Javier Delgado Lijarcio

Pd-catalyzed hydroformylation of styrene using formaldehyde as syngas surrogate

Supervised by Dr Cyril Godard (URV)

and Dr Aitor Gual (CTQC/EURECAT)

FINAL DEGREE PROJECT

Chemistry degree

UNIVERSITAT ROVIRA I VIRGILI

Tarragona, June 2019

TABLE OF CONTENTS

ABSTRACT

Hydrocinnamaldehyde is an interesting compound to be used in perfumery for hyacinth and floral fragrances due to its odor. This compound is currently produced by selective hydrogenation of cinnamaldehyde, whose production is very complex, requires multi-step procedures and is poor sustainable. The metal-catalyzed hydroformylation allows the direct production of hydrocinnamaldehyde in a more sustainable manner, since, the reaction is 100% atom economy and involves only one step.

To date, the production of hydrocinnamaldehyde by rhodium-catalyzed hydroformylation of styrene is not optimized enough, since the current process provides moderate regioselectivites. Recently, a new palladium-catalytic system has been proved to be an excellent alternative due to its better regioselectivity using CO-surrogate molecules.

This work aims the hydrocinnamaldehyde production by Pd-catalyzed regioselective hydroformylation of styrene using formaldehyde (HCHO) as syngas surrogate agent, and includes an optimization of the catalytic system, mechanistic studies using deuteron-labelled molecules and a preliminary exploration of the reaction kinetics.

El hidrocinamaldehído es un compuesto muy interesante usado en perfumerías y fragancias florales debido a su potente olor florar. Este compuesto se produce mediante la hidrogenación selectiva del cinamaldehído, cuya producción es muy compleja, y requiere de un proceso con múltiples etapas, además de ser un proceso que carece de sostenibilidad. La hidroformilación catalizada por metales de transición permite directamente la producción de hidrocinamaldehído de un modo más sostenible, involucrando una sola etapa y siendo económica atómicamente.

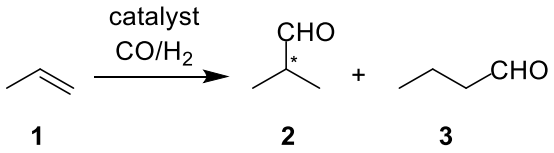
Actualmente, la producción de hidrocinamaldehído mediante hidroformilación de estireno catalizada por rodio no está suficientemente optimizada, ya que se obtienen valores moderados en cuanto a regioselectividad. Recientemente, un nuevo sistema catalítico con paladio ha demostrado ser una excelente alternativa debido a su mejor regioselectividad usando moléculas carboxílicas como sustitutas del gas de síntesis.

Este trabajo tratará la producción de hidrocinnamaldehído mediante la hidroformilación de estireno catalizada por Pd, usando formaldehído como sustituto al gas síntesis, donde se incluye una optimización de las condiciones óptimas del sistema catalítico, estudios para entender el mecanismo de la reacción usando compuestos marcados con deuterio y una exploración preliminar de la cinética de la reacción.

INTRODUCTION

Hydroformylation process.

The hydroformylation of alkenes, which was originally discovered by Otto Roelen in 1938 [1], is nowadays one of the most important industrial applications of homogeneous catalysis (Scheme 1.).[2],[3] Today, over 9 million tons of so-called *oxo*-products are produced per year, a number which is still rising. Most *oxo*-products are obtained from the hydroformylation of propene **1**, which is a fraction of the steam-cracking process. The resulting products *iso*-butyraldehyde **2** and *n*-butanal **3** are important intermediates to produce esters, acrylates and 2-ethylhexanol. [2]



Scheme 1. Hydroformylation of propene.

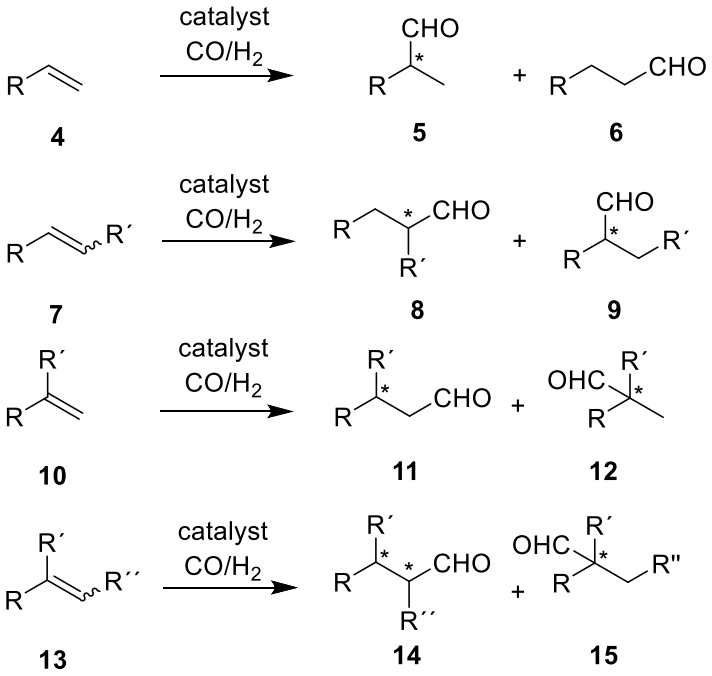
From a synthetic point of view, the reaction is an one-carbon chain elongation caused by the addition of carbon monoxide and hydrogen across the π system of a C=C double bond.[4],[5] As a pure addition reaction, the hydroformylation reaction meets all requirements of an atom economic process.[6] Furthermore, the synthetically valuable aldehyde function is introduced, which allows subsequent skeleton expansion that may even be achieved in one-pot sequential transformations.[7],[8]

In 1968, Wilkinson discovered that phosphine-modified rhodium complexes display a significantly higher activity and selectivity compared to the first generation of cobalt catalysts. [9] Since this time, ligand modification of the rhodium catalyst has been the method of choice in order to influence the catalyst activity and selectivity. [10]

In the low-pressure hydroformylation of internal alkenes, the chemoselectivity (and simultaneously regioselectivity) is one of the remaining problems to be solved in industry. This issue originates from the exponential drop of alkene reactivity when increasing the number of alkene substituents. The known hydroformylation catalysts for internal alkene hydroformylation operating under low-pressure conditions rely on the use of strong π-acceptor ligands, such as bulky phosphites and phosphabenzene systems.[11]

However, the high activity of the corresponding rhodium catalysts is usually associated with a high tendency towards alkene isomerization, which renders a position-selective hydroformylation of an internal alkene extremely challenging, although over the last years, some examples started to appear in the literature.

The regioselectivity of the hydroformylation of alkenes is a function of many factors and quantum chemical calculations have been frequently used to gain useful insight into its origin. [12] These include inherent substrate preferences, directing effects exerted by functional groups as part of the substrate, as well as catalyst effects. In order to appreciate inherent substrate regioselectivity trends, alkenes must be classified according to the number and nature of their substituents (*Scheme 2*).[4],[5]



Scheme 2. Regioselectivity trends on hydroformylation of different alkenes.

The regioselectivity issue usually arises for terminal and 1,2-disubstituted alkenes **7**. For alkyl-substituted terminal alkenes **4,** there is a slight preference for the linear product **6**. For terminal alkenes 4 containing an electron-withdrawing substituent, the formation of the branched product **5** is favored, and sometimes is exclusive. This tendency is unaffected by the catalyst structure. Both 1,1-disubstituted **10** and tri-substituted **13** alkenes generally provide only one regioisomer (**11** and **14**, respectively) based on Keuleman´s rule, which states that the formyl group is usually added in order to avoid the formation of a quaternary carbon center.[13]

Asymmetric hydroformylation is a very promising catalytic reaction that produces chiral aldehydes from inexpensive feedstock (alkenes and *syngas*) in a single step under neutral reaction conditions. Even though asymmetric hydroformylation offers great potential for the fine chemical industry, this reaction has not yet been utilized on an industrial scale due to several technical challenges. [2] Among the most significant issues are (a) the low reaction rates at low temperature where good selectivities are usually observed, (b) the difficulty to control simultaneously the regio- and the enantioselectivity, and (c) the limited substrate scope for any single ligand.

Mechanism for Rh-hydroformylation of styrene.

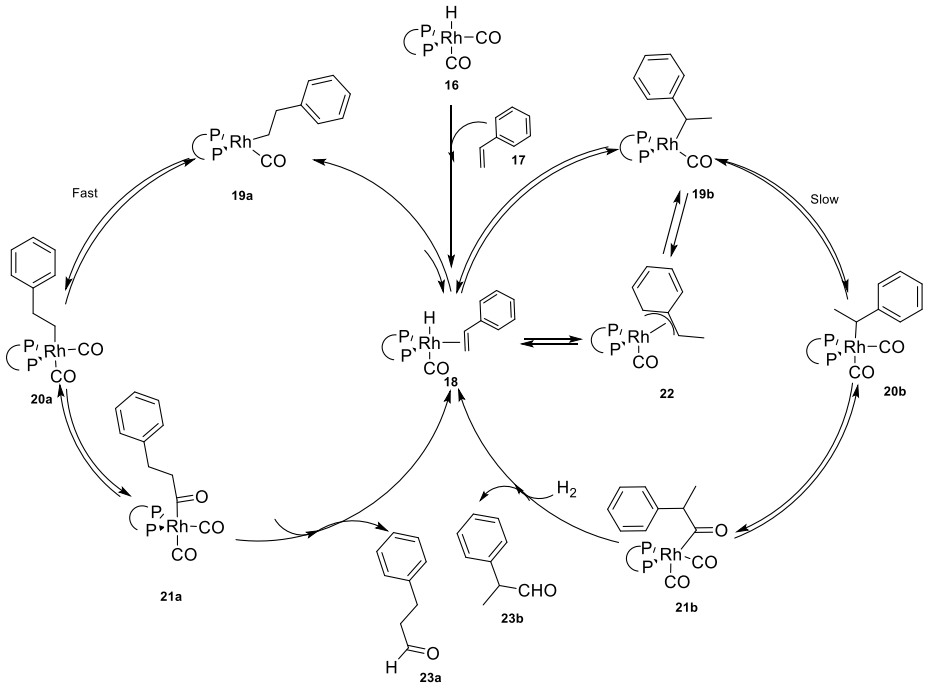
The accepted mechanism for this process is the well-known mechanism proposed by Heck.[14] It corresponds to Wilkinson's so-called dissociative mechanism.[9] The associative mechanism involving 20-electron intermediates for ligand/substrate exchange will not be considered. In this process, a great understanding of the mechanism has been possible due to the observation and structural characterization of the resting state of the catalyst by *in situ* spectroscopic techniques (HP-IR, HP-NMR).[10],[15] Recently, the full catalytic cycle for mono- and bis-ligated monophosphine rhodium complexes has been investigated using DFT calculations.[16]

Although short olefins such as ethylene, propene and butenes are the main substrates in industrial Rh-catalyzed hydroformylation, the transformation of styrene into the corresponding aldehydes has been largely reported. [17] As mentioned previously, for terminal alkenes **4** containing an electron-withdrawing substituent, the formation of the branched product **5** is favored. This is the case when styrene is the substrate in this reaction.

The mechanism of the rhodium-catalyzed hydroformylation of styrene has been studied.[18] The proposed catalytic cycle is shown in *Scheme 3*.

In this mechanism, the formation of the rhodium alkyl intermediates **19a** and **19b** from the Rh hydride species **18** is the key step controlling the regioselectivity. Lazzaroni and co-workers showed that in this reaction, the kinetic product is the branched aldehyde and is therefore favored when the reaction is conducted at low temperature.[12r] The formation of this product is also favored by the formation of the stable Rh(η^3-allyl) species **22**, which is in equilibrium with the branched Rh-alkyl species **19b** that is at the origin of the production of the branched aldehyde. The presence of this species tends to displace the equilibrium towards the catalytic cycle giving rise to the branched product.

In these studies, the effect of temperature was shown to affect the regioselectivity of this process and isotopic labeling experiments demonstrated that the formation of both linear and branched Rh-alkyl species is irreversible at low temperature but becomes reversible at high temperature. [18]



Scheme 3. Proposed mechanism for the Rh-catalyzed hydroformylation of styrene.[12r]

There are only a few reports on the selective formation of the linear aldehyde using Rh systems. [12i] To date, two types of P-based ligands were shown to improve the regioselectivity of this reaction towards the formation of the linear aldehydes: large bite angle ligands such as Xantphos and derivatives [19] and diphosphite ligands containing an atropoisomeric backbone. This latter type of ligands provided a l/b ratio of up to 26.

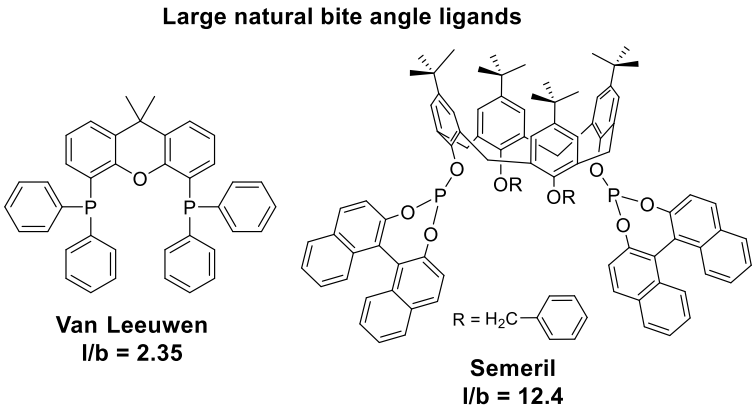


Fig 1. Ligands with large natural bite angle to improve the regioselectivity of hydroformylation.

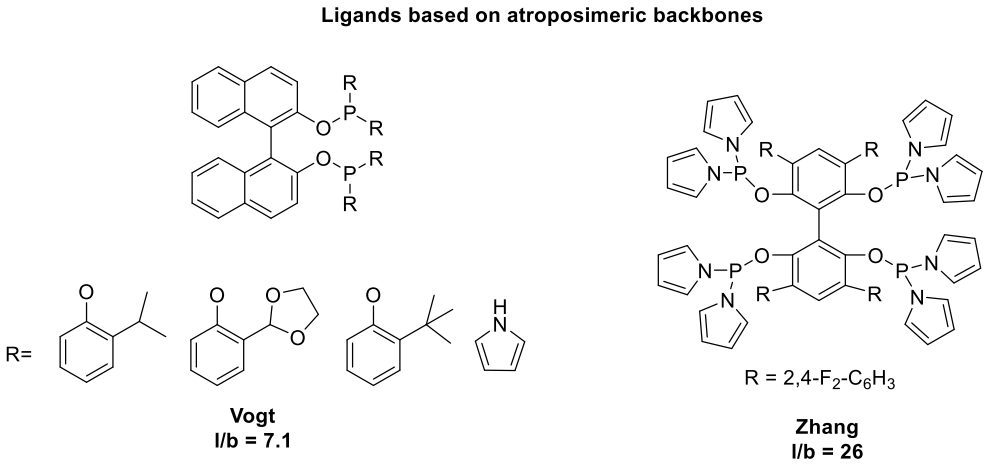
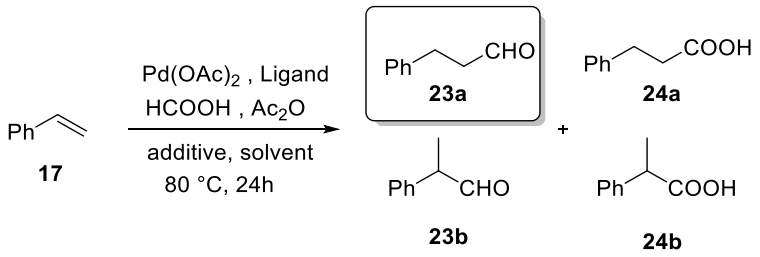


Fig 2. Diphosphite ligands containing an atropoisomeric backbones.

Alternative syngas surrogates

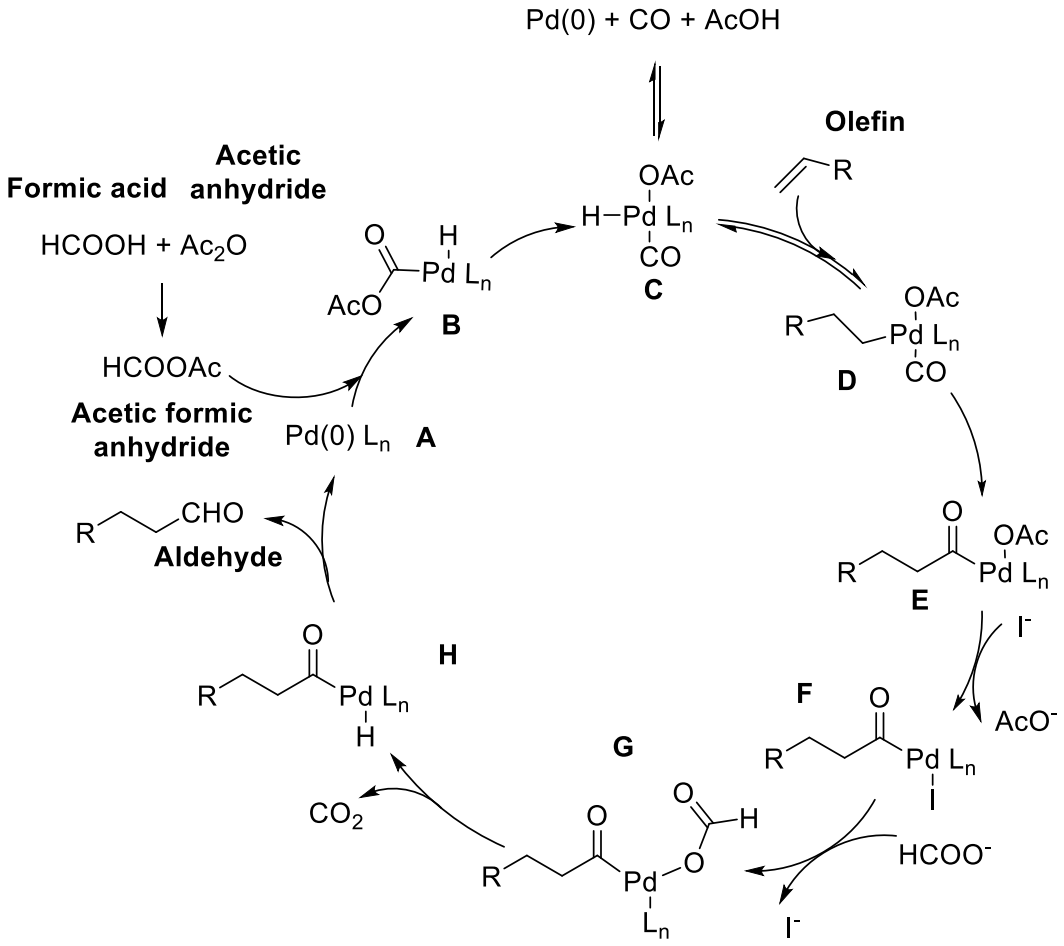
The functionalization of substrates using CO as the carbonyl source comes in as one of the most important industrial process for the manufacture of bulk and fine chemicals. [21] The most common CO and H_2 source for hydroformylation until now has been the synthesis gas (syngas). The synthesis gas is the mixture of CO and H_2 that can be derived from almost every carbon source, such as natural gas, naphtha or coal. [22] The use of CO surrogates serves as a convenient and safe approach for the synthesis of carbonyl derivatives avoiding the need to use gaseous CO.

Recently, Shi and co-workers reported the use of formic acid and acetic anhydride as CO and hydrogen surrogates to selectively form hydrocinnamaldehyde from styrene using palladium based catalysts. In this study, the authors demonstrated that at 80 °C using diphenylphosphine propane (dppp) as ligand, tetrabutylammonium iodide (Bu_4NI) as additive and toluene as solvent, high linear regioselectivity can be obtained for a range of alkene substrate.[23] In this study, the nature of the ligand and solvent, as well as the presence of additive, were key parameters to obtain high regioselectivities (> 99 % Sel. Linear aldehyde).



Scheme 4. Pd-catalyzed hydroformylation of styrene using formic acid and acetic anhydride as CO and hydrogen surrogates reported by Shi and co-workers.[23]

It should be noted that before this study reported by Shi and co-workers, literature examples in rhodium hydroformylation processes reporting the use of formic acid (HCOOH) as hydrogen source (HCOOH = CO_2 + H_2) and required the addition of CO gas. [24] In the Pd-catalyzed reaction reported by Shi and co-workers, CO was generated from the formic acid and the acetic anhydride (HCOOH + Ac_2O = CO + 2 AcOH). The authors proposed a catalytic cycle that is shown in *Scheme 5*.



Scheme 5. Pd-catalyzed hydroformylation mechanism proposed by Shi and co-workers.

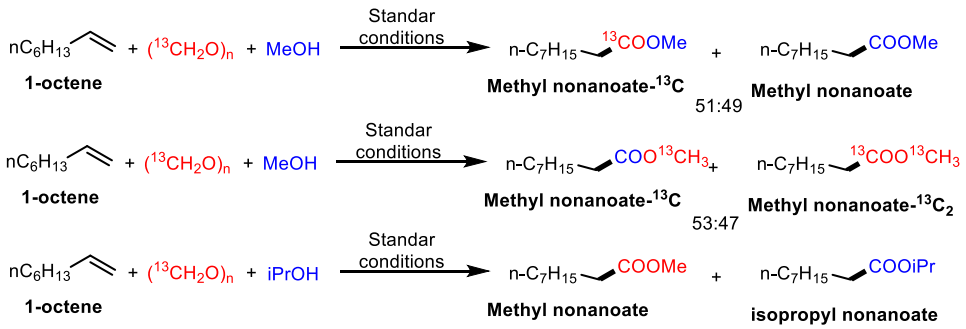
In the proposed catalytic cycle, the catalytically active palladium (0) complex (**A**) reacts with in situ formed acetic formic anhydride (HCOOAc) to give by an oxidative insertion the palladium (II) hydride complex (**B**)**.** This complex (**B**) rearranges to produce palladium(II)-hydride-carbonyl complex (**C**). The olefin reacts with these complex **(C)** to generate palladium(II)-alkyl-complex (**D**) by an insertion step. This complex (**D**) undergoes migratory insertion to give palladium(II)

acyl-complex (**E**). The Pd(II)-acetate complex (**E**) provides Pd(II)−iodide complex (**F**) by ligand metathesis, and further reaction of complex (**F**) with formic acid provides complex Pd(II)-acyl-formate complex (**G**). The palladium(II)-hydride-acyl complex (**H**) is formed via β-elimination and release of CO_2 from complex (**G**). Reductive elimination of palladium(II)-hydride-acyl complex (**H**) would then lead to aldehyde and regenerate the Pd(0) catalyst (**A**).

This study evidenced that high selectivity can be achieved in the transformation of styrene into hydrocinnamaldehyde without syngas using a Pd catalyst bearing dppp as ligand under mild reaction conditions.

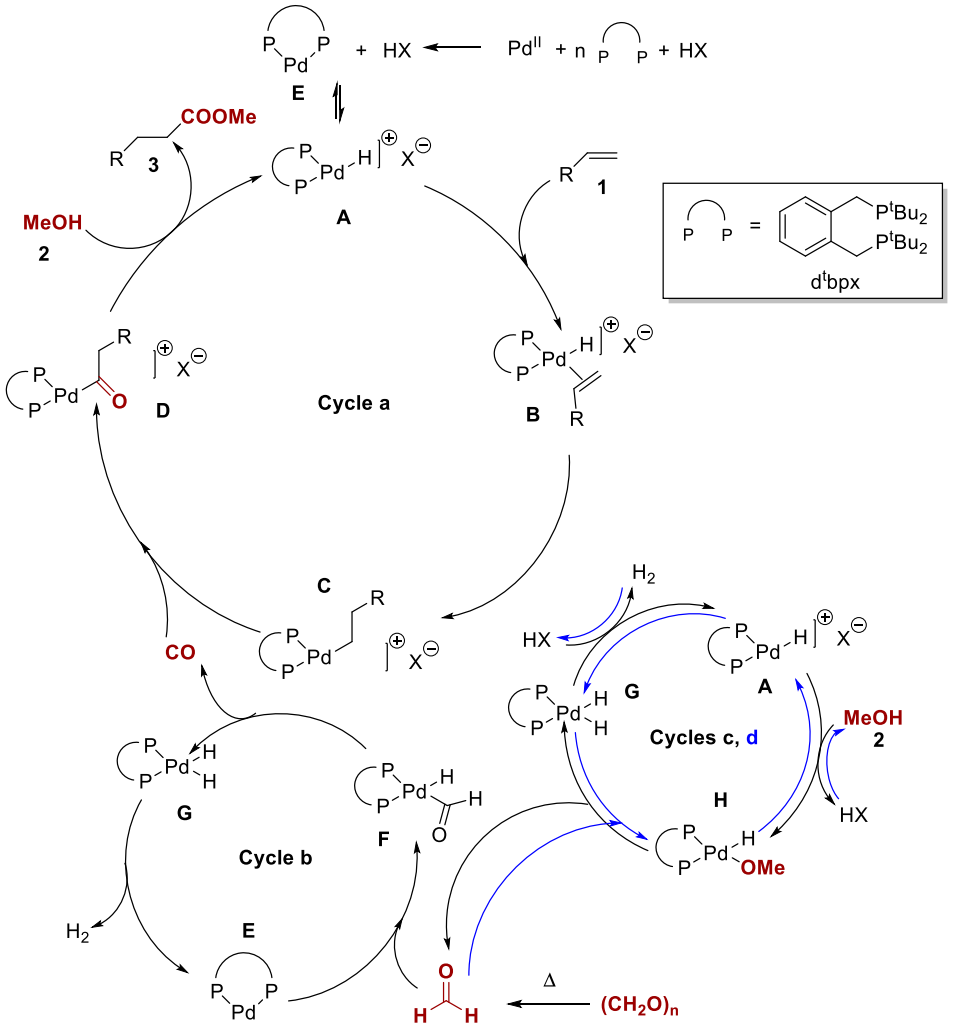
Another example of alternative syngas surrogate is the use of both paraformaldehyde and methanol. Beller and co-workers reported a regioselective Pd-catalyzed methoxycarbonylation of alkenes using both reagents.[25] They reported the effect of the amounts of both the ligand 1,2-bis((di-tert-butylphosphino)methyl)benzene) (d^{t}bpx) and the acid co-catalyst *p*-toluene-sulfonic acid (PTSA) were investigated using $Pd(OAc)_2$ as the catalyst precursor, formalin as syngas surrogate and a scope of olefins (i.e., 1-ocetene, styrene and related compounds). Under optimized conditions quantitative conversions with moderate-to-excellent regioselectivities (i.e., 78-99 % linear sel.) were reported.

Then, to gain further insights into the reaction, ^{13}C isotope labelling experiments were implemented, using both ^{13}C-labelled paraformaldehyde and ^{13}C-labelled methanol as solvent.



Scheme 6. ^{13}C labelling experiments from Beller and co-workers[25]

These results indicate that both formaldehyde and methanol act as the carbonyl source in this process simultaneously. Apparently, CO release from methanol from methanol proceeds by sequential dehydrogenation and decarbonylation processes. Based on the results they obtained, Beller proposed a mechanism for Pd-catalyzed methoxycarbonylation, incorporating synchronous quadruple catalytic cycles. The mechanism is shown in *Scheme 6*.



Scheme 7. Proposed reaction mechanism by Beller.[25]

On his reaction mechanism, Beller reported that Pd^{II} catalyst precursor can be reduced in situ to $Pd^{(0)}$ species (**E**) in the presence of excess phosphine ligands.[26] Under acidic conditions, Pd^0 complex (**E**) is in an equilibrium with Pd^{II} hydride complex (**A**),[27] which is the key catalytically active species to initiate the methoxycarbonylation cycle **a**. Subsequent insertions of alkene **1** and CO followed by alcoholysis of the acyl Pd^{II} complex (**D**) from ester **3** and regenerate the Pd hydride species (**A**). The CO consumed in cycle a was produced from catalytic cycle **b**.

More specifically, at elevated temperature paraformaldehyde can depolymerize to produce formaldehyde, which will undergo an oxidative addition with Pd^0 species (**E**) to generate the (hydrido)(acyl)palladium(II) complex (**F**) and releases CO gas for the methoxycarbonylation process. The reductive elimination of (**G**) regenerates Pd^0 catalyst (**E**) and produces hydrogen.

Meanwhile, the dehydrogenation of methanol **2** is also catalyzed by Pd^{II} hydride (**A**) to afford formaldehyde through catalytic cycle **c**. In this cycle, the coordination of methanol to complex (**A**) provides (hydrido)(methoxy)palladium(II) species (**H**), which gives Pd^{II} dihydride complex (**G**) by b-hydride elimination. Finally, intermediate (**G**) undergoes reductive elimination and oxidative addition with HX to close this catalytic cycle and liberate hydrogen. Simultaneously, formaldehyde can enter catalytic cycle **d**, which is the reverse process of cycle **c**.

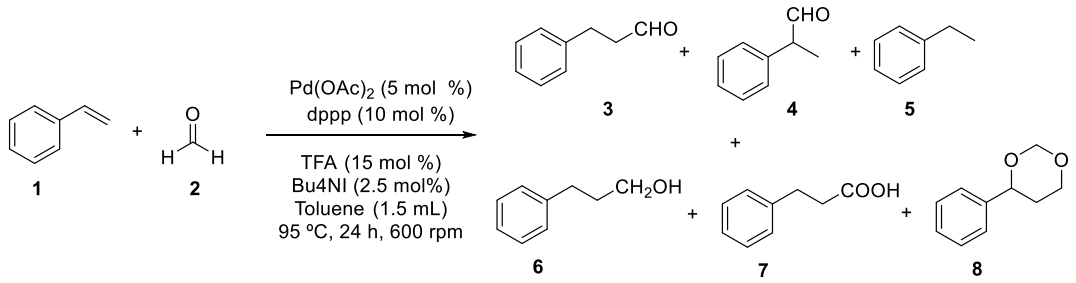
To sum up, as different as the mechanism proposed by Shi and co-workers (shown in *Scheme 5*), Beller reported the presence of three Pd active catalytically species: Pd^0 complex (**E**), Pd^{II} hydride complex (**A**) and Pd^{II} dihydride complex (**G**). These species catalyzed three different reaction

mechanism: (**a**) methoxycarbonylation of alkenes, (**b**) decomposition of formaldehyde into CO and H_2, (**c**) transfer hydrogen reaction of methanol to form formaldehyde, respectively.

Previous work in our group

Our group has been working on the Pd-catalyzed hydroformylation of styrene during the last years. MSc Beatriz García reported in her master project the optimization of the catalytic system and reaction conditions, as well as some mechanistic studies (i.e., NMR monitoring of the reaction and characterization of some reaction intermediates and GC-MS detection of CO).[28] Below, we collected a summary of the most important results and general trends observed during this study. (*Table 1*)

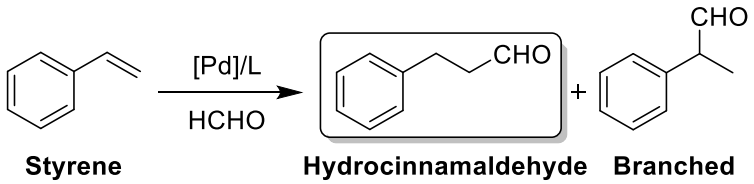
Table 1. Previous optimization of Pd-catalyzed hydroformylation of styrene.[28]



Effect	Variables studied	General behavior
Formaldehyde source	Paraformaldehyde vs. Formalin.	Using 5 equivalents and Ac_2O and TFA: (a) no conversion with PFA, (b) with formalin, 54% conversion with 75% of linear aldehyde and a 25% of ethylbenzene.
Solvent	DCE, Toluene, DCM, Hexane, THF, Dioxane, Water	Similar conversion and selectivity with DCE and Toluene.Much lower conversions and selectivities with other solvents.
Additive	Bu_4NI, Bu_4NBr, Me_4NBr, KI, none	The reaction only proceeds in presence of Bu_4NI. Better with 2.5 mol% than 5 mol%.
Acid	Ac_2O, AcOH (pKa: 4.8), TFA (pKa: 0.23) TfOH (pKa: - 14) and p-TsOH (pKa: -2.8)	In general, Trifluoroacetic acid (TFA), Triflic acid (TfOH) and p-toluensulfonic acid (pTsOH) provided higher chemoselectivities to the hydrogenation product **5** than AcOH and Ac_2O. (**7**) was formed as byproduct with AcOH, and (**8**) was formed as byproduct with TFA, TfOH and pTsOH. Evaluation of acid conc. effect the best compromise between activity and selectivity is 15 mol %.
Temperature	75, 85 and 95 ºC	Higher temperatures provided the best compromise between conversion and selectivity.
Pd precursor	$PdCl_2$, $Pd(OAc)_2$, $Pd(TFA)_2$ and $Pd(acac)_2$	$PdCl_2$ and $Pd(TFA)_2$ show very low conversion. $Pd(AcO)_2$ and $Pd(acac)_2$ provided similar results.
Ligands	PPh_3, dppe and dppp	Only dppp/Pd display activity. dppp/Pd ratio was evaluated: 1:1, 2:1, and 3;1. Best compromise with activity and selectivity with 2:1.
Monitoring the reaction with time	Samples collected at regular intervals between 0-24 h	Formation of hydrogenation product is favored at the early reaction stages, while the aldehyde formation is favored after a certain reaction time.

OBJECTIVES

The main objective of this work was to gain insights into the hydrocinnamaldehyde production by Pd-catalyzed regioselective hydroformylation of styrene using formaldehyde as syngas surrogate.



Scheme 8. Pd-catalyzed hydroformylation of styrene using formaldehyde as syngas surrogate.

The partial objectives were:

1. To complete the previous studies by evaluating new parameters:
   a) Scope of ligands: effect of the bite angle in bidentate phosphines.

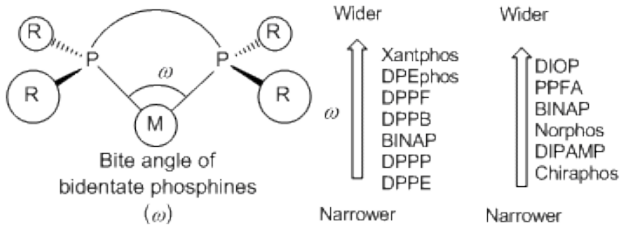


Fig. 3. Bite angle effect on different bidentate phosphines.

   b) To test the effect of new Pd precursors: Pd(0) vs. Pd(II) cationic vs. Pd(II) neutral.
   c) To test the effect of solventand formaldehyde source.
2. To perform mechanistic studies by evaluating deuterium-incorporation and kinetic isotopic effect (KIE) related with rate determining step (rds) using formaldehyde-d_2 D_2O.
3. To perform a preliminary exploration of the reaction kinetics: determination of reagents/catalyst order, rate equation, rate constants, energy of activation (Ea) and enthalpy ($\Delta H^{\#}$).

EXPERIMENTAL PART

General

All reactions were carried out in a Schleck tube dried by heating under reduced pressure and under argon atmosphere. The reaction temperatures were electronically controlled by heating oil baths.

All chemical reagents were purchased from Aldrich Chemical CO, Johnson Matthey, and Strem Chemicals, and were used as received. All the solvents were deoxygenated before to be used.

For the conversions, an Agilent GC System 789A with 7693 Auto-sample instrument was used with Agilent 5975 inert MSD with triple-Axis detector.

The method used was: temperature of inlet 250 °C; temperature of auxiliary line 250 °C; Split = 50:1 ; N_2 as the carrier (constant flow 1.5 mL min^{-1},12.675 psi); temperature program from 50 °C (3 min) to 280 °C at a heating rate of 20 °C min^{-1}, isotherm 270 °C (4.5 min); HP-5 MS column (30 m × 0.25 mm × 0.25 µm).

The deutereted compounds (D_2O and paraformaldehyde-d_2) were purchased from Eurisotop and Sigma-Aldrich, respectively, and used as received.

Catalytic experiments

Palladium precursor (5 mol %), ligand (10 mol %), Bu_4NI (2.5 mol %), 1.5 ml of toluene (or solvent tested), styrene (0.5 mmol), formalin (2.5 mmol) and TFA as acid co-catalyst (15 mol %) were introduced into a 15 mL Schlenk. The reaction mixture was stirred at 95 °C during 24 h.

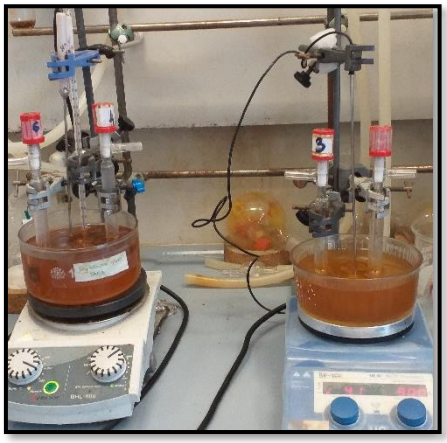


Fig. 4. Reactions in process.

The reaction product was filtered through a Celite-cotton-pipette, then the internal standard was added, and the product was diluted with CH_2Cl_2 in 50 mL (volumetric flask of 50 mL). Finally, the sample was analysed by GC-MS and the conversion and selectivity was determined.

Fig. 5. Filtering process

Analytical method

To determinate the conversion and selectivity by GC-MS, first we have to determinate the response factor of each compound that could appear in our sample. This factor is defined as the ratio between the concentration of a compound being analyzed and the response of the detector to that compound.[29] Among other factors, the response factor of analytes can be affected by the GC system and the nature of the detector used (i.e., FID vs MS).[30]

To determine the response factor, a calibration curve was obtained for each compound, using bicyclohexyl as internal standard (IS).

5 calibration samples were prepared in 50 mL volumetric flasks with different known concentration. More details of the calibration samples are collected in the supporting information. For each compound the ratio between the area of the compound and internal standard (Y-label) and the ratio between the concentration of the compound and internal standard (X-label) were used to make the plot. (*Fig. 6*)

Finally, the slope of the plot will be the response factor for that compound. For an unknown sample, the concentration will be determined using that response factor. (*Eq 1*) shows how to find the concentration of an unknown sample with the use of an internal standard and the response factor:

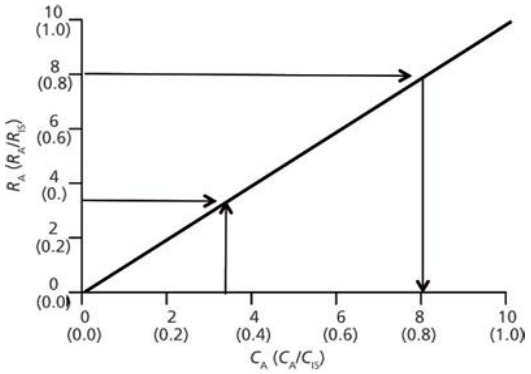


Fig 6. Calibration curve to determine the response factor.

$$\text{Response factor (Rf)} = \frac{[(\text{Aa})(\text{Cis})]}{[(\text{Ca})(\text{Ais})]} \quad (1)$$

Cx = (Aa)(Cis)/((Ais)(Rf))

Ax = Area of compound.

Cx = Concentration of compound.

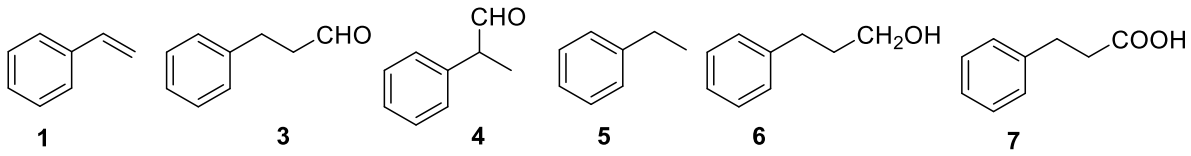
Ais = Area internal standard (Bicyclohexyl).

Cis = Concentration internal standard (Bicyclohexyl).

Table 2 shows the results obtained from the calibration method. This method has been evaluated by using a fabricated sample with 333.3 mM concentration of styrene, dissolved in reaction solvent (Toluene) with formaline.

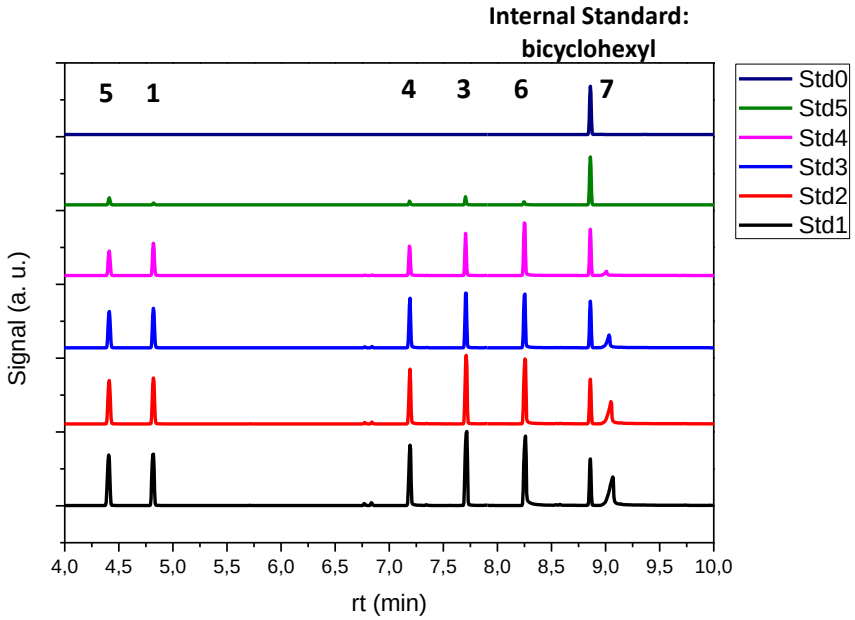
Mass balance was 99%, and the measured product is styrene. The conclusion of this experiment is that our analytical method was valid.

Table 2. Response factor of each compound obtained from the calibration curves.



1 3 4 5 6 7

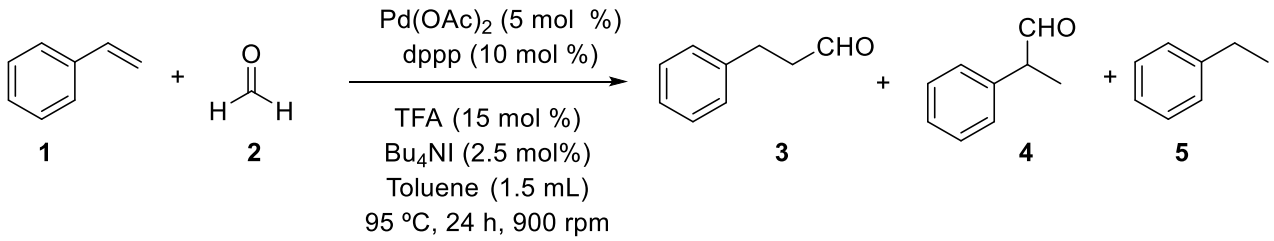
Number	Response Factor	Compound	RT / min.
1	0,4928	Styrene	4,819
3	0,5180	hydrocinnamaldehyde	7,715
4	0,4337	2-phenyl propanaldehyde	7,193
5	0,5459	Ethylbenzene	4,408
6	0,6139	3-phenyl propanol	8,258
7	0,3990	3-phenyl propionic acid	9,066
Toluene	-	Toluene	3,021



RESULTS AND DISCUSSION

Pd-catalyzed hydroformylation of styrene using formaldehyde as syngas surrogate

As previously mentioned, optimization of the reaction conditions was carried out previously in our group by the MSc project of Beatriz Garcia. Our initial objective was to reproduce the results under optimized reaction conditions. The reaction was performed at 95 °C using $Pd(OAc)_2$ as Pd precursor, toluene as solvent, dppp as ligand, Bu_4NI as additive, TFA as acid co-catalyst and formaldehyde (formalin solution) as syngas surrogate. Under these conditions, we obtained 96% conversion of the substrate and the formation of 52% of aldehyde, including a 99,1% regioselectivity to the linear aldehyde. Hydrogenation product (ethylbenzene) was also observed in a 48% of chemoselectivity. With this first results in our hands, blank tests were performed.

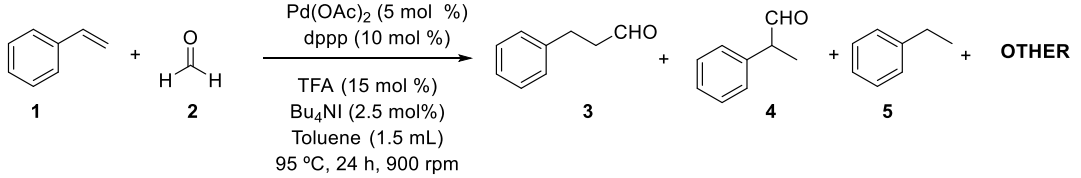


Scheme 9. Previous reaction conditions for Pd-catalyzed hydroformylation.

Blank tests

The absence of part of our catalytic system were tested in this experiment to understand the reaction behavior without it. $Pd(OAc)_2$ as Pd precursor without ligand, dppp as ligand without Pd precursor, and a system without neither Pd precursor nor ligand were tested (see entries 1-4, *table 3*).

Table 3. Pd-catalyzed hydroformylation of styrene. Blank tests.



Entry[a]	Blank	Conv. (%)[b]	CHEMO: (3+4) / 5 / Other (%)[b]	REGIO: 3/ (3 + 4) (%)	RATIO: 3 / 4 [b]	TON [c]
1	$Pd(AcO)_2$ + dppp	96	52 / 48 / 0	99.1	104.6	19.2
2	$Pd(AcO)_2$	0	-	-	-	-
3	dppp	0	-	-	-	-
4	-	17	0 / 0 / 100	-	-	-

Reaction conditions:*[a] Styrene* ***1*** *(0.5 mmol, 58.1 uL),* ***2*** *(2.5 mmol, 197 uL), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), dppp (0.050 mmol, 21.0 mg), TFA (0.075 mmol, 5.8 uL), Bu_4NI (0.013 mmol, 4.6 mg), toluene (1.5 mL), 95ºC, 24 h, 900 r.p.m.; [b] Conversion, chemoselectivity and regioselectivity determined by GC-MS using bicyclohexyl as internal standard; [c] TON defined as the mole of styrene converted divided by the moles of Pd.*

It is noticeable that without using Pd precursor and ligand, 17% of styrene is converted in other byproduct, 4-phenyl-1, 3-dioxane (*Fig. 7*) was obtained (*Table 3*, entry 4), whereas no conversions are observed in the blank tests with only Pd and with only dppp.

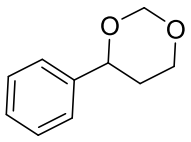
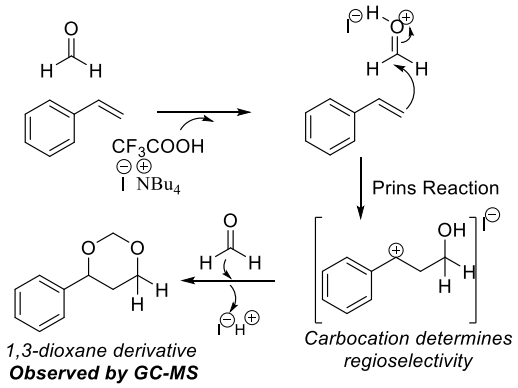


Fig. 7. Structure of the byproduct 4-phenyl-1, 3-dioxane

The electrophilic addition of an aldehyde to an alkene followed by capture of a nucleophile is called Prins reaction.[31] In the presence of water, protic acids and formaldehyde the 1, 3- diol is formed, and if an excess of formaldehyde is added the resulting product is a dioxane. The reaction between styrene and formalin using TfOH as catalyst was previously reported[32], obtaining the dioxane as the main product.



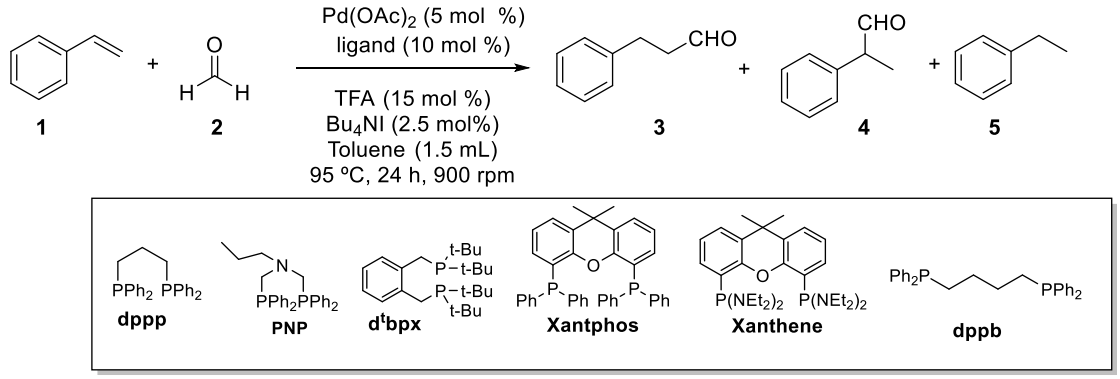
Scheme 10. Prins mechanism reaction.

Next, the effect of the structure of the ligand in our reaction was evaluated.

Effect of the ligand

In most homogeneous catalytic reactions, the steric and electronic properties of the ligands have a great influence on the activity and selectivity of the corresponding catalysts. For this reason, bidentate ligands with different bite angle were tested. The results are displayed in *Table 4*.

Table 4. Pd-catalyzed hydroformylation of styrene. Effect of ligand.



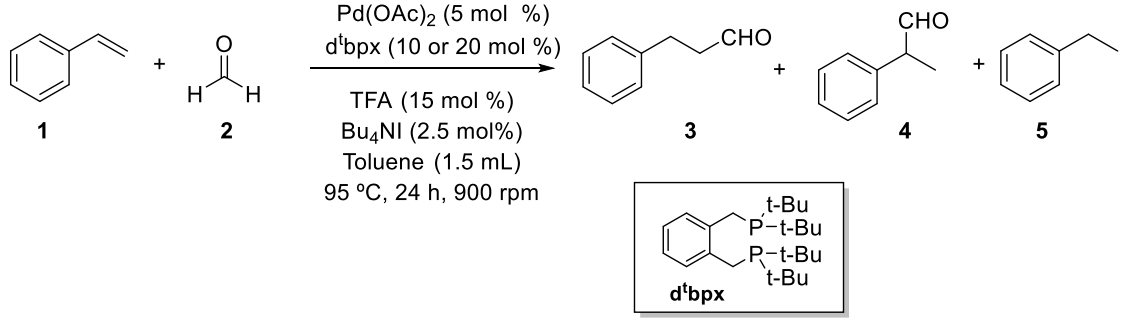
Entry[a]	Ligand	Conv. (%)[b]	CHEMO: (3+4) / 5 (%)[b]	REGIO: 3/ (3 + 4) / %	RATIO: 3 / 4 [b]	TON[c]
1	-	0	-	-	-	-
2	dppp	96	52 / 48	99.1	104.6	19.2
3[d]	dppp	19	0 / 100	-	-	3.7
4	PNP	10	0 / 100	-	-	1.9
5	dppb	6	0 / 100	-	-	1.2
6	Xantphos	0	-	-	-	-
7	Xanthene	5	0 / 100	-	-	1.0
8	dtbpx	0	-	-	-	-

Reaction conditions:*[a] Styrene **1** (0.5 mmol, 58.1 uL), **2** (2.5 mmol, 197 uL), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), ligand (0.050 mmol), TFA (0.075 mmol, 5.8 uL), Bu_4NI (0.013 mmol, 4.6 mg), toluene (1.5 mL), 95ºC, 24 h, 900 r.p.m.; [b] Conversion, chemoselectivity and regioselectivity determined by GC-MS using bicyclohexyl as internal standard; [c] TON defined as the mole of styrene converted divided by the moles of Pd; [d] Exposed to moisture*

Strikingly, in these experiments, the catalytic system dppp/Pd (*Table 4*, entry 2) was the only one that displayed reasonable activity and selectivity to hydroformylation product. Low conversions with full seleticivity to hydrogenation products were measured using Pd-catalyst with the ligands dppb and PNP (*Table 4*, entries 4 and 5), whereas the system is unactive with Xantphos or d^{t}bpx as ligands (*Table 4*, entries 6 and 8). The low activity of the rest of the ligands could be related with the poor coordination of the ligand to the metal catalyst. To check that, different amount of ligand that provides 0% conversion like d^{t}bpx was tested.

The reaction was carried out using 20% mol of d^{t}bpx ligand, quantity reported by Beller[25]. Increasing the amount of d^{t}bpx, the conversion was higher (*Table 5*, entry 2 vs entry 1), but with total chemoselectivity to the formation of hydrogenation product. This behavior was explained because the formation of Pd/dtppx complex was favorured at high L/Pd ratios, and the formed complex displayed mainly hydrogenation activity probably due to the fast decomposition of the HCHO into CO and H_2. Whereas at low L/Pd ratios the coordination of the ligand to Palladium was unfavoured, and this system is unactive. However, no evident explanation for the lack of aldehyde chemoselectivity can be extracted. Our hyphotesis is that the Pd/dppp forms a really stable catalytic system able to perform the activation of formaldehyde to form the Pd-hydrido-acyl species (Pd(H)(HCO)) and this species is stable enough and reacts with the substrate before its decomposition to the Pd-dihydride species responsible for the hydrogenation activity.

Table 5. Pd-catalyzed hydroformylation of styrene. Effect of ligand amount.



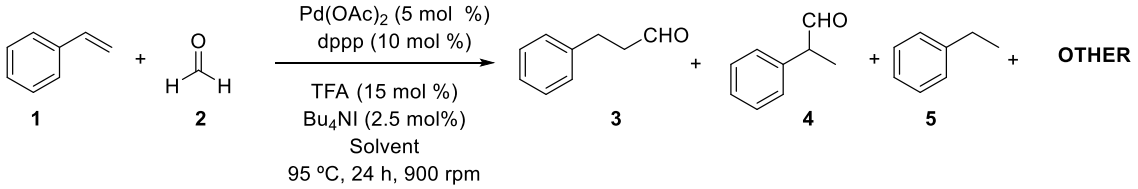
Entry[a]	d^{t}bpx Ligand (mol %)	Conv. (%)[b]	CHEMO: (3+4) / 5 (%)[b]	REGIO: 3/ (3 + 4) / %	RATIO: 3 / 4 [b]	TON [c]
1	10	0	-	-	-	-
2	20	9	0 / 100 / 0	-	-	1.8

Reaction conditions:*[a] Styrene **1** (0.5 mmol, 58.1 uL), **2** (2.5 mmol, 197 uL of solution at 37%), Pd(OAc)$_2$ (0.025 mmol, 5.6 mg), d^{t}bpx (0.050 mmol and 0.100 mmol, 19.6 mg and 39.5 mg), TFA (0.075 mmol, 5.8 uL), Bu$_4$NI (0.013 mmol, 4.6 mg), toluene (1.5 mL), 95ºC, 24 h, 900 r.p.m.; [b] Conversion, chemioselectivity and regioselectivity determined by GC-MS using bicyclohexyl as internal standard; [c] TON defined as the mole of styrene converted divided by the moles of Pd.*

Effect of the solvent

Next, several solvents with different polarity were tested. $Pd(OAc)_2$ was used as Pd precursor, and dppp as ligand. The results are collected in *table 6*.

Table 6. Pd-catalyzed hydroformylation of styrene. Effect of the solvent.



Entry[a]	Solvent	Conv. (%)[b]	CHEMO: (3+4) / 5 / Other (%)[b]	REGIO: 3/ (3 + 4) / %	RATIO: 3 / 4 [b]	TON [c]
1	MeOH	0	-	-	-	-
2	iPrOH	51	10 / 90 / 0	97.3	36.1	10.2
3	Toluene	96	52 / 48 / 0	99.1	104.6	19.2

Reaction conditions:*[a] Styrene **1** (0.5 mmol, 58.1 uL), **2** (2.5 mmol, 197 uL of solution at 37%), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), dppp (0.050 mmol, 21.0 mg), TFA (0.075 mmol, 5.8 uL), Bu_4NI (0.013 mmol, 4.6 mg), toluene (1.5 mL), 95ºC, 24 h, 900 r.p.m.; [b] Conversion, chemoselectivity and regioselectivity determined by GC-MS using bicyclohexyl as internal standard; [c] TON defined as the mole of styrene converted divided by the moles of Pd.*

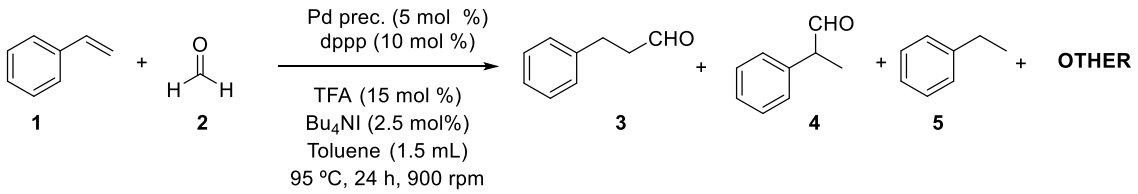
Toluene shows the best result as solvent, obtaining a 96% conversion of styrene, with chemoselectivity of 52% to aldehyde product and 48% to hydrogenation product (*Table 6*, entry 3). In contrast, no conversion of styrene was observed using MeOH as solvent, whereas a 51% conversion of styrene was obtained using iPrOH, with 10% to aldehyde product and 90% to hydrogenation product (*Table 6*, entry 1 vs entry 2). The fact that we obtain nearly 100% of hydrogenation product using iPrOH can be explained by the possibility of transfer hydrogenation reaction to take place, referring to the addition of hydrogen to a molecule from a non-H_2 hydrogen source. [33].

Next, the effect of the Pd precursor was analyzed.

Effect of the Pd precursor

Several Pd precursor were tested and the results obtained are summarized in *Table 7*.

Table 7. Pd-catalyzed hydroformylation of styrene. Effect of Pd precursor.



Entry[a]	Pd precursor	Conv. (%)[b]	CHEMO: (3+4) / 5 / Other (%)[b]	REGIO: 3/ (3 + 4) %	RATIO: 3 / 4 [b]	TON [c]
1	$Pd(dba)_2$	16	43 / 57 / 0	97.5	39.6	1.3
2[d]	$Pd(dba)_2$	0	-	-	-	-
3	$[Pd(Allyl)(COD)]BF_4$	77	12 / 20 / 68	98.8	80.4	15.4
4	$Pd(OAc)_2$	96	52 / 48 / 0	99.1	104.6	19.2

***Reaction conditions:** [a] Styrene **1** (0.5 mmol, 58.1 uL), **2** (2.5 mmol, 197 uL of solution at 37%), Pd precursor (0.025 mmol), dppp (0.050 mmol, 21 mg), TFA (0.075 mmol, 5.8 uL), Bu_4NI (0.013 mmol, 4.6 mg), toluene (1.5 mL), 95ºC, 24 h, 900 r.p.m.; [b] Conversion, chemoselectivity and regioselectivity determined by GC-MS using bicyclohexyl as internal standard; [c] TON defined as the mole of styrene converted divided by the moles of Pd; [d] Without TFA.*

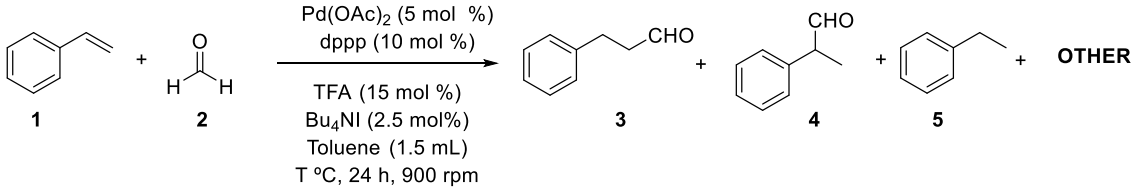
Using $Pd(dba)_2$ as Pd (0) source (*Table 7*, entry 1 vs entry 2) low activity was obtained). The fact that the Pd(0) easily decomposes to Pd(0)-black, observed in our sample once reaction has finished, or Pd(0)-NPs can be hold responsible for the low activity observed. On the other hand, Pd(II) cationic and Pd(II) neutral precursors provided better catalytic results concerning the conversion of styrene (*Table 7*, entry 3 vs entry 4). But the chemoselectivity remained higher using $Pd(OAc)_2$, providing a 52% of aldehyde product and 48% of hydrogenation product. This can be explained because the pH in each reaction is affected by the metal precursor. Pd(II) cationic has BF_4^- as counter-ion, that is the weak conjugated base of the tetrafluoroboric acid (HBF_4), whereas Pd(II) neutral has ^-OAc, a strong conjugated base that can establish an equilibrium with the acid co-catalyst (TFA).

Next, the effect of the temperature was studied.

Effect of the temperature

Three different temperatures were tested in this experiment. The results obtained can be found in *Table 8*.

Table 8. Pd-catalyzed hydroformylation of styrene. Effect of the temperature.



Entry[a]	T (°C)	Conv. (%)[b]	CHEMO: (3+4) / 5 / Other (%)[b]	REGIO: 3/ (3 + 4) %	RATIO: 3 / 4 [b]	TON [c]
1	65	25	72 / 28 / 0	97.7	41.9	5
2	95	96	52 / 48 / 0	99.1	104.6	19.2
3	125	83	0 / 45 / 55	-	-	16.6

Reaction conditions:*[a] Styrene **1** (0.5 mmol, 58.1 uL), **2** (2.5 mmol, 197 uL of solution at 37%), Pd precursor (0.025 mmol), dppp (0.050 mmol, 21 mg), TFA (0.075 mmol, 5.8 uL), Bu_4NI (0.013 mmol, 4.6 mg), toluene (1.5 mL), 95ºC, 24 h, 900 r.p.m.; [b] Conversion, chemoselectivity and regioselectivity determined by GC-MS using bicyclohexyl as internal standard; [c] TON defined as the mole of styrene converted divided by the moles of Pd.*

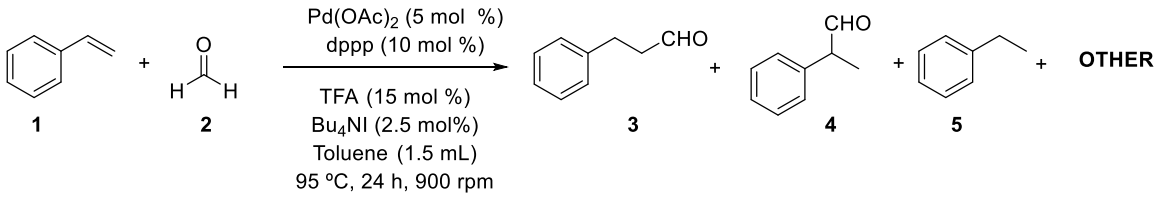
At low temperatures (*Table 8*, entry 1) we obtain lower conversions, only 25% of styrene converted, but higher chemoselectivity was obtained, with 72% of aldehyde product and 28% of hydrogenation product. In contrast, at 95 °C (Table 8, entry 2 vs entry 1), higher conversion was achieved, with 96% of styrene converted, but lower chemoselectivity (52%-48%).

At higher temperatures (*Table 8*, entry 3) side-reactions (hydrogenation and other products) dominated the reaction performance, and hydroformylation products were not detected. To explain that, we consider that could be related with an equilibrium involving the active catalytic specie “Pd-(H)CHO”, that a high temperature shifted the equilibrium to the formation of Pd-dihydride species and CO (gas), resulting in high hydrogenation activity.

Effect of the formaldehyde source

Finally, the effect of the formaldehyde source was evaluated. This is the initial experiment for the evaluation of the reaction's kinetics. We pretend to identify the effect of the solvents in the formalin solution (water and MeOH) and if they are necessary to produce the reaction. So, reactions using formalin, paraformaldehyde alone, with water, and with water and methanol were tested. The results are displayed in *Table 9*.

Table 9. Pd-catalyzed hydroformylation of styrene. Effect of formaldehyde source.



Entry[a]	Formaldehyde source	Conv. (%)[b]	CHEMO: (3+4) / 5 / Other (%)[b]	REGIO: 3/ (3 + 4) %	RATIO: 3 / 4 [b]	TON [c]
1	Formalin[d]	96	52 / 48 / 0	99.1	104.6	19.2
2	PFA	12	35 / 65 / 0	97.9	47.4	2.5
3	PFA + H_2O	95	61 / 36 / 3	99.4	173.2	19.0
4	PFA + H_2O + MeOH	95	56 / 42 / 1 (3-phenylpropanol)	92.2	123.7	19.0

Reaction conditions:*[a] Styrene **1** (0.5 mmol, 58.1 uL), **2** (2.5 mmol, 197 uL of solution at 37%), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), dppp (0.050 mmol, 21.0 mg), TFA (0.075 mmol, 5.8 uL), Bu_4NI (0.013 mmol, 4.6 mg), toluene (1.5 mL), 95ºC, 24 h, 900 r.p.m.; [b] Conversion, chemoselectivity and regioselectivity determined by GC-MS using bicyclohexyl as internal standard; [c] TON defined as the mole of styrene converted divided by the moles of Pd; [d] Formalin is formaldehyde, 37% in aq. soln., ACS, 36.5-38.0%, stab. with 10-15% methanol; [e] Paraformaldehyde, 97%*

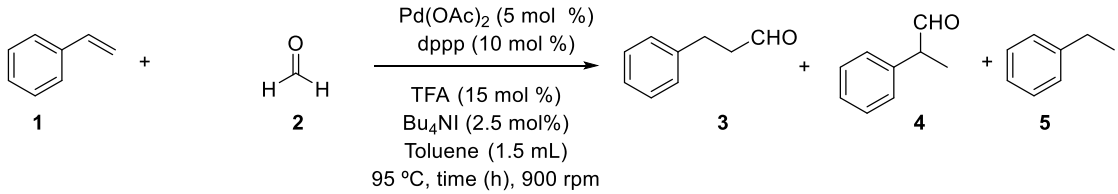
Using only PFA (*Table 9*, entry 2) low catalytic activity was observed, obtaining only 12% of conversion. However, the other conditions provided the same activity (95%), being the system PFA+H_2O which provides the best results in terms of chemoselectivity. So, the kinetic studies were carried out using PFA+H_2O.

Mechanistic studies

To get insights into the mechanism of the reaction, an isotopic labelling experiment was performed. This technique is used to track the path of an isotope (an atom with a detectable variation in neutron count) through a reaction. The reactant is 'labeled' by replacing specific atoms by their isotope. The reactant is then allowed to undergo the reaction. The presence of the isotopes in the product is measured to determine the sequence the isotopic atom has followed in the reaction.

In this work, we evaluate kinetic isotopic effect and relation with rds by testing PFA-d_2 with H_2O, PFA-d_2 solution in D_2O (98 atom % D) and PFA-d_2 in H_2O. The reaction was monitored over time. The data obtained are listed in *Table 10*.

Table 10. Pd-catalyzed hydroformylation of styrene. Kinetic control.



1 2 3 4 5

Entry[a]	Reagents	Time = 0.5 h	
		Conv. (%)[b]	CHEMO: (3+4) / 5 (%)[b]
1	**2** + H_2O	4	11 / 89 / 0
2	**2-d₂** + H_2O	7	8 / 92 / 0
3	**2** + **2-d₂** + H_2O	4	8 / 92 / 0
4	**2** + D_2O	4	11 / 89 / 0

Entry[a]	Reagents	Time = 1 h	
		Conv. (%)[b]	CHEMO: (3+4) / 5 (%)[b]
1	**2** + H_2O	13	17 / 83 / 0
2	**2-d₂** + H_2O	15	11 / 89 / 0
3	**2** + **2-d₂** + H_2O	15	16 / 84 / 0
4	**2** + D_2O	25	12 / 88 / 0

Entry[a]	Reagents	Time = 2 h	
		Conv. (%)[b]	CHEMO: (3+4) / 5 (%)[b]
1	**2** + H_2O	41	39 / 61 / 0
2	**2-d₂** + H_2O	22	15 / 85 / 0
3	**2** + **2-d₂** + H_2O	26	22 / 78 / 0
4	**2** + D_2O	46	28 / 72 / 0

Entry[a]	Reagents	Time = 3 h	
		Conv. (%)[b]	CHEMO: (3+4) / 5 (%)[b]
1	**2** + H_2O	45	31 / 69 / 0
2	**2-d$_2$** + H_2O	24	15 / 85 / 0
3	**2** + **2-d$_2$** + H_2O	31	28 / 72 / 0
4	**2** + D_2O	51	30 / 70 / 0

Reaction conditions:*[a] Styrene **1** (0.5 mmol, 58.1 uL), **2** (2.5 mmol), Water (125 uL), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), dppp (0.050 mmol, 21.0 mg), Bu_4NI (0.013 mmol, 4.6 mg), toluene (1.5 mL), 95ºC, 900 r.p.m.; [b] Conversion, chemioselectivity and regioselectivity determined by GC-MS using bicyclohexyl as internal standard; [c] TON defined as the mole of styrene converted divided by the moles of Pd.*

Concerning reaction rate (rate = d[P]/dt = - d[S]/dt):

- **PFA + H2O vs. PFA + D2O.** Similar apparent product distribution (styrene, ethylbenzene and hydrocinnamaldehyde). No effect was observed on the reaction rate.
- **PFA + H2O vs. PFA-d2 + H2O.** Hydrogenation products are formed at similar rate, whereas the hydroformylation rate is much lower using PFA-d2. Possible kinetic isotopic effect (secondary KIE rate (d)/rate (H) = 1-2 or primary KIE rate (d)/rate (H) = 2-5).

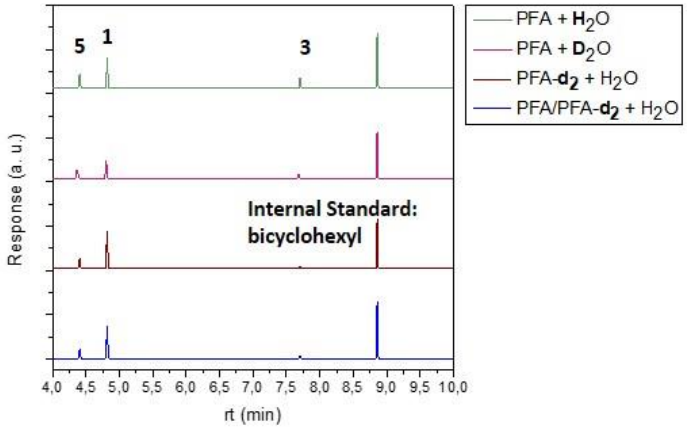


Fig. 8. GC chromatograms from the kinetic studies.

To study the deuterium labelling process, we analyzed the mass spectra obtained by GC-MS analysis.

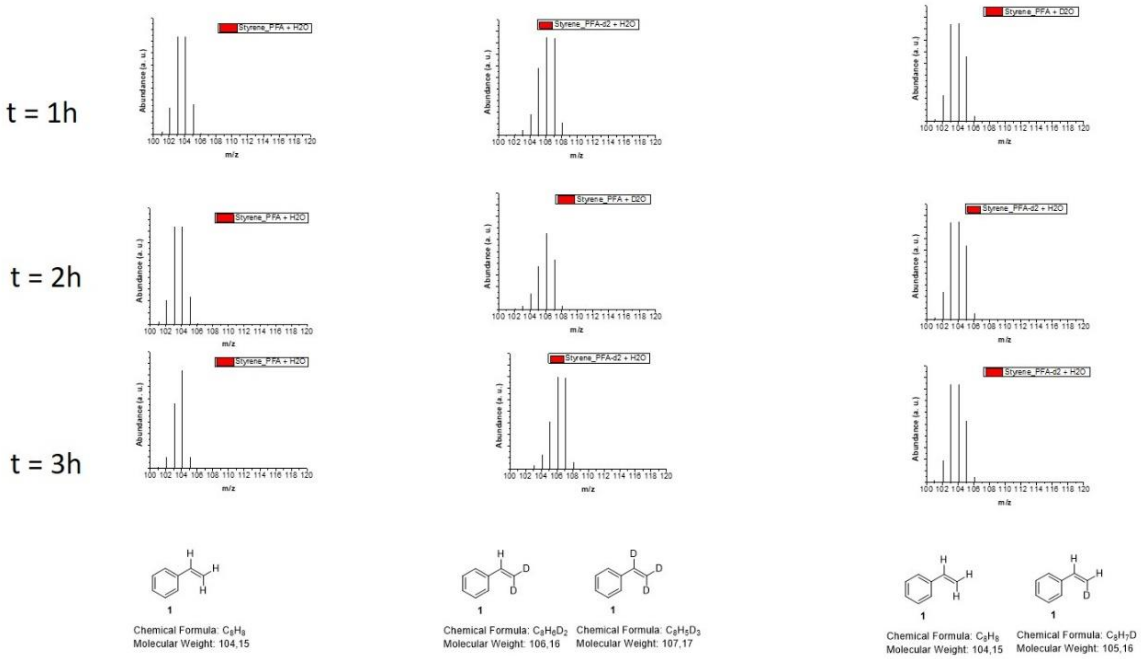


Fig. 9. MS spectra obtained during the isotopic labelling experiments.

For the styrene substrate, some H/D exchange was detected mainly using D_2O, and to a minor extent, from the PFA-d_2 into styrene. The degree of exchange was proportional to the reaction time.

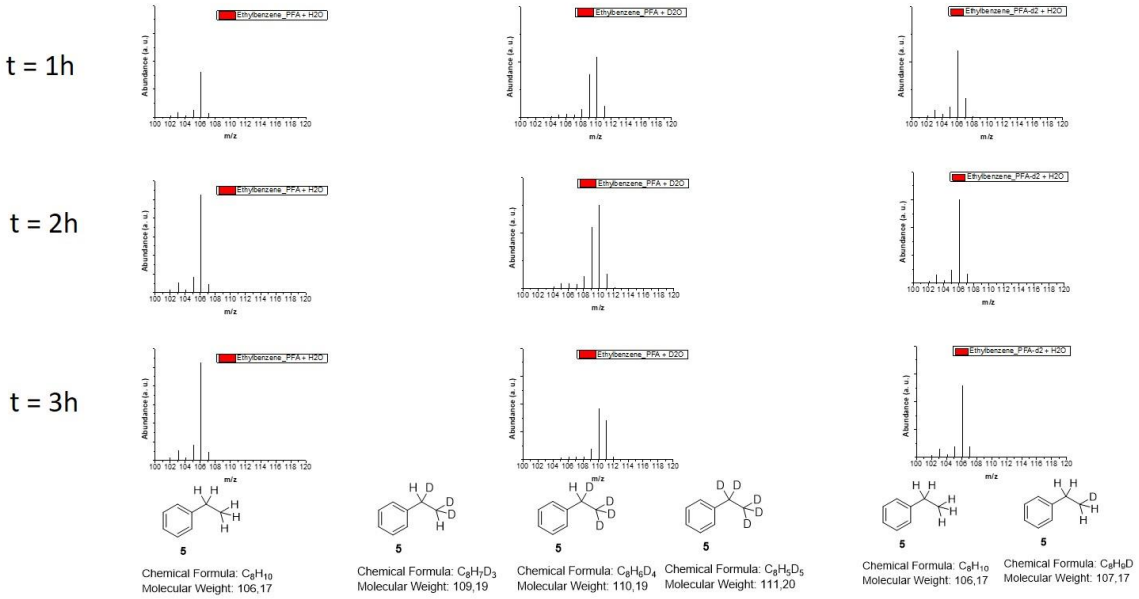
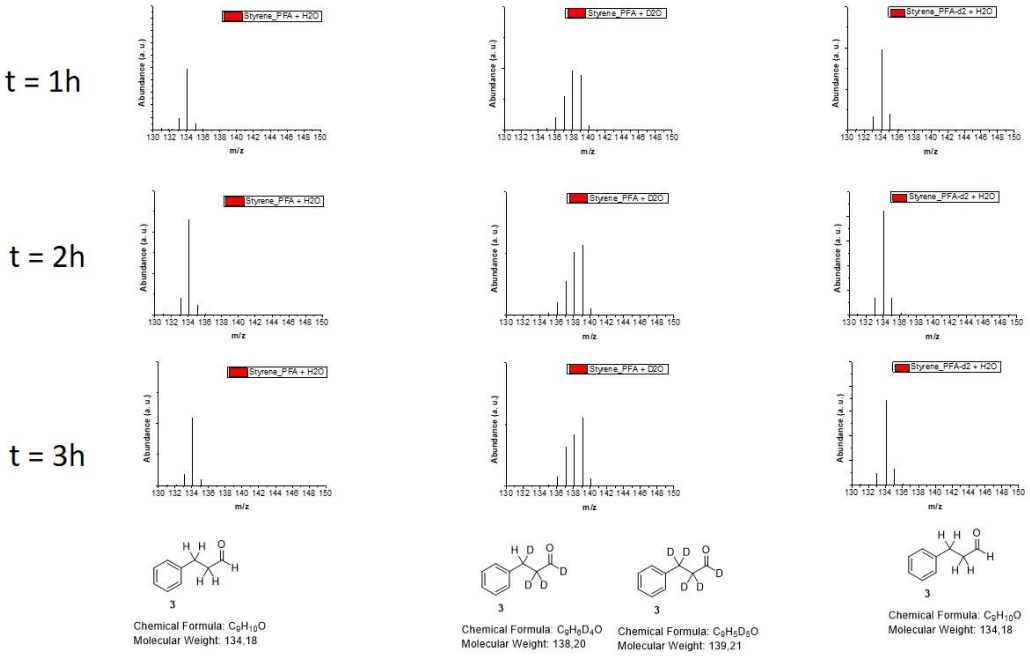


Fig. 10. MS spectrums to study the isotopic labelling effect with hydrogenation product.

As we can see in *figure 10*, the alkylic part of the hydrogenation product is completely deutered, due to the formation of styrene-d_3 in previous step. In case of PFA-d_2, most of hydrogenation product does not have deuterium and only a part has been deuterated with only 1 deuterium.

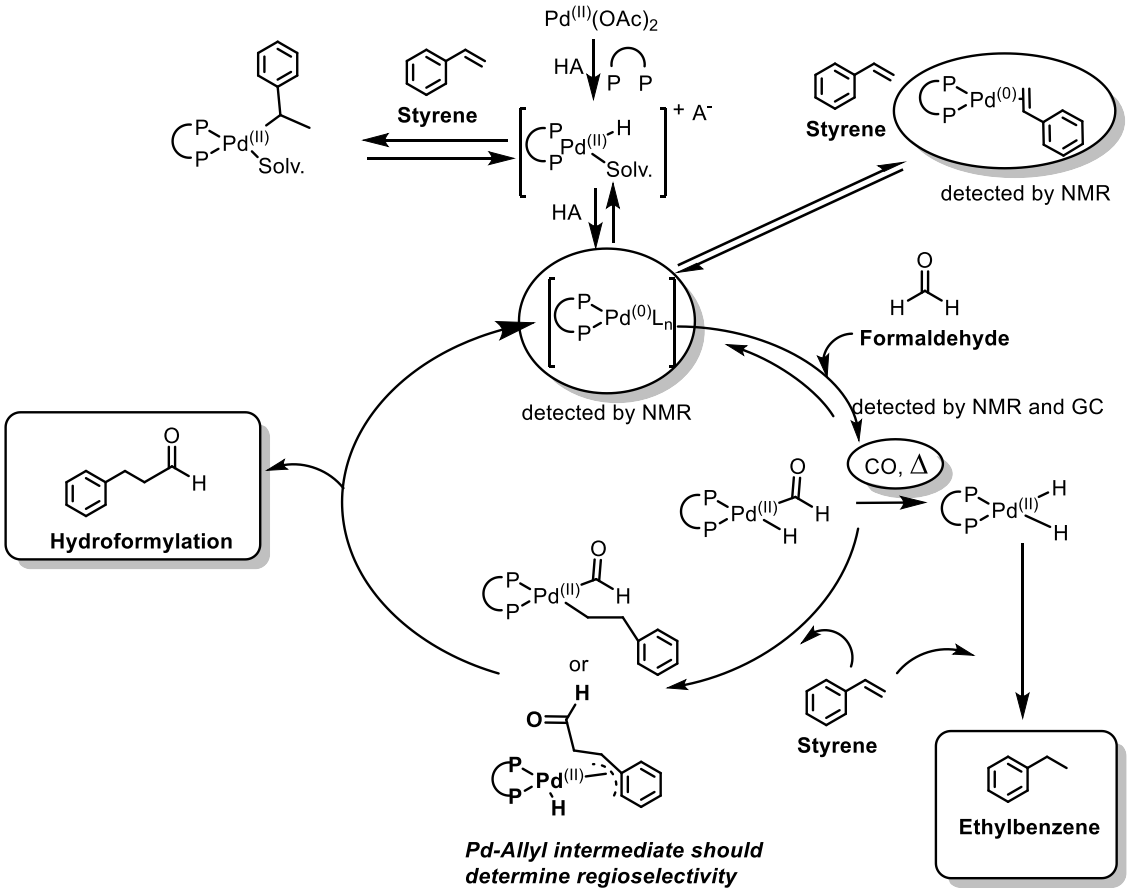
Fig. 11. MS spectrums to study the isotopic labelling effect with hydroformylation product.



Finally, *Figure 11* shows that the hydroformylation product is highly deutered, due to the previous formation of styrene-d_3. When PFA-d_2 was used, most of hydroformylation product does not contain deuterium.

With these results, the conclusions we extracted were that there are different Pd species in the reaction media catalytically active: Pd-H, Pd-$(H)_2$ and Pd-(H)(CHO). On basis the H-D exchange, it was proposed Pd-D was responsible of perdeuteration of styrene by sequential insertion/β-elimination reversible steps. This species was formed by initial formation of Pd-H that undergoes H/D exchange form the D_2O. Pd-$(H)_2$ is responsible of the hydrogenation activity, and Pd-(H)(CHO) is responsible of the hydroformylation activity.

From these results, and the mechanistic studies realized before in our group, the following mechanism for the Pd-catalyzed hydroformylation of styrene using formaldehyde as syngas surrogate is proposed:



Scheme 10. Proposed mechanism for Pd-catalyzed hydroformylation of styrene.

First the equilibrium between insertion and β-elimination is produced. Then, reduction of the Pd(II) precursor forms a Pd(0) species that can either react with styrene to form [Pd(dppp)(styrene)] or oxidatively add formaldehyde to produce a Pd(II)-hydride(formyl) complex.

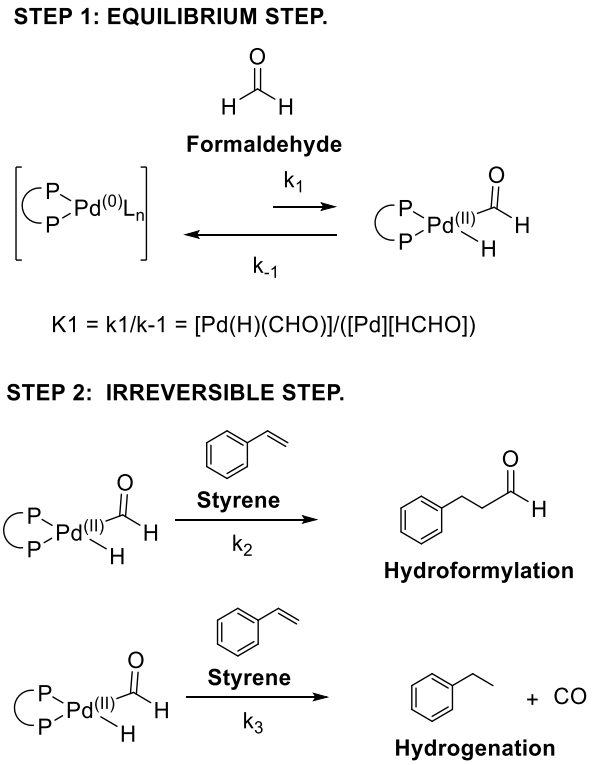
From this species, decarbonylation could release CO (detected by NMR) and forms a Pd(II)-dihydride species that can act as a hydrogenation catalyst under the reaction conditions. Upon reaction with styrene, Pd-hydride(formyl) complex could form a Pd(II)(alkyl)(formyl) of Pd(II)(H)(acyl) intermediate by insertion of the olefin into either the Pd-hydride or the Pd-formyl bonds.

The insertion of styrene into a Pd-H bonds has been reported in several catalytic processes such as methoxycarbonylation of alkenes[25] and the insertion of styrene into a Pd-acyl bond was reported in the Pd-catalyzed CO / styrene copolymerization[34]. From either of these species, reductive elimination would provide the linear aldehyde product.

Kinetic studies

Kinetics constitute the study of rates of chemical reactions. Kinetics allow the chemists to predict how the speed of a reaction will change under the reaction conditions. The study of kinetics is very important because it can provide information about the mechanism of a reaction and can also allow chemists to be more efficient in the laboratory. In a step wise reaction, the rate determining step (RDS) is the step with the highest energy transition state.

First, with the results obtained in the last experiments, we must determine the rate equation.



Scheme 11. Equilibrium and irreversible steps.

Equation: Preequilibrium before the rate determining step (rds)

$$\textit{Rate} = -\frac{d[\text{styrene}]}{dt} = \frac{d[\text{aldehyde}]}{dt} + \frac{d[\text{ethyl benzene}]}{dt} \quad (2)$$

$$\textit{Rate} = k_2\,[\text{styrene}]^a\,[\text{Pd-H-CHO}]^b + k_3\,[\text{styrene}]^a\,[\text{Pd-H-CHO}]^b \quad (3)$$

$$\textit{Rate} = k_{app1}\,[\text{styrene}]^a\,[\text{Pd-H-CHO}]^b, \text{ where } k_{app1} = k_2 + k_3 \quad (4)$$

where [**Pd-H-CHO**] = (k_1/k_{-1}) [**Pd**]^c [**HCHO**]^d

Note that [HCHO] >>> [styrene] and **K1** = equilibrium constant and ***k1*** = rate constant.

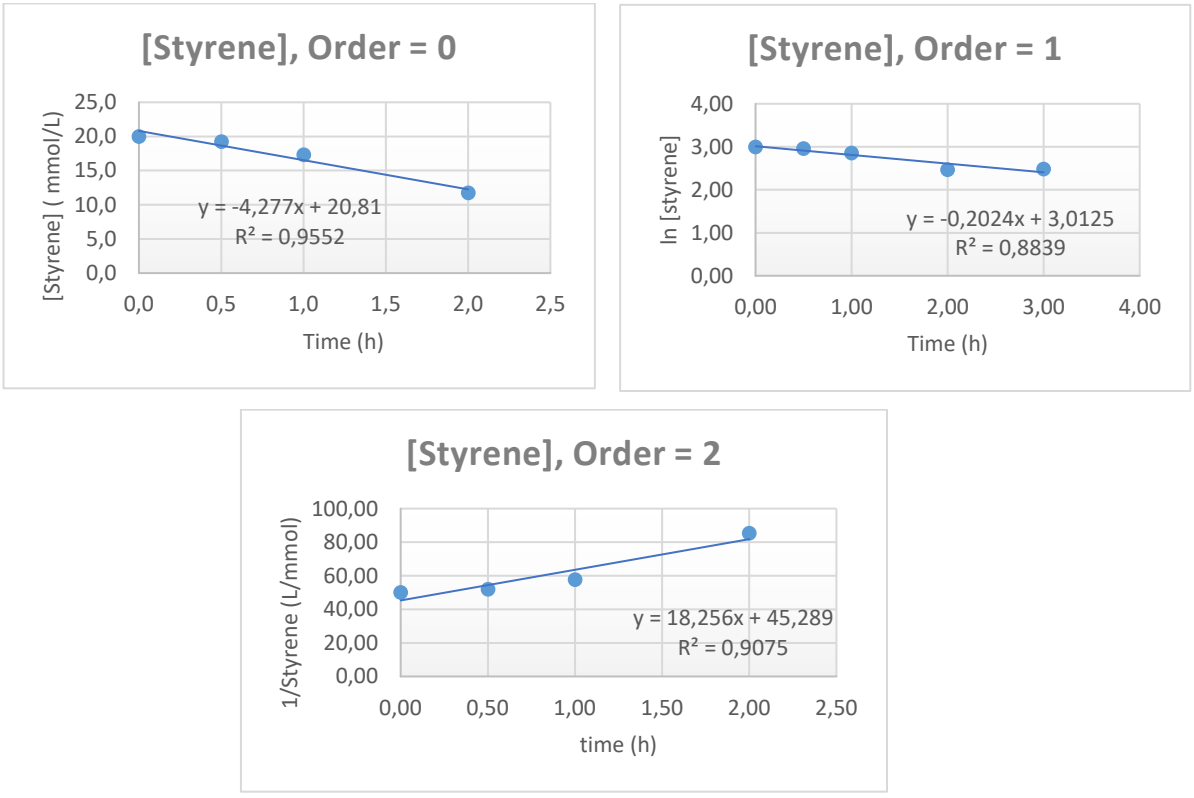
Rate = k_{app2} [**styrene**]^a, where kapp2 = $k_{app1}(k_1/k_{-1})$ [**Pd**]^c [**HCHO**]^d **(5)**

Next, the experiments for kinetics determination will be described:

1. Styrene order. Plot of styrene concentration depending on time. Styrene initial conc.: 333,33 mM (mmol/L).
2. Catalyst order. Maintain constant the L/Pd and TFA/Pd ratio. Plot log k_{app} = f (log [cat]) and slope is equal to the order: 33.3, 16.7 and 6.7 mM.
3. Formaldehyde order. Plot log k_{app} = f (log [HCHO]) and slope is equal to the order: 3333.3, 1666.7 and 833.3 mM.
4. Acid additive order. Plot log k_{app} = f (log [HCHO]) and slope is equal to the order: 100, 50 and 25 mM.
5. Measure k_{app} at different temperatures and estimate the Ea and ΔH: 65 ºC, 75 ºC, 85ºC and 95 ºC, 2h.

To determine the styrene order, experiments using PFA-d_2 + H_2O, PFA/PFA-d_2 and PFA + D_2O as formaldehyde source with different reaction times were carried out. Then, a plot of the concentration of styrene versus the time reaction was created, to determine which order fits better. Here, we only show the results obtained from the PFA + H_2O as formaldehyde source, but similar results were obtained in the rest of experiments.

Fig. 12. Determination of styrene reaction order.



With this graphics, the conclusion is that styrene order is 0, because it fits better.

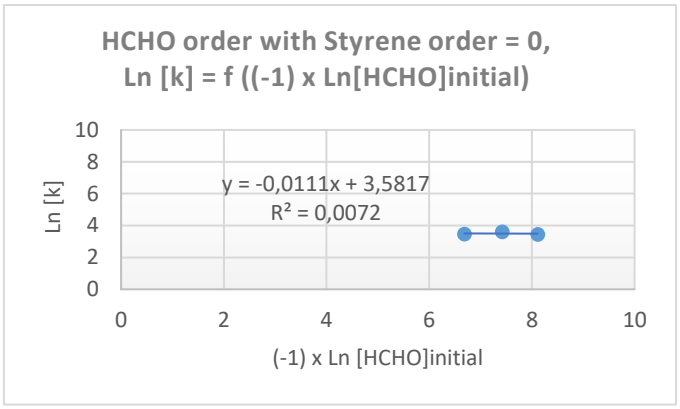
Next, to determine the reaction orders of formaldehyde, Pd catalyst and acid co-catalyst were determined. The reaction order for styrene is 0, so the reaction rate will be the variation of the styrene concentration depending on the time:

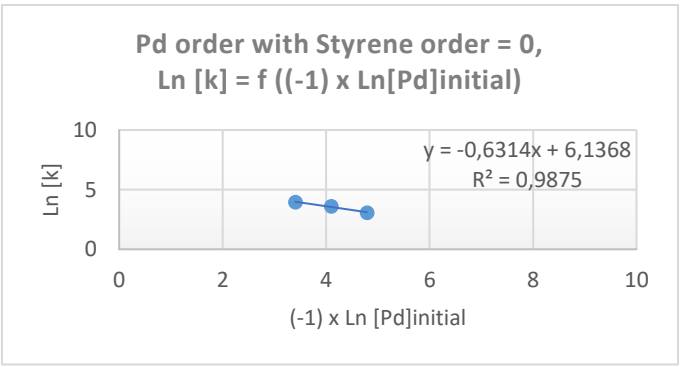
$$\textbf{rate} = -\frac{d[\text{Styrene}]}{dt} = k$$

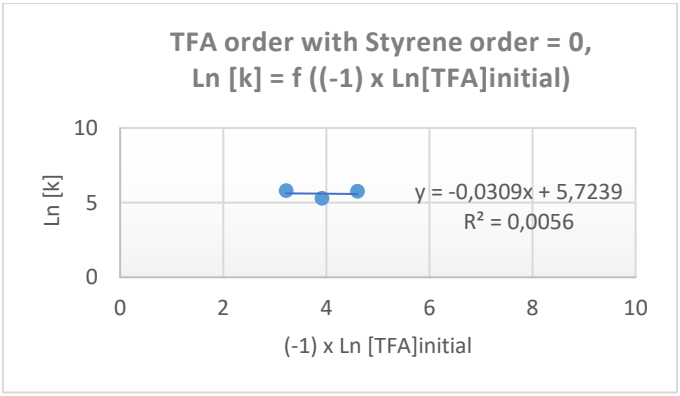
$$k = ([\text{Styrene intial}] - [\text{Styrene final}])/t$$

The reactions were stirred during 2h, so the time will be 7200 s (SI).

Fig. 13. Determination of reaction order of formaldehyde, Pd and TFA.







From these results, it was concluded that the reaction order for Pd catalyst is 1, whereas for HCHO and TFA the reaction order is 0. So, when we are working on the studied concentration range, when Pd concentration increase, the rate also increases. On the other hand, the concentrations of formaldehyde and acid co-catalyst do not present effect. Take note that in the equation established on the "preequilibrium before the rate determining step (rds)":

$$\text{Rate} = -d[\text{styrene}]/dt = d[\text{aldehyde}]/dt + d[\text{ethyl benzene}]/dt = k_{app1}\,[\text{styrene}]^0\,[\text{Pd-H-CHO}]^b \quad \textbf{(6)}$$

$$[\text{Pd-H-CHO}]^b = (k_{-1}/k_1)\,[\text{Pd}]^{0.6}\,[\text{HCHO}]^0$$

$$\textit{rate} = -\,d[\textit{styrene}]/dt = k_{app2}\,[\text{Pd}]^1 \quad \textbf{(7)}$$

If we integrate equation 7:

$$k = ([styrene]^{initial} – [Styrene]^{final})/([Pd] \times t) = TON / t = TOF$$

Making again the graphics with TON to see if the reaction order of styrene is 0, the graphic that presents a better lineal behavior is with styrene order = 0. Now we remake the graphics to determine again the rate, using now TON = f (t). This time all the experiments will be represented to see the similar things they share.

Fig 14. Determination of reaction rate from aldehyde and hydrogenation using PFA + H_2O.

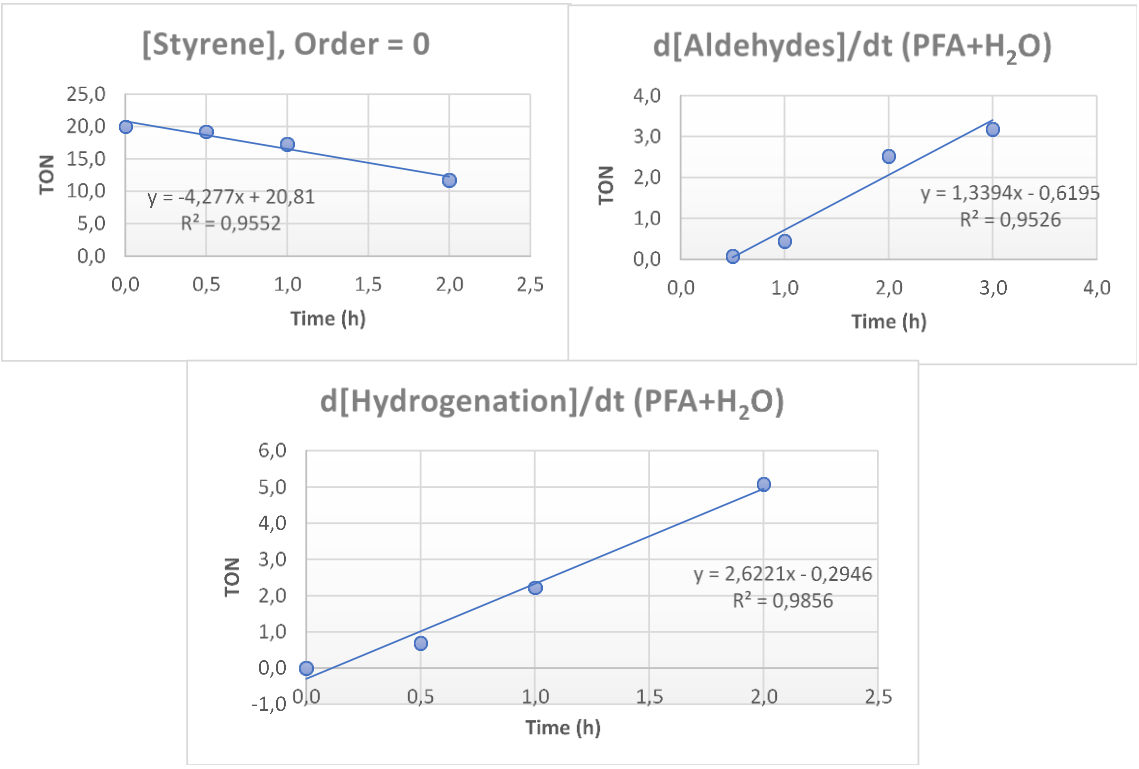


Fig 15. Determination of reaction rate from aldehyde and hydrogenation using PFA-d_2.

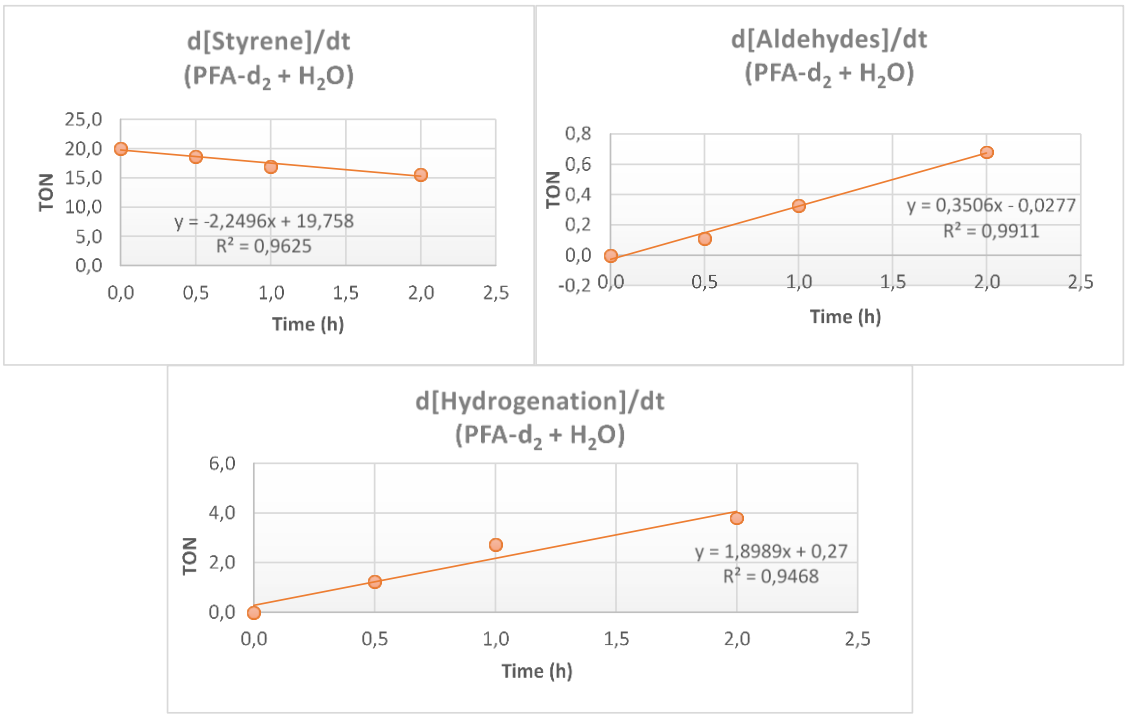


Fig 16. Determination of reaction rate from aldehyde and hydrogenation using PFA/PFA-d_2.

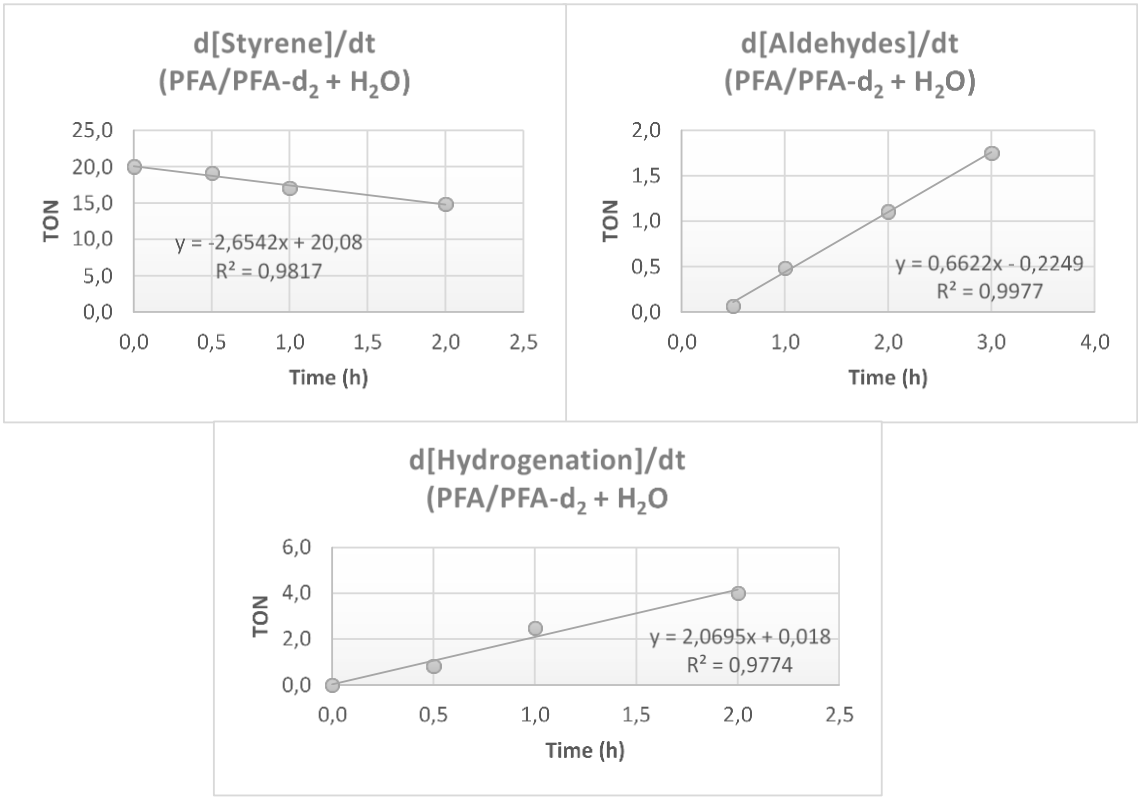
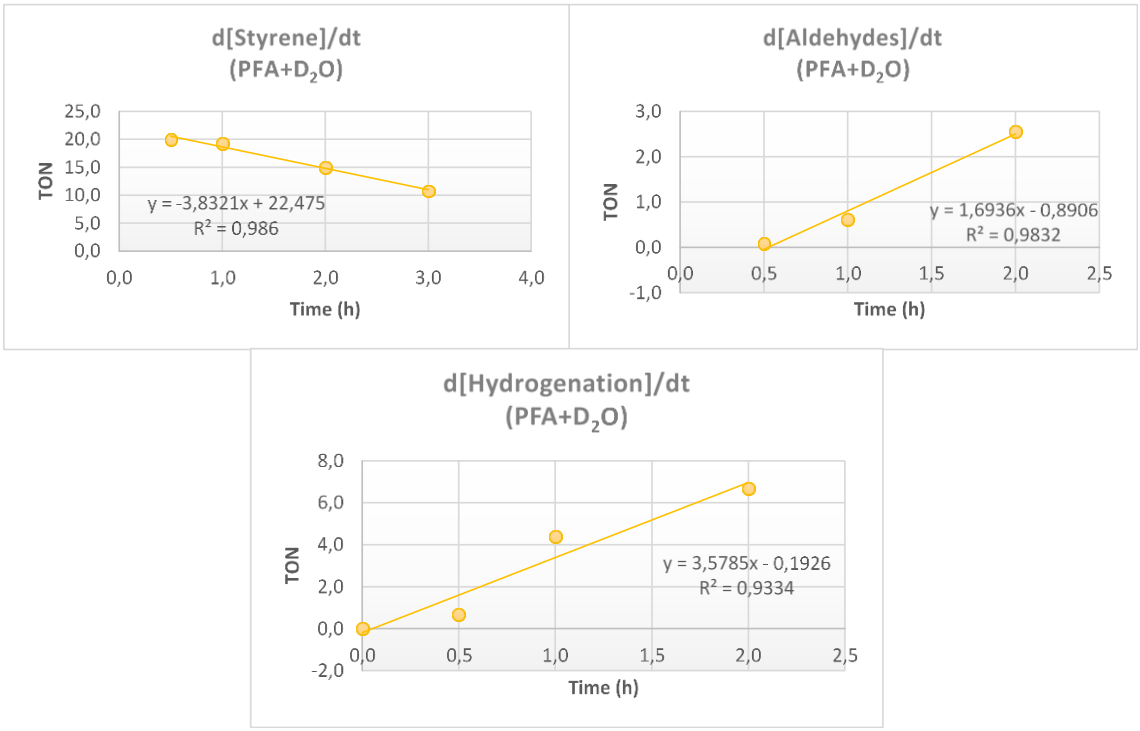


Fig 17. Determination of reaction rate from aldehyde and hydrogenation using PFA + D_2O.



With these results, the KIE is calculated. As we know, the rate global of the reaction is determined by using the rate of hydroformylation and the rate of hydrogenation ($r_{global} = r_{hydroformylation} + r_{hydrogenation}$). The rate values are taken from the slopes on *fig. 15-17*, where the concentrations of styrene, hydrocinnamaldehyde and ethylbenzene depending on time are represented. To be the first approximation the values of R^2 are higher than 0.93, and most of them higher than 0.98. The results of the rate values and isotopic effect are collected in *Tables 11 and 12*.

Table 11. Determination of isotopic effect (I).

	TOF Global (h^{-1}) (k_{app1})	**TOF Hydroformylation (h^{-1}) (k_2)**	**TOF Hydrogenation (h^{-1}) (k_3)**
PFA + H_2O	4.3	1.3	2.7
PFA-d_2 + H_2O	2.2	0.3	1.9
PFA/PFA-d_2 + H_2O	2.6	0.7	2.1
PFA + D_2O	3.8	1.7	3.6

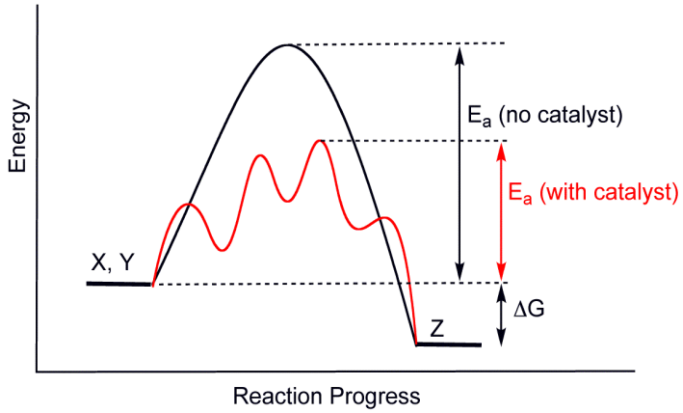
Table 12. Determination of isotopic effect (II).

	Global rH/rD	Hydroformylation rH/rD	Hydrogenation rH/rD
PFA + H_2O	1.0	1.0	1.0
PFA-d_2 + H_2O	1.9	3.9	1.4
PFA/PFA-d_2 + H_2O	1.6	2.0	1.3
PFA + D_2O	1.1	0.8	0.7

Although the global reaction only an apparently isotopic effect is appreciated in PFA-d_2 case, analyzing the hydroformylation and hydrogenation reactions separately, there is an important isotopic effect on the reaction of hydroformylation (rH/rD = 3.9).

Activation energy and reaction enthalpy determination

Activation energy is defined as the minimum energy that is required to active atoms or molecules to a condition in which they can undergo chemical transformation. In transition-state theory, the activation energy is the difference in energy content between atoms or molecules in an activated or transition-state configuration and the corresponding atoms and molecules in their initial configurations.



Scheme 12. Ea from a catalyst reaction vs Ea from a non-catalyst reaction.

When the value of the activation energy increases, the reaction rate decreases since larger amount of energy is required to achieve the transition state, and then, the reaction rate is slower. Comparing a catalyzed reaction with a non-catalyzed reaction, the first one will have a value of activation energy smaller than the second one, because the role of the catalyst in that reactions is to decrease the activation energy, in order to make the reaction possible under milder reaction conditions.[35] Therefore, as indicated in *Scheme 12*, a catalyzed reaction will be faster than a non-catalyzed reaction.

The activation energy is determined using the Ahrrenius equation [36], that relates the constant rate (k) with the temperature. For a given reaction:

$$k = Ae^{\frac{Ea}{RT}} \qquad \textbf{(8)}$$

Where A is constant and has the same units as the constant rate k, Ea is the activation energy (energy units) and R is the gas constant, expressed in compatible units with Ea. In logarithmic form, the equation can be expressed like:

$$\boldsymbol{ln(k) = ln(A) - \frac{Ea}{R}\frac{1}{T}} \qquad \textbf{(9)}$$

(9) is a line equation, where ln(A) is the y-intercept and (– Ea/R) is the slope.

Enthalpy of reaction, also known as heat of reaction, is the change in the enthalpy of a chemical reaction that occurs at a constant pressure. It is a thermodynamic unit or measurement, useful for calculating the amount of energy per mole either released or produced in a reaction.

To determine the enthalpy reaction, the Eyring equation can be used. This equation, like Ahrrenius, describe the relate between the temperature and the rate reaction:

$$k = \frac{k_b T}{h} e^{-\frac{\Delta H}{RT}} e^{\frac{\Delta S}{R}} \qquad \textbf{(10)}$$

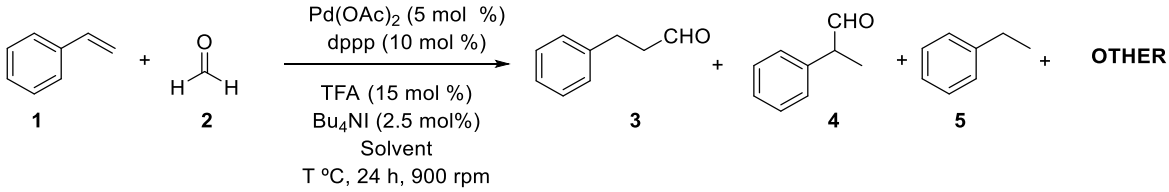
In logarithmic form, the equation can be expressed like:

$$\ln\frac{k}{T} = \frac{-\Delta H}{R}\frac{1}{T} + ln\frac{k_b}{h} + \frac{\Delta S}{R} \qquad \textbf{(11)}$$

(10) is a line equation, where $\ln(k_b/h) + (\Delta S/R)$ is the y-intercept and $(-\Delta H/R)$ is the slope.

So, to determine the activation energy and the reaction enthalpy, 3 reactions were performed at different temperatures:

Table 13. Determination of the activation energy and the reaction enthalpy.



Entry[a]	Temperature (ºC)	Conv. (%)[b]	CHEMO: (3+4) / 5 / OTHER (%)[b]	REGIO: 3/ (3 + 4) %	RATIO: 3 / 4 [b]	TON [c]
1	95	41.0	**39 / 61 / 0**	97.9	47.6	8.30
2	85	8.0	25 / 75 / 0	92.7	12.7	1.65
3	75	1.0	53 / 47 / 9	77.1	3.4	0.12
4	65	0.2	68 / 32 / 0	73.7	2.8	0.04

Reaction conditions:*[a] Styrene **1** (0.5 mmol, 58.1 uL), **2** (2.5 mmol, 77.4 mg), Water (125 uL), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), dppp (0.050 mmol, 21.0 mg), TFA (0.075 mmol, 5.8 uL), Bu_4NI (0.013 mmol, 4.6 mg), toluene (1.5 mL), 95ºC, 2 h, 900 r.p.m.; [b] Conversion, chemio-selectivity and regio-selectivity determined by GC-MS using bicyclohexyl as internal standard; [c] TON defined as the mole of styrene converted divided by the moles of Pd.*

Then, using the reaction rate (TOF), Ahrrenius plot and Eyring plot were created:

Fig 18. Ahrrenius plot to determinate de activation energy (Ea)

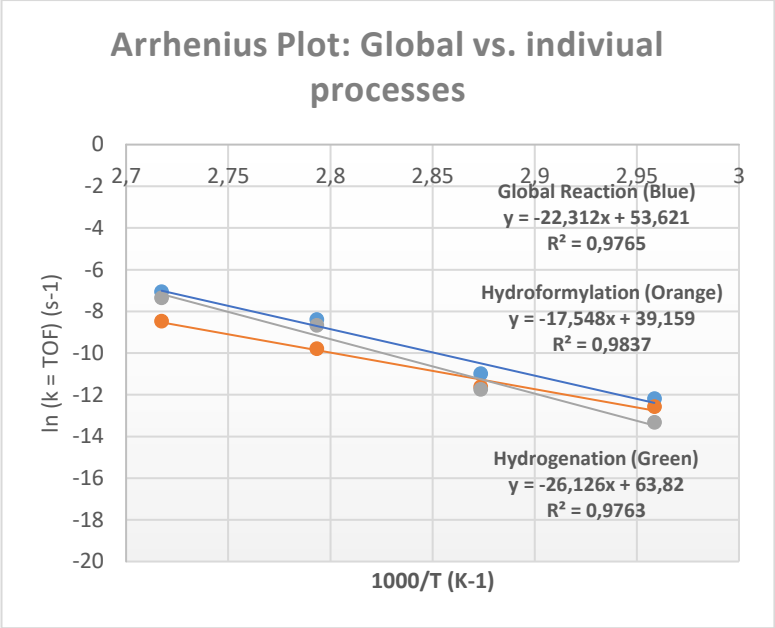
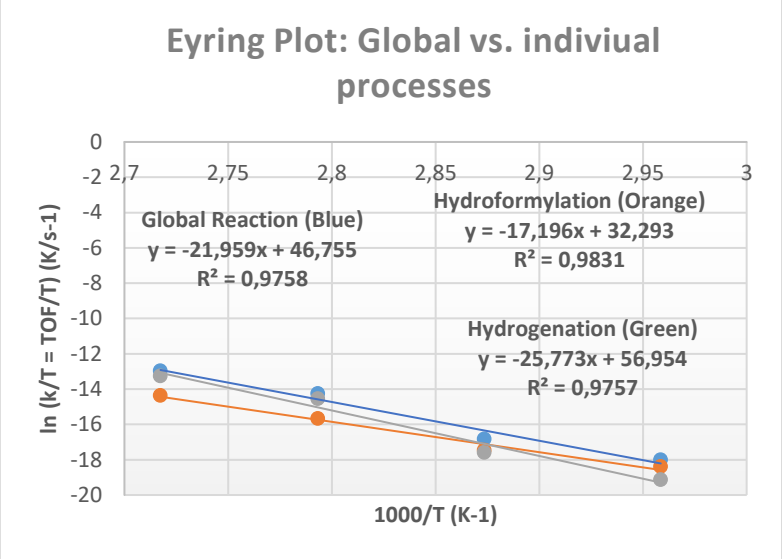


Fig 19. Eyring plot to determinate the reaction enthalpy.



Using equations (9) and (11), activation energy and enthalpy was obtained. Take note that:

R = 8,314 $J \cdot K^{-1} \cdot mol^{-1}$

h = $6{,}62 \cdot 10^{-23}$ J·s

kB = $1{,}38 \cdot 10^{-23}$ $J \cdot K^{-1}$

1 Kcal = 4,18 J

The results of these experiment are in *Table 14*.

Table 14. Results for the determination of the activation energy and the reaction enthalpy.

	Energy Activation Ea (Kcal/mol)	Enthalpy ΔH^{+} (Kcal/mol)
Global Reaction	44,4	43,7
Hydroformylation	34,9	34,2
Hydrogenation	51,9	52,0

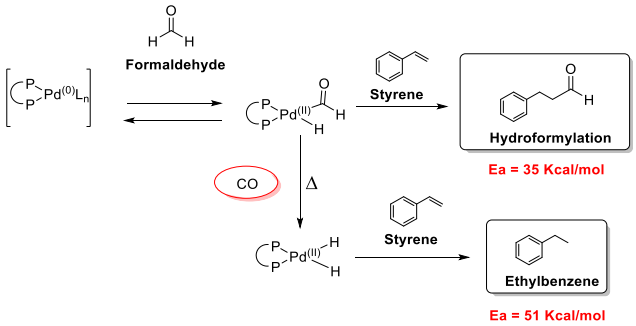
For hydrogenation process we obtained the highest values of activation energy and enthalpy, whereas the hydroformylation process provides the lowest values. This can confirm that, just like other carbonylation process[37], hydroformylation is favored at low temperatures (kinetic control) compared with the hydrogenation process.

CONCLUSIONS

The main objective of this work, which was to gain insights into the hydrocinnamaldehyde production by Pd-catalyst regioselective hydroformylation of styrene, was successfully completed.

Concerning the partial objectives:

1. An experimental set-up has been completed and the development and validation of analytical method was achieved.
2. The study of the effect of the reaction conditions and optimization has been completed, providing the best result of chemoselectivity at 65 °C: 25% conversion, 72% chemoselectivity and 97.7 regioselectivity (l/b ratio of 41.9)
3. Concerning mechanistic studies, there are various Pd species in the reaction media that are catalytically active. On basis of H-D exchange, a sequential styrene insertion- β-elimination reversible steps is hypothesized.
4. The rate reaction has been established: $r = (k_2 + k_3)(k_1/k_{-1})\,[Pd]^1$
5. There is an isotopic effect on the hydroformylation process, but in the hydrogenation process was not observed. This could be because the activation energy (Ea) of hydrogenation process is different and much higher than the Ea from hydroformylation process. With that, we propose that the rate determining step (rds) of hydroformylation process is the activation of C-H bond from HCHO, and the formation of the active specie.



Scheme 13. Results obtained from the kinetic studies.

REFERENCES

[1] O. Roelen, *Chem. Abstr.* **1994**, *38*.

[2] (a) B. H. Cornils, W.A. , *Applied Homogeneous Catalysis with Organometalic Compounds, Vol. 1*, Weinheim, **2002**; (b) K. A. Weissermel, J.P., *Industrial organic chemistry*, Weinheim, **2003**.

[3] (a) J. L. Klosin, C.R., *Acc. Chem. Res.* **2007**, *40*, 1251-1259; (b) B. Breit, *Top. Curr. Chem.* **2007**, *279*, 139-172; (c) F. Ungvári, *Coord. Chem. Rev.* **2007**, *251*, 2087-2102; (d) K. D. O. Wiese, D. , *Top. Organomet. Chem.* **2006**, *18*, 1-33; (e) Gual, A.; Godard, C.; Castillón, S.; Claver, C. , *Tetrahedron: Asymm.* **2010**, *21*, 1135-1146; (f) A. F. R. Börner, *Hydroformylation: Fundamentals, Processes and Applications in Organic Synthesis*, **2016**; (g) M. Taddei, Mann, A., *Hydroformylation for Organic Synthesis*, **2013**; (h) F. Ungvári, *Coord. Chem. Rev.* **2007**, *251*, 2072-2086; (i) P. W. N. M. K. van Leeuwen, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. , *Chem. Rev.* **2011**, *111*, 2077-2118.

[4] B. B., *Aldehydes: synthesis by hydroformylation of alkenes Vol. 25*, Thieme, Stuttgart, **2007**.

[5] P. W. N. M. van Leeuwen, *Homogeneous Catalysis: Understanding the Art*, Dordrecht, **2004**.

[6] B. M. Trost, *Science* **1991**, *254*, 1471-1477.

[7] B. Breit, *Acc. Chem. Res.* **2003**, *36*, 264-275.

[8] P. S. Eilbracht, A.M. , *Top. Organomet. Chem.* **2006**, *18*, 65-95.

[9] (a) D. A. O. Evans, J.A.; Wilkinson, G., *J. Am. Chem. Soc.* **1968**, 3133-3142; (b) D. Y. Evans, G.; Wilkinson, G., *J. Chem. Soc. A.* **1968**, 2660-2665; (c) J. F. O. Young, J.A.; Jardine, F.H.; Wilkinson, G., *J.Chem. Soc. Chem. Comm* **1965**, 131-135.

[10] P. W. N. M. C. van Leeuwen, C. , *Rh catalyzed hydroformylation*, Dordrecht, **2000**.

[11] (a) T. C. Jongsma, G.; van Leeuwen, P.W.N.M. , *J. Organomet. Chem.* **1991**, *421*, 121-128; (b) D. W. Selent, K.D.; Röttger, A. Börner, *Angew. Chem. Int. Ed.* **2000**, *39*, 1639-1641; (c) B. W. Breit, R.; Mackewitz, T.; Paciello, R.; Harms, K. , *Chem. Eur. J.* **2001**, 3106-3121.

[12] (a) P. E. M. Siegbahn, *J. Am. Chem. Soc.* **1993**, *115*, 5803-5812; (b) T. K. Matsubara, N.; Ding, Y.; Musaev, D. G.; Morokuma, K., *Organometallics*, *16*, 1065-1078; (c) R. H. Schmid, W. A.; Frenking, G., *Organometallics* **1997**, *16*, 701-708; (d) O. B. Gonzalez-Blanco, V. , *Organometallics* **1997**, *16*, 5556-5562; (e) L. A. B. van der Veen, M. D. K.; Bregman, F. R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M; Kees, G.; Fraanje, J.; Schenck, H.; Bo, C. , *J. Am. Chem. Soc.* **1998**, *120*, 11616-11626; (f) D. S. Gleich, R.; Herrmann, W. A. , *Organometallics* **1998**, *17*, 4828-4834; (g) D. S. Gleich, R.; Herrmann, W. A. , *Organometallics* **1998**, *17*, 2141-2143; (h) D. S. Gleich, R.; Herrmann, W. A. , *Organometallics* **1999**, *18*, 4354-4361; (i) L. A. K. van der Veen, P. H.; Schoemaker, G. C.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. , *Organometallics* **2000**, *19*, 872-883; (j) L. Z. Versluis, T.; Fan, L. , *Inorg. Chem.* **1990**, *29*, 4530-4536; (k) W. A. D. A. Rocha, W. B., *Int. J. Quantum Chem.* **2000**, *78*, 42-51; (l) J. J. M. Carbó, F.; Bo, C.; van Leeuwen, P. W. N. M., *J. Am. Chem. Soc.* **2001**, *123*, 7630-7637; (m) G. G. Alagona, C.; Lazzaroni, R.; Settambolo, R., *Organometallics* **2001**, *20*, 5394-5404; (n) S. A. C. Decker, T. R. , *New J. Chem* **2002**, *26*, 129-135; (o) C. R. U. Landis, J., *J. Chem. Soc., Dalton Trans.* **2002**, 729-742; (p) D. H. Gleich, J. , *Chem. Eur. J.* **2004**, *10*, 2435-2444; (q) E. E. Zuidema, L.; Eichelsheim, T.; Carbó, J. J.; Bo, C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. , *Chem. Eur. J.* **2008**, *14*, 1843-1853; (r) R. S. Lazzaroni, R.; Alagona, G.; Ghio, C., *Coord. Chem. Rev.* **2010**, *254*, 696-706; (s) M. S. Kumar, B.; Chaudhari, R. V.; Jackson, T. A., *Organometallics* **2014**, *33*, 4183-4191; (t) M. C. Kumar, R. V.; Subramaniam, B.; Jackson, T. A. , *Organometallics* **2015**, *34*, 1062-1073.

[13] A. I. M. K. Keulemans, A.; van Bavel, T. , *Rec. Trav. Chim. Pays Bas* **1948**, *67*, 298-308.

[14] R. F. Heck, *Acc. Chem. Res.* **1969**, *2*, 10-16.

[15] P. C. J. v. R. Kamer, A.; Schoemaker, G.C.; van Leeuwen, P.W.N.M., *Coord. Chem. Rev.* **2004**, *248*, 2409-2424.

[16] I. d. B. Jacobs, B.; Reek, J. N. H. , *Chem. Cat. Chem* **2015**, *7*, 1708-1718.

[17] (a) M. P. Dieguez, O.; Ruiz, A.; Castillon, S.; Claver, C., *Chem.Eur. J.* **2001**, *7*, 3086-3094; (b) T. P. L. Clark, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. , *J. Am. Chem. Soc.* **2005**, *127*, 5040-5042; (c) A. T. C. Axtell, C. J. J. Klosin; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. , *Angew. Chem. Int. Ed.* **2005**, *44*, 5834-5838.

[18] A. R. Lazzaroni, R. Settambolo, S. Bertozzi and G. Vitulli, *J. Mol. Catal.* **1989**, *50*, 1-9.

[19] M. Kranenburg, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1998**, 155-157.

[20] J. Pospech, Fleischer, I., Franke, R., Buchholz, S., and Beller, M., *Angew. Chem.* **2013**, *52*, 2852-2872.

[21] P. Gautam, B. M. Bhanage, *Catal. Sci. Technol.* **2015**, *5*, 4663–4702.

[22] L. J. C. Jens Rostrup-Nielsen, *Concepts in Syngas Manufacture*, Imperial College Press, London, **2011**.

[23] W. C. Ren, W.; Dai, J.; Shi, Y.; Li, J.; Shi , Y. , *J. Am. Chem . Soc.* **2016**, 14864-14867.

[24] (a) A. A. Somasunderam, H. , *J. Mol. Catal.* **1994**, *92*, 35-40; (b) B. V. El Ali, G.; Alper, H. , *j. mol. Catal. A. chem.* **1996**, *112*, 195-201.

[25] Liu, Q.; Yuan, K.; Arockiam, B.; Franke, R.; Doucet, H.; Jackstell, R.; Beller, M.; *Angew. Chem. Int.* Ed. **2015**, *54,* 4493-4497.

[26] C. Amatore, E. Carre, A. Jutand, M. A. M'Barki, *Organometallics* **1995**, *14,* 1818-1826.

[27] Liu, Q.; Wu, Jiao H.; Fang, R.; Jackstell, R.; Beller, M.; *Angew. Chem. Int. Ed.* **2013**, *52*, 8064-8068.

[28] Garcia, B.; Díaz, M.; Godard, C.; *"Pd-catalyzed hydroformilation of styrene"*, URV.

[29] Determination of the response factor using internal standard. https://www.chromatography today.com/news/gc-mdgc/32/breaking-news/what-is-a-response-factor/31169 (Visited on 25 May 2019).

[30] How to calculate a response factor. https://sciencing.com/calculate-gc-response-factors-8003137.html (visited on 25 May 2019).

[31] H. J. Prins., *Condensation of formaldehyde with some unsaturated compounds*, *Chem. Week.*, **1919**, *16*, 1072.

[32] F. T. Y. Du, *Catal. Commun.* **2007**, *8*, 2012-2016.

[33] Wang, D.; Astruc, D.; *Chem. Rev.* **2015**, 115, *13*, 6621-6686.

[34] Sperrle, M.; Aeby, A.; Consiglio,G.; Pfaltz, A.; *Helv. Chem. Act.*; **1996**, *79*, 5, 1387-1392

[35] (a) Luza, L.; Rambor, C.P.; Gual, A.; Bernardi, F.; Domingos, J.B.; Grehl, T.; Brüner, P.; and Dupont, J.; *ACS Catal.* **2016**, *6*, 6478-6486. Luza, L.; Rambor, C.P.; Gual, A.; Fernandes, J.A.; Eberhardt, D.; Dupont, J.; *ACS Catal.* **2017**, *7*, 2791-2799.

[36] Leu, M.; Vicente, I.; Ferndendes, J.A.; de Pedro, I.; Dupont, J.; Sans, V.; Licence.; Gual, A.; Cano, I.; *Appl. Catal. B. Eviron.*, **2019**, *245*, 240-250.

[37] (a) Murzin, D.; Salmi, T.; *Catalytic kinetics*, 2nd Ed., *Elsevier Science*, **2016**. (b) House, J.E.; *Principles of Chemical Kinetics*, 2nd Ed., Elsevier Science, **2007**.

[38] van Leeuwen, P. W. N. M.; *Homogenous Catalysis Understanding the Art*, *Ed. Kluwer Academic Publishers*, Dordretch, **2004**, *7*, 126.