an etheric compound that produced via acid catalysed nucleophilic addition reaction (**Table 1**, *entry 1*) [144]. The addition of oxalic acid and trichloroacetic acid led to the production of low esters amount (*entries 2* and *3*, respectively), the addition of phenol to styrene substrate in both cases was not observed. A remarkable increase in catalytic activity was observed when concentrated hydrochloric acid was used. It was noticed that the reaction was accelerated upon increasing the amount of added acid. However, after adding more than 3 drops of cc. HCl to the reaction mixture a small decrease in the activity of the reaction can be noticed (*entries 4-6*). Besides, since using excess alcoholic nucleophiles over the stoichiometric amount in the hydroalkoxycarbonylation reaction showed to afford better activity results, the effect of using excess amount of phenol in our investigation seemed to be realistic. Therefore, after examining the effect of excess phenol addition trials, we found that the optimal reaction condition can be achieved by applying substrate: nucleophile ratio of 1:6. A slight enhancement in activity was observed when further increase of phenol addition was applied to the reaction (*entries 7* and *8*).

The next step was to explore the effect of introducing achiral and chiral bidentate ligands on the activity of the reaction and compare the results with that obtained from using PPh_3 and $Pd(OAc)_2$. It is worth noting that in addition to $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$ catalyst was tested in this stage and found that the *in situ* generated complexes afforded from $Pd(PhCN)_2Cl_2$ exhibited a slightly higher activity compared to the *in situ* generated species analogues afforded by $Pd(OAc)_2$ precursor. Besides, all experiments concerning the bidentate ligands and $Pd(PhCN)_2Cl_2$ showed lower catalytic activity than that obtained from the monodentate phosphine ligand and $Pd(OAc)_2$ (compare *entries 9-14* and *1-8*). Interestingly, two observations can be concluded from the results obtained from introducing bidentate ligands. First, the use of ligands with smaller bite angles such as BDPP, DPPP, DPPB, BINAP and JOSIPHOS were ineffective or produced esters with low conversions. Second, the introduction of larger bite angle ligands like XANTPHOS, DIOP and PHANEPHOS demonstrated better activity and resulted in the formation of the desired esters. Out of the *in situ* generated bidentate systems,

DIOP-containing system was selected for further optimisation and investigation. The regioselectivity results of the branched ester (**3aa**) obtained from using bidentate ligands were much lower than that obtained in case of PPh_3 and confirms our expectation that the monodentate phosphine ligand favoured the branched ester formation in the Pd-catalysed hydrophenoxycarbonylation reaction.

Table 1. Optimisation of hydrophenoxycarbonylation reaction[a]

Entry	Ligand	Acid	Time [h]	Conv.[a] [%]	R_{br}[b] [%] (ee. abs. conf.)
1[c]	PPh_3	TsOH	24	>99	47
2	PPh_3	$(COOH)_2$	24	6	>99
3	PPh_3	CCl_3COOH	24	1	-
4	PPh_3	HCl (1 drop)	24	50	81
5	PPh_3	HCl (3 drops)	24	90	96
6	PPh_3	HCl (5 drops)	24	78	75
7[d]	PPh_3	HCl	24	8	94
8[e]	PPh_3	HCl	24	98	75
9	DPPB	HCl	48	12	25
10	XANTPHOS	HCl	24	28	16
11	(*S*,*S*)-BDPP	HCl	72	0	-
12	(*R*)-BINAP	HCl	24	0	-
13	(*R*)-(*S*)-JOSIPHOS	HCl	24	0	-
14	DPPP	HCl	24	2	45
15	(*R*)-PHANEPHOS	HCl	48	45	24(18 R)
16	(*R*)-DIOP	HCl	24	22	18
17	(*R*)-DIOP	HCl	48	77	16(2 R)
18	(*R*)-DIOP	HCl	72	>99	14(2 R)
19[f]	(*R*)-DIOP	HCl	144	85	9(2 R)
20[g]	(*R*)-DIOP	HCl	72	50	20(6 R)
21[h]	(*R*)-DIOP	HCl	24	>99	18(1 R)

[a] Reaction conditions: 0.01 mmol of $Pd(OAc)_2$ (entries 1-8) or 0.01 mmol of $PdCl_2(PhCN)_2$ (entries 9-21), 0.06 mmol monodentate P-ligand or 0.04 mmol of bidentate P-ligands, 6 mmol phenol, 1 mmol styrene, T= 100°C, p(CO)= 100 bar, solvent: 10 mL of toluene, HCl= 3 drops≈ 30 µL≈ 0.35 mmol, other acids= 0.35 mmol. Conversion values were determined by GC.

[b] Regioselectivity towards branched ester (**3aa**). [moles of 3aa/ (moles of 3aa + moles of 4aa) ×100].

[c] Chemoselectivity towards ester is 17%. High extent of ether formation was observed.

[d] Styrene nucleophile ratio was 1:2.

[e] Styrene nucleophile ratio was 1:10.

[f] p(CO)= 10 bar, [g] T= 80°C, [h] T= 120°C.

Temperature parameter was also investigated in the optimisation and it was shown from **Table 1** that, while the activity of the catalyst system using Pd-DIOP catalyst can be significantly affected by changing the temperature parameter, the regioselectivity towards the branched ester was not strongly influenced (*entries 20* and *21*). With regard to CO pressure, it was noticed that longer reaction times were required to carry out the reaction when low CO pressure values

were introduced to attain good reaction activity. Additionally, a decrease in the regioselectivity values were observed under such conditions (*entry 19*). Moreover, only side product formation, that is, styrene-phenol adduct and styrene dimers were detected under atmospheric conditions (1 bar CO).

Our next task was to explore the influence of 4-substituted derivatives (phenols and styrenes) on regio- and enantioselectivity for the hydroaryloxycarbonylation reaction in the presence of the *in situ* generated systems afforded by $Pd(PhCN)_2Cl_2$ and (*R*)-DIOP. Seven (**1a-g**) and ten representatives (**2a-j**) of styrenes and phenols respectively, were selected to investigate whether these substituted derivatives have an impact on the hydroaryloxycarbonylation reaction. These experiments were conducted under optimised conditions (*Scheme 2*).

No significant variances in regioselectivity values for the branched esters (**3**(**a-g**)(**a-j**)) (those obtained from *para*-substituted styrenes/parent phenol and of the ones obtained from *para*-substituted phenols/parent styrene) can be found. Styrene derivatives possessing electron donating properties ((**1b**) (**1c**) (**1d**)) slightly enhanced the formation of the branched ester (**Table** 2, *entries 2-4*). A reversed influence on the regioselectivity towards the branched ester can be observed when electron withdrawing substituents were used. For instance, the preference formation of the branched ester in case of trifluoromethyl substituent was low (*entry 8*) (the ester of (**3ga**) which formed by the reaction of (**1g**) and the parent phenol (**2a**)).

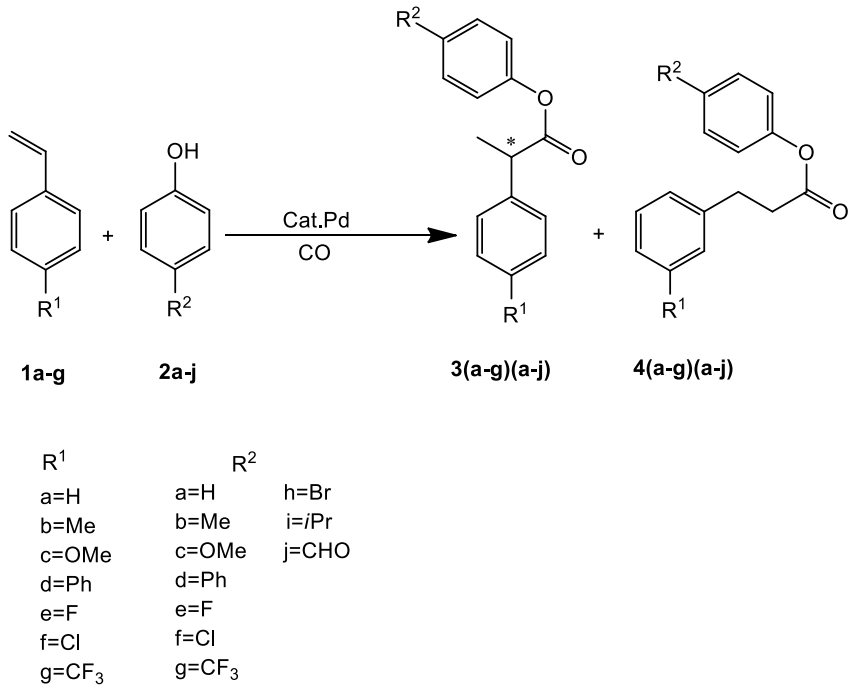
Interestingly, it was observed that in spite of the variation for substituents' electronic properties of phenols, similar regioselectivity values toward the branched esters were achieved in all cases. No strong dependence between phenol substituents and the ester selectivities can be inferred from the obtained results. Moreover, the regioselectivity obtained for the ester (**3aa**) produced from the parent styrene (**1a**) and phenol (**2a**) was close to those obtained for substituted phenols.

It is worth mentioning that ester enantiomers separation of the obtained branched ester derivatives was not successful by using various GC chiral columns, hence, we carried out the derivatisation process for the branched esters by reduction process using $LiAlH_4$ reagent to produce 2-arylpropanols. Fortunately, separable isomers can be obtained ((*S*) isomer was eluted before the (*R*) isomer). Additionally, it can be seen from **Table 2**, that the formation of the enantiomer aryl (*R*)-2-aryl propanoates were favoured in all cases. Some experiments revealed the formation of racemic or close to racemic mixtures. All the hydroaryloxycarbonylation reactions afforded low enantioselectivities (ee-s up to 14%). Depending on the Hammett substituents constants (σ_p) which in our case can be used to express the electronic properties

for the *para*-substituted styrenes and phenols, it can be stated that no clear correlation can be found between the electronic properties and the optical yields of the branched esters.

Methyl and chloro substituents gave the best optical yield values with respect to styrene substrates (*entries 2* and *6*). Reduction of the temperature to 80 °C increased the e.e. value (*entry 7*). The best ee-s with regard to phenol nucleophiles were provided by bromo and formyl phenol substituents (*entries 15* and *17*). Methoxy, fluoro and trifluoromethyl substituents afforded no optical yields purity. On the other side chloro and isopropyl substituents had similar effect on regioselectivity that is, close to racemic mixtures can be seen in these cases. Moreover, substituted styrenes and phenols were selected and allowed to react together under the same optimised conditions. The optical yield of the produced enantiomers was studied and it was shown from e.e. values that the presence of substituents on both styrene and phenol at the same time did not support each other. Surprisingly, in some cases they afforded lower e.e. values when compared to experiments that involve the presence of only one substituent either on styrene or phenol. For instance, compare e.e. values for ((**3fh**), (**3fa**) and (**3ah**)) and ((**3bc**), (**3ba**) and (**3ac**)).

It is worth mentioning that the generally accepted mechanism of the hydroalkoxycarbonylation of alkenes that was used to interpret the formation of alkyl esters (*Scheme 24* in the **Introduction** part) can be used to rationalise the formation of aryl esters too.



Scheme 2. Hydroaryloxycarbonylation using 4-substituted styrenes as substrates and 4-substituted phenol nucleophiles

Table 2. Palladium-catalysed hydroaryloxycarbonylation of styrenes.[a]

Entry	Styrene (substituent)	Phenol (Substituent)	Time [h]	Conversion[a] [%]	Regioselectivity Branched ester[b] [%]	Enantiomeric excess[c] [%]
1	(**1a**) H	(**2a**) H	48	77	16	2 (R)
2	(**1b**) Me	(**2a**) H	96	96	22	7 (R)
3	(**1c**) OMe	(**2a**) H	96	>99	20	0
4	(**1d**) Ph	(**2a**) H	96	91	18	n.d.
5	(**1e**) F	(**2a**) H	72	>99	16	0
6	(**1f**) Cl	(**2a**) H	48	75	14	10 (R)
7[d]	(**1f**) Cl	(**2a**) H	120	77	17	14 (R)
8	(**1g**) CF_3	(**2a**) H	96	>99	9	0
9	(**1a**) H	(**2b**) Me	48	53	16	1 (R)
10	(**1a**) H	(**2c**) OMe	48	56	20	5 (R)
11	(**1a**) H	(**2d**) Ph	48	98	18	1 (R)
12	(**1a**) H	(**2e**) F	48	68	19	5 (R)
13	(**1a**) H	(**2f**) Cl	48	68	19	<1 (R)
14	(**1a**) H	(**2g**) CF_3	48	37	15	5 (R)
15	(**1a**) H	(**2h**) Br	48	65	17	9 (R)
16	(**1a**) H	(**2i**) $CH(CH_3)_2$	48	52	20	<1 (R)
17	(**1a**) H	(**2j**) CHO	72	>99	25	8 (R)
18	(**1f**) Cl	(**2j**) CHO	120	42	17	11 (R)
19	(**1f**) Cl	(**2h**) Br	48	83	16	4 (R)
20	(**1b**) Me	(**2c**) OMe	48	87	20	2 (R)

[a] Reaction conditions: 0.01 mmol of $PdCl_2(PhCN)_2$, 0.04 mmol (*R,R*)-DIOP, 6 mmol nucleophile, 1 mmol substrate, T= 100 °C, p(CO) = 100 bar, solvent: 10 mL of toluene. Conversion values were determined by GC.

[b] Regioselectivity towards branched ester (**3a**). [moles of 3/ (moles of 3 + moles of 4) × 100].

[c] Enantioselectivities were determined after reduction by chiral GC. (*S*)-2-phenylpropanol was eluted before the (R) enantiomer.

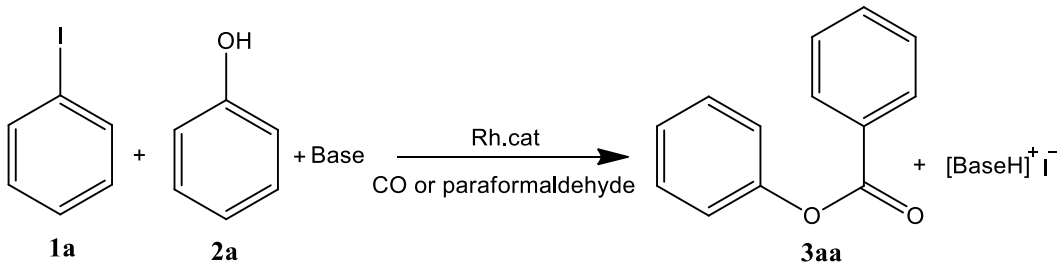
[d] T = 80°C.

Based on the results above, it could be stated that the variety of different *para*-substituents on both styrene substrates and phenol nucleophiles allowed the preparation of both branched and linear ester derivatives, aryl 2-arylpropanoates and aryl 3-arylpropanoates, respectively, in the presence of the catalyst system composed of $Pd(PhCN)_2Cl_2$-DIOP-HCl. The regioselectivity of the branched esters were found to be between 9-25% and the electronic properties of the substituents (on both sides) showed no clear effects on regioselectivity. For non-racemic mixture cases of the branched ester derivatives, a preference formation towards the (*R*) isomers can be noticed for all cases. The highest ee value was 14% and was afforded from chloro-substituted styrene and the parent phenol.

3.2. Rhodium-catalysed aryloxycarbonylation of iodo-aromatics by 4-substituted phenols with carbon monoxide or paraformaldehyde

The use of substituted haloarenes as substrates in the carbonylation reactions has found various applications in organic synthesis. Pd-catalysed alkoxy- and aryloxycarbonylation reactions of iodoarenes are well known in the literature. In this study we aimed at studying the Rh-catalysed aryloxycarbonylation reactions of iodoarenes, *i.e.*, Rh precursors were used instead of Pd systems. Hence, the optimisation conditions of esterification reaction using iodobenzene as substrate with phenol as *O*-nucleophile were carried out under carbon monoxide atmosphere as well as using paraformaldehyde as a CO source [145].

Initially, iodobenzene (**1a**) and phenol (**2a**) were selected as a model reaction to carry out the carbonylation process to produce phenyl benzoate ester (**3aa**) in the presence of Rh catalysts (*Scheme 3)*. As mentioned above, either conventional CO gas or paraformaldehyde as CO surrogate were conducted for this model reaction and sufficient ester synthesis was observed considering both strategies. Generally, Rh precursors as well as the used ligands were varied to conduct the optimisation for the reaction. In addition to that, the reaction conditions were also modified and tested. The optimised reaction parameters and conditions were adapted to conduct and test carbonylation reaction for *para*-substituted iodoarenes and *para*-substituted phenols.



Scheme 3. Rhodium-catalysed phenoxycarbonylation of iodobenzene

3.2.1. Reaction under carbon monoxide atmosphere

To identify the optimal conditions for the phenoxycarbonylation of iodobenzene substrate and the parent phenol all conditions and parameters were tested. Generally, the reaction involved the addition of triethylamine as a base, toluene solvent and a fixed ratio of catalyst to substrate of 1:100. The general feature for the reaction was the formation of the desired ester (**3aa**) as well as the production of small extent of side products such as the formation of benzene which can be formed due to the reduction of iodobenzene and the production of carboxylic acids

which can be afforded by hydrolysis. The time required to carry out the reaction is 48 h in order to obtain satisfying conversions which enable facile isolation of the products in analytical purity. Attempts to enhance the conversions by increasing reaction times were unsuccessful. Ester-selectivities were in the range between 57-96% and higher yields of (**3aa**) were obtained when the reaction was carried at elevated temperatures 120 °C.

Various ligands were screened in the optimisation, that is, monodentate PPh_3 as well as phosphorous bidentate ligands were tested. Apparently, based on the activity and selectivity values we can deduce that active catalytic systems were formed in the conducted experiments (**Table 3**, *entries 1, 3, 5, 6, 10* and *14*). DPPB ligand exhibited lower activities and (**3aa**) yields (*entries 11* and *12*). Similar conversions were achieved when DPPP, DPPF and Xantphos ligands were used. However, an extra advantage of the use of the latter ligand, due to the higher ester selectivity, afforded by its addition (67%, 82%, 95%, respectively). High chemoselectivity towards ester compound and near complete conversion of the parent substrate were achieved when PPh_3 ligand and 0.33 mmol of the parent substrate were used. Applying 1.0 mmol of iodobenzene substrate in the reaction under similar conditions resulted in 53% substrate conversion and 49% ester yield. Relying on the obtained results, Rh-Xantphos system was chosen to carry out further experiments to explore the reaction scope by investigating different substituted substrates and phenols (**Table 4**).

Table 3. Optimisation of the phenoxycarbonylation reaction under CO atmosphere.[a]

Entry	precursor	Ligand (eq.)	Temp. [°C]	p(CO) [bar]	Conversion [b] [%]	Yield (3aa)	Chemosel.[c] [%]
1	$Rh(CO)_2(acac)$	PPh_3 (4)	90	90	53	49	92
2	$Rh(CO)_2(acac)$	Xantphos (2)	90	90	62	51	82
3	$Rh(CO)_2(acac)$	Xantphos (2)	120	90	80	76	95
4	$Rh(CO)_2(acac)$	Xantphos (2)	90	60	58	52	90
5	$[Rh(nbd)Cl]_2$	Xantphos (4)	120	90	79	76	96
6	$Rh(CO)_2(acac)$	DPPP (2)	90	90	76	72	95
7	$Rh(CO)_2(acac)$	DPPP (2)	120	90	92	62	67
8	$[Rh(nbd)Cl]_2$	DPPP (4)	90	90	27	21	78
9	$[Rh(nbd)Cl]_2$	DPPP (4)	90	60	8	6	75
10	$[Rh(nbd)Cl]_2$	DPPP (4)	120	90	60	53	88
11	$Rh(CO)_2(acac)$	DPPB (2)	90	90	20	19	95
12	$[Rh(nbd)Cl]_2$	DPPB (4)	90	90	7	4	57
13	$Rh(CO)_2(acac)$	DPPF (2)	90	90	64	57	89
14	$Rh(CO)_2(acac)$	DPPF (2)	120	90	82	67	82

[a] Reaction conditions: precursor: 0.01 mmol, Et_3N: 1.2 mmol, phenol: 2mmol, substrate: 1 mmol, toluene: 10 mL, time: 48 h.

[b] Determined by GC.

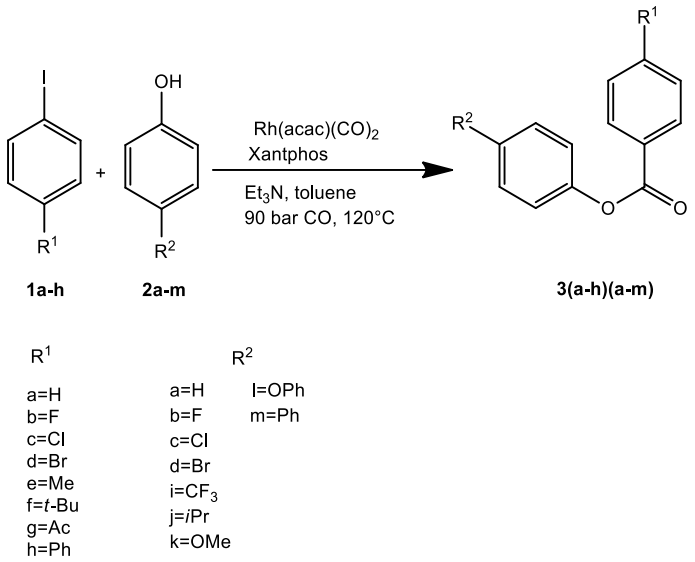
[c] Chemoselectivity towards ester (**3aa**) product [moles of **3aa**/ moles of converted **1a**) × 100].

Comparing data gained from both precursors used in the phenoxycarbonylation reaction indicated an interesting feature regarding both the catalyst system efficiency and the ester selectivity (compare *entries 7* and *10*; *11* and *12*). As can be shown in **Table 3** that the performance of the precursor $Rh(CO)_2(acac)$ was superior compared to that of the dinuclear complex $[Rh(nbd)Cl]_2$. The reason behind such observation might be attributed to the formation of the catalytically active species $Rh(CO)_n$(diphosphine) (n= 1,2), that is, the easier formation of that active species in case of the mononuclear complex might explain the higher efficiency of the $Rh(acac)(CO)_2$ complex. Two reasons can be introduced to clarify the easier tendency for the formation of the active species in case of $Rh(CO)_2(acac)$. The first is that no need for dehalogenation process (in case of Rh(I) species) and dehydrohalogenation step which require the presence of base (in case of Rh(III) species formed in the catalytic cycle) to initiate the suggested active species in the catalytic cycle. It is well known that the primary role of the added base is to abstract HI, so, the presence of hydrohalogenated-containing species in the catalytic cycle will affect the role of the added base. The second factor is that it is obviously shown from the structure of the dinuclear compound that it requires the pre-activation of CO to generate the active species, while the pre-activation of CO in case of the mononuclear complex was not required as the starting compound (precursor) contains CO in its structure.

Both precursors exhibited a resemblance with respect to activity and selectivity when Xantphos ligand was used as can be manifested in the former table (**Table 3**, *entry 3* and *5*). It is worth noting that 1:2 ratio of metal to ligand was used in both cases. However, more equivalents of Xantphos ligand were used in case of the dinuclear complex. Moreover, the CO pressure parameter was also studied in the optimisation experiments and according to our data, lower conversions were achieved when lower CO pressures were applied (for comparison see *entries 2* and *4; 8* and *9*).

It can be stated that the optimum experiment conditions that can be adapted to conduct further experiments regarding aryloxycarbonylation reactions was that one which involved the addition of Xantphos ligand to $Rh(acac)(CO)_2$ precursor under CO pressure of 90 bar in toluene solvent at 120 ℃ (*entry 3*).

Various *para*-substituted iodobenzenes and *para*-substituted phenols can be utilised to investigate the effect of substrate and phenol substitution on the activity of the carbonylation reaction when the optimum conditions were applied (*Scheme 4*).



Scheme 4. Rh-catalysed aryloxcarbonylation of substituted iodobenzene

Regarding *para*-substituted iodobenzenes, they afforded more reactivity than the parent iodobenzene compound in the aryloxycarbonylation reaction, without any dependence on the electronic properties of the substituents whether they are electron-donating or withdrawing groups (**Table 4)**. Esters formed in these cases (phenyl 4-substituted benzoates) (**3ba**-**3ha**) were afforded between 72% and 97% even though lower yield value of the ester derivative (*entry* 5) was given when *tert*-butyl group was located in the *para*-position of iodobenzene substrate. Aryl iodide bearing acetyl group in the *para* position (**1g**) had the highest impact concerning the ester yield (97%) and the reaction activity as well.

The effect of phenols' substituents was also studied in the aryloxycarbonylation reaction. *para*-Substituted phenols afforded ester derivatives (4-substituted aryl benzoates) (**3ab**-**3am**) in higher yields (91%-98%) compared to the result obtained from the parent iodobenzene and the parent phenol (**3aa**). No correlation was found between the ester yields and the electronic properties of the phenol substituents, in other words, either electron-withdrawing or donating groups were located in *para*-position on phenol, the corresponding ester yields were close to each other.

Findings obtained from Pd-catalysed aryloxycarbonylation reaction of 4-iodotoluene substrate were in agreement with the above-mentioned results, in which an enhanced reactivity for the 4-iodotoluene substrate was observed when *para*-substituted phenols were employed regardless of their nature [146].

It is well known that the electronic properties of substituents can be expressed by the (σ_p)-Hammett constant values. These constants can be either negative or positive values depending

on the properties of the substituents whether they are electron-donating or withdrawing groups, respectively. The *para*-Hammett constant values for the corresponding substituents are: F (0.062), Cl (0.227), Br (0.232), CHO (0.420), $COCH_3$ (0.500), CF_3 (0.540), Ph (-0.010), OPh (-0.030), *i*Pr (-0.150), Me (-0.170), *t*Bu (-0.200), OMe (-0.268) [146].

Additionally, the observations from **Table 4** assured that both substituents types on iodoarenes, *i.e.*, electron-withdrawing and donating groups, resulted in enhanced reaction activity compared to the reaction involving the parent substrate and phenol irrespective to the positive or negative (σ_p)-Hammett constant values (*vide supra*). The same trend was found for phenol substituents as well.

Table 4. Rhodium-catalysed aryloxycarbonylation of iodoarenes using gaseous CO.[a]

Entry	Iodobenzene (Substituent, R^1)	Phenol (Substituent, R^2)	Conversion[b] [%]	Ester yield[c] [%]
1	F (**1b**)	H (**2a**)	80	72 (**3ba**)
2	Cl (**1c**)	H (**2a**)	95	88 (**3ca**)
3	Br (**1d**)	H (**2a**)	97	87 (**3da**)
4	Me (**1e**)	H (**2a**)	97	88 (**3ea**)
5	*t*Bu (**1f**)	H (**2a**)	27	12 (**3fa**)
6	Ac (**1g**)	H (**2a**)	>99	97 (**3ga**)
7	Ph (**1h**)	H (**2a**)	96	86 (**3ha**)
8	H (**1a**)	F (**2b**)	>99	94 (**3ab**)
9	H (**1a**)	Cl (**2c**)	>99	98 (**3ac**)
10	H (**1a**)	Br (**2d**)	>99	95 (**3ad**)
11	H (**1a**)	CF_3 (**2i**)	98	93 (**3ai**)
12	H (**1a**)	*i*Pr (**2j**)	98	95 (**3aj**)
13	H (**1a**)	OMe (**2k**)	98	91 (**3ak**)
14	H (**1a**)	OPh (**2l**)	99	95 (**3al**)
15	H (**1a**)	Ph (**2m**)	>99	98 (**3am**)

[a] Reaction conditions: 0.01 mmol of $Rh(acac)(CO)_2$, 0.02 mmol Xantphos, 2 mmol nucleophile, 1.2 mmol Et_3N, 1.0 mmol substrate, T = 120°C, p(CO) = 90 bar, solvent: 10 mL of toluene, time= 48 h.

[b] Determined by GC.

[C] Isolated esters.

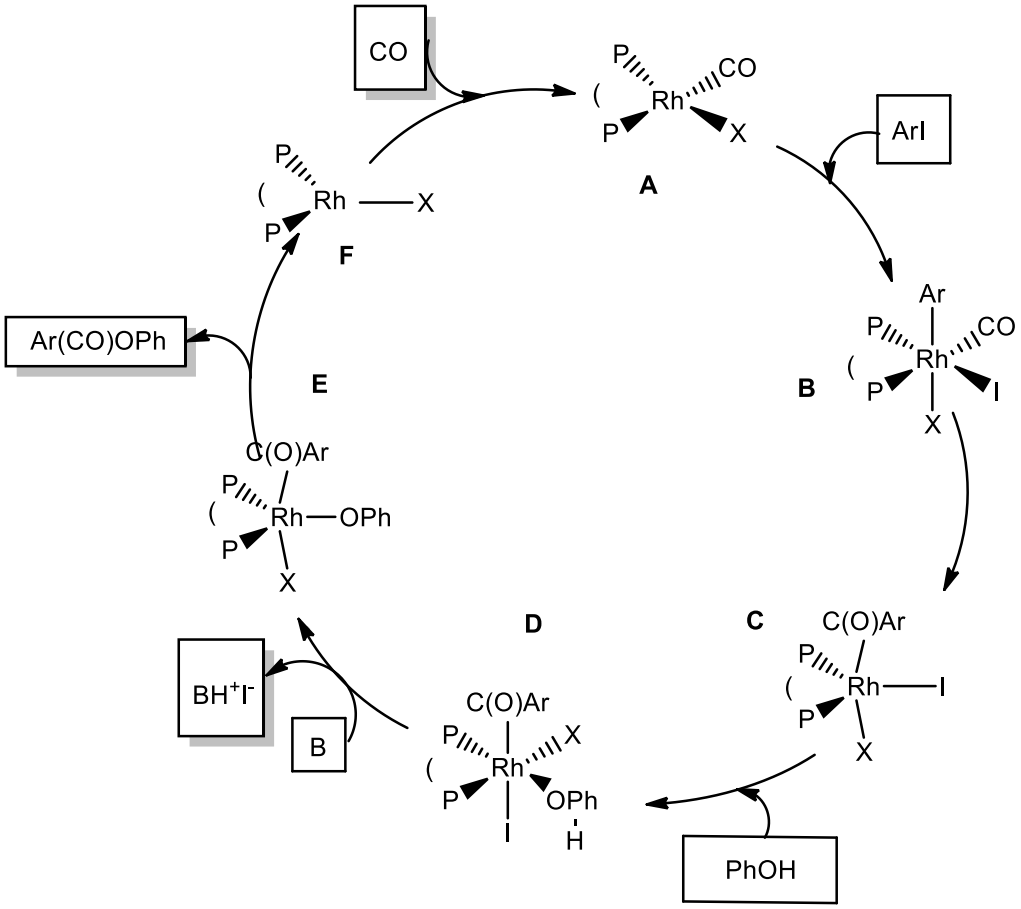
Accordingly, the rate determining step and the selectivity of the aryloxycarbonylation reaction should be after the Rh(III)-acyl complex, therefore, the steps after the oxidative addition step of Rh(I)-active species in the catalytic cycle (see proposed catalytic cycle below, (*Scheme 5*)) can be considered as choices to determine the rate determining step for the reaction as well as the activity and selectivity.

The well-known mechanism of Pd-catalysed alkoxycarbonylation reaction [147, 148] and the results obtained by Miura *et al* concerning the catalytic studies of the Pd-catalysed aryloxycarbonylation of *para*-iodotoluene substrate [146] can be considered as beneficial

sources for us to postulate a reasonable catalytic cycle for the Rh-catalysed aryloxycarbonylation of 4-substituted iodoarenes.

Initially, we assume that the active starting species that is formed in the catalytic cycle (*Scheme 5*) is Rh(I), namely, Rh(CO)(diphosphine)X (**A**). The first step in the cycle is the transformation of the Rh(I) active complex to Rh(III) species (**B**) by oxidative addition reaction of aryl iodide to the *in situ* generated active intermediate (**A**). The next step involves the CO insertion into Rh-C bond which resulted in the formation of the (acyl)Rh(III) complex (**C**). The complex (**D**) that is formed by the nucleophilic attack of phenol on complex (**C**) is converted to (acyl)(phenoxy) Rh(III) complex (**E**) by HI elimination assisted via base addition. Thereafter, the targeted ester compound, phenyl benzoate, was generated by reductive elimination process of the former complex (**E**) and the unstable Rh(I) species (**F**) was produced. The coordinatively unsaturated (**F**) intermediate transformed to the starting active species in the catalytic cycle by CO coordination.

As mentioned formerly, neither electronic properties of phenolic substituents nor aryl iodide substituents were causing variations in the carbonylation reaction activities as well as ester selectivity. Regarding elucidating the rate determining step in the catalytic cycle, the step related to the formation of (**B**) intermediate can be excluded. Moreover, the formation of (**C**) or (**D**) complexes cannot be appointed as the rate determining step, as obviously mentioned formerly, due to the non-dependence of the reaction activity on the electronic properties of phenols. In other words, a correlation between electronic properties of the phenol substituents and the corresponding activities should be found ((σ_p)-Hammett plot can be noticed). Since this is not the case, then (**C**) and (**D**) might not represent the determining step in the catalytic cycle. Based on the former description, we can assume that mutual interference of both substituents of phenols and iodoarenes are responsible together for tuning the reaction activity and selectivity. Hence, the transformation process of (**E**) complex that involved the phenolic cleavage of the (acyl)(phenoxy)Rh(III) intermediate can be chosen to express the reaction rate. In other words, the reductive elimination step of the intermediate (**E**) to produce ester compound is the rate determining step in the catalytic cycle.



Scheme 5. Catalytic cycle for Rh-catalysed aryloxycarbonylation of iodo-aromatics under CO atmosphere

3.2.2. Reactions in the presence of paraformaldehyde as CO source

The second approach dealing with carrying out carbonylation reaction, more specifically, the aryloxycarbonylation of iodobenzene substrates and phenols as *O*-nucleophilic donor compounds was also initiated by applying the same formerly-mentioned precursors in the absence of carbon monoxide atmosphere, but using a surrogate instead, namely, paraformaldehyde which acts as a CO source (*Scheme 6*). Thus, both methodologies (CO atmosphere and paraformaldehyde as CO source) might provide versatile sources of results which can assist in making comparison studies between the two protocols.

The starting point was to optimise the reaction conditions for the Rh-catalysed phenoxycarbonylation reaction using paraformaldehyde by applying both iodobenzene (**1a**) and the parent phenol compound (**2a**) (**Table 5**). The Rh *in situ* formed catalysts were generated in these experiments by applying catalyst to substrate ratio of 1:50. The starting complexes (precursors) that were used in the optimisation were similar to that ones used in phenoxycarbonylation reaction under CO atmosphere.

Performing the reaction in conventional toluene solvent resulted in higher conversion and ester yield when $[Rh(nbd)Cl]_2$ precursor, DPPP ligand and Et_3N were used as the catalyst system (metal to ligand ratio 1:1) (*entry 1*) compared to the results obtained of (*entry 2*) which involved the application of the same catalyst system but in DMF solvent instead of toluene (low conversion and negligible ester yield obtained in case of DMF). The general feature of both experiments was the obtaining of side products formation such as acid and hydrodeiodinated compound of the corresponding substrate. The formation of many side products explained the low preference formation of the target ester.

Apparently, testing different precursors and ligands did not incorporate in enhancing neither the conversion nor the ester selectivity (*entries 1-6*). Unlike the significant effort of Xantphos in obtaining high reaction activities and ester selectivites under high pressure of CO environment, moderate performance for Xantphos ligand regarding the paraformaldehyde-based carbonylation reaction was afforded (*entry 6*).

Additionally, more exploration of the optimisation conditions was conducted by testing various solvents and bases. It was found that replacing triethylamine base with Na_2CO_3 enhanced the optimisation results. Besides, the undesired acid formation caused by the ester hydrolysis was reduced by the addition of $MgSO_4$ which acted as a drying agent, so a better chemoselectivity of the target ester was achieved.

To test the effect of the equivalents of the tested ligands, 5 equivalents of DPPP ligand was used instead of 2 (compare entry *1* and *7*). The ester selectivity was enhanced by increasing number of equivalents of DPPP ligand as well as using Na_2CO_3 base and $MgSO_4$ drying agent (side products were supressed and or eliminated). Disappointingly, lower activity value was obtained (see the substrate conversion value reduction from 45% to 26%).

Our group aimed at obtaining good conversion and ester selectivity values in parallel, so we decided to think how to increase the dissolution of paraformaldehyde in the reaction mixture which might increase the conversion value. We noticed that adding ethyl acetate as a co-solvent to toluene solvent was satisfactory in achieving good conversion value (*entry 8*), near to that found of (*entry 1*), when only 2 equivalents of DPPP ligand were used. Moreover, better ester selectivity was afforded compared to the result of (*entry 1*), Unfortunately, the ester selectivity was reduced compared to the result of (*entry 7*).

One very important factor we were thinking about in order to get better experimental results, was the incorporation of an additive compound or a cocatalyst. In this context, we decided of testing the effect of copper(I) chloride compound addition. It is worth noting that CuCl compound was used in a previous study concerning palladium-catalysed aryloxycarbonylation

reactions and the effect of the CuCl addition was the increasing of the reaction activity. The role of CuCl according to the authors was its ability to remove PPh_3 ligand(s) from palladium systems and as a result the creation of active species in the catalytic cycle [146]. It can be concluded from (*entry 7*, **Table 5**) that the low conversion of 26% is due to the increased number of bis-diphosphine rhodium complexes that will be formed upon increasing the added ligand to precursor ratio which in turn might supress the number of the catalytically active species that is required in the catalytic cycle. Since CuCl possess the ability of removing ligands from the coordination sphere of the Pd complex as mentioned before, we believe that its addition in the optimisation experiments will have an impact and considerable advantage by creating vacant sites on the coordination sphere of the intermediate complexes and thus generating catalytically active Rh species from the *in situ* generated bis-diphosphine complexes.

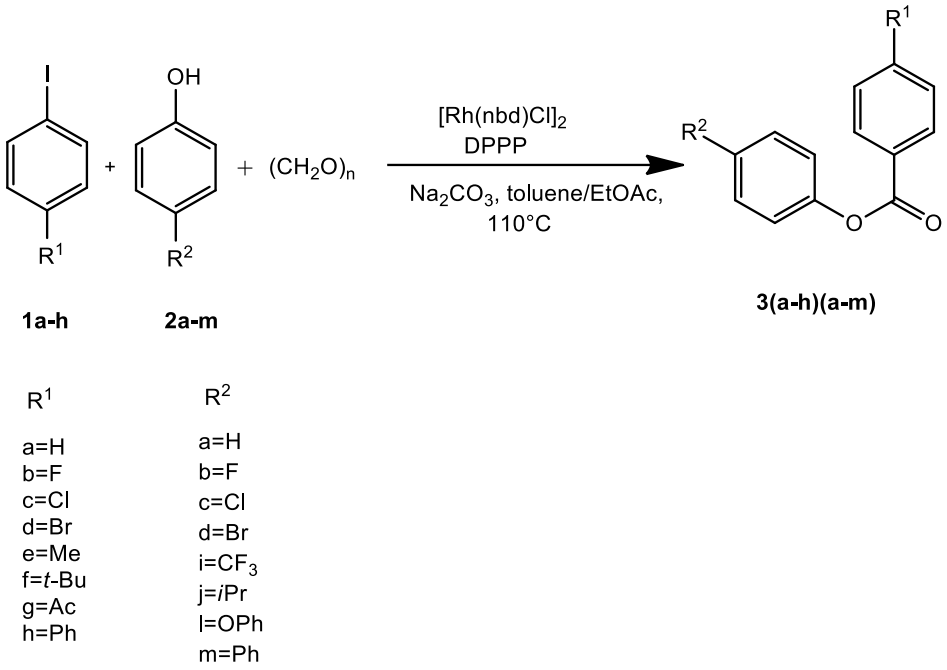
We can conclude from the previous findings that three factors seemed to be effective to enhance the progress of the paraformaldehyde-mediated carbonylation reaction. The first is the increase number of the equivalents from 2 to 5 of DPPP ligand (good ester selectivity and poor conversion). The second is the use of EtOAc as a co-solvent (good conversion and low ester selectivity). The third factor is the CuCl addition which might solve the problem of low substrate conversion in case of using 5 equivalents of DPPP ligand. Based on these factors, the investigation of the effect and performance of the combined factors in one experiment seemed to be rational.

Interestingly, a promising result regarding both conversion and selectivity was achieved when the former factors were combined together in the reaction mixture (*entry 9*). The reaction conditions of (*entry 9*) were applied for further experiments replacing DPPP ligand with DPPB and DPPF maintaining the catalyst to ligand ratio. Both conversion and selectivity values were lower compared to the experiment where DPPP ligand was used. Attempts to enhance the result afforded form (*entry 9*) by increasing the ratio of added EtOAc solvent from 60% to 75% were failure and low catalyst activities were obtained instead (compare *entries 9* and *13*).

Next, further experiments were conducted by keeping the optimised conditions obtained of (*entry 9*) untouched as well as maintaining the catalyst: ligand ratio, but only changing the catalyst systems by varying precursors and ligands (*entries 10-12*). Lower activity and selectivity results compared to the obtained result of (e*ntry 9*) were obtained.

With regard to the used precursors, we found that the efficiency performance of $[Rh(nbd)Cl]_2$ was superior over the mononuclear $Rh(acac)(CO)_2$. Besides, the comparison between carbonylation reactions occurred under CO atmosphere and paraformaldehyde as a CO source

confirmed that the latter complex provided much better performance in case of CO atmospheric carbonylation-based reaction.



Scheme 6. Rh-catalysed aryloxycarbonylation of iodoarenes and phenols by using paraformaldehyde as CO source

Table 5. Optimisation of the phenoxycarbonylation reaction in the presence of paraformaldehyde.[a]

Entry	precursor	Ligand (eq.)	solvent	Conversion[b] [%]	Ester Yield[b] [%]
1[c]	[Rh(nbd)Cl]$_2$	DPPP (2)	Toluene	45	19
2[c]	[Rh(nbd)Cl]$_2$	DPPP (2)	DMF	29	2
3[c]	Rh(CO)$_2$(acac)	DPPB (1)	Toluene	32	15
4[c]	[Rh(nbd)Cl]$_2$	DPPB (2)	Toluene	47	15
5[c]	[Rh(nbd)Cl]$_2$	DPPF (2)	Toluene	44	14
6[c]	[Rh(nbd)Cl]$_2$	XANTPHOS (2)	Toluene	24	11
7[d]	[Rh(nbd)Cl]$_2$	DPPP (5)	Toluene	26	26
8[d]	[Rh(nbd)Cl]$_2$	DPPP (2)	EtOAc:Tol. (6:4)	40	25
9[d,e]	[Rh(nbd)Cl]$_2$	DPPP (5)	EtOAc:Tol. (6:4)	76	76
10[d,e]	[Rh(nbd)Cl]$_2$	DPPB (5)	EtOAc:Tol. (6:4)	38	25
11[d,e]	[Rh(nbd)Cl]$_2$	DPPF (5)	EtOAc:Tol. (6:4)	43	18
12[d,e]	Rh(CO)$_2$(acac)	DPPB (2.5)	EtOAc:Tol. (6:4)	22	11
13[d,e]	[Rh(nbd)Cl]$_2$	DPPP (5)	EtOAc:Tol. (8:4)	5	5

[a] Reaction conditions: precursor: 0.01 mmol, phenol: 3mmol, substrate: 0.5 mmol, solvent: 10 mL, paraformaldehyde: 16 mmol, temperature 110°C, reaction time: 24 h. Mixed solvents (*entries 7-12*) are given in v/v%. [b] Determined by GC, [c] 0.5 mmol Et_3N was added, [d] $MgSO_4$: 1.25 mmol and Na_2CO_3: 1.5 mmol were added, [e] 1.0 mmol CuCl was added.

Table 6. Rhodium-catalysed aryloxycarbonylation of iodoarenes using paraformaldehyde as CO source.[a]

Entry	Iodobenzene (substituent, R^1)	Phenol (Substituent, R^2)	Conversion[b] [%]	Ester yield[b] [%]
1	F (**1b**)	H (**2a**)	28	19 (**3ba**)
2	Cl (**1c**)	H (**2a**)	67	3 (**3ca**)
3	Br (**1d**)	H (**2a**)	>99	6 (**3da**)
4	Me (**1e**)	H (**2a**)	43	35 (**3ea**)
5	*t*Bu (**1f**)	H (**2a**)	40	13 (**3fa**)
6	Ac (**1g**)	H (**2a**)	>99	2 (**3ga**)
7	Ph (**1h**)	H (**2a**)	89	9 (**3ha**)
8	H (**1a**)	F (**2b**)	>99	86 (**3ab**)
9	H (**1a**)	Cl (**2c**)	51	51 (**3ac**)
10	H (**1a**)	Br (**2d**)	87	83 (**3ad**)
11	H (**1a**)	CF_3 (**2i**)	49	43 (**3ai**)
12	H (**1a**)	*i*Pr (**2j**)	65	61 (**3aj**)
13	H (**1a**)	OPh (**2l**)	61	61 (**3al**)
14	H (**1a**)	Ph (**2m**)	58	58 (**3am**)

[a] Reaction conditions: 0.01 mmol of $[Rh(nbd)Cl]_2$, 0.05 mmol of DPPP, 3 mmol nucleophile, 0.5 mmol substrate, 16 mmol paraformaldehyde, 1.5 mmol Na_2CO_3, 1.25 mmol $MgSO_4$, 1.0 mmol CuCl, T = 110°C, solvent total volume: 10 mL, toluene: ethyl acetate (4:6), reaction time = 24 h. [b] Determined by GC.

The variety of different groups on both substrates and phenols enabled the synthesis of numerous aryl 4-substituted-benzoates (**Table 6**). From the data in **Table 6** above we can see that the conversion values for the aryloxycarbonylation reaction of iodoarenes and phenols using paraformaldehyde as a CO source were lower than the achieved conversion values concerning the same iodobenzenes and phenols by carbonylation reaction under CO atmosphere in most of the cases. Besides, it was found that the ester yields were dramatically decreased in all cases that are involving the reaction of substituted iodobenzenes and parent phenol (*entries 1-7*) compared to the yield value afforded from the phenoxycarbonylation of the parent iodobenzene substrate and the parent phenol (*entry 9*, **Table 5**). The reason behind affording low chemoselectivity values of ester products can be explained by observing the formation of the hydrodeiodinated compounds, that is, the reduction pathway is obviously dominating against the carbonylation reaction pathway (*entries 1-7*). This pathway was studied by other authors [121] as well as the study introduced by Lee and co-workers in their publication dealing with paraformaldehyde assisted palladium-catalysed hydrodehalogenation reaction [149]. On the other hand, the oxidation reaction can be represented by alcohol nucleophiles transformation to aldehydes or formate products.

Actually, the chemoselectivity values toward esters formation were high in all cases concerning that ones involving substituted phenols and were irrespective to the nature of the substituents

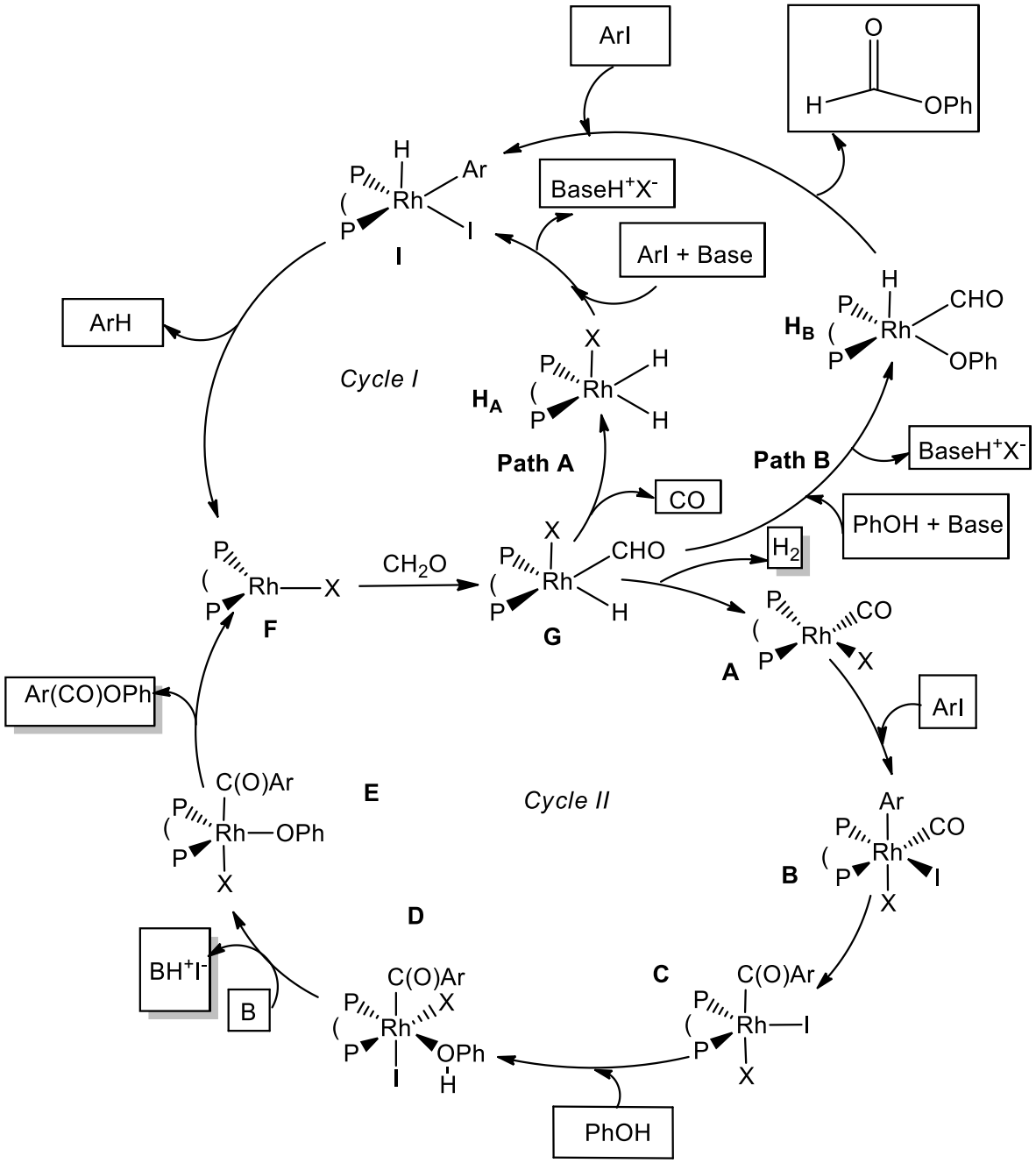
and found to be over 86% in all cases. The chloro-, phenoxy- and phenyl substituted phenols afforded exclusive ester derivatives (*entries 9*, *13* and *14* respectively). The conversion of the substrate in these cases were varied between 49% and full conversion and no hydrodeiodination pathway was noticed (*entries 8-14*).

The experiment involving the reaction of parent phenol and parent iodobenzene (*entry 9*, **Table 5**) gave higher conversion than most of the substituted phenols, but not for fluoro- and bromophenol derivatives (*entries 8* and *10*). As mentioned before, some iodobenzenes showed high chemoselectivity values toward hydrodeiodinated products and low ester selectivity values. The observation of hydrodeiodinated products in these cases is not related to the nature of the iodobenzene substitution, whether they are electron withdrawing or donating groups. It can be stated that there is no clear dependence between both reaction activity and selectivity and the electronic properties of the substituents either on substrate or phenol.

Concerning both phenoxycarbonylation methodologies of iodoaromatics and the reduction pathway to generate the hydrodeiodinated compounds a plausible reaction mechanism can be proposed (*Scheme 7*) based on our experimental results and reported publications [114, 147-149]. Initially, formaldehyde can be generated from depolymerisation of paraformaldehyde at elevated temperatures which can be readily subjected to an oxidative addition step to the Rh(I) complex (**F**) to afford (hydrido)(formyl)rhodium(III) complex (**G**). The intermediate species (**G**) can undergo two routes in the catalytic cycle; the first is the formation of the (carbonyl)rhodium(I) complex (**A**) by H_2 reductive elimination step. This species is responsible for the aryloxycarbonylation pathway of iodoaromatics (*cycle II*). The same steps sequence observed in the former mechanism can also be applied to this mechanism, that is, (**B**), (**C**), (**D**) and (**E**) intermediates in both mechanisms are similar to each other.

The other route is that complex (**G**) can be converted to the (dihydrido)rhodium species ($\mathbf{H_A}$) by (CO) dissociation which might be incorporated for the iodoarenes reduction process generating the hydrodeiodinated derivatives (*Cycle I*, **path A**). Another possibility is the formation of (phenoxy)(formyl)rhodium(III) intermediate ($\mathbf{H_B}$) which in turn could be involved in the production of phenyl formate as a side product (**path B**). Both possibilities lead to the formation of complex (**I**) ((hydrido)(aryl)rhodium(III)) complex which can be considered as a key intermediate for observing the hydrodehalogenated compounds and the unsaturated complex (**F**).

In this chapter, the application of $Rh(acac)(CO)_2$-Xantphos-Et_3N and $[Rh(nbd)Cl]_2$-DPPP-Na_2CO_3-CuCl catalytic systems for the aryloxycarbonylation of iodobenzenes and phenols was studied. The aryloxycarbonylation reaction carried out either in the presence of gaseous CO or paraformaldehyde as a CO source afforded the corresponding aryl 4-substituted benzoates. In the presence of CO atmosphere, the former system afforded higher conversion as well as higher ester yields than the conversion and the ester yield obtained from the reaction of parent iodobenzene and parent phenol irrespective to the electronic properties of substituents positioned either on iodobenzenes or phenols. In the presence of paraformaldehyde as CO source in the latter system, when substituted iodobenzenes and parent phenol were reacted, lower ester yields were afforded compared to the ester yield obtained from the parent iodobenzene and the parent phenol due to the formation of hydrodeiodinated derivatives. Besides, lower ester yields in most of the cases were obtained when parent iodobenzene and substituted phenols were reacted compared to the ester yield obtained from parent iodobenzene and parent phenol.



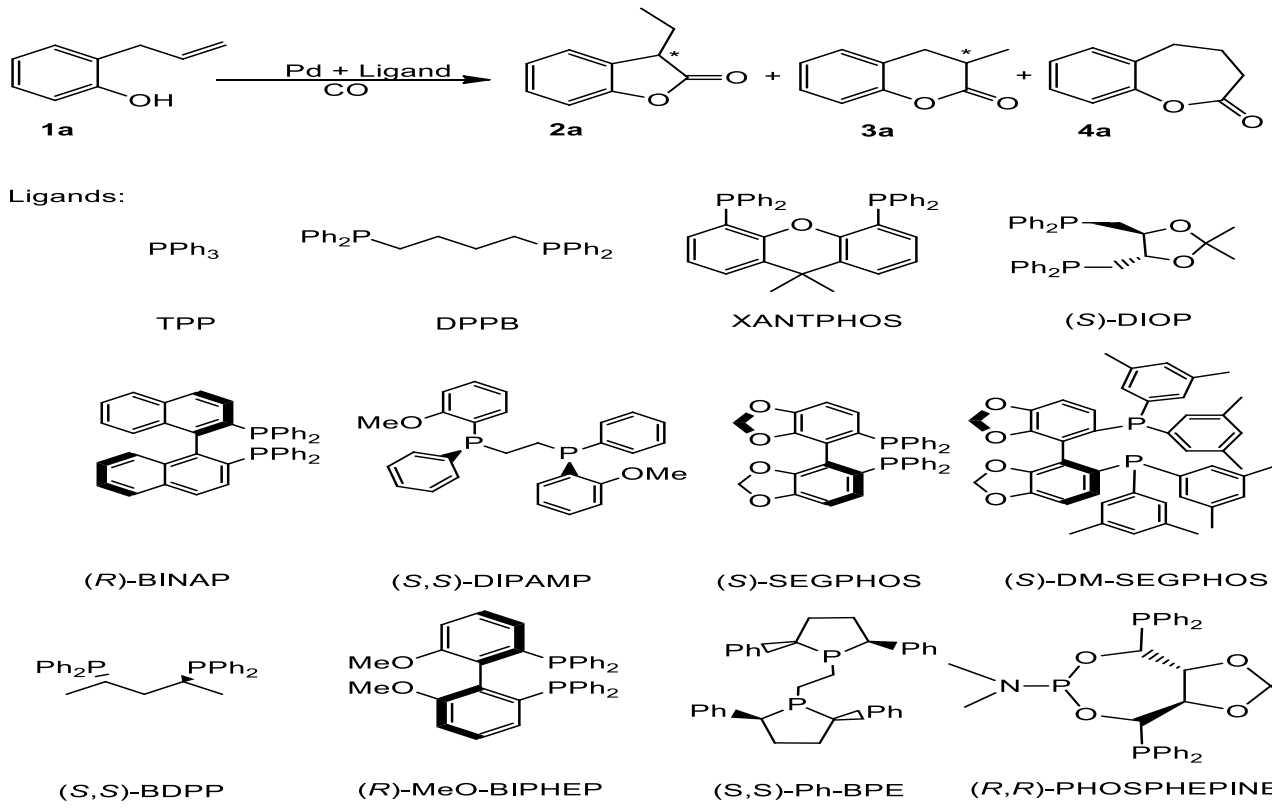
Scheme 7. A plausible mechanism of the phenoxycarbonylation and hydrodeiodination of iodoarenes with formaldehyde

3.3. Palladium-catalysed intramolecular asymmetric cyclohydroaryloxy-carbonylation of 2-allylphenol derivatives. Synthesis of chiral lactones via cyclocarbonylation

The investigation of the cyclohydroaryloxycarbonylation reaction of 2-allylphenols to synthesise lactone compounds with greater emphasis on the selective formation towards the chiral 6-membered lactone derivatives and the enantioselective investigation of these chiral compounds seemed to be realistic. Investigating the optimisation conditions under H_2 gas absence was an additional aim in our study [150].

3.3.1. Optimisation of the cyclohydrophenoxycarbonylation reaction

Initially, the investigation of the optimisation reaction for 2-allylphenol substrate was established by performing Pd-catalysed cyclohydrophenoxycarbonylation experiments for the parent substrate (**1a**) to afford the corresponding five-, six-, or seven-membered lactones ((**2a**), (**3a**) and (**4a**), respectively)) (*Scheme 8*).



Scheme 8. Palladium-catalysed cyclohydrophenoxycarbonylation of 2-allylphenol

Our intention was to accomplish different goals as in Alper's work [138] including the obtaining of good results concerning lactones chemoselectivity and enhancing the formation

yield of the chiral lactone regioisomer (6-membered lactone) as well as observing good catalytic activity performance, hence, a detailed optimisation was necessary. $Pd(OAc)_2/PPh_3$ system was our starting catalyst system to initiate the optimisation conditions. The selection was based on preceeding experiments and the reaction was performed under 100 bar of CO pressure. This system afforded no conversion under the selected reaction conditions (**Table 7**, *entry 1*). Replacing PPh_3 with the chelating ligand DPPB (bis(diphenylphosphino)butane) resulted in the formation and identification of the desired lactone products (*entry 2*) with good chemoselectivity and preference regioselective formation towards the seven-membered lactone (**4a**). Besides, formation of an isomerised by-product, 2-propenylphenol, was also detected. Unfortunately, lower than 1% of substrate conversion was obtained upon testing the chiral ligand (*S,S*)-DIOP under the same conditions (*entry 3*). In an attempt to obtain higher catalytic activity, we decided to add various acids to the reaction mixture and to study their effect based on the results obtained from reports concerning hydroalkoxycarbonylation [56] as well as our hydrophenoxycarbonylation experimental results [143]. Surprisingly, it was noticed that a drastic decrease of catalytic activity when DPPB ligand and hydrochloric acid were used, while a notable increase in the catalytic activity can be observed when DIOP ligand and the same acid were added (*entries 4* and *5* respectively). Another nominated catalyst precursor tested in the cyclocarbonylation reaction was bis(benzonitrile)palladium(II) chloride which showed a better performance with the applied ligands, that is to say, a full conversion was afforded when (*S,S*)-DIOP ligand was used (*entry 10*). Besides, various chiral ligands were tested under the same conditions (*entries 11-13*; *15* and *16*) to compare the efficiency of the prepared *in situ* catalytic system with that of (*entry 10*). The results showed that some of the tested ligands were insufficient and disappointingly our search for enhancing the enantioselective transformation was not satisfying.

Additionally, concerning the regioselectivity, the tested ligands were divided into two categories: the first one which includes TPP and XANTPHOS ligands was found to favour the formation of the 6-membered lactone (**3a**) whereas the second set that involves the other tested chiral diphosphine ligands was in favour of the formation of the dominant 7-membered derivative. It is worth mentioning that the formation of minor compounds such as the 5-membered benzofuran derivative and the isomerised version of the 2-allylphenol to 2-propenylphenol was detected during the optimisation experiments. The significant role of the acid in forming active catalytic systems can be inferred from the first set of reactions. Accordingly, the thought of testing the effect of other acids seemed to be realistic. In this manner, *para*-toluenesulfonic acid was used. Despite achieving high catalytic activity, the

percent of the isomerisation was increasing considerably and 44% of the 2-propenylphenol was detected in the crude mixture. Also, a drop in the percentage formation of the 7-membered lactone was occurred might be due to the enriched isomerisation pathway (compare *entries 10* and *14*).

The application of oxalic acid was ineffective and resulted only in 23% conversion (*entry 17*). In contrary to oxalic acid, formic acid was sufficient in the cyclocarbonylation and afforded comparable results to HCl under the same conditions (*entry 18*). The idea of applying both HCl and TsOH acids in one experiment (*entries 10* and *14*) in order to get better regioselectivity for the 6-membered regioisomer as in case of (*entry 14*) and to maintain the catalytic activity observed by using HCl as in (*entry 10*) seemed to be realistic. Interestingly, both targets were accomplished (*entry 19*) and a significant increase of the chromanone derivative yield was observed. A quadrable elevation in the regioselectivity for the 6-membered lactone can be noticed (compare *entries 10* and *19*), nevertheless a drastic decrease of the optical yield was afforded under the selected conditions. The addition of the former acid mixture in a 1:1 molar ratio and XANTPHOS ligand instead of DIOP gave the highest percentage yield for the chromanone derivative with 64% (*entry 20*). The optimisation of the carbonylation reaction was also investigated by testing additional solvents. Surprisingly, while the addition of CH_2Cl_2 incorporated in the giving of low lactones chemoselectivity and modest enantioselective values for the target 6-membered lactone, the chromanone regioisomer constituted the highest percent among the formed lactones with 90% (*entry 21*).

The *in situ* generated Pd-DIOP catalysts afforded moderate optical yields in case of HCl and formic acid (52% and 42%, respectively). However, the catalyst system composed of Pd-BINAP species afforded lower ee-s. Moreover, optical yields in some cases were not determined because of the low yields of the 6-membered lactone. Temperature modification parameter was applied to the experiment of (*entry 10*) and resulted in the notice of a slight increase of ee when the temperature was varied from 120 to 100 °C, although a loss in catalytic activity was observed (*entry 22*). The effect of CO pressure was also examined and it was found that conducting the reaction under 55 bar instead of 100 bar led to a dramatic decrease of ee values (*entry 23*).

Finally, further experiments were carried out in order to broaden the search for more optimised conditions. The aim was to get either comparable or enhanced results compared to those obtained by using $Pd(PhCN)_2Cl_2$-DIOP-HCl, $Pd(PhCN)_2Cl_2$-DIOP-HCOOH or $Pd(PhCN)_2Cl_2$-XANTPHOS-HCl/TsOH catalyst systems (*entries 10*, *18* and *20* respectively). Accordingly, various catalytic systems were chosen for this purpose by testing other

precursors, chiral phosphine ligands as well as different Lewis acids (*entries 25-34*). It seems that replacing $Pd(PhCN)_2Cl_2$ precursor with other precursors in the cyclocarbonylation reaction dramatically decreased the catalytic activity under the same conditions (*entries 25-27*). The introduction of chiral ligands instead of DIOP was not satisfactory in achieving comparable ee values for the 6-membered lactone and some of these tested ligands caused a deactivation of the catalytic system (*entries 28-31*). Based on reports dealing with the effect of Lewis acids on transition metal-catalysed reactions [151], we found that the use of aluminium chloride or tris(pentafluorophenyl)borane in our cyclohydroaryloxycarbonylation reaction were applicable and afforded full substrates conversion and comparable regioselectivity for the 6-membered ring lactone compound (*entries 32* and *33*).

Table 7. Optimisation of hydrophenoxycarbonylation reaction[a]

Entry	Precursor	Ligand	Acid	Conv.	Product yields[b]		
					2a	3a (e.e.)	4a
1	$Pd(OAc)_2$	TPP	-	<1	-	-	-
2	$Pd(OAc)_2$	DPPB	-	36	1	4	30
3	$Pd(OAc)_2$	(*S*,*S*)-DIOP	-	<1	-	-	-
4	$Pd(OAc)_2$	DPPB	HCl	2	-	-	2
5	$Pd(OAc)_2$	(*S*,*S*)-DIOP	HCl	42	2	5 (42)	35
6	$Pd(PhCN)_2Cl_2$	DPPB	-	<1	-	-	-
7	$Pd(PhCN)_2Cl_2$	DPPB	HCl	7	0	1	6
8	$Pd(PhCN)_2Cl_2$	TPP	HCl	70	6	41	21
9	$Pd(PhCN)_2Cl_2$	XANTPHOS	HCl	>99	1	54	42
10	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	HCl	>99	2	14 (52)	80
11	$Pd(PhCN)_2Cl_2$	(*R*)-PHANEPHOS	HCl	>99	5	3 (n.d.)	86
12	$Pd(PhCN)_2Cl_2$	(*R*)-BINAP	HCl	69	0	8 (22)	61
13	$Pd(PhCN)_2Cl_2$	(*S*)-SEGPHOS	HCl	3	0	0	3
14	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	TsOH	>99	7	39 (6)	10
15	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIPAMP	HCl	0	-	-	-
16	$Pd(PhCN)_2Cl_2$	(*S*)-DM-SEGPHOS	HCl	0	-	-	-
17	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	Oxalic acid	23	2	15 (16)	5
18	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	HCOOH	>99	5	17 (42)	78
19	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	HCl/TsOH	93	11	58 (6)	20
20	$Pd(PhCN)_2Cl_2$	XANTPHOS	HCl/TsOH	>99	12	64	24

21[c]	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	HCl	53	1	27 (5)	2
22[d]	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	HCl	60	0	6 (59)	51
23[e]	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	HCl	>99	4	13 (30)	73
24	-	(*S*,*S*)-DIOP	HCl	0	-	-	-
25	$PdCl_2$	(*S*,*S*)-DIOP	HCl	<1	-	-	-
26	$Pd(PPh_3)_2Cl_2$	(*S*,*S*)-DIOP	HCl	20	0	3 (n.d)	13
27	$Pd(acac)_2$	(*S*,*S*)-DIOP	HCl	<1	-	-	-
28	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-BDPP	HCl	97	28	40 (36)	9
29	$Pd(PhCN)_2Cl_2$	(*R*)-MeO-BIPHEP	HCl	>99	2	14 (13)	77
30	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-Ph-BPE	HCl	-	-	-	-
31	$Pd(PhCN)_2Cl_2$	(*R*,*R*)-PHOSPHEPINE	HCl	6	-	-	-
32	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	$(C_6F_5)_3B$	>99	3	11 (38)	82
33	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	$AlCl_3$	>99	10	25 (36)	64
34	$Pd(PhCN)_2Cl_2$	(*S*,*S*)-DIOP	Cl_3CCOOH	9	-	-	-

[a] Reaction conditions: Pd precursor: 0.01 mmol, Ligand: 0.04 mmol (0.08 mmol in case of TPP), 2-Allylphenol: 1.0 mmol, Solvent (toluene): 10 mL, Acid: 0.35 mmol, T= 120 °C, p(CO)= 100 bar, t= 48 h; Yields and e.e. were determined by GC.

[b] Sum of products' yields (**2a**, **3a**, **4a**) and the yield of isomerisation product (2-propenylphenol) give conversion values.

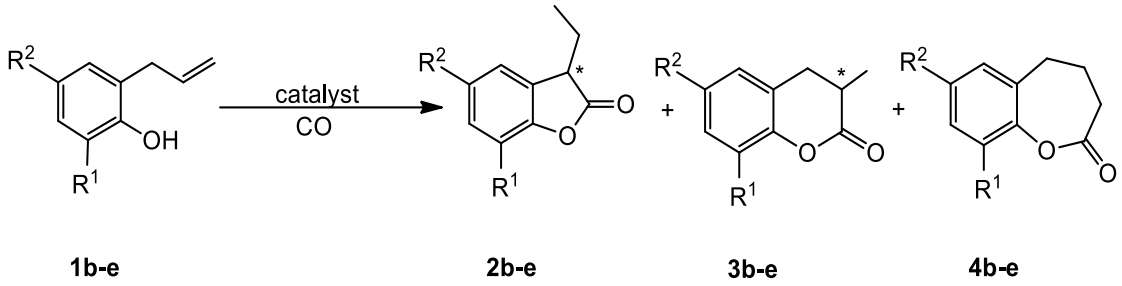
[c] CH_2Cl_2 was used as a solvent.

[d] T= 100°C. [e] p(CO)= 55 bar

3.3.2. Substituent effect

Our investigation regarding the study of the cyclohydroaryloxycarbonylation reaction was broadened in order to get a deeper insight about the effect of the substituents on the regio- and enantioselectivity for this reaction. Hence, the substrate scope including the parent substrate (2-allylphenol (**1a**)) and numerous substituted 2-allylphenol derivatives (6-methyl-2-allylphenol (**1b**), 6-methoxy-2-allylphenol (**1c**), 4-acetyl-2-allylphenol (**1d**), 3-allylsalicylaldehyde (**1e**)) were chosen to carry out the investigation (*Scheme 9*). It is worth mentioning that two ligands were utilised in this investigation for set purposes; namely: (*S*,*S*)-DIOP and the achiral diphosphine ligand (XANTPHOS) (**Table 8**). While the former ligand containing-system was utilised to examine the substituent effect on the reaction enantioselectivity, the latter ligand containing-catalyst was used to maintain the high regioselectivity values for the prepared and desired substituted chromanone derivatives as the

highest selectivity value for the chromanone compound obtained in the optimisation experiments was afforded when XANTPHOS ligand was applied.



1b-e **2b-e** **3b-e** **4b-e**

1-4b R^1=CH_3, R^2=H; **1-4c** R^1=OCH_3, R^2=H; **1-4d** R^1=H, R^2=$COCH_3$; **1-4e** R^1=CHO, R^2=H

Scheme 9. Cyclohydroaryloxycarbonylation reactions using substituted 2-allylphenol derivatives

The initial experiments that were carried out for the 2-allylphenol derivatives (6-methyl (**1b**) and 6-methoxy (**1c**)) with (*S*,*S*)-DIOP and HCl and their catalytic activities (*entries 1* and *2*, respectively) gave an indication about the poor or moderate conversion which might be afforded by such system. Accordingly, we replaced HCl acid with HCOOH acid and above 95% conversion was noticed for all tested substrates (*entries 3-6*). In these cases, traces or negligible amount of 5-membered lactone derivatives were noticed. Additionally, the isomerisation pathway of the substituted allylphenols was also found to be negligible, which might explain the low preference formation of the benzofuran derivatives in these cases. Under the same conditions, it was found that the substituted allylphenols gave higher regioselectivity values for the 6-membered lactone derivatives compared to that obtained from the parent 2-allylphenol. For instance, a near 1:1 ratio can be seen for 6- and 7-membered lactones formed from 3-allylsalicylaldehyde (**1e**) and the highest regioselectivity towards the six-membered lactone derivative of 46% was afforded (*entry 6*). Unlike the regioselectivity increasing tendency found for the substituted allylphenols, a slight decrease of enantioselectivity values were found and, in some cases, e.e. values are comparable to the e.e. value of the 6-membered lactone induced from the unsubstituted 2-allylphenol.

As mentioned above the addition of XANTPHOS ligand and the application of both HCl and TsOH acids enhanced the regioselectivity of the chromanone derivative as can be seen in the optimisation section. Consequently, we conducted the cyclocarbonylation of the allylphenols by applying both ligand and acid mixture to search the effect of such addition on the regioselectivities. Surprisingly, the conversion of all tested substrates was fallen off compared to the obtained conversion of the parent allylphenol under similar conditions (*entries 7* and *9*)

with only one exception where a full conversion was detected for the acetyl substituted substrate (**1d**) (*entry 10*). Interestingly, our prediction of enhancing the regioselectivities of the substituted chromanones was accomplished by the previously-mentioned addition. In addition to the formation of the 7-membered lactones a dominant formation of the six-membered lactone derivatives was observed for all of the substituted allylphenols (5-membered lactone formation was only noticed in case of acetyl substitution (**1d**)). Besides, and under these conditions it can be observed that only traces of propenylphenol derivatives appeared in the corresponding reaction mixtures. Thus, the extremely low tendency formation of the benzofuran derivatives in these experiments (except (**1d**) 13%) can be understood as a result of the terminal alkene isomerisation pathway suppression. Since the e.e. values and regioselectivities of the substituted lactones were not affected significantly by substitutions, it can be inferred that the cyclocarbonylation reaction of allylphenols was relatively independent on the phenyl ring substitution.

Table 8. Hydroaryloxycarbonylation reaction of 2-allylphenol derivatives[a]

Entry	Substrate	Ligand	Acid	Conversion	Lactone yields[b] **2** / **3** / **4**	6-membered lactone (**3**)	
						Regiosel.[c]	e.e.
1	**1b**	(*S*,*S*)-DIOP	HCl	55	6 / 11 / 36	21	44
2	**1c**	(*S*,*S*)-DIOP	HCl	17	0 / 0 / 17	0	-
3	**1b**	(*S*,*S*)-DIOP	HCOOH	>99	1 / 27 / 71	27	48
4	**1c**	(*S*,*S*)-DIOP	HCOOH	95	0 / 37 / 54	41	23
5	**1d**	(*S*,*S*)-DIOP	HCOOH	>99	4 / 25 / 71	26	43
6	**1e**	(*S*,*S*)-DIOP	HCOOH	95	0 / 40 / 44	46	16
7	**1b**	XANTPHOS	HCl/TsOH	33	0 / 19 / 11	63	-
8	**1b**	XANTPHOS	HCOOH	30	0 / 17 / 12	59	-
9	**1c**	XANTPHOS	HCl/TsOH	29	0 / 16 / 12	57	-
10	**1d**	XANTPHOS	HCl/TsOH	>99	13 / 74 / 13	74	-
11	2-propenylphenol	(*S*,*S*)-DIOP	HCOOH	>99	87 / 13 / 0	13	0

[a] Reaction conditions: $Pd(PhCN)_2Cl_2$: 0.01 mmol, Ligand: 0.04 mmol, Substrate: 1.0 mmol, Toluene: 10 mL, Acid: 0.35 mmol, T= 120 °C, t= 48 h; Yields and e.e. were determined by GC.

[b] Sum of products' yields (**2**, **3**, **4**) and the yield of isomerisation product give conversion values. [c] Regioselectivity = (**3** / (**2** + **3** + **4**)) *100.

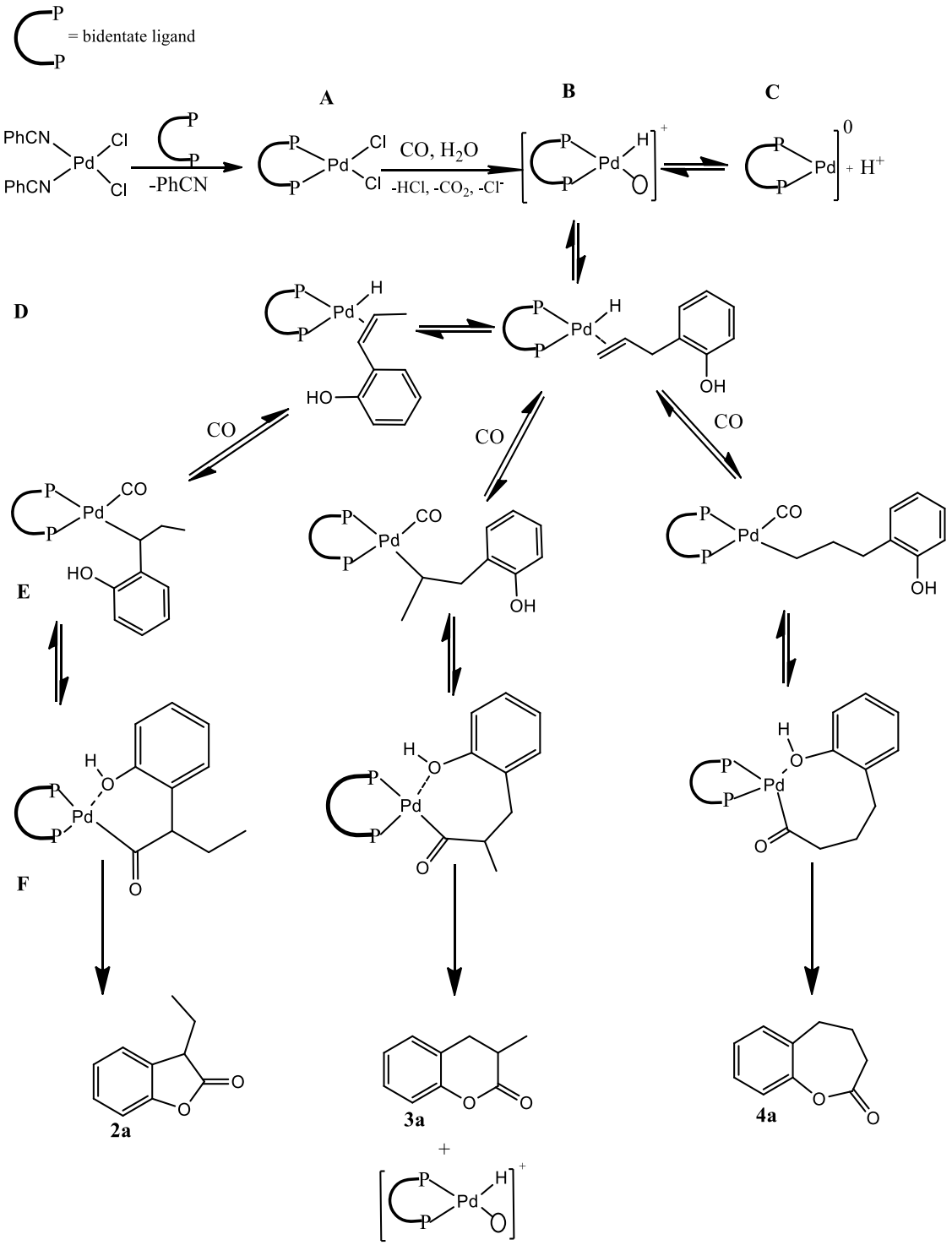
2-Propenylphenol was also studied in this investigation so it was subjected to carry out the cyclohydrocarbonylation experiment using (*S*,*S*)-DIOP ligand and HCOOH (*entry 11*). The substrate tended to produce the 5-membered lactone in a remarkable yield (87%) as well as the formation of no 7-membered lactone which assumed that the isomerisation pathway to produce the allyl moiety was not favoured by this substrate under the selected conditions. Despite the successful obtaining of good optical purity percent for the 2-allylphenol, a failure in getting a good e.e. value was obtained and a racemic mixture for the 6-membered lactone compound was formed instead in case of 2-propenylphenol substrate.

In the meantime, and based on reports dealing with the mechanism of the Pd-catalysed hydroaryloxycarbonylation reactions [152-154] as well as our previous results we can assume that this mechanism can be applied to our studied cyclohydroaryloxycarbonylation reaction, even though, setting a clear evidence about the occurrence of the cyclohydroaryloxycarbonylation reaction via that route needs more study and investigation. Initially, the formation of the cationic Pd-H intermediate (**B**) can be considered as the key step in the proposed mechanism (*Scheme 10)*. The precursor $Pd(PhCN)_2Cl_2$ can be transformed into di(chloro)di(phosphino)palladium(II) complex, (**A**), which is considered as a source of (**B**) intermediate generation which can reversibly transformed to Pd(0) species (**C**). The coordination of the alkene functionality of the substrate on the vacant site of (**B**) will afford two intermediates of (**D**) as terminal and internal alkene functionality containing-Pd intermediates can be reversibly transformed to each other by alkene insertion into Pd-H bond followed by β-hydride elimination. The detection of isomerised compounds (propenylphenols) in the reaction mixture is a proof for the existence of reversible isomerisation pathway. Alkene insertion in the palladium-hydrido bond followed by CO coordination gave the isomeric Pd-alkyl complexes (**E**). Finally, CO insertion into Pd-alkyl bond and the *O*-nucleophilic donation of the OH group resulted in the formation of the oxo(acyl)Pd species (**F**) which in turn transformed readily to the desired lactone derivatives and the active Pd(hydrido) species can be generated to initiate the catalytic cycle. It is worth mentioning that both 6- and 7-membered lactones can be derived from the allyl moiety Pd-containing species while the 5-membered lactone derivatives can be derived from the propenyl moiety Pd-containing intermediate.

The other factor that should be investigated in the cyclohydroaryloxycarbonylation reaction is the acid effect. Two perspectives from the previous results can be set. The first one is the acid effect on the reaction activity which can be best seen from the 'cyclohydroaryloxycarbonylation reaction of substituted allylphenols' section. For instance, the reaction of both (**1b**) and (**1c**) in the cyclocarbonylation with HCl afforded much lower

conversion values compared to that observed from the reaction of the same substrates in the presence of HCOOH acid (compare *entries 1* and *3*; *2* and *4*, **Table 8**). The same trend can be viewed in **Table 7** (see *entries 10* and *17*). It is worth mentioning that the effect of the acid promoters on the activity of the carbonylation reaction is described in the literature [55]. The addition of free acids as promoters may activate the reaction by forming Pd(II) active species according to the following reaction $Pd^0 + HX = HPd^{II}X$ which can induce the generation of the Pd-hydride intermediate (key intermediate for Pd-catalysed hydroalkoxycarbonylation reaction). The second perspective which can be drawn from our findings concerning the acid effect on our carbonylation reaction is its effect on the reaction regioselectivity. The ability of both TsOH and oxalic acid to alter the regioselectivity preference towards the 6-membered lactone when compared to HCl acid for example is a confirmation about such acid effect (calculated regioselectivities for chromanone compounds in **Table 7** for *entries 10*, *14* and *17*, are 15, 70 and 68%, respectively) and that effect might not due to the presence of protons only, but to the acid anion as well which might affect the regioselective outcome.

Two catalyst systems, $Pd(PhCN)_2Cl_2$-DIOP-HCOOH and $Pd(PhCN)_2Cl_2$-XANTPHOS-HCl/TsOH, were used to carry out the cyclohydroaryloxycarbonylation reaction of the 2-allylphenol derivatives. The former system afforded high catalytic activity (conversion values were varied between 95-99%). Additionally, higher regioselectivities were observed for the substituted chromanone derivatives than for the chromanone compound produced from the parent 2-allylphenol substrate under the same conditions. A reversal influence on ee values for chromanone derivatives can be noticed, as lower ee values were obtained in most of the cases than for the chromanone compound obtained from the parent 2-allylphenol under the selected conditions. The application of the latter catalyst system resulted in lower conversion for the tested substrates and higher regioselectivity for the chromanone derivatives compared to that obtained from the application of $Pd(PhCN)_2Cl_2$-DIOP-HCOOH system. Moreover, HCOOH demonstrated better reaction activity than HCl which reflected the effect of the used acid on the cyclohydrocarbonylation reaction of allylphenols.



Scheme 10. Proposed mechanism of cyclohydroaryloxycarbonylation reaction

4. Experimental

4.1. Palladium-catalysed enantioselective hydroaryloxycarbonylation of styrenes by 4-substituted phenols

4.1.1. General

The $PdCl_2(PhCN)_2$ precursor was synthesised from $PdCl_2$ (Aldrich) according to standard procedures [155]. The ligands (TPP, DIOP, XANTPHOS, *etc*.) were purchased from Sigma-Aldrich Kft., Budapest, Hungary. Toluene was distilled and purified by standard methods and stored under argon. All reactions were carried out under argon using standard Schlenk techniques. The ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker Avance-III 500 spectrometer. Chemical shifts are reported in ppm relative to TMS (downfield) for ^{1}H- and ^{13}C NMR spectroscopy. Conversions and selectivities were determined using GC and GC–MS. The enantiomeric excess was determined by using a chiral capillary column (CycloSil-B (30m × 0,25 mm)): (injection temperature: 250 °C; starting oven temperature: 50 °C; 1st rate: 2 °C/min; final temperature: 150 °C; 2nd rate 25 °C/min; final temperature: 230 °C/min; carrier gas: He 1.30 mL/min).The esters were purified by column chromatography (Silica gel, 0.063 mm; $CHCl_3$) and isolated as colorless liquids.

4.1.2. Hydroaryloxycarbonylation experiments

In a typical experiment, a solution of $PdCl_2(PhCN)_2$(3.8 mg; 0.01 mmol) and (*R*)-DIOP (19.9 mg; 0.04 mmol) in toluene (10 mL) containing 1 mmol substrate, 6 mmol nucleophile and 3 drops of concentrated HCl was transferred under argon atmosphere into a 100 mL stainless steel autoclave. The autoclave was pressurized with carbon monoxide to 100 bar total pressure and placed in a pre-heated oil bath. The mixture was stirred with a magnetic stirrer for the required time. The pressure was monitored throughout the reaction. After cooling and venting of the autoclave, the solution was removed, filtered and immediately analysed by GC and GC–MS.

4.1.3. Reduction of esters

2 mL of $LiAlH_4$ solution (1 mol/dm^3 in THF) was transferred into a dry two-necked flask equipped with a magnetic stirrer. Condenser and dropping funnel containing solution of the esters (1 mmol in 5 mL THF, purified by column chromatography) was connected to the flask. From the dropping funnel the solution was added slowly to the reducing agent under continuous stirring (5 min). After adding the whole amount of solution, the mixture was heated to reflux temperature (66 °C) and stirred for overnight. After the reaction was completed, the reaction mixture was cooled in water and ice, then cold water was added cautiously to the reaction

mixture to decompose the excess of the reagent. When no hydrogen was evolved by water addition, diluted sulphuric acid (10%) was added to dissolve the $Al(OH)_3$ precipitate. The products were extracted with diethyl ether (10 mL) and the organic phase was washed with saturated NaCl solution and dried over Na_2SO_4. After filtration and evaporation of the solvent the alcohols were analysed by chiral GC to determine the enantiomeric excess.

4.2. Rhodium-catalysed aryloxycarbonylation of iodo-aromatics by 4-substituted phenols with carbon monoxide or paraformaldehyde

4.2.1. General

The $[Rh(nbd)Cl)]_2$ precursor was synthesized from rhodium trichloride according to the standard procedure [156]. The $[Rh(acac)(CO)_2]$ was also synthesized by published method [157]. Ligands (TPP, DPPP, Xantphos, DPPB, DPPF) phenols, iodoarenes and dry toluene were purchased from Sigma-Aldrich and used without further purification. All reactions were carried out under argon atmosphere using standard Schlenk-techniques. The esters were purified by column chromatography (Silica gel, 0.063 mm; $CHCl_3$) and isolated as pure solids.

4.2.2. Aryloxycarbonylation of iodoarenes under carbon monoxide atmosphere

In a typical experiment, catalyst precursor $[Rh(acac)(CO)_2]$ (2.68 mg; 0.01 mmol) and Xantphos (11.57 mg; 0.02 mmol) in toluene (10 mL) containing 1.0 mmol substrate, 2.0 mmol nucleophile and 1.2 mmol Et_3N were transferred under argon atmosphere into a 100 mL stainless steel autoclave followed by its pressurization with CO up to total 90 bar and placed in a pre-heated oil bath at 120 °C. The mixture was then stirred with a magnetic stirrer for 48 h. The pressure was monitored throughout the reaction. After cooling and venting of the autoclave the solution was removed, filtered and immediately analyzed by GC and GC–MS.

4.2.3. Aryloxycarbonylation of iodoarenes using paraformaldehyde as CO surrogate

In a typical experiment, complex precursor $[Rh(nbd)Cl)]_2$ (4.80 mg; 0.01 mmol) and DPPP (20.62 mg; 0.05 mmol) in 10 mL of solvent mixture consists of toluene: ethyl acetate (4:6) containing 0.5 mmol substrate, 3 mmol of nucleophile, 16 mmol paraformaldehyde, 1.5 mmol Na_2CO_3, 1.25 mmol $MgSO_4$, and 1.0 mmol CuCl were transferred under argon atmosphere into three-necked round bottom flask and placed in a pre-heated oil bath. The mixture was then refluxed at 110 °C under atmospheric pressure using a balloon and stirred with a magnetic stirrer for 24 h. After cooling of the flask, the solution was removed, filtered and immediately analyzed by GC and GC–MS.

4.3. Palladium-catalysed intramolecular asymmetric cyclohydroaryloxy-carbonylation of 2-allylphenol derivatives. Synthesis of chiral lactones via cyclocarbonylation

4.3.1. General

Catalyst precursor $PdCl_2(PhCN)_2$ was synthesized from $PdCl_2$ according to the literature [155]. Palladium(II) acetate, phosphine ligands, solvents and acids were purchased from Sigma-Aldrich Kft., Budapest, Hungary and were used without further purification. The reactions were performed under inert argon atmosphere. Conversion and selectivity were determined by THERMO FOCUS gas chromatograph, using splitless injection and FID detector (column: DB-1MS (30m x 0.250mm x 0.25μm) inlet temperature: 250 ºC; starting oven temperature: 50 ºC; rate: 15 ºC/min; final temperature: 320 ºC, carrier gas: He 1.30 mL/min). Chiral separations were conducted using Cyclosil-B chiral column (30m x 0.250mm x 0.25μm)) inlet temperature: 250 ºC; starting oven temperature: 50 ºC; rate: 1st step: 1.5 ºC/min; final temperature: 160 ºC; 2nd step 25 ºC/min, final temperature: 230 ºC, hold final temperature: 5 min. Carrier gas: He 1.30 mL/min). For MS measurements Hewlett Packard 5830A GC-MS with electron spray ionisation (ESI). The data are given as mass unit per charge (m/z) and intensities are given in brackets.

4.3.2. General procedure for palladium-catalysed cyclocarbonylation reactions

The reactions were carried out in stainless steel autoclave (100 mL). $PdCl_2(PhCN)_2$ (3.8 mg; 0.01 mmol) (*S*,*S*)-DIOP (19.9 mg; 0.04 mmol) and a magnetic stir bar were placed in the reaction vessel. Then, toluene (10 mL), 1 mmol substrate and acid (0.35 mmol) were transferred into the autoclave, which was purged 3 times with argon, pressurized to 100 bar of carbon monoxide and placed in 100 ˚C oil bath for 48 hours. After the given reaction time the autoclave was cooled to room temperature and vented. The solution was filtered and analysed by gas chromatography (2 drops of the reaction mixture was dissolved in 1.5 mL of CH_2Cl_2, and 1 μL was injected from the solution). Purification was carried out by column chromatography on silica gel (63-200 μm) using $CHCl_3$ as eluent.

5. Characterisation of all prepared compounds during my PhD laboratory work

5.1 Palladium-catalysed enantioselective hydroaryloxycarbonylation of styrenes by 4-substituted phenols

Phenyl 3-phenylpropanoate (**4aa**). δ_H (500 MHz, $CDCl_3$) 7.06-7.49 (10 H, m, *Ph* + O*Ph*), 3.15 (2 H, t, 7.7 Hz, Ph*CH*$_2$), 2.95 (2 H, t, 7.7 Hz, C(O)*CH*$_2$). δ_C (125.7 MHz, $CDCl_3$) 171.4, 150.7, 140.2, 129.5, 128.7, 128.5, 126.5, 125.9, 121.6, 36.1, 31.0. MS m/z (rel int.): 226 (5, M^+), 133 (79), 105 (100), 91 (83), 77 (24), 65 (24), 51 (10).

Phenyl 2-phenylpropanoate (**3aa**). δ_H (500 MHz, $CDCl_3$) 7.06-7.49 (10 H, m, *Ph* + O*Ph*), 4.04 (1H, q, 7.15, PhC*H*), 1.69 (3H, d, 7.15, CHC*H*$_3$). δ_C (125.7 MHz, $CDCl_3$) 173.1, 150.9, 140.2, 129.4, 128.8, 127.6, 127.4, 125.8, 121.4, 45.7, 18.6. MS m/z (rel int.): 226 (1, M^+), 132 (43), 105 (100), 91 (7), 77 (17), 65 (8), 51 (5).

Phenyl 3-(4-methylphenyl)propanoate (**4ba**). δ_H (500 MHz, $CDCl_3$) 7.07-7.45 (9H, m, C$_6$*H*$_4$+ O*Ph*), 3.12 (2H, t, 7.6 Hz, PhC*H*$_2$), 2.94 (2H, t, 7.6 Hz, C(O)C*H*$_2$), 2.42 (3H, s, PhC*H*$_3$). δ_C (125.7 MHz, $CDCl_3$) 171.5, 150.8, 137.2, 136.0, 129.5, 129.4, 128.4, 125.8, 121.6 36.2, 30.6, 21.1. MS m/z (rel int.):240 (18, M^+), 147 (78), 133 (30), 119 (37), 105 (100), 91 (18), 77 (12), 65 (10).

Phenyl 2-(4-methylphenyl)propanoate (**3ba**). δ_H (500 MHz, $CDCl_3$) 7.07-7.45 (9H, m, C$_6$*H*$_4$+ O*Ph*), 4.01 (1H, q, 7.2, PhC*H*), 2.44 (3H, s, PhC*H*$_3$), 1.69 (3H, d, 7.2 Hz, CHC*H*$_3$). δ_C (125.7 MHz, $CDCl_3$) 173.2, 150.9, 137.2, 137.0, 129.6, 129.4, 127.5, 125.8, 121.5, 45.3, 21.2, 18.7. MS m/z (rel int.): 240 (2, M^+), 146 (41), 119 (100), 91 (13), 77 (5), 65 (7).

Phenyl 3-(4-methoxyphenyl)propanoate (**4ca**). δ_H (500 MHz, $CDCl_3$) 6.89-7.40 (9H, m, C$_6$*H*$_4$+ O*Ph*), 3.83 (3H, s, OC*H*$_3$), 3.05 (2H, t, 7.5 Hz, PhC*H*$_2$), 2.88 (2H, t, 7.5 Hz, C(O)C*H*$_2$). δ_C (125.7 MHz, $CDCl_3$) 171.5, 158.2, 150.1, 132.2, 129.4, 128.6, 125.8, 121.6, 114.0, 55.3, 36.3, 30.2. MS m/z (rel int.): 256 (63, M^+), 162 (32), 121 (100), 94 (9), 77 (9), 65 (4), 51 (2).

Phenyl 2-(4-methoxyphenyl)propanoate (**3ca**). δ_H (500 MHz, $CDCl_3$) 6.89-7.40 (9H, m, C$_6$*H*$_4$+ O*Ph*), 3.94 (1H, q, 7.1 Hz, PhC*H*), 3.84 (3H, s, OC*H*$_3$), 1.62 (3H, d, 7.1 Hz, CHC*H*$_3$). δ_C (125.7 MHz, $CDCl_3$) 173.2, 157.9, 150.5, 132.5, 129.3, 128.6, 125.7, 121.4, 114.2, 55.3, 45.6, 18.9. MS m/z (rel int.): 256 (19, M^+), 162 (9), 135 (100), 105 (4), 91 (4), 77 (5), 65 (4), 51 (4).

Phenyl 3-(1,1'-biphenyl-4-yl)propanoate (**4da**). δ_H (500 MHz, $CDCl_3$) 7.09-7.67 (14H, m, *Ph-Ph*+ O*Ph*), 3.18 (2H, t, 7.6 Hz, PhC*H*$_2$), 2.99 (2H, t, 7.6 Hz, C(O)C*H*$_2$). δ_C (125.7 MHz, $CDCl_3$) 171.4, 150.7, 140.9, 139.5, 139.3, 129.5, 128.9, 128.8, 127.4, 127.2, 127.0, 125.8, 121.6, 36.0, 30.7. MS m/z (rel int.): 302 (40, M^+), 208 (50), 180 (24), 167 (100), 152 (18), 115 (72), 94 (56), 65 (11).

Phenyl 2-(1,1'-biphenyl-4-yl)propanoate (**3da**). δ_H (500 MHz, $CDCl_3$) 7.09-7.67 (14H, m, *Ph*-*Ph*+ O*Ph*), 4.08 (1H, q, 7.1 Hz, PhC*H*), 1.72 (3H, d, 7.1 Hz, CHCH_3). (δ_C (125.7 MHz, $CDCl_3$) 173.0, 150.9, 140.7, 140.4, 139.2, 129.4, 128.8, 128.0, 127.6, 127.2, 127.1, 125.8, 121.5, 45.4, 18.6. MS m/z (rel int.): 302 (19, M+), 208 (15), 181 (100), 165 (26), 153 (4), 114 (4), 94 (9), 65 (6).

Phenyl 3-(4-fluorophenyl)propanoate (**4ea**). δ_H (500 MHz, $CDCl_3$) 6.88-7.70 (9H, m, *Ph*+ O*Ph*), 3.10 (2H, t, 7.5 Hz, PhCH_2), 2.92 (2H, t, 7.5 Hz, C(O)CH_2). δ_C (125.7 MHz, $CDCl_3$) 171.3, 161.7 (d, 244.2 Hz), 150.1, 135.9, 129.9 (d, 7.8 Hz), 129.5, 125.9, 121.6, 115.4 (d, 21.2 Hz), 36.1, 30.2. MS m/z (rel int.): 244 (18, M^+), 151 (16), 123 (38), 109 (100), 94 (73), 77 (7), 65 (5), 51 (3).

Phenyl 2-(4-fluorophenyl)propanoate (**3ea**). δ_H (500 MHz, $CDCl_3$) 6.88-7.70 (9H, m, *Ph*+ O*Ph*), 4.01 (1H, q, 7.2 Hz, PhC*H*), 1.67 (3H, d, 7.2 Hz, CHCH_3). δ_C (125.7 MHz, $CDCl_3$) 172.9, 162.1 (d, 245.6 Hz), 150.8, 132.8, 129.4, 129.2 (d, 8.1 Hz), 125.9, 121.4, 115.6 (d, 21.5 Hz), 45.0, 18.6. MS m/z (rel int.): 244 (2, M^+), 150 (52), 123 (100), 103 (20), 94 (10), 77 (6), 65 (4).

Phenyl 3-(4-chlorophenyl)propanoate (**4fa**). δ_H (500 MHz, $CDCl_3$) 7.04-7.43 (9H, m, *Ph*+ O*Ph*), 3.09 (2H, t, 7.5 Hz, PhCH_2), 2.91 (2H, t, 7.5 Hz, C(O)CH_2). δ_C (125.7 MHz, $CDCl_3$) 171.1, 150.7, 138.7, 132.3, 129.9, 129.5, 128.7, 125.9, 121.6, 35.8, 30.3. MS m/z (rel int.): 260 (38, M^+), 166 (25), 139 (62), 125 (100), 103 (33), 94 (71), 77 (15), 65 (13).

Phenyl 2-(4-chlorophenyl)propanoate (**3fa**). δ_H (500 MHz, $CDCl_3$) 7.04-7.43 (9H, m+ *Ph*, O*Ph*), 4.05 (1H, q, 7.2 Hz, PhC*H*), 1.66 (3H, d, 7.2 Hz, CHCH_3). δ_C (125.7 MHz, $CDCl_3$) 172.6, 150.8, 138.6, 132.2, 129.8, 129.4, 129.0, 125.9, 121.4, 45.1, 18.5. MS m/z (rel int.): 260 (2, M^+), 166 (62), 139 (100), 103 (20), 77 (7), 65 (5).

Phenyl 3-(4-trifluoromethylphenyl)propanoate (**4ga**). δ_H (500 MHz, $CDCl_3$) 7.03-7.68 (9H, m, *Ph*+ O*Ph*), 3.16 (2H, t, 7.6 Hz, PhCH_2), 2.94 (2H, t, 7.6 Hz, C(O)CH_2). δ_C (125.7 MHz, $CDCl_3$) 171.2, 150.7, 144.4, 129.7, 129.1 (q, 32.1 Hz), 129.0, 126.1, 125.8 (q, 3.6 Hz), 124.5 (q, 270.0 Hz), 121.6, 35.7, 30.9. MS m/z (rel int.): 294 (7, M^+), 173 (48), 159 (28), 133 (11), 94 (100).

Phenyl 2-(4-trifluoromethylphenyl)propanoate (**3ga**). δ_H (500 MHz, $CDCl_3$) 7.03-7.68 (9H, m, *Ph*+ O*Ph*), 4.06 (1H, q, 7.1 Hz, PhC*H*), 1.67 (3H, d, 7.1 Hz, CHCH_3). δ_C (125.7 MHz, $CDCl_3$) 172.5, 150.8, 144.2, 130.0 (q, 32.4 Hz), 129.6, 128.2, 126.2, 126.0 (q, 3.8 Hz), 124.3 (q, 270.4 Hz), 121.5, 45.7, 18.7. MS m/z (rel int.): 275 (3), 200 (100), 173 (83), 133 (17), 94 (38), 65 (5).

4-Methylphenyl 3-phenylpropanoate (**4ab**). R_f ($CHCl_3$) 0.911; δ_H (500 MHz, $CDCl_3$) 6.72-7.73 (9 H, m, *Ph* + OC_6H_4), 3.11 (2H, t, 7.5 Hz, PhCH_2), 2.91 (2H, t, 7.5 Hz, C(O)CH_2), 2.37 (3H, s, PhCH_3). δ_C (125.7 MHz, $CDCl_3$) 171.6, 148.5, 140.2, 135.4, 132.2, 129.9, 128.6, 127.6, 126.4, 36.0, 31.0, 20.8. MS m/z (rel int.): 240 (9, M^+), 133 (4), 108 (100), 105 (31), 91 (44), 77 (19), 65 (8), 51 (5).

4-Methylphenyl 2-phenylpropanoate (**3ab**). R_f ($CHCl_3$) 0.911; δ_H (500 MHz, $CDCl_3$) 6.72-7.73 (9 H, m, *Ph* + OC_6H_4), 3.99 (1 H, q, 7.5 Hz, Ph*CH*), 2.35 (3H, s, PhCH_3), 1.65 (3H, d, 7.5Hz, CHCH_3). δ_C (125.7 MHz, $CDCl_3$) 173.0, 148.6, 140.2, 135.3, 132.2, 129.8, 128.4, 127.3, 126.4, 45.7, 20.8, 18.6. MS m/z (rel int.): 240 (1, M^+), 132 (82), 109 (40), 105 (100), 77 (28), 63 (2), 51 (9).

4-Methoxyphenyl 3-phenylpropanoate (**4ac**). R_f ($CHCl_3$) 0.676; δ_H (500 MHz, $CDCl_3$) 6.88-7.47 (9 H, m, *Ph* + OC_6H_4), 3.82 (3H, s, OCH_3), 3.10 (2H, t, 7.5 Hz, PhCH_2), 2.89 (2H, t, 7.5 Hz, C(O)CH_2). δ_C (125.7 MHz, $CDCl_3$) 171.8, 157.3, 144.5, 140.2, 128.6, 127.5, 126.4, 122.2, 114.4, 55.6, 36.0, 31.0. MS m/z (rel int.): 256 (6, M^+), 124 (100), 109 (19), 105 (16), 91 (28), 77 (8), 65 (6), 51 (4).

4-Methoxyphenyl 2-phenylpropanoate (**3ac**). R_f ($CHCl_3$) 0.676; δ_H (500 MHz, $CDCl_3$) 6.88-7.47 (9 H, m, *Ph* + OC_6H_4), 3.97 (1H, q, 7.0 Hz, Ph*CH*), 3.80 (3H, s, OCH_3), 1.63 (3H, d, 7.0 Hz, CHCH_3). δ_C (125.7 MHz, $CDCl_3$) 171.8, 157.3, 144.5, 140.2, 128.4, 127.3, 126.4, 122.1, 114.3, 55.6, 45.6, 18.6. MS m/z (rel int.): 256 (7, M^+), 132 (44), 124 (100), 105 (84), 77 (18), 63 (4), 51 (6).

1,1'-Biphenyl-4-yl 3-phenylpropanoate (**4ad**). R_f ($CHCl_3$) 0.923; δ_H (500 MHz, $CDCl_3$) 7.09-7.63 (14H, m, *Ph-Ph* + OC_6H_4), 3.13 (2H, t, 7.5 Hz, PhCH_2), 2.94 (2H, t, 7.5 Hz, C(O)CH_2). δ_C (125.7 MHz, $CDCl_3$) 171.4, 150.1, 140.4, 140.1, 139.0, 128.7, 128.6, 128.4, 128.1, 127.6, 127.3, 127.1, 126.5, 36.0, 31.0. MS m/z (rel int.): 302 (3, M^+), 170 (100), 141 (8), 119 (8), 105 (13), 91 (23), 77 (5), 66 (4), 51 (3).

1,1'-Biphenyl-4-yl 2-phenylpropanoate (**3ad**). R_f ($CHCl_3$) 0.923; δ_H (500 MHz, $CDCl_3$) 7.09-7.63 (14H, m, *Ph-Ph* + OC_6H_4), 4.02 (1H, q, 7.0 Hz, Ph*CH*), 1.66 (3H, d, 7.0 Hz, CHCH_3). δ_C (125.7 MHz, $CDCl_3$) 173.0, 150.3, 140.4, 140.1, 139.0, 128.8, 128.6, 128.4, 128.0, 127.6, 127.4, 127.1, 126.5, 45.7, 18.5. MS m/z (rel int.): 302 (4, M^+), 170 (100), 141 (13), 132 (63), 119 (13), 105 (75), 77 (13), 63 (2), 51 (2).

4-Fluorophenyl 3-phenylpropanoate (**4ae**). R_f ($CHCl_3$) 0.909; δ_H (500 MHz, $CDCl_3$) 6.97-7.73 (9H, m, *Ph* + OC_6H_4), 3.10 (2H, t, 7.5 Hz, PhCH_2), 2.92 (2H, t, 7.5 Hz, C(O)CH_2). δ_C (125.7 MHz, $CDCl_3$) 171.4, 160.2 (d, 243.9 Hz) 146.5, 140.0, 128.6, 127.5 (d, 8.8 Hz), 126.5,

122.9 (d, 8.8 Hz), 116.0 (d, 22.6 Hz), 35.9, 30.9. MS m/z (rel int.): 244 (2, M^+), 133 (67), 112 (33), 105 (100), 91 (98), 77 (22), 65 (12), 51 (11).

4-Fluorophenyl 2-phenylpropanoate (**3ae**). R_f ($CHCl_3$) 0.909; δ_H (500 MHz, $CDCl_3$) 6.97-7.73 (9H, m, *Ph* + OC_6H_4), 3.99 (1H, q, 7.0 Hz, Ph*CH*), 1.64 (3H, d, 7.0 Hz, CH*CH*$_3$). δ_C (125.7 MHz, $CDCl_3$) 173.0, 160.2 (d, 243.9 Hz), 146.5, 139.9, 128.4, 127.5 (d, 8.8 Hz), 126.5, 122.8 (d, 8.8 Hz), 115.9 (d, 23.9 Hz), 45.6, 18.5. MS m/z (rel int.): 132 (37), 105 (100), 77 (17), 63 (3), 51 (5).

4-Chlorophenyl 3-phenylpropanoate (**4af**). R_f ($CHCl_3$) 0.889; δ_H (500 MHz, $CDCl_3$) 6.95-7.40 (9H, m, *Ph* + OC_6H_4), 3.10 (2H, t, 7.5 Hz, Ph*CH*$_2$), 2.91 (2H, t, 7.5 Hz, C(O)*CH*$_2$). δ_C (125.7 MHz, $CDCl_3$) 171.1, 149.1, 139.9, 131.2, 129.4, 128.6, 127.5, 126.5, 122.9, 35.9, 30.9. MS m/z (rel int.): 260/262 (9/3, M^+), 133 (57), 105 (100), 91 (94), 77 (20), 66 (11), 51 (9).

4-Chlorophenyl 2-phenylpropanoate (**3af**). R_f ($CHCl_3$) 0.889; δ_H (500 MHz, $CDCl_3$) 6.95-7.40 (9H, m, *Ph* + OC_6H_4), 3.98 (1H, q, 7.5 Hz, Ph*CH*), 1.64 (3H, d, 7.5 Hz, CH*CH*$_3$). δ_C (125.7 MHz, $CDCl_3$) 172.8, 149.3, 139.8, 131.2, 129.3, 128.4, 127.4, 126.5, 122.8, 45.6, 18.4. MS m/z (rel int.): 260/262 (1/0, M^+), 132 (31), 105 (100), 77 (14), 63 (4), 51 (5).

4-(Trifluoromethyl)phenyl 3-phenylpropanoate (**4ag**). R_f ($CHCl_3$) 0.886; δ_H (500 MHz, $CDCl_3$) 7.14-7.20 (9H, m, *Ph* + OC_6H_4), 3.11 (2H, t, 7.5 Hz, Ph*CH*$_2$), 2.94 (2H, t, 7.5 Hz, C(O)*CH*$_2$). δ_C (125.7 MHz, $CDCl_3$) 170.8, 153.2, 139.8, 128.6, 128.2 (q, 32.9 Hz), 127.5, 126.7 (q, 3.8 Hz), 126.6, 123.9 (q, 272.0 Hz), 122.0, 35.9, 30.9. MS m/z (rel int.): 294 (2, M^+), 143 (11), 133 (67), 105 (100), 91 (91), 77 (18), 65 (11), 51 (9).

4-(Trifluoromethyl)phenyl 2-phenylpropanoate (**3ag**). R_f ($CHCl_3$) 0.886; δ_H (500 MHz, $CDCl_3$) 7.14-7.20 (9H, m, *Ph* + OC_6H_4), 4.0 (1H, q, 7.0 Hz, Ph*CH*), 1.65 (3H, d, 7.0 Hz, CH*CH*$_3$). δ_C (125.7 MHz, $CDCl_3$) 172.6, 153.2, 139.8, 128.4, 128.2 (q, 32.9 Hz), 127.6, 126.7 (q, 3.8 Hz), 126.6, 123.9 (q, 272.0 Hz), 121.9, 45.7, 18.4. MS m/z (rel int.): 143 (4), 132 (14), 105 (100), 77 (11), 63 (2), 51 (5).

4-Bromophenyl 3-phenylpropanoate (**4ah**). R_f ($CHCl_3$) 0.938; δ_H (500 MHz, $CDCl_3$) 6.92-7.71 (9H, m, *Ph* + OC_6H_4), 3.10 (2H, t, 7.5 Hz, Ph*CH*$_2$), 2.92 (2H, t, 7.5 Hz, C(O)*CH*$_2$). δ_C (125.7 MHz, $CDCl_3$) 171.0, 149.7, 139.9, 132.5, 128.6, 127.5, 126.5, 123.4, 118.9, 35.9, 30.9. MS m/z (rel int.): 304/306 (6/6, M^+), 172/174 (45/45), 133 (50), 105 (100), 91 (93), 77 (20), 66 (28), 51 (10).

4-Bromophenyl 2-phenylpropanoate (**3ah**). R_f ($CHCl_3$) 0.938; δ_H (500 MHz, $CDCl_3$) 6.92-7.71 (9H, m, *Ph* + OC_6H_4), 3.99 (1H, q, 7.0 Hz, Ph*CH*), 1.64 (3H, d, 7.0 Hz, PhCH*CH*$_3$). δ_C (125.7 MHz, $CDCl_3$) 171.0, 149.7, 139.9, 132.4, 128.4, 127.5, 126.5, 123.2, 118.9, 45.6, 18.5.

MS m/z (rel int.): 304/306 (1/1, M^+), 172/174 (6/6), 132 (45), 105 (100), 77 (15), 63 (5), 51 (4).

4-Isopropylphenyl 3-phenylpropanoate (**4ai**). R_f ($CHCl_3$) 0.907; δ_H (500 MHz, $CDCl_3$) 6.94-7.47 (9H, m, *Ph* + OC_6H_4), 3.11 (2H, t, 7.5 Hz, PhCH_2), 2.94 (2H, t, 7.5 Hz, C(O)CH_2), 2.90 (1H, heptett, 7.0 Hz, C*H*$(CH_3)_2$), 1.26 (6H, d, 7.0 Hz, CH(CH_3)$_2$. δ_C (125.7 MHz, $CDCl_3$) 171.6, 148.6, 146.3, 140.2, 128.6, 127.6, 127.3, 126.4, 121.2, 36.0, 33.6, 31.0, 24.0. MS m/z (rel int.): 268 (9, M^+), 136 (92), 121 (100), 105 (36), 91 (62), 77 (15), 65 (11), 51 (4).

4-Isopropylphenyl 2-phenylpropanoate (**3ai**). R_f ($CHCl_3$) 0.907; δ_H (500 MHz, $CDCl_3$) 6.94-7.47 (9H, m, *Ph* + OC_6H_4), 3.98 (1H, q, 7.5 Hz, Ph*CH*), 2.90 (1H, heptett, 7.0 Hz, *CH*$(CH_3)_2$, 1.64 (3H, d, 7.5 Hz, CHCH_3), 1.25 (6H, d, 7.0 Hz, CH(CH_3)$_2$). δ_C (125.7 MHz, $CDCl_3$) 171.6, 148.6, 146.3, 140.2, 128.4, 127.6, 127.3, 126.4, 121.0, 45.7, 33.6, 24.0, 18.6. MS m/z (rel int.): 268 (2, M^+), 136 (14), 132 (95), 121 (43), 105 (100), 91 (11), 77 (20), 65 (3), 51 (3).

4-Formylphenyl 3-phenylpropanoate (**4aj**). δ_H (500 MHz, $CDCl_3$) 10.00 (1H, s, C*H*O), 7.21-7.93 (9H, m, *Ph*+ O*Ph*), 3.11 (2H, t, 7.5 Hz, PhCH_2), 2.95 (2H, t, 7.5 Hz, C(O)CH_2). δ_C (125.7 MHz, $CDCl_3$) 190.1, 172.3, 155.3, 142.9, 139.8, 131.2, 128.7, 128.4, 126.6, 122.3, 36.0, 30.9. MS m/z (rel int.): 254 (2, M^+), 133 (61), 105 (100), 91 (73), 77 (12), 65 (12), 51 (5).

4-Formylphenyl 2-phenylpropanoate (**3aj**). δ_H (500 MHz, $CDCl_3$) 9.95 (1H, s, C*H*O), 7.21-7.93 (9H, m, *Ph*+ O*Ph*), 4.01 (1H, q, 7.1 Hz, PhC*H*), 1.65 (3H, d, 7.1 Hz, CHCH_3). δ_C (125.7 MHz, $CDCl_3$) 191.0, 171.2, 155.1, 139.8, 132.2, 128.7, 128.4, 126.6, 122.6, 122.3, 45.1, 18.5. MS m/z (rel int.): 254 (1, M^+) 132 (17), 105 (100), 77 (10), 65 (4), 51 (2).

4-Formylphenyl 3-(4-chlorophenyl)propanoate (**4fj**). δ_H (500 MHz, $CDCl_3$) 10.00 (1H, s, C*H*O), 6.97-7.93 (8H, m, *Ph*+ O*Ph*), 3.06 (2H, t, 7.6 Hz), 2.92 (2H, t, 7.6 Hz). δ_C (125.7 MHz, $CDCl_3$) 190.8, 171.2, 155.2, 138.3, 131.2, 129.8, 129.0, 128.7, 128.2, 127.4, 35.8, 30.2. MS m/z (rel int.): 228 (7, M^+), 207 (4), 167 (43), 139 (57), 125 (100), 104 (23), 77 (13), 65 (7).

4-Formylphenyl 2-(4-chlorophenyl)propanoate (**3fj**). δ_H (500 MHz, $CDCl_3$) 9.87 (1H, s, C*H*O), 6.97-7.93 (8H, m, *Ph*+ O*Ph*), 3.98 (1H, q, 7.1 Hz), 1.64 (3H, d, 7.1 Hz). δ_C (125.7 MHz, $CDCl_3$) 190.0, 170.4, 155.2, 137.9, 134.0, 131.2, 129.7, 129.1, 128.7, 127.8, 45.1, 18.3. MS m/z (rel int.): 165 (19), 139 (100), 103 (25), 77 (7), 65 (4).

4-Bromophenyl 3-(4-chlorophenyl)propanoate (**4fh**). R_f ($CHCl_3$) 0.894; δ_H (500 MHz, $CDCl_3$) 6.73-7.71 (8H, m, CC_6H_4 + OC_6H_4), 3.06 (2H, t, 7.5 Hz, PhCH_2), 2.88 (2H, t, 7.5 Hz, C(O)CH_2). δ_C (125.7 MHz, $CDCl_3$) 170.7, 149.6, 138.4, 132.5, 129.8, 128.7, 123.2, 118.9, 117.3, 35.7, 30.2. MS m/z (rel int.): 338/340/342 (10/13/3, M^+), 172/174 (80/78), 167 (9) 139 (45), 131 (13), 125 (100), 103 (33), 89 (10), 77 (20), 63(13), 51 (5).

4-Bromophenyl 2-(4-chlorophenyl)propanoate (**3fh**). R_f ($CHCl_3$) 0.894; δ_H (500 MHz, $CDCl_3$) 6.73-7.71 (8H, m, CC_6H_4 + OC_6H_4), 3.95 (1H, q, 7.0 Hz, Ph*CH*), 1.62 (3H, d, 7.0 Hz, CH*CH*$_3$). δ_C (125.7 MHz, $CDCl_3$) 170.7, 149.6, 138.4, 132.4, 129.0, 128.9, 123.1, 118.9, 117.3, 45.0, 18.4. MS m/z (rel int.): 338/340/342 (1/2/0, M^+), 172/174 (5/5), 166 (46), 141 (33), 139 (100), 103 (35), 77 (17), 63 (8), 51 (4).

4-Methoxyphenyl 3-(4-methylphenyl)propanoate (**4bc**). R_f ($CHCl_3$) 0.633; δ_H (500 MHz, $CDCl_3$) 6.89-7.36 (8H, m, CC_6H_4 + OC_6H_4), 3.82 (3H, s, O*CH*$_3$), 3.06 (2H, t, 7.5 Hz, Ph*CH*$_2$), 2.87 (2H, t, 7.5 Hz, C(O)*CH*$_2$), 2.37 (3H, s, *CH*$_3$). δ_C 171.8, 157.2, 144.2, 137.1, 135.9, 129.2, 128.3, 122.3, 114.5, 55.6, 36.1, 30.6, 21.0. MS m/z (rel int.): 270 (9, M^+), 124 (100), 109 (19), 105 (44), 91 (8), 77 (8), 65 (5), 51 (4).

4-Methoxyphenyl 2-(4-methylphenyl)propanoate (**3bc**). R_f ($CHCl_3$) 0.633; δ_H (500 MHz, $CDCl_3$) 6.89-7.36 (8H, m, CC_6H_4 + OC_6H_4), 3.93 (1 H, q, 7.0 Hz, Ph*CH*), 3.80 (3H, s, O*CH*$_3$), 2.38 (3H, s, *CH*$_3$), 1.61 (3H, d, 7.0 Hz, CH*CH*$_3$). δ_C 173.5, 157.3, 144.5, 137.2, 135.9, 129.5, 127.4, 122.1, 114.4, 55.6, 45.2, 21.0, 18.6. MS m/z (rel int.): 270 (3, M^+), 146 (83), 124 (45), 119 (100), 91 (20), 77 (8), 65 (5), 51 (2).

5.2. Rhodium-catalysed aryloxycarbonylation of iodo-aromatics by 4-substituted phenols with carbon monoxide or paraformaldehyde

Phenyl benzoate (**3aa**): δ_H (500MHz, $CDCl_3$) 8.23–8.24 (2H, m, Ph), 7.65–7.68 (1H, m, Ph), 7.54 (2H, t, 7.5 Hz, Ph), 7.46 (2H, t, 7.5 Hz, Ph), 7.31 (1H, d, 7.5 Hz, Ph), 7.24–7.26 (2H, m, Ph). δ_C (125.7 MHz, $CDCl_3$) 165.2, 151.1, 133.7, 130.3, 129.7, 129.6, 128.7, 126.0, 121.8. IR (KBr (cm^{-1})): 3070, 3050, 1742, 1590, 1495, 1450, 1260, 1200, 1170, 1060, 830, 700. MS m/z (rel int.): 198 (11, M^+),141 (1), 105 (100), 93 (1), 77 (52), 65 (7), 51 (17).

Phenyl 4-fluorobenzoate (**3ba**): δ_H (500 MHz, $CDCl_3$) 8.263 (2H, dd, 9.0 Hz, 5.5 Hz, Ph), 7.469 (2H, t, 8.0 Hz, Ph), 7.314 (1H, t, 7.5 Hz, Ph), 7.203–7.252 (4H, m, Ph). δ_C (125.7 MHz, $CDCl_3$) 166.2 (d, 255.2 Hz), 164.2, 150.9, 132.8 (d, 8.8 Hz), 129.5, 126.0, 125.8, 121.7, 115.8 (d, 22.6 Hz). IR (KBr (cm^{-1})): 3075, 3064, 1734, 1597, 1506, 1273, 1193, 1166, 1078, 854, 759, 687. MS m/z (rel int.): 216 (8, M+), 123 (100), 95 (40), 75 (15), 65 (5), 51 (4).

Phenyl 4-chlorobenzoate (**3ca**): δ_H (500 MHz, $CDCl_3$) 8.179 (2H, d, 8.5 Hz, Ph), 7.527 (2H, d, 8.5 Hz, Ph), 7.472 (2H, t, 7.5 Hz, Ph), 7.320 (1H, t, 7.5 Hz, Ph), 7.246 (2H, dd, 8.0 Hz, 1 Hz, Ph). δ_C (125.7MHz, CDCl3) 164.4, 150.8, 140.2, 131.6, 129.6, 129.0, 128.1, 126.1, 121.6. IR (KBr (cm^{-1})): 3092, 3056, 1732, 1612, 1495, 1280, 1076, 853, 756, 723. MS m/z (rel int.): 232/ 234 (7/2, M+), 139/141 (100/33), 111/113 (33/11), 93 (2), 75 (20), 65 (7), 50 (9).

Phenyl 4-bromobenzoate (**3da**): δ_H (500 MHz, $CDCl_3$) 8.101(2H, d, 8.5 Hz, Ph), 7.694 (2H, d, 8.5 Hz, Ph), 7.457–7.488 (2H, m, Ph), 7.320 (1H, t, 7.5 Hz, Ph), 7.235–7.251 (2H, m, Ph). δ_C (125.7MHz, CDCl3) 164.5, 150.8, 132.0, 131.7, 129.6, 128.8, 128.5, 126.0, 121.6. IR (KBr (cm^{-1})): 3091, 3053, 1731, 1563, 1492, 1287, 1162, 1083, 850, 753, 668. MS m/z (rel int.): 276/278 (6/6, M+), 183/185 (100/100), 155/157 (29/29), 104 (6), 76 (24), 65 (13), 51 (6).

Phenyl 4-methylbenzoate (**3ea**): δ_H (500 MHz, $CDCl_3$) 8.131 (2H, d, 8.0 Hz, Ph), 7.461 (2H, t, 7.5 Hz, Ph), 7.345 (2H, d, 8.0 Hz, Ph), 7.301 (1H, t, 7.5 Hz, Ph), 7.246 (2H, d, 8.0 Hz, Ph), 2.488 (3H, s, *CH_3*). δ_C (125.7 MHz, $CDCl_3$) 165.3, 151.1, 144.4, 130.2, 129.5, 129.3, 126.9, 125.8, 121.8, 21.8. IR (KBr (cm^{-1})): 3088, 3039, 2954, 2923, 2856, 1725, 1610, 1477, 1271, 1193, 1080, 751, 688. MS m/z (rel int.): 212 (5, M+), 119 (100), 91 (43), 65 (23), 51 (3).

Phenyl 4-tert-butylbenzoate (**3fa**): δ_H (500 MHz, $CDCl_3$) 8.166 (2H, d, 8.0 Hz, Ph), 7.559 (2H, d, 8.5 Hz, Ph), 7.456 (2H, t, 7.5 Hz, Ph), 7.282–7.349 (1H, m, Ph), 7.235 (2H, d, 8.0 Hz, Ph), 1.402 (9H, s, *tert-butyl*). δ_C (125.7 MHz, $CDCl_3$) 165.2, 157.4, 151.1, 130.1, 129.5, 126.8, 125.8, 125.6, 121.8, 35.2, 31.1. IR (KBr (cm^{-1})): 3057, 2963, 2932, 2901, 2870, 1735, 1606, 1495, 1269, 1184, 1072, 765, 702. MS m/z (rel int.): 254 (1, M+), 239 (4), 161 (100), 146 (11), 118 (14), 91 (10), 77 (6), 65 (7), 50 (3).

Phenyl 4-acetylbenzoate (**3ga**): δ_H (500 MHz, $CDCl_3$) 8.322 (2H, d, 8.0 Hz, Ph), 8.106 (2H, d, 8.5 Hz, Ph), 7.476 (2H, t, 7.5Hz, Ph), 7.325 (1H, t, 7.5Hz, Ph), 7.260 (2H, d, 8 Hz, Ph), 2.704 (3H, s, CO*CH3*). δ_C (125.7 MHz, $CDCl_3$) 197.4, 164.3, 150.8, 140.8, 133.4, 130.4, 129.6, 128.4, 126.2, 121.6, 26.9. IR (KBr (cm^{-1})): 3057, 2963, 2834, 1732, 1678, 1489, 1405, 1317, 1271, 1215, 1162, 1091, 859, 762, 691. MS m/z (rel int.): 240 (6, M+), 147 (100), 119 (15), 104 (11), 91 (17), 76 (14), 65 (11), 51 (4).

Phenyl 4-phenylbenzoate (**3ha**): δ_H (500 MHz, $CDCl_3$) 8.312 (2H, d, 8.5 Hz, Ph), 7.774 (2H, d, 8.5 Hz, Ph), 7.691–7.709 (2H, m, Ph), 7.529 (2H, t, 7.5 Hz, Ph), 7.442–7.498 (3H, m, Ph), 7.321 (1H, t, 7.5Hz, Ph), 7.277 (2H, dd, 8.0 Hz, 1 Hz, Ph). δ_C (125.7MHz, $CDCl_3$) 165.1, 151.0, 146.4, 140.0, 130.7, 129.5, 129.0, 128.3, 127.4, 127.3, 125.9, 121.8. IR (KBr (cm^{-1})): 3039, 1730, 1608, 1494, 1404, 1266, 1190, 1083, 825, 742. MS m/z (rel int.): 274 (3, M+), 181 (100), 152 (42), 127 (3), 102 (1), 76(2), 65 (7), 51 (3).

4-Fluorophenyl benzoate (**3ab**): δ_H (500 MHz, $CDCl_3$) 8.233 (2H, dd, 8 Hz, 1 Hz, Ph), 7.668–7.698 (1H, m, Ph), 7.555 (2H, t, 7.5 Hz, Ph), 7.200–7.241 (2H, m, Ph), 7.125–7.177 (2H, m, Ph). δ_C (125.7 MHz, $CDCl_3$) 165.2, 160.3 (d, 243.9 Hz), 146.8, 133.7, 130.2, 129.3, 128.6, 123.1(d,7.5 Hz), 116.2(d, 22.6 Hz). IR (KBr (cm^{-1})): 3113, 3065, 1731, 1504, 1294, 1188, 1087, 1064, 808, 706. MS m/z (rel int.): 216 (5, M+), 105 (100), 83 (8), 77 (63), 58 (8), 51 (23).

4-Chlorophenyl benzoate (**3ac**): δ_H (500 MHz, $CDCl_3$) 8.230 (2H, dd, 8 Hz, 1 Hz, Ph), 7.671–7.701 (1H, m, Ph), 7.556 (2H, t, 7.5 Hz, Ph), 7.417–7.448 (2H, m, Ph), 7.193–7.223 (2H, m, Ph). δ_C (125.7 MHz, $CDCl_3$) 165.0, 149.4, 133.8, 131.3, 130.2, 129.6, 129.2, 128.7, 123.1. IR (KBr (cm^{-1})): 3083, 3056, 1734, 1489, 1283, 1219, 1082, 1061, 808, 706. MS m/z (rel int.): 232/234 (8/3, M+), 105 (100), 98 (5), 77 (63), 63 (5), 51 (23).

4-Bromophenyl benzoate (**3ad**): δ_H (500 MHz, $CDCl_3$) 8.216–8.232 (2H, m, Ph), 7.670–7.700 (1H, m, Ph), 7.539–7.597 (4H, m, Ph), 7.138–7.168 (2H, m, Ph). δ_C (125.7 MHz, $CDCl_3$) 164.9, 150.0, 133.8, 132.6, 130.2, 129.2, 128.7, 123.6, 119.0. IR (KBr (cm^{-1})): 3083, 3061, 1733, 1486, 1281, 1217, 1060, 806, 707. MS m/z (rel int.): 276/278(5/5, M+), 171/173 (1/1), 143/145 (3/3), 105 (100), 77 (55), 63 (8), 51 (20).

4-Trifluoromethylphenyl benzoate (**3ai**): δ_H (500 MHz, $CDCl_3$) 8.316–8.338 (1H, m, Ph), 8.230–8.269 (1H, m, Ph), 7.696–7.762 (2H, m, Ph), 7.500–7.596 (2H, m, Ph), 7.427–7.456 (1H, m, Ph), 7.384–7.409 (1H, m, Ph), 7.205–7.270 (1H, m, Ph). δ_C (125.7 MHz, $CDCl_3$) 164.7, 153.5, 134.0, 130.3, 129.0, 128.7, 128.2 (q, 32.8 Hz), 126.9 (q, 3.8 Hz), 123.9 (q, 271.6 Hz), 122.3. IR (KBr (cm^{-1})): 3066, 2923, 1734, 1612, 1600, 1517, 1453, 1340, 1272, 1134, 1071, 817, 705. MS m/z (rel int.): 266 (1, M+), 133 (4), 113 (2), 105 (100), 83 (2), 77 (56), 63 (2), 51 (19).

4-Isopropylphenyl benzoate (**3aj**): δ_H (500 MHz, $CDCl_3$) 8.233–8.252 (2H, m, Ph), 7.651–7.683 (1H, m, Ph), 7.531–7.562 (2H, m, Ph), 7.303–7.331 (2H, m, Ph), 7.155–7.183 (2H, m, Ph), 2.980 (1H, septet, 7.0 Hz, $(CH_3)_2CH$), 1.308 (6H, d, 7.0 Hz, $(CH_3)_2CH$). δ_C (125.7 MHz, $CDCl_3$) 165.4, 148.9, 146.4, 133.5, 130.2, 129.8, 128.6, 127.4, 121.4, 33.7, 24.0. IR (KBr (cm^{-1})): 3052, 3030, 2972, 2960, 2932, 2892, 1732, 1508, 1450, 1268, 1195, 1081, 1064, 809, 712. MS m/z (rel int.): 240 (13, M+), 105 (100), 91 (8), 77 (48), 65 (3), 51 (11).

4-Methoxyphenyl benzoate (**3ak**): δ_H (500 MHz, $CDCl_3$) 8.238 (2H, d, 7 Hz, Ph), 7.668 (1H, t, 7.5 Hz, Ph), 7.545 (2H, t, 7.5 Hz, Ph), 7.156–7.189 (2H, m, Ph), 6.964–6.997 (2H, m, Ph), 3.863 (3H, s, OCH_3). δ_C (125.7 MHz, $CDCl_3$) 165.6, 157.4, 144.5, 133.5, 130.2, 129.7, 128.6, 122.5, 114.6, 55.6. IR (KBr (cm^{-1})): 3113, 3070, 2999, 2959, 2932, 2834, 1730, 1505, 1271, 1195, 1087, 1064, 808, 709. MS m/z (rel int.): 228 (19, M+), 123 (3), 105 (100), 95 (3), 77 (48), 63 (1), 51 (13).

4-Phenoxyphenyl benzoate (**3al**): δ_H (500 MHz, $CDCl_3$) 8.247 (2H, dd, 8.0 Hz, 1 Hz, Ph), 7.663–7.698 (1H, m, Ph), 7.556 (2H, t, 7.5Hz, Ph), 7.369–7.411 (2H, m, Ph), 7.207–7.239 (2H, m, Ph), 7.139–7.173 (1H, m, Ph), 7.074–7.117 (4H, m, Ph). δ_C (125.7 MHz, $CDCl_3$) 165.3, 157.3, 154.9, 146.4, 133.7, 130.2, 129.8, 129.5, 128.6, 123.4, 122.9, 119.7, 118.9. IR (KBr

(cm^{-1})): 3055, 1735, 1600, 1586, 1498, 1488,1450, 1269, 1184, 1093, 1066, 810, 710. MS m/z (rel int.): 290 (25, M+), 185 (3), 157 (1), 129 (4), 105 (100), 77 (56), 63 (3), 51 (17).

4-Biphenyl benzoate (**3am**): δ_H (500 MHz, $CDCl_3$) 8.263–8.280 (2H, m, Ph), 7.671–7.706 (3H, m, Ph), 7.629–7.646 (2H, m, Ph), 7.569 (2H, t, 7.5 Hz, Ph), 7.476–7.506 (2H, m, Ph), 7.399 (1H, t, 7.5 Hz, Ph), 7.322–7.351 (2H, m, Ph). δ_C (125.7 MHz, $CDCl_3$) 165.3, 150.4, 140.4, 139.1, 133.7, 130.2, 129.6, 128.8, 128.6, 128.3, 127.4, 127.2, 122.0. IR (KBr (cm^{-1})): 3057, 3027, 1732, 1486, 1272, 1220, 1087, 1065, 759, 703. MS m/z (rel int.): 274 (20, M+), 169 (3), 141 (6), 115 (9), 105 (100), 77 (40), 51 (9).

5.3. Palladium-catalysed intramolecular asymmetric cyclohydroaryloxy-carbonylation of 2-allylphenol derivatives. Synthesis of chiral lactones via cyclocarbonylation

3-Ethylbenzofuran-2(3*H*)-one (**2a**). δ_H (500 MHz, $CDCl_3$) 1.006 (3H, t, 7.5 Hz), 2.097 (2H, q, 7.5 Hz), 3.738 (1H, t, 6 Hz), 7.138 (1 H, d, 8 Hz), 7.184 (1H, t, 7.5 Hz), 7.308-7.359 (2H, m). δ_C (125.7 MHz, $CDCl_3$) 10.2, 24.3, 44.6, 110.7, 124.1, 124.2, 127.2, 128.8, 154.0, 177.2. MS m/z (rel int.): 162 (100, M^+), 147 (1), 133 (74), 119 (84), 105 (29), 91 (68), 77 (45), 63 (17), 51 (54).

3-Methyl-2-chromanone (**3a**). δ_H (500 MHz, $CDCl_3$) 1.399 (3H, d, 5.5 Hz), 2.769-2.885 (2H, m), 3.002 (1H, dd, 4.5 Hz, 14.5 Hz), 7.061 (1H, d, 8 Hz), 7.111 (1H, t, 7 Hz), 7.208 (1H, t, 7.5 Hz), 7.266 (1H, d, 7.5 Hz). δ_C (125.7 MHz, $CDCl_3$) 15.4, 31.7, 34.3, 116.6, 122.9, 124.2, 128.0, 128.2, 151.8, 171.6. MS m/z (rel int.): 162 (100, M^+), 147 (1), 134 (68), 119 (74), 107 (20), 91 (61), 78 (35), 63 (18), 51 (34).

4,5-Dihydro-1-benzoxepin-2(3*H*)-one (**4a**). δ_H (500 MHz, $CDCl_3$) 2.211 (2H, q, 7.0 Hz), 2.498 (2H, t, 7.0 Hz), 2.854 (2H, t, 7.0 Hz), 7.124 (1H, d, 8 Hz), 7.197-7.228 (2H, m), 7.305 (1H, d, 8 Hz). δ_C (125.7 MHz, $CDCl_3$) 26.6, 28.3, 31.1, 119.4, 125.9, 128.4, 129.7, 130.1, 151.9, 171.7. MS m/z (rel int.): 162 (32, M^+), 147 (1), 134 (4), 119 (1), 107 (100), 91 (10), 77 (19), 63 (6), 55 (47).

2-Propenylphenol. δ_H (500 MHz, $CDCl_3$) 1.904 (3H, d, 7 Hz), 6.185-6.256 (1H, m), 6.656 (1H, d, 16.0 Hz), 6.792 (1H, d, 8 Hz), 6.840 (1H, t, 7.5 Hz), 7.032 (1H, s), 7.058 (1H, t, 8 Hz), 7.322 (1H, d, 7.5 Hz). δ_C (125.7 MHz, $CDCl_3$) 18.9, 115.6, 116.6, 120.2, 125.2, 125.6, 127.0, 127.7, 153.1. MS m/z (rel int.): 134 (100, M^+), 119 (41), 105 (26), 91 (55), 77 (30), 63 (13), 51 (23).

3-Ethyl-7-methylbenzofuran-2(3*H*)-one (**2b**). δ_H (500 MHz, $CDCl_3$) 1.007 (3H, t, 7.5 Hz), 2.054-2.110 (2H, m), 2.357 (3H, s), 3.734 (1H, t, 6 Hz), 7.063-7.168 (3H, m). δ_C (125.7 MHz,

$CDCl_3$) 10.2, 15.0, 24.4, 45.0, 121.0, 121.3, 123.8, 126.7, 130.2, 152.5, 177.3. MS m/z (rel int.): 176 (70, M^+), 161 (1), 148 (71), 133 (100), 119 (6), 105 (39), 91 (33), 77 (20), 65 (24), 51 (18).

3,8-Dimethyl-2-chromanone (**3b**). δ_H (500 MHz, $CDCl_3$) 1.405 (3H, d, 7.0 Hz), 2.334 (3H, s) 2.75-2.915 (2H, m), 2.975 (1H, dd, 5.5 Hz, 14.5 Hz), 6.993-7.034 (2H, m), 7.130 (1H, dd, 2 Hz, 8.5 Hz). δ_C (125.7 MHz, $CDCl_3$) 15.4, 15.7, 31.9, 34.3, 122.7, 123.8, 125.4, 126.0, 129.7, 150.2, 171.8. MS m/z (rel int.): 176 (91, M^+), 161 (1), 148 (68), 133 (100), 115 (18), 105 (41), 91 (45), 77 (27), 65 (18), 51 (23).

9-Methyl-4,5-dihydro-1-benzoxepin-2(3*H*)-one (**4b**). δ_H (500 MHz, $CDCl_3$) 2.198 (2H, q, 7.5 Hz), 2.313 (3H, s) 2.487 (2H, t, 7.5 Hz), 2.832 (2H, t, 7.5 Hz), 7.040-7.096 (2H, m), 7.158 (1H, d, 7.0 Hz). δ_C (125.7 MHz, $CDCl_3$) 16.2, 26.6, 28.4, 31.2, 122.5, 127.1, 128.5, 129.9, 130.0, 150.1, 171.8. MS m/z (rel int.): 176 (33, M^+), 161 (6), 148 (7), 133 (16), 121 (100), 105 (3), 91 (24), 77 (18), 65 (9), 55 (22).

8-Methoxy-3-methyl-2-chromanone (**3c**). δ_H (500 MHz, $CDCl_3$) 1.407 (3H, d, 7.0 Hz), 2.782-2.891 (2H, m,), 2.991 (1H, dd, 5.5 Hz, 14.5 Hz), 3.917 (3H, s), 6.783 (1H, d, 7.5 Hz), 6.866 (1H, d, 8.5 Hz), 7.059 (1H, t, 8.0 Hz). δ_C (125.7 MHz, $CDCl_3$) 15.4, 31.9, 34.1, 56.1, 111.1, 119.5, 124.0, 124.2, 141.1, 147.5, 170.9. MS m/z (rel int.): 192 (100, M^+), 177 (1), 164 (69), 149 (40), 131 (34), 115 (8), 103 (25), 91 (23), 77 (38), 65 (29), 51 (25).

9-Methoxy-4,5-dihydro-1-benzoxepin-2(3*H*)-one (**4c**). δ_H (500 MHz, $CDCl_3$) 2.210 (2H, q, 7.5 Hz), 2.519 (2H, t, 7.5 Hz), 2.850 (2H, t, 7.5 Hz), 3.892 (3 H, s), 6.809 (1H, d, 7.5 Hz), 6.920 (1H, d, 8.5 Hz), 7.137 (1H, t, 8.5 Hz). δ_C (125.7 MHz, $CDCl_3$) 26.5, 28.3, 31.1, 56.1, 111.6, 121.0, 126.1, 131.5, 140.7, 149.6, 171.3. MS m/z (rel int.): 192 (37, M^+), 175 (1), 164 (10), 149 (6), 137 (100), 122 (13), 103 (6), 91 (14), 77 (20), 66 (4), 55 (25).

2-Propenyl-6-methoxyphenol. δ_H (500 MHz, $CDCl_3$) 1.938 (3H, d, 7.0 Hz), 3.918 (3H, s), 5.857 (1H, s), 6.289-6.362 (1H, m), 6.709 (1H, d, 16 Hz), 6.751 (1H, d, 7.5 Hz), 6.815(1H, t, 8 Hz), 7.024 (1H, d, 7.5 Hz). δ_C (125.7 MHz, $CDCl_3$) 18.9, 56.1, 108.7, 118.9, 119.4, 124.4, 125.1, 126.9, 142.6, 146.7. MS m/z (rel int.): 164 (100, M^+), 149 (34), 131 (36), 121 (31), 103 (40), 91 (31), 77 (42), 65 (14), 51 (16).

5-Acetyl-3-ethylbenzofuran-2(3*H*)-one (**2d**). δ_H (500 MHz, $CDCl_3$) 1.012 (3H, t, 7.5 Hz), 2.095-2.186 (2H, m), 2.642 (3H, s), 3.789 (1H, t, 6.0 Hz), 7.209 (1H, d, 8.5 Hz), 7.959 (1H, d, 1.5 Hz), 7.993 (1H, dd, 1.5 Hz, 8.5 Hz). δ_C (125.7 MHz, $CDCl_3$) 10.1, 24.2, 26.5, 44.3, 110.5, 124.4, 127.8, 130.4, 133.7, 157.5, 176.3, 196.5. MS m/z (rel int.): 204 (34, M^+), 189 (30), 176 (2), 161 (100), 147 (1), 133 (4), 115 (3), 103 (5), 89 (4), 77 (12), 63 (5), 51 (8).

6-Acetyl-3-methyl-2-chromanone (**3d**). δ_H (500 MHz, $CDCl_3$) 1.420 (3H, d, 6.5 Hz), 2.613 (3H, s), 2.837-2.879 (2H, m), 3.088 (1H, dd, 5.5 Hz, 15.5 Hz), 7.128 (1H, d, 8.5 Hz), 7.869 (1H, d, 2 Hz) 7.916 (1H, dd, 2 Hz, 8.5 Hz). δ_C (125.7 MHz, $CDCl_3$) 15.4, 26.5, 31.6, 34.1, 116.8, 123.1, 128.5, 129.0, 133.5, 155.3, 170.6, 196.6. MS m/z (rel int.): 204 (36, M^+), 189 (60), 176 (1), 161 (100), 147 (1), 133 (7), 115 (5), 103 (6), 91 (4), 77 (18), 63 (7), 51 (14).

7-Acetyl-4,5-dihydro-1-benzoxepin-2(3*H*)-one (**4d**). δ_H (500 MHz, $CDCl_3$) 2.257 (2H, q, 7.5 Hz), 2.523 (2H, t, 7.0 Hz), 2.630 (3H, s) 2.925 (2H, t, 7.5 Hz), 7.193 (1H, d, 8.5 Hz), 7.869 (1H, d, 2.0 Hz), 7.915 (1H, dd, 2 Hz, 8.5 Hz). δ_C (125.7 MHz, $CDCl_3$) 26.4, 26.6, 28.4, 31.2, 119.6, 129.1, 130.0, 130.5, 134.9, 155.4, 170.3, 196.7. MS m/z (rel int.): 204 (13, M^+), 189 (9), 176 (14), 161 (11), 149 (48), 133 (6), 121 (3), 105 (4), 91 (7), 77 (16), 65 (5), 55 (100).

***3*-Methyl-2-oxochroman-8-carbaldehyde** (**3e**). δ_H (500 MHz, $CDCl_3$) 1.460 (3H, d, 6.0 Hz), 2.877-2.967 (2H, m), 3.093 (1H, dd, 5.0 Hz, 14.5 Hz), 7.229 (1H, t, 7.5 Hz), 7.463 (1H, d, 7.5 Hz), 7.849 (1H, d, 7.5 Hz), 10.560 (1H, s). δ_C (125.7 MHz, $CDCl_3$) 15.4, 31.5, 33.9, 123.8, 123.9, 124.2, 126.9, 133.9, 153.8, 169.8, 188.1. MS m/z (rel int.): 190 (63, M^+), 175 (1), 162 (100), 147 (39), 133 (47), 116 (80), 105 (44), 91 (50), 77 (56), 63 (28), 51 (58).

2-Oxo-2,3,4,5-tetrahydro-1-benzoxepin-9-carbaldehyde (**4e**). δ_H (500 MHz, $CDCl_3$) 2.288 (2H, q, 7.5 Hz), 2.605 (2H, t, 7.5 Hz), 2.949 (2H, t, 7.5 Hz), 7.315 (1H, t, 7.5 Hz), 7.518 (1H, d, 7.5 Hz), 7.892 (1H, d, 7.5 Hz), 10.500 (1H, s). δ_C (125.7 MHz, $CDCl_3$) 26.5, 28.2, 31.3, 126.1, 126.4, 126.9, 131.1, 135.7, 153.8, 169.8, 188.4. MS m/z (rel int.): 190 (8, M^+), 173 (4), 162 (20), 144 (19), 135 (69), 115 (9), 105 (13), 91 (9), 77 (24), 66 (9), 55 (100).

4-(3-Formyl-2-hydroxyphenyl)butanoic acid. δ_H (500 MHz, $CDCl_3$) 2.015 (2H, q, 7.5 Hz), 2.437 (2H, t, 7.5 Hz), 2.773 (2H, t, 7.5 Hz), 6.991 (1H, t, 7.5 Hz), 7.424-7.470 (2H, m), 9.914 (1H, s), 11.308 (1H, s), 11.340 (1H, s). δ_C (125.7 MHz, $CDCl_3$) 24.2, 28.4, 33.4, 119.6, 120.3, 129.9, 131.9, 137.3, 159.8, 179.4, 196.8. MS m/z (rel int.): 208 (38, M^+), 190 (18), 174 (4), 162 (16), 148 (93), 135 (100), 120 (39), 105 (16), 91 (24), 77 (76), 66 (14), 55 (60).

6. Summary

In this thesis, various transition metal-catalysed carbonylations were investigated aiming at using alternative carbon monoxide sources. Styrenes and aryl halides were used as substrates. Chemo-, regio- and enantioselectivity of these model reactions were studied as well.
In the light of the previous findings, the following general points can be mentioned.

1. A set of styrenes was hydroaryloxycarbonylated by using palladium catalysts under carbon monoxide atmosphere to prepare the corresponding propanoic acid aryl esters. Various achiral and chiral phosphine ligands were utilised to afford the *in situ* generated Pd catalysts. The reaction conditions were optimised by varying different factors such as temperature, CO pressure, reaction time, catalyst precursor, reaction solvent and different phosphine ligands. Generally, monophosphine ligands favoured the formation of branched ester derivatives, while diphosphine ligands favoured the formation of the linear ester regioisomers.
2. DIOP-containing palladium catalyst generated *in situ* in the hydroaryloxycarbonylation reaction of styrenes was the most efficient catalyst among various tested chiral ligands concerning enantioselectivity. Substituents on both phenols and styrenes were also studied regarding the effect on the regio- and enantioselectivity of the hydroaryloxycarbonylation reaction by using Pd-DIOP catalyst system. A preference formation of the linear ester derivatives and low enantiomeric excess of branched isomers were noticed. Besides, the hydroesterification reaction of substituted styrenes and phenols showed high functional group tolerance.
3. Carbon monoxide or paraformaldehyde as a CO source was utilised to carry out the Rh-catalysed aryloxycarbonylation reaction of aryl iodides. The reaction conditions were optimised in both strategies by varying different factors such as temperature, reaction time, catalyst precursor, reaction solvent and the phosphine ligands. The corresponding phenyl ester derivative was synthesised successfully according to both protocols.
4. The application of the direct CO gas in the aryloxycarbonylation reaction of iodoarenes resulted in the formation of good ester selectivity. Comparing to Pd systems used in the same reaction, Rh systems afforded lower activity. Using paraformaldehyde as a CO surrogate in the aryloxycarbonylation reaction showed dramatic changes during the optimisation reactions. Ligand structure and solvent composition had an impact effect on both activity and chemoselectivity.

5. Substituents on both phenols and iodoarenes were also studied regarding the effect on the activity and chemoselectivity of the aryloxycarbonylation reaction by using Rh-diphosphine catalyst systems. In the presence of CO atmosphere, substitution of both substrate and nucleophile exhibited higher reaction activity when compared to the phenoxycarbonylation reaction of iodobenzene and the parent phenol. In the presence of paraformaldehyde, concerning the electronic properties of phenol substitution, no definite effect on the aryloxycarbonylation reactivity was observed. However, instead of obtaining ester compounds in good yields when applying substituted iodobenzenes and phenol, a hydrodeiodination pathway was favoured, thus, the formation of the corresponding arenes was observed in these cases.
6. Palladium complexes were utilised to carry out cyclohydroaryloxycarbonylation reaction of 2-allylphenol substrates to afford the corresponding lactone derivatives. The cyclocarbonylation reaction of the allylphenol derivatives were conducted under carbon monoxide atmosphere in the absence of hydrogen gas. Various phosphine ligands and precursors were tested and exploited to generate the active catalytic species in the presence of acid derivatives.
7. A dominant formation of the chiral 6- and achiral 7-membered lactones were obtained, while trace amount formation of the 5-membered lactone derivatives can be noticed. Higher regioselectivity values regarding the chiral chromanone derivatives can be achieved by applying achiral phosphine ligands. The application of chiral ligands, resulted in the formation of moderate to good enantioselectivity regarding the chiral 6-membered chromanone derivatives (up to 59%). The catalyst composition and the acid co-catalysts were found to have an effect on the reaction regioselectivity, while no such influence of allylphenol substitution was observed. The experimental results were rationalised by considering a generally accepted mechanism. Based on the above findings, a catalytic cycle was suggested.

7. References

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