

UNIVERSITY OF PÉCS

Doctoral School of Chemistry

**TRANSITION METAL-CATALYSED
(HYDRO)ARYLOXYCARBONYLATION REACTIONS**

PhD thesis

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1. Introduction

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.

A very important class of compounds in organic chemistry is the one that involves compounds containing carbonyl group(s) in their structures. Fortunately, this class can be prepared by homogeneous catalytic reactions, specifically, by conducting carbonylations which incorporated in the introduction of at least one CO group to the structure of reacted substrates.

The production of fine chemicals and the preparation of optically active compounds that can serve as intermediates or building blocks in pharmaceutical industry is of great importance. Non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen, ketoprofen, fenoprofen and ibuprofen can be prepared by transition metal-catalysed carbonylation of the corresponding alkenes.

Esterification is a very important and fundamental transformation as it provides the esters formation which in turn can be widely used in the production of fragrances, flavours, natural products, polymers as well as fine chemicals. Methyl methacrylate (MMA) is a crucial compound which can be afforded by carbonylation reaction of propyne in the presence of palladium-containing catalyst system. Due to the high importance of esters formation, our interests in studying transition metal-catalysed esterification reactions seems to be realistic.

Hydroalkoxycarbonylation (hydroesterification) reaction term is used to describe transition metal-catalysed carbonylation process of unsaturated substrates like alkenes and alkynes to their corresponding alkyl esters in the presence of alcohols as *O*-nucleophiles.

To the best of my knowledge, sporadic results and reports concerning the hydroaryloxycarbonylation reaction which involves the use of phenols as the *O*-nucleophiles and alkenes as the substrates can be found in the literature.

Alkoxycarbonylation or 'Heck-carbonylation' reaction term is used to describe the carbonylation process of organic halides such as aryl-, alkenyl-, allyl- and benzyl halides (chlorides, bromides or iodides) to produce ester derivatives in the presence of alcohols as the nucleophilic source. It is worth mentioning that numerous reports can be found regarding Pd-catalysed alkoxycarbonylation reaction of aryl halides. Nevertheless, Rh-catalysed alkoxy- or aryloxycarbonylation (aryloxy stands for phenol nucleophiles addition instead of alcohols) reaction is less studied.

Both gaseous CO or CO surrogates such as metal carbonyls, formaldehyde and paraformaldehyde can be used as carbonylating agents. Generally, the great importance of CO surrogates was stemmed from the well-accepted properties they own when compared to systems where gaseous CO was applied. Toxicity, flammability and the need of special equipment to handle carbonylation reactions are all disadvantages of using gaseous CO-based carbonylation.

Cyclohydroalkoxycarbonylation and cyclohydroaryloxycarbonylation reactions of potential unsaturated alcohols and phenols substrates, respectively are very important protocols that enabled the synthesis of cyclic esters (lactones). These categories have gained special interests due to the biological and pharmacological applications they own.

Various reports on the cyclohydrocarbonylation reaction of unsaturated alcohols can be found in the literature, nevertheless, few reports concerning cyclohydroaryloxycarbonylation reaction of unsaturated phenols are present in the literature, especially, for 2-allylphenols. Intramolecular hydroaryloxycarbonylation for allylphenols was investigated by using the *in situ* generated palladium catalyst system (Pd(OAc)₂-DPPB) in the presence of H₂ gas to synthesize the corresponding cyclic esters; 5-, 6- and 7-membered lactones.

2. Aims

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 as well as various substrates use such as terminal alkenes, aryl halides and allyl phenol derivatives under mild 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 investigate the Rh-catalysed aryloxycarbonylation reactions of substituted iodobenzenes and substituted phenols in the presence of the gaseous CO as well as paraformaldehyde as a CO source (CO surrogate).
- To carry out cyclohydroaryloxycarbonylation of 2-allylphenol derivatives leading to the preparation of different lactones and investigate the asymmetric carbonylation.

3. Methods

3.1. General

All reactions were carried out under argon using standard Schlenk techniques. The ^1H 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 ^1H 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. The esters were purified and isolated by column chromatography (Silica gel, 0.063 mm; CHCl_3).

3.2. Synthetic methods for Pd-catalysed hydroaryloxycarbonylation of styrenes and phenols, and for Pd-catalysed cyclohydroaryloxycarbonylation of allylphenols

The reactions were carried out in stainless steel autoclave (100 mL). $\text{PdCl}_2(\text{PhCN})_2$ (3.8 mg; 0.01 mmol), DIOP (19.9 mg; 0.04 mmol), phenol in case of Pd-catalysed hydroaryloxycarbonylation of styrenes (6 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 three times with argon, pressurized to 100 bar of carbon monoxide and placed in oil bath for 48 hours at 100 °C (for styrenes) or 120 °C (for allylphenols). 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 CH₂Cl₂, and 1 µL was injected from the solution).

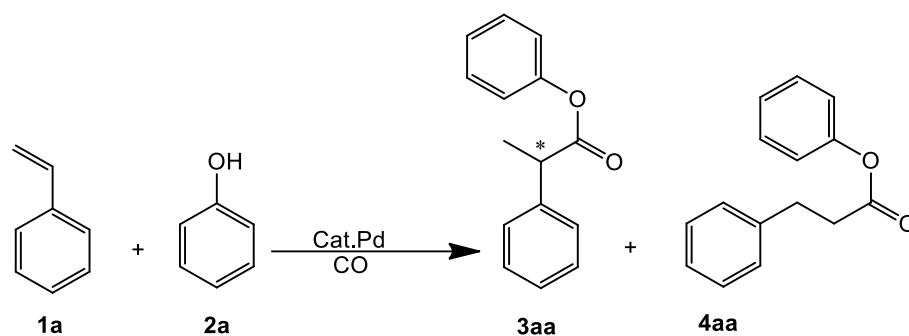
3.3. Synthetic methods for Rh-catalysed aryloxy carbonylation of iodobenzenes and phenols in the presence of CO gas or paraformaldehyde

In the presence of gaseous CO, 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 (phenol) and 1.2 mmol Et₃N were transferred under argon atmosphere into a 100 mL stainless steel autoclave followed by 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. After cooling the mixture, the solution was removed and immediately analyzed by GC and GC–MS.

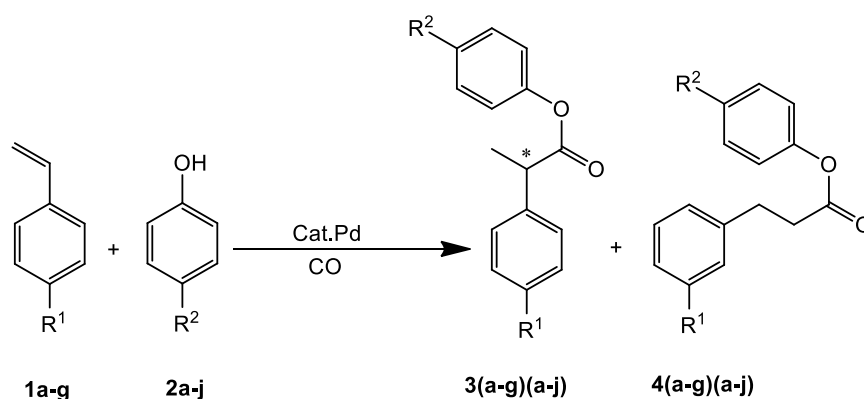
For reactions carried out in the presence of paraformaldehyde, complex precursor [Rh(nbd)Cl]₂ (4.80 mg; 0.01 mmol) and DPPP (20.62 mg; 0.05 mmol) in 10 mL of solvent mixture consists of toluene:ethyl acetate (4:6) containing 0.5 mmol substrate, 3 mmol of nucleophile, 16 mmol paraformaldehyde, 1.5 mmol Na₂CO₃, 1.25 mmol MgSO₄, 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 the mixture, the solution was removed and immediately analyzed by GC and GC–MS.

4. Thesis results

1) The optimisation conditions of hydrophenoxy carbonylation reaction of parent styrene (**1a**) and parent phenol (**2a**) were scanned by testing several phosphine ligands (achiral mono- and bidentate, chiral bidentate), Pd precursors, acids and solvents. Parameters such as temperature, CO pressure and metal: ligand ratio were also studied. Both branched and linear ester isomers, (**3aa**) and (**4aa**), respectively were produced from the hydrophenoxy carbonylation reaction (*Scheme 1*). The optimal conditions, (Pd(PhCN)₂Cl₂-(*R*)-DIOP-HCl catalyst system, 100 bar of carbon monoxide and carrying the reaction at 100 °C were adapted to carry out the hydroaryloxy carbonylation reaction of *para*-substituted styrenes and *para*-substituted phenols as well (*Scheme 2*).



Scheme 1. Palladium-catalysed hydrophenoxy-carbonylation of styrene and phenol

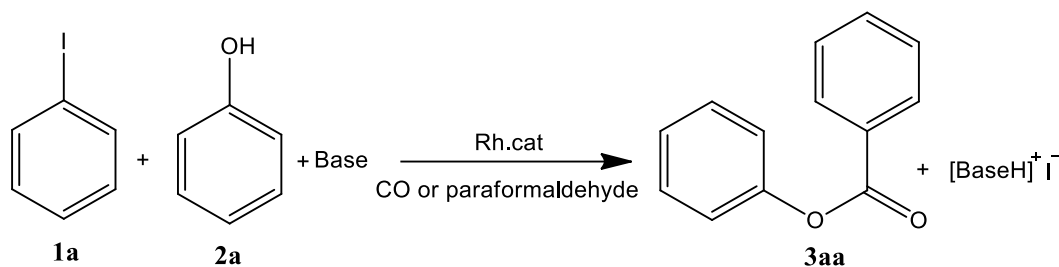


R^1	R^2	
a =H	a =H	h =Br
b =Me	b =Me	i = <i>i</i> Pr
c =OMe	c =OMe	j =CHO
d =Ph	d =Ph	
e =F	e =F	
f =Cl	f =Cl	
g =CF ₃	g =CF ₃	

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

2) The regioselectivity of the reaction toward branched esters were found to be between 9-25% and independent of the nature of the substitution either on styrenes or phenols. 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.

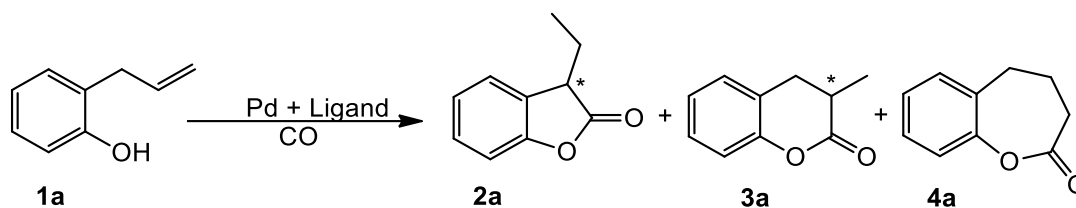
3) The optimisation conditions of Rh-catalysed phenoxyoxycarbonylation reaction of iodobenzene substrate (**1a**) with phenol as *O*-nucleophile (**2a**) were investigated in the presence of gaseous carbon monoxide as well as paraformaldehyde (CO source) to produce phenyl benzoate ester (**3aa**) (**Scheme 3**).



Scheme 3. Rhodium-catalysed phenoxy carbonylation of iodobenzene

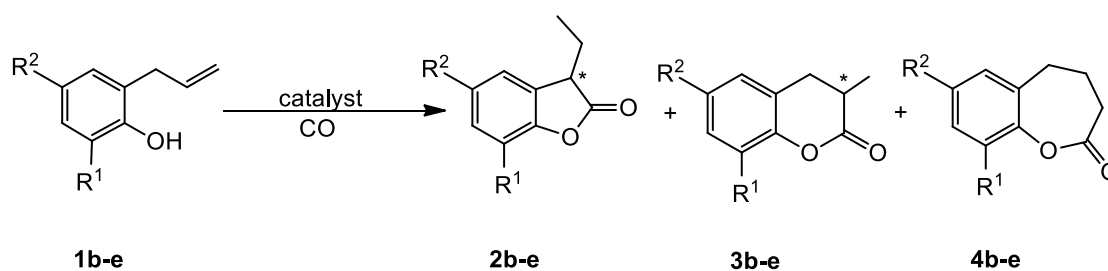
4) The application of $\text{Rh}(\text{acac})(\text{CO})_2\text{-Xantphos-Et}_3\text{N}$ and $[\text{Rh}(\text{nbd})\text{Cl}]_2\text{-DPPP-Na}_2\text{CO}_3\text{-CuCl}$ catalytic systems for the aryloxy carbonylation of iodobenzenes and phenols was studied. The aryloxy carbonylation reaction carried 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.

5) The investigation of the cyclohydrophenoxy carbonylation reaction of 2-allylphenol to synthesise lactone compounds in the absence of H_2 gas and in the presence of the *in situ* generated Pd catalyst system was established. 5-, 6- and 7-membered lactone derivatives were formed in the optimisation reactions (**Scheme 4**). In general, diphosphine ligands favoured the formation of the 7-membered lactone isomer, while PPh_3 and Xantphos ligands favoured the formation of the 6-membered lactone isomer. The highest ee values for the chromanone compound (6-membered lactone) were afforded by HCl and HCOOH and found to be 52 and 42%, respectively.



Scheme 4. Palladium-catalysed cyclohydrophenoxy carbonylation of 2-allylphenol

6) Two catalyst systems, $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ -DIOP-HCOOH and $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ -Xantphos-HCl/TsOH, were used to carry out the cyclohydroaryloxy carbonylation reaction of the 2-allylphenol derivatives (**Scheme 5**). 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 conversions for the tested substrates and higher regioselectivity for the chromanone derivatives compared to that obtained from the application of $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ -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.



1-4b $\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{H}$; **1-4c** $\text{R}^1=\text{OCH}_3$, $\text{R}^2=\text{H}$; **1-4d** $\text{R}^1=\text{H}$, $\text{R}^2=\text{COCH}_3$; **1-4e** $\text{R}^1=\text{CHO}$, $\text{R}^2=\text{H}$

Scheme 5. Cyclohydroaryloxy carbonylation reactions using substituted 2-allylphenol derivatives

5. Publications related to the PhD thesis:

- [1] P. Pongrácz, A. Abu Seni, L. T. Mika, L. Kollár. Palladium-catalysed enantioselective hydroaryloxy-carbonylation of styrenes by 4-substituted phenols. *Mol. Catal.* 438 (2017) 15. (IF: 4.397).
- [2] A. Abu Seni, L. Kollár, L. Mika, P. Pongrácz. Rhodium-catalysed aryloxy-carbonylation of iodo-aromatics by 4-substituted phenols with carbon monoxide or paraformaldehyde. *Mol. Catal.* 457 (2018) 67. (IF: 5.008).
- [3] A. Abu Seni, L. Kollár, P. Pongrácz. Palladium-catalysed intramolecular asymmetric cyclohydroaryloxy-carbonylation of 2-allylphenol derivatives. Synthesis of chiral lactones via cyclocarbonylation. *Mol. Catal.* (2019). (In press). (IF: 5.008).

6. Other Publications:

- [1] M. El-khateeb, K. J. Asali, A. Abuseni, I. Jibril, W. Weigand. *Transition Met. Chem.* 34 (2009) 419.

7. Conferences:

- [1] M. El-khateeb, K. J. Asali, A. Abuseni, I. Jibril, W. Weigand. *Transition Met. Chem.* 34 (2009). Organometallic Complexes of Sulfur or Selenium Ligands: Irbid-Jena relationship (Jordan-Germany), Irbid (Jordan), 2009.
- [2] A. Abu Seni, P. Pongrácz, L. Kollár: Palladium-catalysed enantioselective hydroaryloxy-carbonylation of Styrenes by 4-Substituted Phenols. 20th European Symposium on Organic Chemistry (ESOC-2017) Cologne, 2-6 July, 2017 (CA098).