Mechanistic investigation of CO_2 hydroformylation methods

M.Sc. thesis

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Abstract

The theoretical part of the thesis describes the conventional hydroformylation reaction, which uses carbon monoxide, with many important reaction examples performed by several investigation groups. Reaction examples are divided by substances, and different homogeneous catalytic complexes, also different reaction mechanisms depending on used catalytic complex, are described. As a very important part, also several examples of hydroformylation reaction that uses carbon dioxide are described, together with mostly used homogeneous catalytic complexes, and reaction mechanisms. This contains reverse-water gas shift reaction, which converts carbon monoxide to carbon dioxide, and ionic liquids, which are successfully used as solvents in hydroformylation reaction.

The experimental part aimed to investigate the mechanism of the carbon dioxide-based hydroformylation reaction through investigating the kinetic isotope effect (KIE). Based on that, deuterated substrates were synthesized with good yields and deuteration levels, 1-deuterio-cyclohexene and 1,2,3,3-tetradeuterio-cyclohexene. Unfortunately, the deuterated substrates could not be used in the KIE-experiments, due to the lack of time for this project.

Tiivistelmä

Tämän pro gradu – tutkielman kirjallisessa osassa on käsitelty perinteinen hydroformylaatioreaktio, jossa käytetään hiilimonoksidia reagenssina. Tämä sisältää useiden eri tutkimusryhmien tekemiä reaktioita. Esimerkit reaktioista ovat jaoteltu muun muassa eri lähtöaineiden, sekä erilaisten katalyyttikompleksien mukaan. Katalyyttikompleksien käyttäytymistä reaktiossa on kuvattu reaktiomekanismien avulla. Kirjallisuuskatsauksen tärkeimmässä osassa on käsitelty lukuisia esimerkkejä tähän asti tehdyistä hiilidioksidia käyttävistä hydroformylointireaktioista. Tämäkin osuus sisältää kuvauksen useimmiten käytetyistä katalyyttikomplekseista, ja niiden käyttäytymisen reaktiomekanismeista. Ioninesteitä ja niiden ominaisuuksia on kuvattu, sillä niitä on onnistuneesti käytetty liuottimina hydroformylointireaktiossa. Käänteistä vesi-kaasu siirtoreaktiota on myös käsitelty tarkasti, sillä se muuntaa hiilimonoksidin hiilidioksidiksi, joka toimii lähtoaineena hydroformylointireaktiossa.

Tutkielman kokeellisen osan tavoitteena oli alun perin selvittää tarkemmin hiilidioksidia käyttävän hydroformylointireaktion mekanismia, tutkimalla kineettistä isotooppiefektiä (KIE) leimauskokeiden avulla. Tämän mahdollistamiseksi oli syntetisoitu leimatut lähtöaineet, 1-deuterium-sykloheksseeni sekä 1,2,3,3-tetradeuterium-sykloheksseeni, joiden saannot ja leimautumisprosentit saatiin melko suuriksi. Projektille annetun hyvin lyhyen ajan vuoksi näitä lähtöaineita ei kuitenkaan ehditty käyttämään hydroformylointireaktion mekanismin tutkimiseen.

Preface

This Master's Thesis project was accomplished between June 2020 and March 2021, with the collaboration of the University of Jyväskylä and VTT Technical Research Centre of Finland. The experimental part took place at the Department of Chemistry of the University of Jyväskylä during the autumn period of 2020.

I would like to thank VTT Research Centre for the great opportunity to make my project with the most interesting, and globally important topic. I am very grateful to my supervisors Juha Lehtonen and Pauliina Pitkänen from VTT for useful pieces of advice and help especially with the theoretical part of my project. I would also like to greatly thank my supervisor from the University of Jyväskylä Petri Pihko, for his patient desire to improve my knowledge both in laboratory skills and in chemistry. I also thank Anton Nechaev and Saara Riuttamäki from all my heart, for all their help, and mental support, as well as for guidance, and practical tips in the laboratory. I was shown during this project, how interesting and inspiring chemistry investigation can be, and now I know, that I want to be a part of it in the future. Lastly, I want to thank my dear fiancé, for his endless support and believing in me, even when I did not.

Olga Minchenkova

"Courage is not the absence of fear, but rather the judgement that something else is more important".

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Abbreviations

acac	acetylacetone
AcO	acetoxy group
Boc	tert-butoxycarbonyl
Biphephos	6,60-[(3,30-Di-tert-butyl-5,50-dimethoxy-1,10-biphenyl-2,20-diyl)bis(oxy)]bis(dibenzo[d, f][1,3,2]dioxaphosphepin)
bipy/bpy	bipyridine
bmim	1-*n*-butyl-3-methylimidazolium
[BMMI]Cl	3-butyl-1,2-dimethylimidazoliumchloride
CCU	carbon capture and utilization
CFC	chlorofluorocarbon
cod	1,5-cyclooctadiene
Cy	cyclohexyl group
DMA	dimethylacetamide
DMC	dimethylcarbonate
DME	dimethylether
DMF	dimethylformamide
EDTA	ethylenediaminetetraacetic acid
ee	equatorial-equatorial
ee	enantiomeric excess
emim	1-ethyl-3-methylimidazolium
GHG	greenhouse gas
KIE	kinetic isotope effect
IL	ionic liquid
*i*Pr	*iso*-propyl group

l/b	linear to branched aldehyde ratio
LCA	life cycle assessments
LPO	low-pressure oxo-process
MAB	2-methyl-4-acetoxybutenal
Mim	methylimidazolium
NMP	*N*-methylpyrrolidone
OMe	methoxy group
omim	1-*n*-octyl-3-methylimidazolium
Ph	phenyl group
[PPN]Cl	bis(triphenylphosphine)iminiumchloride
PXL	propane-expanded liquid
R	organic side chain
(r)WGSR	(reverse) water-gas shift reaction
SILP	supported ionic liquid phased
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TPPTS	2,2',3-phosphinetriyltribenzenesulfonate
VAM	vinyl acetate monomer
Xanthphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

LITERATURE PART

1. Introduction

According to the intergovernmental panel on climate change (IPCC), the impacts of climate changes on natural and human systems observed over the past few decades have been significant. With recent emissions of greenhouse gases being the highest in history, it seems obvious that the human influence on these climate changes has been pivotal. The main changes observed are the warming of the atmosphere and ocean, the decreasing amounts of ice and snow, and the rise of sea level. If the greenhouse gases continue their emissions at the current level, many components of the climate system will continue to warm, and undergo long-lasting changes, which may cause many serious and even irreversible effects on ecosystems and people. [1]

The largest fraction of global anthropogenic greenhouse gases (GHG) results from fuel combustion. In general, the use and production of energy have many environmental consequences. The combustion of fossil fuels, which are coal, natural gas, and oil, leads to large emissions of carbon dioxide (CO_2), which forms when the carbon in fuels is oxidized. Carbon dioxide represents about 95 % of all emissions which are related to the use of energy, thus it also represents about 80 % of all GHG emissions. The rest of the emissions are mainly caused by methane, N_2O, and chlorofluorocarbon (CFC)-gases. [1,2]

Recently, the interest in transforming carbon dioxide into other valuable chemicals and fuels has grown dynamically, mainly because of continuously growing emissions of the carbon dioxide produced as a waste by fossil fuel-based energy systems. During the past few decades, methods to catalytically reduce carbon dioxide to many other chemicals, such as methanol, formic acid, methane, and carbon monoxide, have been discovered. Moreover, several innovations in the production of fine chemicals have been made, leading to a broadening in the number of chemicals produced from CO_2, which are made by combining CO_2 reduction, and forming new C-C, C-N, and C-O bonds. [3,4]

In particular, using CO_2 as a surrogate for highly toxic and flammable CO has attracted great interest, especially because CO is produced currently from fossil fuels. Thus, a possibility to efficiently reduce CO_2 to CO, as well as the possibility to use the forming product subsequently would be very valuable in sustainable chemistry. Catalytic transformation of CO_2 has been recently very much exploited in carbonylative alkene functionalization, and thus many good approaches to valuable chemicals, such as esters, carboxylic acids, and alcohols, have been developed. As one of the carbonylation reactions, hydroformylation reaction is important to be reviewed, since it has been one of the most important processes in the industry, producing alcohols and aldehydes. Traditionally, hydroformylation reaction uses toxic CO as a reagent, as well as catalyst complexes and organic solvents. Thus, replacing CO

with CO_2 in catalytic conversion of alkenes to aldehydes or alcohols has been an aim for many research groups over the past decades, especially for Tominaga *et al,* since 1994. [3–6]

The literature part of this Master's Thesis is aimed at the description of conventional hydroformylation reaction that includes the catalytic complexes and organic ligands used, and also the different examples of the important reactions performed so far. As an application to conventional hydroformylation reactions, hydroformylation reactions performed by several research groups using CO_2 as an alternative to CO using the reverse water-gas shift reaction are reviewed. Besides, the features of ionic liquids and the reverse water-gas shift reaction are described more accurately, since both are strongly related to performing CO_2-based hydroformylation reaction reviewed in this thesis. References used are mostly from the past two decades, but in this paper, we also decided to use more recent publications, containing the approaches that some modern methods originate from.

2. CO_2 can be converted from a pollutant to a raw material.

CCU (carbon capture and utilization) is a term, which indicates the capture of carbon dioxide from a source, and its subsequent utilization as a raw material. Carbon dioxide can be used directly, or it can be used for the synthesis of important chemicals as a raw material. For example, carbon dioxide can be utilized in carbonated beverages, or converted into more complicated chemicals, such as polymers. CCU is a very important theme in chemical research nowadays, as it may potentially help to reduce the usage of fossil fuels and emissions of greenhouse gases. However, CCU does not necessarily reduce the amount of atmospheric CO_2, but it delays the release of it, which varies from tens of years to hours. [7,8]

The research lines which refer to carbon dioxide utilization as a carbon source can be divided into three classes, according to the molecular transformation of carbon dioxide (Figure 1). On the left side, are shown molecules **1-2** that are produced from the incorporation of carbon dioxide without formal reduction. In the middle, a large synthetic diversity of molecules **3-11**, which are formed under combined reduction and bond formation, are illustrated. Finally, on the right, there are methane **12** and saturated hydrocarbons (**13)** that are produced after the total reduction of carbon dioxide. [9]

Many important chemicals are produced *via* CCU, for instance, C_1 based chemicals such as carbon monoxide, formic acid, methanol, methane, and syngas (synthetic gas). Moreover, more complex molecules are produced, such as DME (dimethyl ether), DMC (dimethyl carbonate), and methyl propionate. Many LCA (life cycle assessments) studies have been carried out, and it was concluded, that using the chemicals produced via CCU reduces the emissions of greenhouse gases. Especially

production of methane and formic acid has the largest reductions of overall environmental impact, compared to their traditional production. [7]

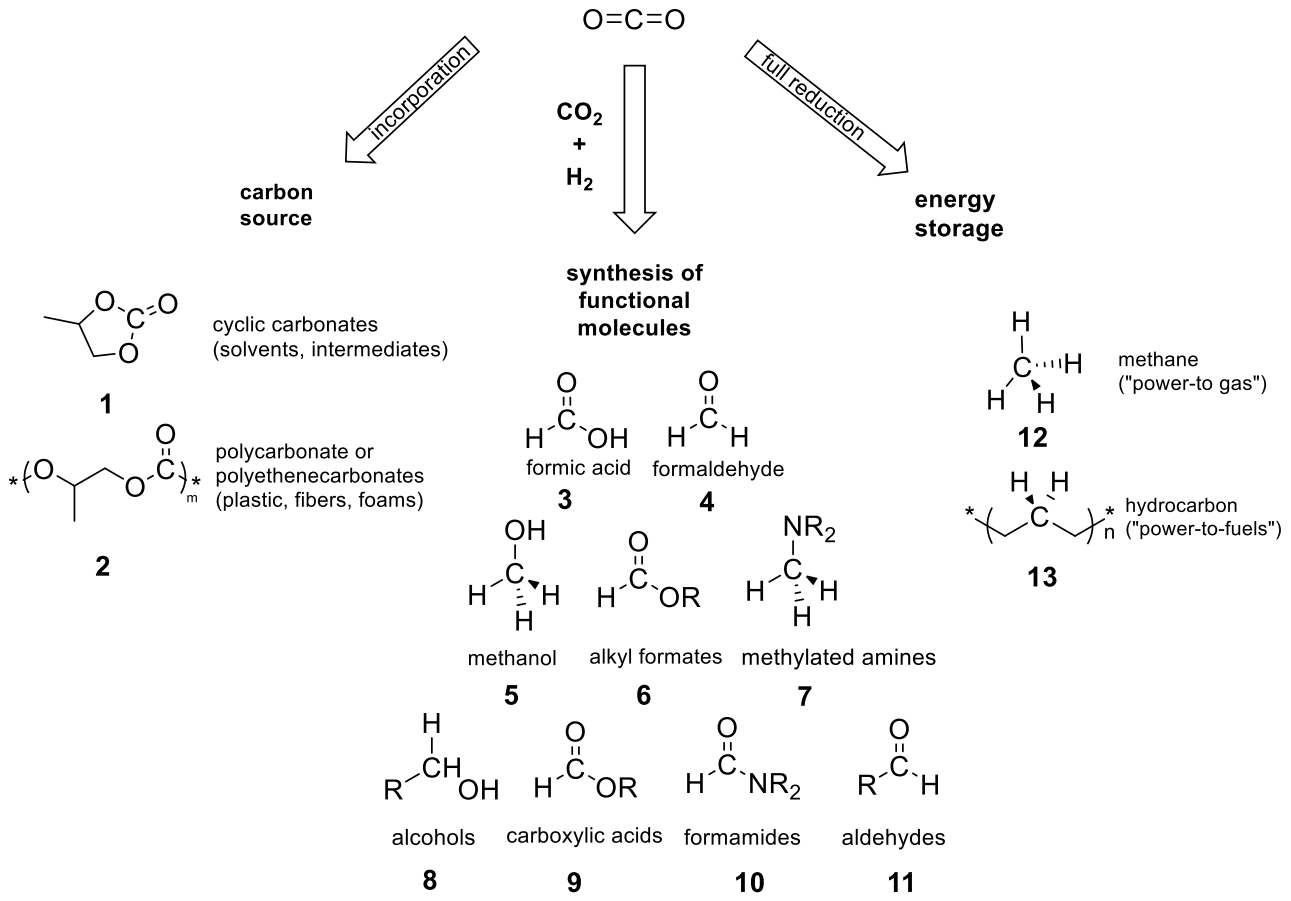


Figure 1. Utilization of carbon dioxide as a carbon source.[9]

Reactions of CO_2 feedstocks to produce methane are important not only in terms of energy defossilization but also because it is a good method for energy storage in chemical bonds if electrolysis is used for hydrogen supplying. The Sabatier process can be considered as the main thermochemical pathway in forming methane from carbon dioxide, where CO_2 reacts exothermically with hydrogen forming methane and water. The most active metal catalyst for CO_2 methanation, as well as for CO methanation, is ruthenium (Ru). [3]

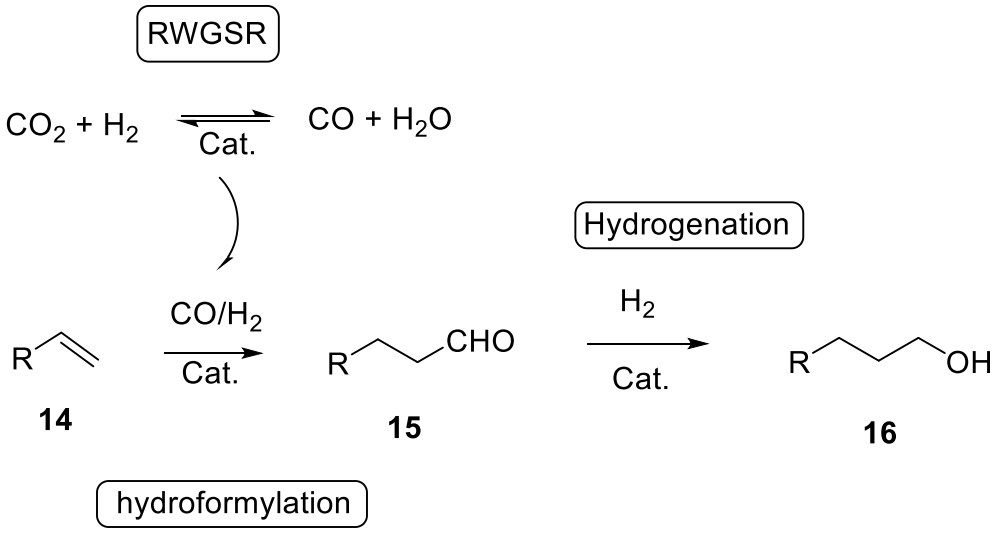
Formic acid **3** is not a very large product in the global market, with an annual production less than 1 Mt/a. The storage of silage is the largest industrial application of formic acid nowadays.[3] In addition to that, it is used for the synthesis of organic chemicals, such as pharmaceuticals, and for the textile, leather, and rubber industry. Most commonly, formic acid is produced via methyl formate, which is

a two-step process of formal carbonylation of water, potassium, or sodium methoxide ($NaOCH_3$, $KOCH_3$) is used as a catalyst for the reaction.[8] There can be two possible pathways for producing formic acid from carbon dioxide; direct hydrogenation of CO_2 to form formic acid or producing CO from CO_2 first, which is followed by carbonylation reaction. The direct hydrogenation can be catalysed by either homogenous or heterogeneous catalysts. Several companies are using patented commercial processes, which use CO_2 hydrogenation in producing formic acid, such as BASF and Reactwell. [8,10]

Though the hydrogenation of CO_2 in the formation of formic acid and its derivatives is a big theme of interest, there are many competing approaches to the same product using CO. CO-based processes are thermodynamically more favored, partly because the reduction of CO_2 to CO always requires energy. Significantly, for those processes, CO_2/H_2 mixture can be used for generating CO as a starting material, by reverse water-gas shift reaction (RWGSR). An important application for that is hydroformylation reaction, which is conventionally a reaction of alkenes with CO/H_2 mixture. [10]

The synthetic gas for hydroformylation reaction can be produced *in situ* by the RWGS reaction, where CO_2 is used as an alternative source of carbon monoxide (Scheme 1). After the reduction of carbon dioxide by hydrogen to form carbon monoxide, it can be used in the previously described hydroformylation reaction in the presence of an alkene **14**, and after that, it can also be converted from aldehyde **15** to alcohol **16** in a hydrogenation reaction. Importantly, both reactions can occur with the same catalyst, and within the same system. Noteworthy, the term “olefin” refers to cyclic and acyclic hydrocarbons, with one or several unsaturated C-C bonds, whereas the term “alkene” refers to hydrocarbons having only one unsaturated C-C bond. Since only the last-mentioned compounds are used in CO_2 - based hydroformylation reaction, it is more appropriate to use the term “alkene” within the framework of this thesis. [11]

The possibility to use CO_2 instead of CO in performing hydroformylation reactions is an important theme for modern research. There are many problems with using carbon monoxide, such as the toxicity and flammability of this gas; also it cannot be called a green gas, as it is produced mainly from fossil fuels. Thus, a possibility to efficiently reduce CO_2 to CO and the subsequent use of obtained carbon monoxide would be valuable for the chemical industry. Therefore, many catalytic transformations using carbon dioxide as a source of alkene functionalization have been recently discovered, and this has made it possible to easily obtain important chemicals, such as alcohols, esters, and carboxylic acids. [4]



Scheme 1. Principle of RWGS reaction, and its connection to hydroformylation reaction[12]

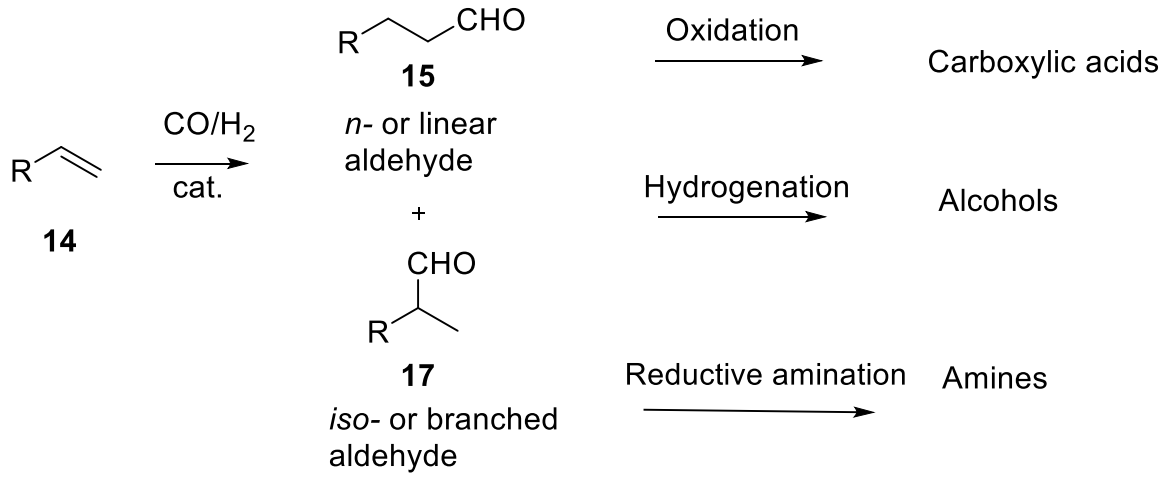
The main difficulty in the use of CO_2 is its bond strength (532 kJ/mol), and as a result, cleavage of the C-O bonds can be challenging.[10] Besides, this kind of approach for performing hydroformylation reaction has some other difficulties, for example, it is a challenge to find such kind of systems, which allows this reaction to proceed in one pot, avoiding alkene hydrogenation. This challenge can be solved though by using appropriate catalytic systems, ligands, and additives when performing the reaction. But there is also an additional drawback related to the activity of the catalytic systems. Catalytic systems used in hydroformylation reaction with CO/H_2 mixture are far more active, than those which produce CO for hydroformylation in the RWGSR. When the CO is generated from CO_2 *in situ*, its partial pressure is lower compared to processes where CO is the feedstock, and, as a consequence, the rate of hydroformylation reaction is also lower. As a result, it has been proposed, that performing the reaction in two distinct steps, and not *in situ*, would be more economical, and would not require developing more active catalysts. [4,13]

3. Hydroformylation reaction forms oxo-products from alkenes and CO/H_2 gas

Hydroformylation reaction was discovered accidentally by Otto Roelen in 1938, and he called it then "oxo process", which term is widely used today, especially by industrial chemists.[14] It is one of the largest industrial processes today, which uses homogenous catalysts. Each year over 10 million metric tons of oxo chemicals made by hydroformylation reaction are produced. Aldehydes that are formed in the reaction, are important reagents for further reactions in bulk chemistry, for example, in the

synthesis of alcohols, amines, and carboxylic acids (Scheme 2). The reason for that is, that the carbonyl group is very reactive, and it can, for example, easily undergo reduction and oxygenation reactions, which lead to carboxylic acids and alcohols.[13]

Hydroformylation reaction is the addition of synthetic gas, "syngas", which is a mixture of carbon monoxide CO and hydrogen H_2, to alkenes (Scheme 2). The term "hydroformylation", can tell us much about the scope of the reaction; it refers to hydrogen and formyl groups that are introduced to the substrate in the reaction. Catalysts are used to run the reaction, such as, transition metal catalysts, e.g. cobalt, ruthenium, rhodium, palladium, and platinum complexes. The main reaction products are aldehydes, which can be branched and linear unless ethylene is used as a starting material. In the reaction, different branched aldehydes can be formed, even if the reactant used is a terminal alkene. The reason for this is that double bond isomerization can take place before the hydroformylation reaction. The formation of different products stresses the importance of regioselectivity in each hydroformylation reaction. [11,13]



Scheme 2. Hydroformylation reaction principle, and products derived from reaction product[13]

The alkene starting material in hydroformylation reaction, is very reactive, as a result of the π-electrons of its double bond. However, the aldehyde group (C=O) that is formed in the reaction, is also very reactive, partly because of oxygen's free electron pairs, which gives it Lewis base properties. The reactivity of the aldehyde group is one of the main reasons for the wide use of compounds containing the carbonyl group in the industry. Noteworthy, hydroformylation reaction can also produce alcohol directly from an alkene in sequential hydroformylation-hydrogenation reaction. Aldehyde, which is conventionally the main product of hydroformylation reaction, can be thus

hydrogenated to alcohol in a one-pot reaction, with the use of certain catalysts, such as ruthenium, for instance. [11]

3.1 Catalytic complexes

Compounds, used to catalyse hydroformylation reactions, are typically hydrido metal carbonyl complexes. Their general structure is $[HM(CO)_xL_y]$, where M refers to the transition metal, and L refers to ligand, which can be an additional CO, or it can be another organic ligand if the catalytic process is modified. Catalytic processes are divided into modified and unmodified processes, in modified processes ligands other than CO are used. The most commonly used ligands are phosphines, phosphonates, and phosphites. In unmodified processes, no modifier ligands are used in the catalytic complex. [11,15]

The use of the modifying ligand in metal complexes has quite a big role in the selectivity of hydroformylation reaction. The selectivity can either refer to side reactions of hydroformylation reaction, such as hydrogenation and isomerization, or to the type of aldehyde that is produced, which can be branched or linear, depending on the ligand. [16]

The most used transition metals in catalytic complexes are cobalt Co and rhodium Rh, but also other metals can be used, e.g. Ru, Pt, and other metals from the VII group. For transition metals in unmodified catalytic complexes, the following order in reactivity for hydroformylation reaction has been established: [11]

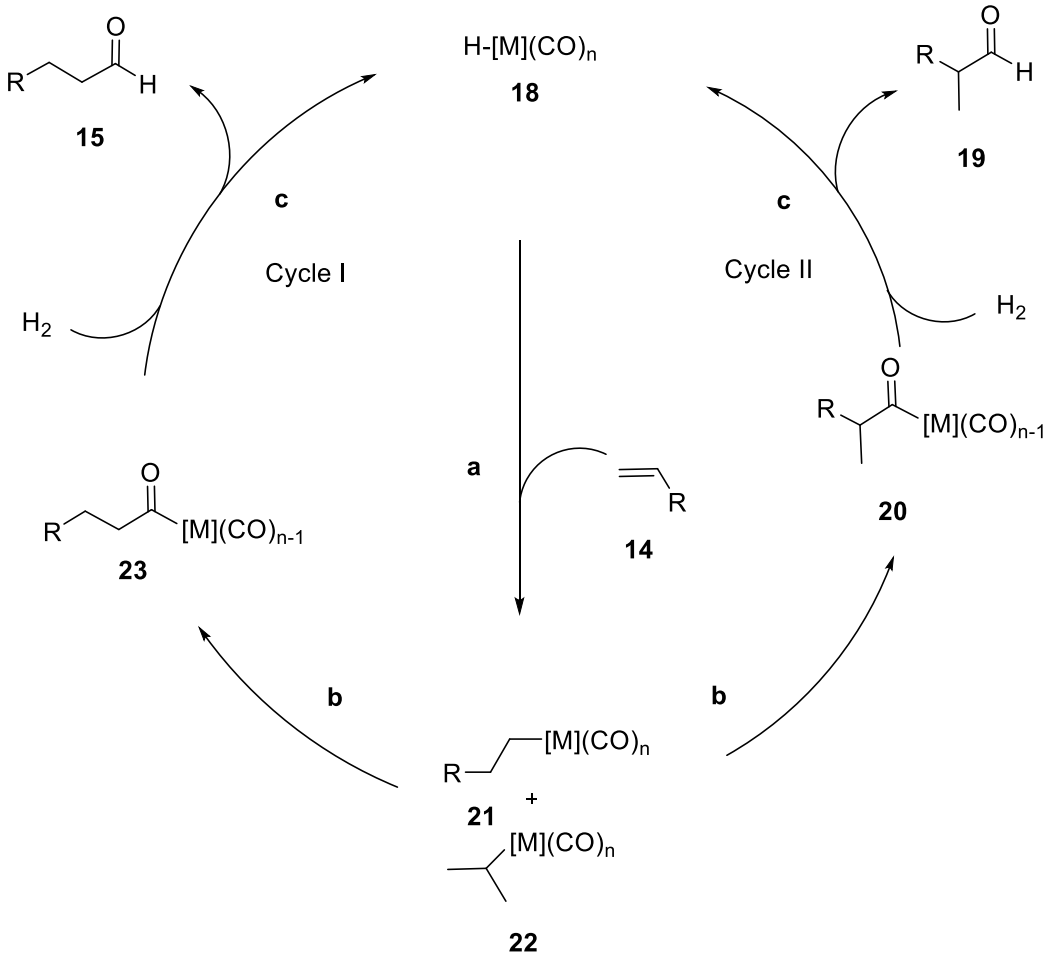
$$Rh >> Co > Ir > Ru > Os \sim Tc > Pt > Pd > Mn > Fe > Ni >> Re$$

The first generation of hydroformylation processes, where cobalt metal complexes were used, was developed by BASF and ICI companies, and in the 1950s the phosphine-modified catalyst system was scaled up for the synthesis of detergent alcohols. Cobalt metal complexes are still widely used, especially for mid-and long-chained alkenes, for example $[HCo(CO)_4]$ and $[HCo\text{-}(CO)_3PR_3]$ are common cobalt catalysts. Still, cobalt complexes have quite poor chemo- and regioselectivity in the hydroformylation reactions, and undesired side products such as alkanes, can be easily formed. This led to the development of Rh-based complexes, in 1965 Wilkinson[17] introduced the new catalyst, $[RhCl(PPh_3)_3]$, which showed excellent chemo- and regioselectivity. The advent of the Wilkinson's catalyst inspired the development of more active Rh -based catalysts, which make a big part of modern catalysts used for the short-chain alkene hydroformylation processes. Typically, organic ligands such as phosphites and phosphine, are used with Rh catalysts. The use of Rh-based complexes

makes a great advantage for the industry because the hydroformylation processes can be performed under much lower pressure, compared with Co-based complexes. [16,18]

A simple catalytic cycle for hydroformylation reaction can be described in few steps (Scheme 3). In step **a** in the mechanism, the metal-alkyl complex **21/22** (linear/branched) forms by addition of the M-H bond to the alkene **14**. In step **b**, the CO ligand migrates and subsequently integrates into the M-alkyl bond, which forms products **23/20**. In step **c**, finally, the product aldehyde **15/19** is released, and the catalyst **18** is reconstructed by hydrogenolysis of the M-alkyl bond. The mechanism is divided into two cycles, in Cycle I the formation of linear aldehyde is presented, and in Cycle II there is the formation of branched aldehyde. The formation of two isomers of aldehyde **15/19** is related to the formation of different M-alkyl complexes **21/22**, which are momentary intermediates. [11]

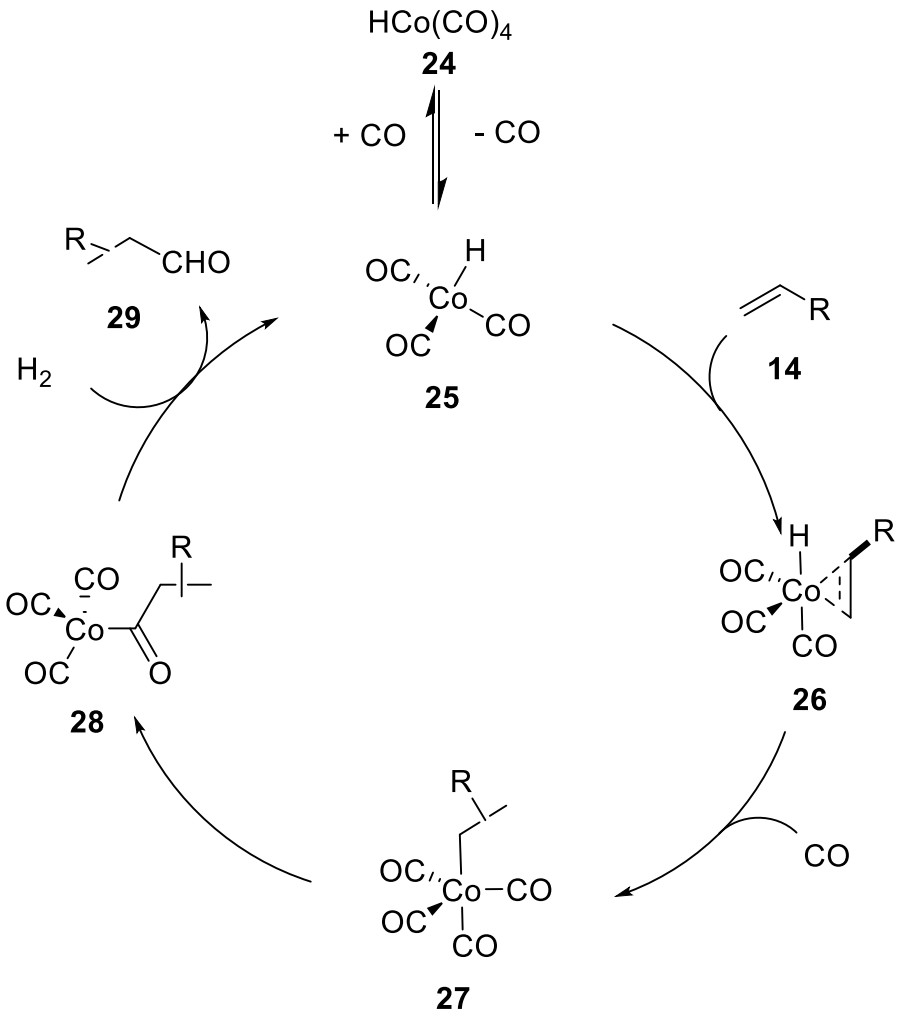
It is quite important to choose appropriate metal complexes and ligands when performing the hydroformylation reaction, for crucial steps and intermediates of the cycle to take place. Proper reaction conditions are also important. It is thought, that the hydroformylation activity of metal carbonyl complexes relates to the polarity of the M-H bond in the complex[19]. The addition to the alkene, as well as the hydrogenolysis of the M-alkyl bond, can be facilitated by the high acidity. [11]



Scheme 3. A simplified catalytic cycle of hydroformylation reaction[11]

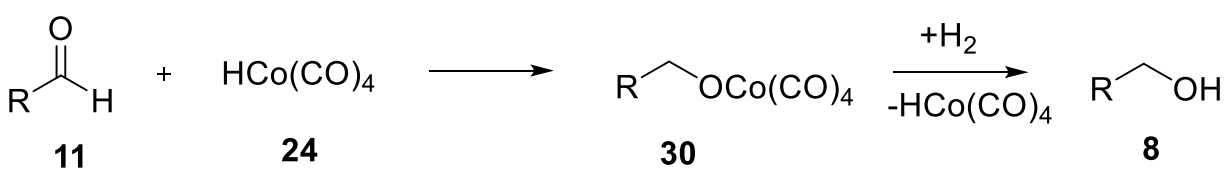
3.1.1 Cobalt-catalysed hydroformylation reaction

The original mechanism for cobalt-catalysed hydroformylation reaction was presented by Heck and Breslow[20] in the 1961, and it is still considered valid in many modern kinds of research (Scheme 4). In the mechanism, there is used the originally developed Co-based catalyst, $HCo(CO)_4$ **24**, which is unmodified. The mechanism starts with CO loss from the original catalyst **24**, resulting in catalytically active 16 e^- $HCo(CO)_3$ **25**. Then the alkene **14** coordinates to this active catalyst, and two isomeric Co-alkyl complexes **26** are formed, the branched Co-alkyl complex leads to branched, or *iso*-aldehyde in the alternative pathway of the mechanism, and linear complex leads to linear, or *n*-aldehyde **29**, respectively. In the mechanism, only the formation of the linear isomer is shown. Side reaction to form alkane is also possible (not shown in the mechanism), which is caused by the fact, that the C-C bond in the alkyl complex can react with hydrogen in the hydrogenolysis reaction. [11]



Scheme 4. The mechanism for cobalt-catalysed hydroformylation reaction[18]

This reaction with the unmodified $HCo(CO)_4$ **24** catalyst must be performed under high pressure, even up to 100 bar of the total partial pressures, since there is a risk for the catalyst to decompose to cobalt metal. Therefore, when performing the reaction, the partial pressure of CO must be increased dramatically, as the temperature rises. [21,22] Furthermore, alcohol **8** can be produced from aldehyde **11** formed in the described catalytic process; aldehyde **11** undergoes addition to $HCo(CO)_4$ complex **24**, then the formation of the Co-complex **30** takes place, and it reacts with hydrogen (Scheme 5). [11]



Scheme 5. Formation of alcohols in Co-catalysed hydroformylation reaction[11]

After the hydroformylation reaction and the originally described unmodified Co-catalyst was developed, it was used under harsh conditions, in high pressure (almost 100 atm) and temperature (up to 80 °C). The biggest problem with this catalyst was very low selectivity (low l/b ratio) between linear and branched aldehydes formed in the reaction. This led to the development of modified Co-catalysts, where monodentate phosphine ligands were used with $HCo(CO)_3(PR)_3$ catalytic system, developed in the 1960s.[11] It is formed through salts $[Co(CO)_4]^+[Co(CO)_3P_2]$, which are in turn, formed by mixing an excess of the *P*-based ligand with $Co_2(CO)_8$. Those salts are converted through a dimer structure to active precatalysts $[HCo(CO)_3P]$, which are made with hydrogen or syngas. [11,22]

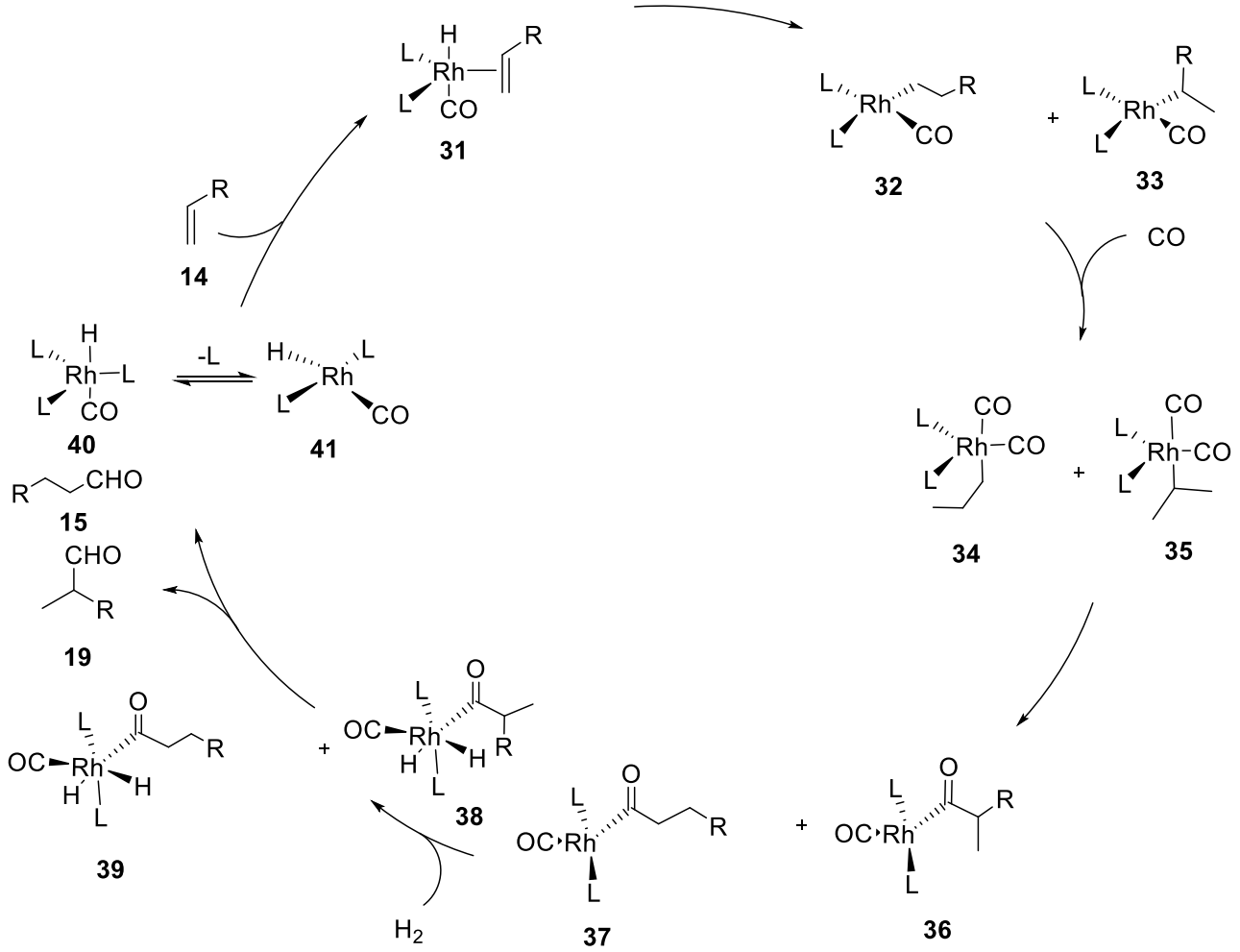
This modified $HCo(CO)_3(PR)_3$ system is more stable than $HCo(CO)_4$ since the electron-donating phosphine increases π – back bonding to carbonyl ligands. That allows its use under much lower pressures than with unmodified catalysts.[22] Phosphine modified cobalt catalysts also have high regioselectivity towards linear aldehydes, because ligands around the cobalt coordination cause larger steric demand, which leads to the different orientation of the alkene insertion into the Co-H bond. Nevertheless, these modified catalysts have some problems. The activity of the catalysts decreases by the cause of modification, which leads to competition between isomerization and hydrogenation reactions, and to the need of using higher reaction temperatures and high catalyst concentrations. These problems have led to the use of the Rh-based catalyst, which is the most used catalyst in the hydroformylation reaction in modern industry and research. [11]

Nevertheless, modern researchers are developing new ways for using Co-based catalysts. For example, recently cationic cobalt (II) biphosphine hydrido-carbonyl catalyst, has been reported.[22] It has shown to be far more active, than the traditional Co (I)-based catalysts, and they even approach Rh-based catalysts in their activity in hydroformylation reaction.[22] Moreover, a Co-based catalyst with novel phosphine ligands has been described, with following $NaBH_4$ reduction to alcohol, producing mostly linear aldehydes in good yields. [23]

3.1.2 Rhodium-catalysed hydroformylation reaction

The catalytic cycle for the Rh-based hydroformylation reaction mechanism is supported by kinetic and spectroscopic evidence (Scheme 6). In the proposed cycle, L refers to a neutral monodentate ligand, which can be for example CO, TPPTS, PPh_3, or $P(OR)_3$. The mechanism begins, when the coordinatively unsaturated catalytic intermediate **31** is formed, by the ligand dissociation of the

precatalyst **40** or **41**. There are also two insertion steps, the first one where the alkene **14** inserts into the Rh-H bond of **40** or **41**, and the second step where the CO ligand inserts into the Rh-C bond of **32** or **33**. If the insertion follows the anti-Markovnikov pathway, the reaction is highly regioselective towards the linear isomer **15** of the product. The rate-determining step of the mechanism is generally the oxidative addition of dihydrogen. The concentration of the used ligand is thought to be inversely proportional to the rate of the hydroformylation reaction.[24]



Scheme 6. The catalytic cycle for Rh-based hydroformylation reaction[24]

As previously described, Rh is the most active metal used so far in the alkene hydroformylation reaction. Rh-based catalysts are found to be almost a thousand times more active, than Co-based catalysts.[15] Furthermore, when compared to Co-based catalysts, ligand modified Rh-based catalysts are more active than analogous unmodified catalysts. Ligand modified Rh-based catalysts used for

hydroformylation reaction are synthesized with the desired ligand, either with CO/H_2 or *in situ.* Typical metal catalyst precursors include, for example, $Rh(OAc)_3$, $RhCl_3{\cdot}(H_2O)_x$, and $Rh(acac)(CO)_2$, with the latter being the most used in laboratory-scale due to its stability and facility to handle.[15,25] The unmodified Rh-based catalysts have been, due to their minor activity, much less widely used, than the corresponding phosphorus liganded modified catalysts. But still, some unmodified catalyst precursors are still a worthy theme for research, such as $[Rh\ (COD)(OAc)]_2$ and $Rh_4(CO)_{12}$.[26] This is must probably due to several advantages for the unmodified catalysts, such as their availability, well-known properties, and rather easiness of handling. Hydroformylation using unmodified Rh – catalysts can be carried out under very mild reaction conditions, some of the catalysts are active even at room temperature.[26] It is found, that phosphites are more suitable ligands in the catalyst modifying process than phosphines since they are better π-acceptors. Thus, they facilitate CO dissociation in the catalytic cycle, which leads to a faster reaction rate. Though, the less basic phosphines also make reaction rates faster and give higher *l/b* ratios. [15]

Phosphorus modified Rh-based catalysts, used with low syngas pressure (1,8 – 6,0 MPa), and medium temperatures (85-130 ℃), are called low-pressure oxo-processes (LPOs). That kind of process is still utilized in many large companies and used preferably in the transformation of short unfunctionalized alkenes, such as ethene, propene, and butenes.[11] These processes make about 70 % of the total hydroformylation reaction capacity. Production of butanal from propene is one of the largest of the processes, which produce oxo-aldehydes. Other important industrial processes using Rh-based catalysts are, for example, the synthesis of 1,2 propanediol by hydroformylation reaction of vinyl acetate monomer (VAM) and the synthesis of an intermediate of vitamin A, 2-methyl-4-acetoxy butenal (MAB), by hydroformylation reaction of 1,4 diacetoxy-2-butene or 1,5 diacetoxy-2-butene. Moreover, the Kuraray technology should also be mentioned. This techlonogy, where 1,4 butanediol is synthesized by hydroformylation reaction of allyl alcohol, and subsequent hydrogenation of 2-hydroxytetrahydrofuran, the intermediate of the reaction. The technology has been commercialized by ARCO. [15]

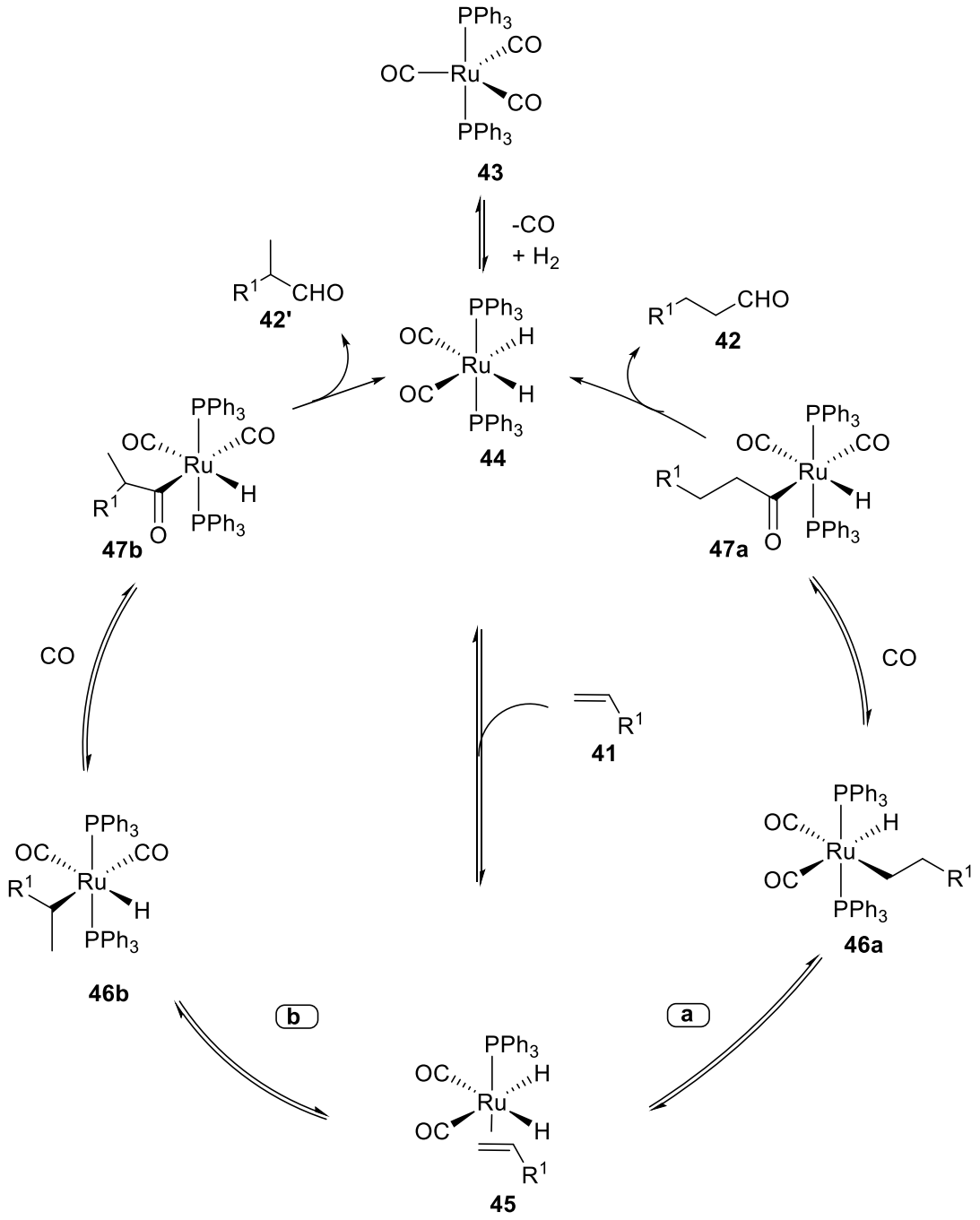
The main problem with Rh-based catalysts is their very high and volatile price, which leads to the need to avoid the losses of precious metal catalysts even in the ppm range. Therefore, it makes great importance and a challenge for the industry to be able to recycle the catalyst. This involves the recycling of both metal catalyst and ligand from the reaction mixture. [13,16]

3.1.3 Ruthenium-catalysed hydroformylation reaction

Rhodium has been the most preferred catalyst in hydroformylation reaction, due to its activity and technical success. Thus, because of the high demand for this metal catalyst, its originally high price has increased further, and this has led to the need for the development of alternative transition metal complexes for hydroformylation reaction.[18] Transition metal complexes, such as Ru, Fe, Ir, and Pd – based complexes can potentially catalyse the hydroformylation reaction. Among these, ruthenium complexes have been tested since the 1960s as potential catalysts, but they have shown relatively low activity, especially compared to rhodium. Despite this, $Ru_3(CO)_{12}$ has been studied as a catalyst for hydroformylation reaction of propene, 1,3 dienes, and 1-hexene, for instance. However, the results of these investigations were more applicable to qualitative scale of a research laboratory.[18,27] Despite this, the group of Beller was first to develop successful ruthenium-based catalytic systems, which give linear aldehydes from alkenes with high yields (80 %) and regioselectivity (<95 %), with the use of imidazole-substituted phosphine ligands.[28,29]

The same reaction mechanism has been proposed in different studies for several different Ru-based catalytic complexes, such as $[Ru(edta)(H_2O)]^-$, $[Ru_3H(CO)_{11}]^-$, and also for well-defined complex $[Ru(CO)_3(PPh_3)_2]$, which was first developed by Wilkinson and co-workers in 1965.[30] This phosphine-based catalyst is found to be capable of catalysing the hydroformylation reaction of 1-pentene to aldehydes, as well as pentene to alcohols. For this catalytic complex, a reaction mechanism has been proposed by Wilkinson. (Scheme 7). [18,30]

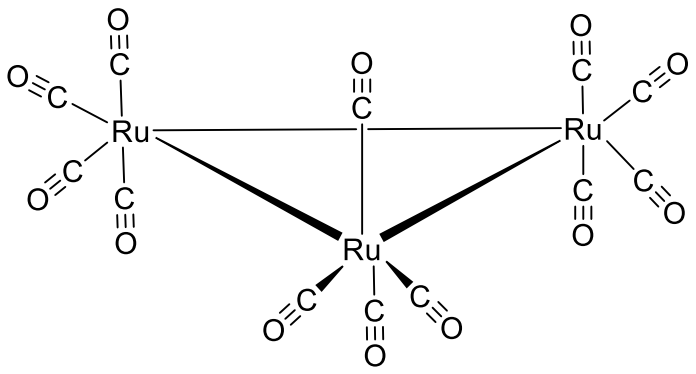
The rate-determining step of the reaction mechanism seems to be oxidative addition of hydrogen to metal complex center, which is followed by dissociation of one carbonyl ligand. [30] Then phosphine complex dissociates also, enabling the formation of the π-complex **45** by alkene (**41)** coordination. Subsequently, CO inserts into the metal-alkyl bond, which leads to the formation of acyl species **47**. Then the desired product is formed, and the active complex **44** regenerates, which is a result of a transfer of the second hydrogen atom. The electron density in the metal complex center grows, and the polarization of the M-H bond enforces when phosphine ligands are coordinated.[18,30] The increasing polarization favors anti-Markovnikov addition, which in turn, leads to increased *n*-selectivity (path **a**). Therefore, the formation of the linear alkyl complex **46a** is favored, because of the steric and electronic effects of the phosphine ligand. The conversion of **46** to **47** is the CO migration step, which can be assisted by the excess of CO, occurs significantly faster than the competitive elimination of β-hydride. Hence, with the use of $[Ru(CO)_3(PPh_3)_2]$ complex, the alkene isomerization was on the minimum level. [18,30]



Scheme 7. Proposed catalytic cycle for $[Ru(CO)_3(PPh_3)_2]$-based hydroformylation reaction.[30]

Nowadays, the most commonly used Ru-based catalyst complex in hydroformylation reaction is $Ru_3(CO)_{12}$ **48** (Figure 2). However, several unmodified ruthenium complexes have been also tested, and oxidation states Ru(0), Ru(II), and Ru(III) have all found to be suitable. Modification of the catalyst, by replacing CO ligand with nitrogen or phosphorus ligands, for example, allows modification of the essential properties of the central metal. Moreover, organic ligands may prevent

the high activity of Ru-complexes towards the hydrogenation of alkenes. Besides, unmodified Ru-complexes also tend to isomerize alkenes used as substrates, which is not always desirable. [11]



48

Figure 2. Triruthenium dodecacarbonyl ($Ru_3(CO)_{12}$) **48**

Ru-complexes also have a tendency to act as catalysts in the reduction of aldehydes. The reducing activity may be enhanced using *N*- or *P*-based ligands (Figure 3). Typically used *N*-ligands are, for instance, pyridine 4**9**, 2,2'-bipyridine **50**, 2,2'-bipyrimidine **51,** 1,10'-phenanthroline **52,** and saturated cyclic amines (**53**). In addition to *N*-based ligands, also trivalent PPh_3 ligands have been used, as well as imidazole-substituted dialkyl phosphines **54, 55,** and **56**, bulky diphosphines, such as bis(dicyclohexylphosphino)methane **56** and bis[bis(pentafluorophenyl)phosphino]ethane **58**.[11] Apart from PPh_3, which has been shown to even diminish the activity of Ru-catalyst, *P*-based ligands lead to increased activity of Ru-catalysts, producing aldehydes in high yields, and achieving good chemo- and regioselectivity. In particular, the use of Xantphos-ligand **59** has been reported to lead to excellent *l/b* selectivity. Generally, bidentate phosphine ligands seem to give higher yields of aldehydes, than monodentate ligands.[28,31]

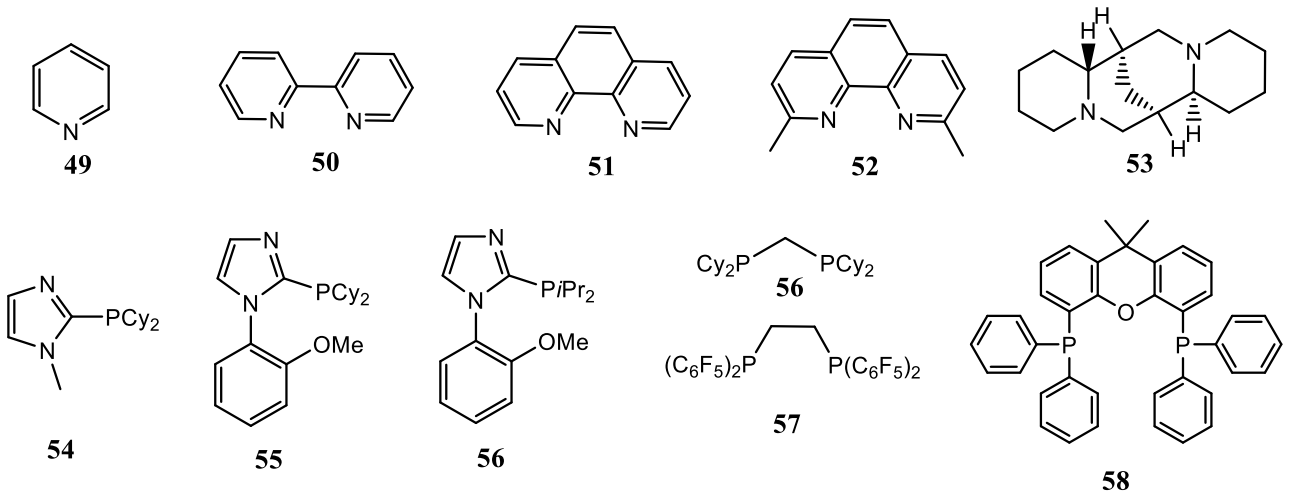
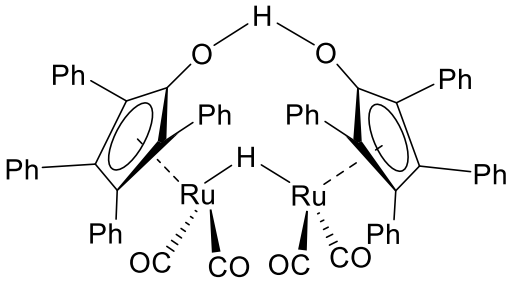


Figure 3. Phosphorus and nitrogen ligands that are suitable for Ru-based hydroformylation reaction.[11]

Aldehydes formed in conventional hydroformylation reaction can be also converted to other valuable chemicals, such as alcohols, by tandem or domino reactions, where hydroformylation reaction acts as the first step. As previously mentioned, Ru-catalysts possess the activity for hydrogenation. Often this hydrogenation takes place with the alkene, which is undesirable. But this hydrogenation tendency can also be used for aldehyde hydrogenation, which can be the aim of the study.[11] Hence, Bell and co-workers showed using $RuCl_2(PPh3)_3$ as the catalyst, that both hydroformylation reaction and product aldehyde hydrogenation is possible using the same Ru-catalyst in a one-pot sequence.[32] In 2013, Beller and co-workers demonstrated the conversion of many cyclic and acyclic alkenes to primary alcohols using imidazole substituted dialkyl phosphine **13** and $Ru_3(CO)_{12}$ as the catalyst, with alcohol yields up to 99 %. Interestingly, the best results were obtained using linear α-alkenes, but also styrene gave good yields for alcohol. [29]

Interestingly, a novel Ru-Rh catalyst system $[Rh(CO)_2(acac)]$/Shvo-complex **60** has been recently reported (Figure 4), which successfully converts different alkenes, aromatic and aliphatic, to mainly linear alcohols. Noteworthy, also tetrasubstituted alkenes, that don't have so active internal C-C double bond, can be converted to corresponding alcohol, for example, 2,3-dimethyl-but-2-ene, with 90 % yield of the corresponding *n*-alcohol. [33]



60

Figure 4. Shvo's catalyst **60**

3.1.4 Properties of organic ligands

With the use of different organic ligands, it is possible to modify the catalytic properties of a metal complex used in hydroformylation reaction. Ligands can drastically affect not only the reactivity of the catalyst but also its stereo-, chemo- and regioselective properties. Sometimes, ligands are even named as co-catalysts, since their concentration towards the metal and electronic and steric construction is pivotal for the hydroformylation reaction to succeed. The whole catalytic cycle of the reaction can be either blocked or accelerated, because of the properties of the ligands used. Different reactions can be favored, side reactions, or consecutive. In particular, when the cobalt catalyst is modified with phosphines, its thermal stability is improved, but activity in hydroformylation reaction is decreased. Moreover, the undesired direct hydrogenation of an alkene becomes favored. Furthermore, phosphine modified rhodium catalysts improve the thermal stability, but, in contrast to cobalt catalysts, they also drastically increase the rate of hydroformylation reaction. In particular, the use of trialkylphosphines with rhodium results in alcohol formation as the main product of hydroformylation reaction. [11]

Only trivalent phosphorus compounds are used for rhodium and cobalt-based catalysts, in industrial applications. Although several other coordinating elements, such as N, As, Sb, and Bi, have been proposed to act as suitable ligands. Compared to phosphorus-based ligands, their activity in the hydroformylation reaction decreases in the order of Ph_3P >> Ph_3N > Ph_3As, Ph_3Sb > Ph_3Bi.[13] Phosphines, which are also called phosphanes, can be usually characterized as central phosphorus atom, which is surrounded by three carbon atoms (Figure 5). There are only a few exceptions, such as primary or secondary phosphines, or *P*-heterocycles. [11,13]

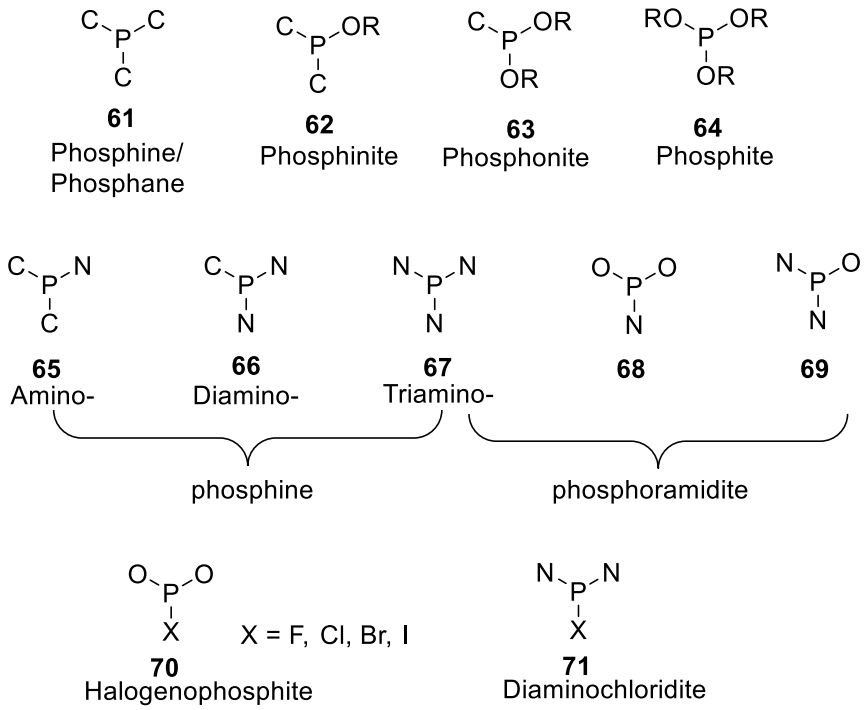


Figure 5. The trivalent P-ligands are classified by the nature of α-atom next to the phosphorus.[13]

As shown in Figure 5, phosphinites (**62)**, or esters of phosphinous acids, are formed when one C-substituent in phosphines (**61)** is replaced by an oxy-group. When phosphinites are substituted with alcohol, phosphonites (**63)**, or esters of phosphonous acid, and phosphites (**64**), or esters of phosphorus acid, are formed. Besides, *N*-substituents can be incorporated stepwise, forming amino (**65**)- diamino (**66**)- or triaminophosphines (**67**). Moreover, different heteroatoms can be combined, which forms additional variations, e.g. (**70**). [11,13]

As discussed in Section 3.1.1, the activity of cobalt complexes is reduced, when they are modified with phosphorus ligands. Within those trivalent ligands, only phosphines can be used, when the product aldehyde is desired, because Co-catalyst has a high reductive potential, and can thus form alcohols from aldehydes.[13] When there is an excess of product alcohol, transesterification can occur with ligands with P-N or P-O bond. Among *P*-ligands used in rhodium catalysts, the use of phosphites leads to higher reaction rates, since they force CO dissociation within the catalytic cycle. This can be explained by the fact, that phosphites are better π-acceptors than phosphines. [11,13]

For the hydroformylation reaction to proceed with maximum practicality and effeciency, the regio- and enantioselectivities must be controlled, so that only one desired isomer would form. Besides, the catalyst system must be optimized, so that mild reaction conditions would be enough for substituted and thus sterically hindered alkenes to be functionalized. These tasks can be achieved by careful

design of the ligands. This theme has been studied carefully, and new catalytic systems are developed, for successful linear or branched selective hydroformylation reaction for internal and terminal alkenes when both regio- and enantioselectivity are controlled. There are several ways to confirm the effectiveness of a ligand towards favoring only one isomer. First, the Tolman angle is used to determine the bulkiness of the coordinated ligand for monodentate ligands, and natural bite angle is used for the same thing for bidentate ligands (Figure 6). [15]

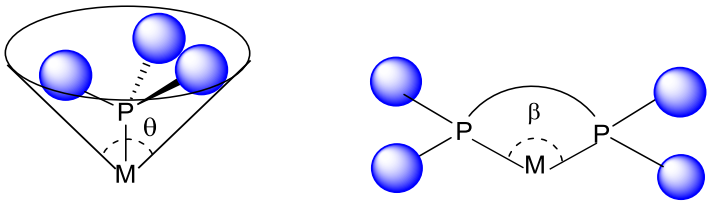


Figure 6. Tolman angle θ and natural bite angle β. [15]

Second, for bidentate P-ligands, their coordination ability is strongly affected by the stiffness of the space between the two phosphorus atoms. And finally, a ligand -metal coordination may occur in either equatorial-equatorial (*ee*) **72** or equatorial-axial (*ea*) **73** mode, which depends on the stiffness and bulkiness of the ligand (Figure 7). [15]

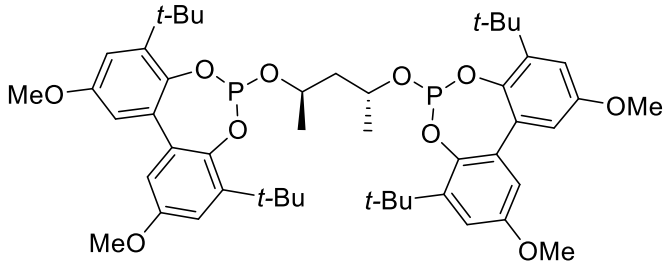
ee **72** *ea* **73**

Figure 7. Bis-equatorial(*ee*) **72** and equatorial–axial (*ea*) **73** coordination modes of bidentate ligands (L–L) in the$[HRh(CO)_2(L–L]$. [15]

Modifying Co and Rh metal complexes with ligands started with the use of PPh_3, and it has been widely used because it is quite inexpensive, accessible, and air-stable. Nevertheless, substantial progress has been made, and many new *P*-ligands have been developed, with various regioselective properties. In hydroformylation reaction, both alkenyl carbons can react, and hence, linear selective hydroformylation reaction can be achieved, when a ligand can orient the formyl group to the terminal position. For that target, bulky *P*-ligands, and bidentate *P*-ligands seem to be the most appropriate,

since they are sterically hindered, and thus reduce the access toward the metal atom. As previously mentioned, the natural bite angle is a concept, applied for measuring the degree of congestion around the metal atom for the bidentate *P*-ligands. The steric hindrance of *P*-ligand increases when the natural bite angle increases.[13] The steric hindrance between phosphorus substituents and the alkenyl substrate is an explanation for the formation of linear alkyl intermediates. Besides, linear selective hydroformylation reaction is favored, when the chelating *P*-ligand is coordinated in a bis-equatorial (*ee*) manner. Furthermore, besides the steric effect induced by large natural bite angle, there is also an electronic effect, which is supported by general observation, that bidentate *P*-ligand favors or disfavors electronically certain geometries of transition metal intermediates. Biphephos and Xantphos – ligands have hegemony in most linear selective applications.[13,15,34,35] However, successful use of the Rh/Yantphos system in linear selective hydroformylation reaction, with *ee* (enantiomeric excess) from 90 % to 99 % towards linear aldehydes has been reported recently. Yantphos is a family of phosphine-amidophosphite chiral bidentate ligands. [36]

The synthesis of fine chemicals can be performed using branched-selective hydroformylation reaction. For instance, 2-aryl-propionic acid drugs, such as (*S*)-naproxen, can be synthesized via Rh-based hydroformylation reaction using biphosphite ligand (2*R*, 4*R*) – chiraphite **74** (Figure 8). [37] Since then, many other ligands have been developed for the enantioselective and regioselective approach to fine chemicals, to enlarge the scope of substrates. For example, there are many important chemicals, the synthesis of which requires branched selective hydroformylation reaction of the terminal alkene. *Iso*-butanal is proposed to be one of the most industrially important chemicals, the global demand for it approached 0,5 million tonnes in 2014. It can be branched-selectively synthesized from propene with Rh-based hydroformylation reaction, using bidentate phospholane-phosphite system **75** (also referred to as BOBPHOS, Figure 8). With that system, also, for example, 1-hexene can be effectively converted to corresponding *iso*-aldehyde, although it normally reacts to give mainly the *n*-aldehyde. [15,38]



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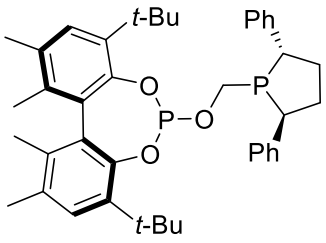


75

Figure 8. Biphosphite ligand (2*R*, 4*R*) – chiraphite **74** and bidentate phospholane-phosphite system (BOBPHOS) **75**. [15]

Generally, monodentate phosphines have been observed to be poorly enantioselective, which has shown the necessity of the use of multidentate ligands. Besides, at least as the substrate is coordinated to the metal complex, the rigidity and bulkiness of the ligand are not as important in branched selective hydroformylation reaction, as it is in linear selective hydroformylation reaction. Moreover, branched selective hydroformylation reaction requires ligands with lower natural bite angle and/or more adaptable ligands. [15]

3.2. Hydroformylation reactions of alkenes

When speaking about bulk chemical processes, unfunctionalized alkenes are most used as substrates for hydroformylation reaction, with various chain lengths. However, also functionalized alkenes make interest as substrates.[11,39] Generally, double C-C bonds of internal alkenes react slower in hydroformylation reaction, than bonds of terminal alkenes. Therefore, when the steric hindrance of the substrate increases, the rate of hydroformylation reaction goes down (Figure 9). This observation is found to be independent of the metal complex used, Rh or Co-based. [13,39]

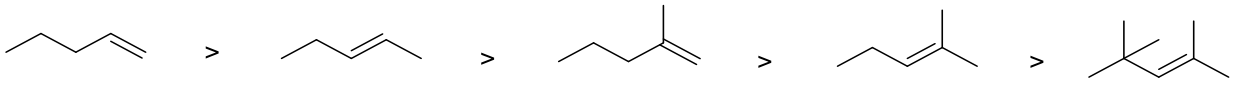


Figure 9. The rate of hydroformylation reaction decreases when the steric hindrance of the substrate grows.[13]

The hydroformylation reaction of branched alkenes usually requires either a more active catalyst or more severe reaction conditions. According to Keulemans' rule, the hydroformylation reaction of sp^2-configured and triply substituted C-atoms is not favorable.[40] Exceptions to this rule are possible, but only for alkenes, which have neighboring activating groups, such as ester or hydroxyl groups. Those groups allow chelation of the substrate to the metal complex center. Besides, the "normal" regioselectivity of the hydroformylation reaction of alkene may be altered because of its functional groups, which is due to an electronic effect. Styrene is a good example of that, which produces mainly branched aldehydes in hydroformylation reaction. [13]

The original structure of the substrate may be changed by the migration of the double bond. For example, it was observed, that before hydroformylation reaction, 1-octene can be immediately transformed into *cis*- and *trans*-2-octene, in the presence of a small amount of Rh diphosphite catalyst.[41] Usually, a mixture of alkenes isomers is used as feedstock in bulk industrial processes since the use of pure alkenes is not affordable. Thus, the hydroformylation reaction of dimerized butene, trimerized 2-butene, and di-and tricyclopentadiene, which reacted as a mixture, has been reported.[42] Besides terminal alkenes, also branched and internal substrates are present in mixtures of acyclic alkenes. Therefore, promoting isomerization before hydroformylation reaction may be desirable if the desired product is a terminal or linear aldehyde. This is the case when the substrate alkene is not terminal. The success of this reaction depends on the choice of suitable reaction conditions, metal catalyst, and ligand, which can be for instance Rh catalyst based on sterically demanding bidentate ligands. If, on the other hand, the desired product is branched, it may be achieved by using a catalyst with a low tendency towards isomerization, and high activity towards hydroformylation reaction, together with an internal alkene. [11,13]

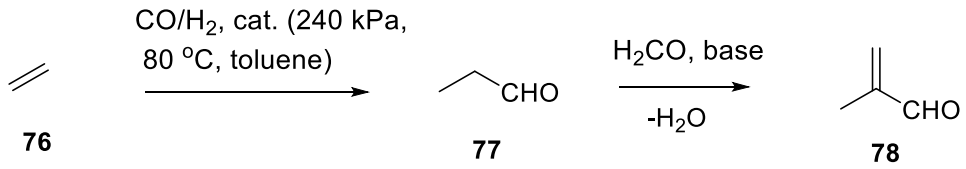
3.2.1 Unfunctionalized alkenes, dienes, and alkynes

Ethene, propene, isomeric butenes, octenes, and alkenes with chain length up to C_{18} are the most important unfunctionalized acyclic alkenes used in the industry for the hydroformylation reaction. Generally, oxo products formed in the hydroformylation reaction of these unfunctionalized alkenes can be divided into short-chain (C_3, C_4), medium-chain (C_5-C_{12}) and long-chain (C_{13}-C_{19}) products. [11]

For hydroformylation reaction of ethene to produce propanal, rhodium-based catalysts have been preferentially used. This process has been studied in gas-phase using metal complexes, which are supported on inorganic or organic surfaces. CO hydrogenation may be a potential undesired side-

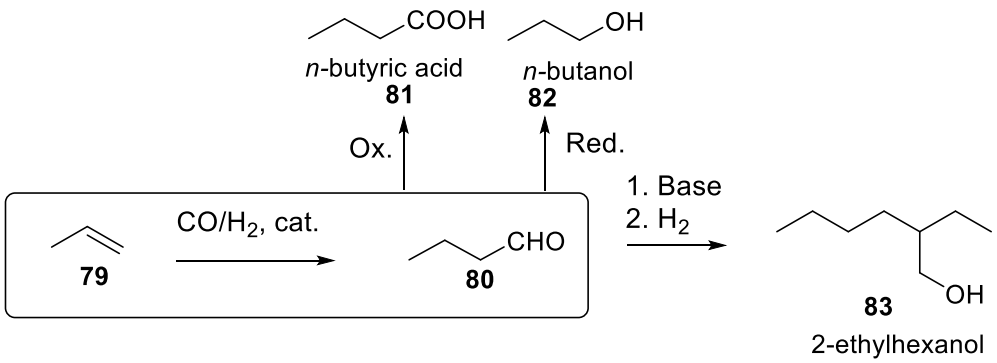
reaction, resulting in the production of C_2 oxygenates and methanol. Moreover, alkyne impurities can make another difficulty, which can be however overcome using homogeneous rhodium catalysts, such as the Wilkinson complex [$RhCl(PPh_3)_3$].[11,13] Besides, homogeneous rhodium catalysts or rhodium nanoparticles have been used either in ionic liquids ([BMIM][BF_4])[43], or in supercritical carbon dioxide.[44]

Industrially important reaction, which involves hydroformylation reaction of ethene **76** to form propanal **77**, and its linear form subsequently undergo aldol reaction with formaldehyde to produce methacrolein **78**, is patented by BASF (Scheme 8).[13] An aqueous two-phase system may be also used in proceeding tandem hydroformylation/aldol condensation reaction.[45] Besides, a possibility of hydroformylation reaction of ethene-containing gas mixtures in the presence of the rhodium-phosphine catalyst, with conversion to propanal up to 99 % has been reported recently. [46]



Scheme 8. Production of methacrolein via hydroformylation reaction of ethene. [13]

The products of hydroformylation reaction of propene are linear and branched butanal, from which the linear butanal **79** is used as a precursor for many industrially important chemicals, such as 2-ethylhexanol **82** (Scheme 9), very used plasticizer alcohol, and butanol **82**, widely used for producing pharmaceuticals, pyroxylin plastics, and polymers. In particular, the production of *n*-butanal makes over 50 % of the consumption of all oxo-aldehydes. Important products derived from it are *n*-butanol and *n*-butyric acid (Scheme 9). [11,47]

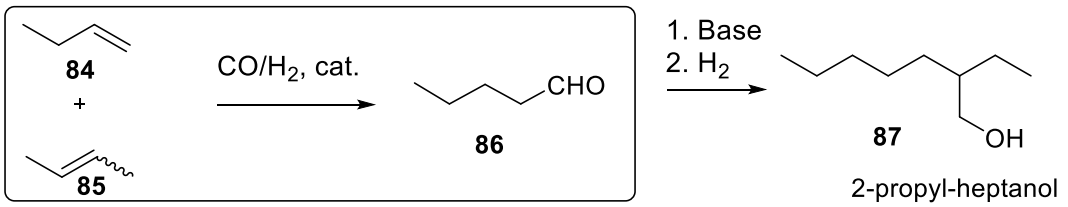


Scheme 9. *n*-Butanol **82**, *n*-butyric acid **81**, and 2-ethylhexanol **83** are important products derived from *n*-selective propene **79** hydroformylation reaction [11]

Rh-based catalysts are preferentially used for propene hydroformylation reaction, due to their good regioselectivity, high activity, and allowing mild reaction conditions. For the hydroformylation reaction of propene, there are two main Rh-based commercial process pathways, that are currently dominating the industry: the aqueous biphasic oxo process (Ruhrchemie/Rhone Poulenc process), and homogeneous low-pressure oxo-process (LP Oxo^{SM}). [11] In the biphasic process, the catalyst is dissolved in the aqueous phase, while organic and nonpolar reactants and the products remain in separate, immiscible phase. To avoid the expensive separation of the catalyst and the products, water-soluble trisodium 2,2',3-phosphinetriyltribenzenesulfonate (TPPTS) is used as a ligand. The homogeneous oxo-process is one of the most important oxo-processes in the world, where butanal is produced using triphenylphosphine (TPP)-rhodium complexes. Bis-phosphite-modified rhodium catalysts have also been developed for these processes, because of their highly regioselectivity and activity. Conventionally, polymer-grade propene, which is up to 99,5 % purity, is used for that process. [11] However, recently it has been shown, that also refinery-grade propene with 60-70 % purity, a mixture with propane, can be used for hydroformylation reaction of propene. This process occurs in propane-expanded liquid (PXL), and it has been indicated to be a more sustainable and greener process for butyraldehyde production, than the conventional process. [47]

From the hydroformylation reaction of linear butenes **84-85**, such important products as *n*-pentanal and *iso*-pentanal are produced. The *n*-pentanal **86** can act as a precursor for 2-propylheptanol **87**, which is produced by aldol condensation and subsequent hydrogenation of the aldehyde (Scheme 10). Both 2-ethylhexanol and 2-propylheptanol are also used as important precursors for plasticizers.[13]There are several studies for producing *n*-pentanal in a regioselective way, one successful example of that is Rh(acac)$(CO)_2$ catalysed hydroformylation reaction of 1-butene with an excess of *N*-pyrrolylphosphine ligands, which produces the corresponding aldehyde with high

regioselectivity. The importance of producing *iso*-pentanal by hydroformylation reaction is economically minor, however, the use of calixarene based diphosphines as ligands has been suggested. [48]

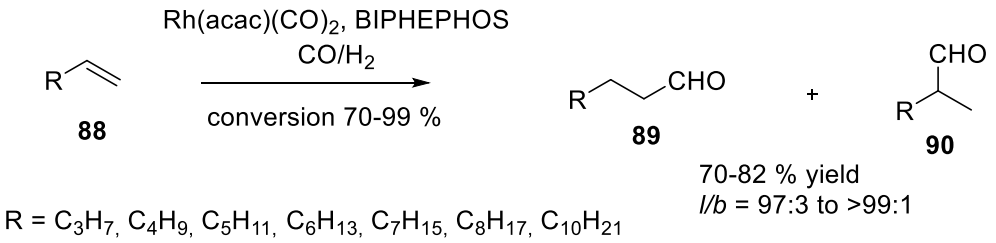


Scheme 10. 2-Propyl-heptanol **86** is one of the important products derived from the *n*-selective butene hydroformylation reaction.[11]

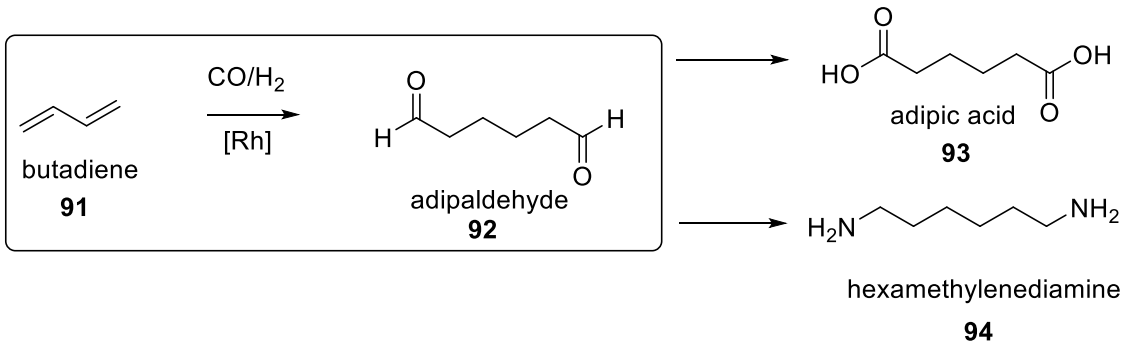
Many long-chain alkenes, such as octene, decene, and especially hexene have been used as substrates in different studies, that investigated the properties of different catalytic systems and ligands.[11] As an example, Kragl and co-workers investigated rhodium-based hydroformylation reaction with the use of BIPHEPHOS ligand and used long-chained alkenes from 1-pentene to 1-dodecene (Scheme 11). Excellent conversion of alkenes to corresponding aldehydes and regioselectivity towards *n*-aldehydes was achieved in this study. [49] Besides, recently, Liu and co-workers investigated $HRh(CO)(TPPTS)_3$ – catalysed hydroformylation reaction of different long-chain alkenes (**88)**, from 1-hexene to 1-dodecene. The use of methanol CH_3OH in the reaction makes the reaction proceed homogeneously. The conversions of the aldehydes (**89**) from long-chained alkenes reached 97,6 %. [50]

The hydroformylation reaction of conjugated dienes offers an excellent potential opportunity for the synthesis of many important branched chemicals. For example, 1,3-butadiene, 1,3-pentadiene, and 2-methyl-1,3-butadiene can act as substrates for the synthesis of commodity products. Moreover, the fragrance industry has an interest in generating aldehydes, which can be possible by hydroformylation reaction of 1,3-diene moieties of natural products. However, the hydroformylation reaction of conjugated dienes occurs much slower, than with alkenes, and is very difficult to achieve, and also it shows poor regioselectivity. Good reaction rates require high ligand concentrations, unusually high pressure, or temperature.[11,51] For example, hydroformylation of 1,3-butadiene **91** to give adipaldehyde **92** has shown to proceed with two separate steps. First, the hydroformylation reaction of butadiene gives monoaldehyde (4-pentenal), and second, the hydroformylation reaction of monoaldehyde gives adipaldehyde. These reactions proceed with several competing reactions.

Adipaldehyde can act as a substrate to such valuable chemicals, as hexamethylenediamine **94** and adipic acid **93** (Scheme 12). [52]

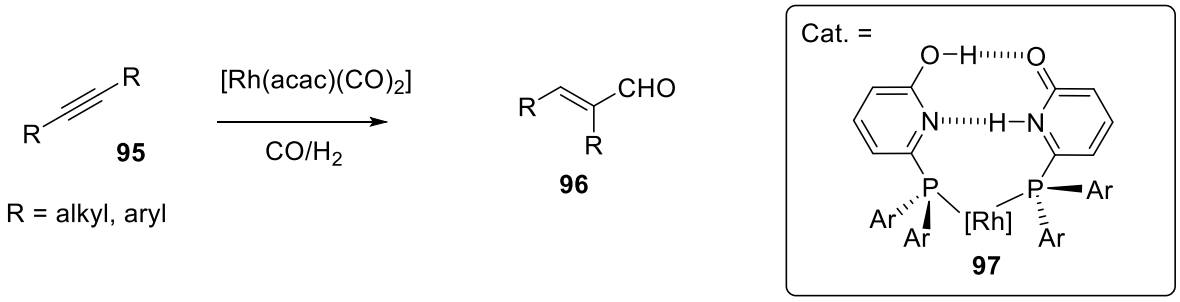


Scheme 11. *n*-Regioselective hydroformylation reaction of different alkenes using Rh(BIPHEPHOS).[49]



Scheme 12. Preparation of commodity chemicals such as adipic acid and hexamethylenediamine from butadiene.[52]

The hydroformylation reaction of alkynes is one of the most effective ways of producing α, β – unsaturated aldehydes. Those aldehydes are pivotal in the preparation of fine chemicals, pharmaceuticals, agrochemicals, and biologically active molecules. Several groups have reported different catalytic systems for alkyne hydroformylation reaction. For example, Breit and co-workers discovered, that unfunctionalized alkynes (**95**) can be effectively hydroformylated to aldehydes (**96**) with rhodium catalysts (**97**) modified with self-assembling ligands, with the yield as high as 93 % (Scheme 13). [53]



Scheme 13. Hydroformylation reaction of alkynes with a self-assembling Rh catalyst.[11,53]

Despite the success, the hydroformylation reaction of alkynes can be described as far more difficult, than the hydroformylation reaction of alkenes. It is challenging to control the regioselectivity of the reaction, and the formation of undesired by-products, such as saturated aldehydes and hydrogenated products of alkynes.[54]

3.2.2 α- and β-Functionalized alkenes

With the hydroformylation reaction of functionalized alkenes, it becomes possible to generate aldehydes with one or more functional groups. Those aldehydes can be used in the synthesis of different bulk chemicals, fragrances, and pharmaceuticals. Functional group or heteroatom may significantly affect the hydroformylation reaction, and it can thus differentiate from the reaction with unfunctionalized alkenes. Formation of stable metallacycles and electronic effects, which lead to the different stability of alkyl-rhodium intermediates, refer to these differences (Figure 10). The cleavage of the metallacycle often requires specific reaction conditions, such as high syngas pressure, which can also lead to hydrogenation of vinyl groups, which are conjugated with a carbonyl moiety. [11,55]

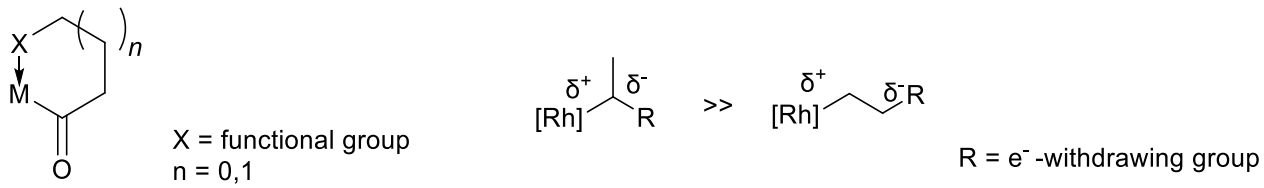
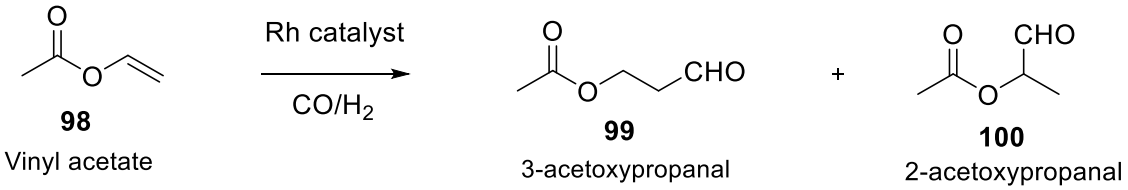


Figure 10. Functionalized alkene chelation during the formation of metal-acyl complex, and stability comparison of rhodium alkyl intermediates.[11]

α-Functionalized alkenes refer to alkenes, where heteroatoms, such as oxygen, nitrogen, halogen, or sulfur, are connected to the C=C double bond.[11] If the rhodium catalyst is unmodified, the formyl

group is incorporated in α-position, which is directed by a heteroatom. The consequence of that branched alkyl-rhodium intermediate is proposed to be more stabilized, than its linear isomer (Figure 9). Modifying the catalyst with a bulky ancillary organic ligand, which can coordinate to the active metal, is the way of avoiding this directing tendency. In the contrast, unmodified cobalt catalyst often directs the formyl group in the β-position of the product aldehyde. [26]

Several groups of α-functionalized alkenes have been hydroformylated in different studies, such as vinyl halogenides (e.g vinyl chloride), acyclic and cyclic vinyl ethers, vinyl acetates, vinyl carbonates, also vinyl amines, vinyl sulfoxides, and acrylic esters.[11] In particular, the hydroformylation reaction of vinyl acetate **98** with Rh – catalyst produces 3-acetoxypropanal **99**, and 2-acetoxypropanal **100** (Scheme 14). The first mentioned is widely used industrially for plasticizers and detergents, and its production exceeds 10 million tons each year. [56]



98
Vinyl acetate

99
3-acetoxypropanal

100
2-acetoxypropanal

Scheme 14. The Rh-based hydroformylation reaction of vinyl acetate.[56]

The hydroformylation reaction of functionalized allyl compounds, or β-functionalized alkenes, is affected by the nature of the functional group, as it is also for vinyl substrates. The dependence of regioselectivity for the allylic compounds by their functional group was tested using a rhodium catalyst modified by chiral bidentate phosphine-phosphoramidite ligand (Figure 11). It seems that electron-withdrawing groups have a stronger linear-regioselective effect. However, the functional group did not affect the enantioselectivities of the products. But in contrast to vinyl compounds, aldehydes which are produced by the hydroformylation reaction of β-functionalized alkenes, may participate in the further reaction employing their first functional group. Hence, for example, ring closure can occur. [11,57]

In general, allylic compounds may undergo double bond migration, and for that reason, they are quite challenging substrates for the hydroformylation reaction. Linear aldehydes are mostly predominant products; good examples are allylamines and allylbenzene. But also branched aldehydes have been

reported to form from allylic alcohol derivatives when substrate bounding catalyst-directing phosphine groups were used. [57]

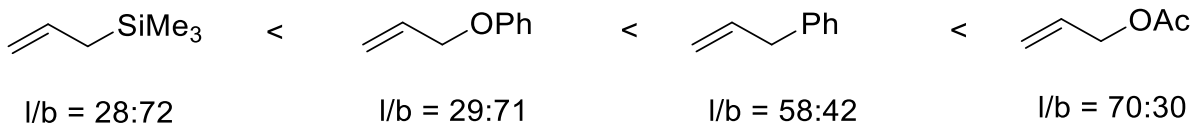
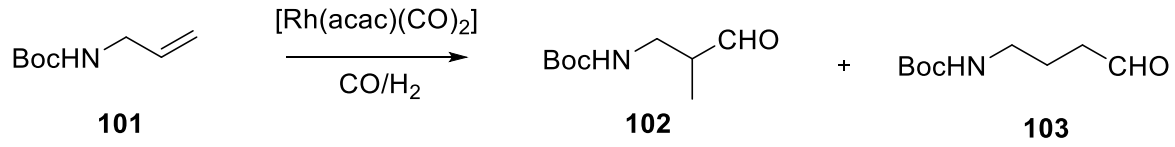


Figure 11. Dependence of the regioselectivities of allylic compounds on the functional group.[11,57]

Such groups of allylic substrates have been investigated for the hydroformylation reaction, as allyl and homoallyl alcohols, allyl ethers, allyl amides, and β, γ– unsaturated acetals. For example, the group of Zhang has successfully performed the hydroformylation reaction of *N*-allylamides **101** for the synthesis of b2-amino aldehydes **102** (Scheme 15). This kind of amino aldehyde is a key building block for the synthesis of natural product cyclamenol A **103**. [57]



Scheme 15. Asymmetric hydroformylation reaction of *N*-allylamide **101**.[57]

4. Ionic liquids are attractive solvents and promoters for hydroformylation reaction.

Generally, ionic liquids (ILs) can be defined as liquid electrolytes, which are entirely composed of ions. They are salts, which are typically based on a heterocyclic substituted cation, and with an organic or inorganic anion, and which exist at room temperature at liquid state. Since one or both the ions of the salt are large, the cation has a low degree of symmetry. Hence, the lattice energy of the salts crystalline form is reduced, and the melting point is lower. In these compounds, an anion, cation, or both can incorporate a covalently bound functional group and it thus makes a part of the ion structure. This functional group can modulate the ions with chemical or physical properties of the ions or to modify their reactivity. These parts, the anion, cation, and the substituent of either cation

or anion, of the IL, can be modified and altered, and thus, the physical properties of the IL can be tuned by the large diversity of different combinations of cationic and anionic components. Therefore, ILs are also commonly called “designer solvents”. [58,59]

Physical properties that may be altered, can be, for example, hydrophobicity, density, solubility, viscosity, and the melting point of an IL, and they can be tailored for each reaction, depending on the requirements. The miscibility of water in ILs is also an important property, which changes with the structure of IL. Different ILs can be synthesized with different combinations of ions, in an endless number of ways. Besides, the separation of the reaction products may proceed more easily with an IL used as a solvent, than with conventional solvents. ILs do not have detectable vapor pressure at ordinary conditions, and thus do not contribute any volatile organic compounds (VOCs) in the atmosphere. [58–60]

Because of those significant benefits, the use of ILs as solvents have been very attractive for different fields of chemistry, including catalysis, electrochemistry, electrocatalysis, synthetic chemistry, biocatalysis, chemical separation, chemical fixation of carbon dioxide, and metal extraction. Furthermore, ILs have been applied in such important homogeneous catalytic reactions, as hydrogenation, oxidation, Heck reaction, carbonylation, and hydroformylation reaction. The typical structures of IL cations **104-120** (on the left) and anions **121-140** (on the right) are presented in Figure 12. It is noteworthy, that the cations are organic, and have larger molecular volumes when anions have better geometric symmetry and are inorganic. [58,60]

Usually, ILs are classified by the most important functional group. Moreover, presently, a well-established division can be made, between protic ILs (PILs), which are proton donating, and aprotic ILs (AILs). Most used PILs include primary, secondary, or tertiary ammonium, mono- or di-imidazolium ions, triazolium and guanidinium, and the coupled anions, such as $[NO_3]^-$, $[NTf_2]^-$ and methylsulfate. However, also dicationic ILs have been characterized with one aprotic and one protic center, and thus with both functionalities. Hence, this classification cannot be considered ideal. Classification can be made also by the presence or absence of the stereogenic centers; to achiral ILs and chiral ILs. Furthermore, a new class of ILs can be identified, such as polymeric ILs with a polymerizable ion, magnetic ILs with a paramagnetic atom/group. solvate ILs, divalent ILs, and amino acid ILs, and aryl alkyl ILs, which are named from the functional groups, which are introduced on the ions. [60]

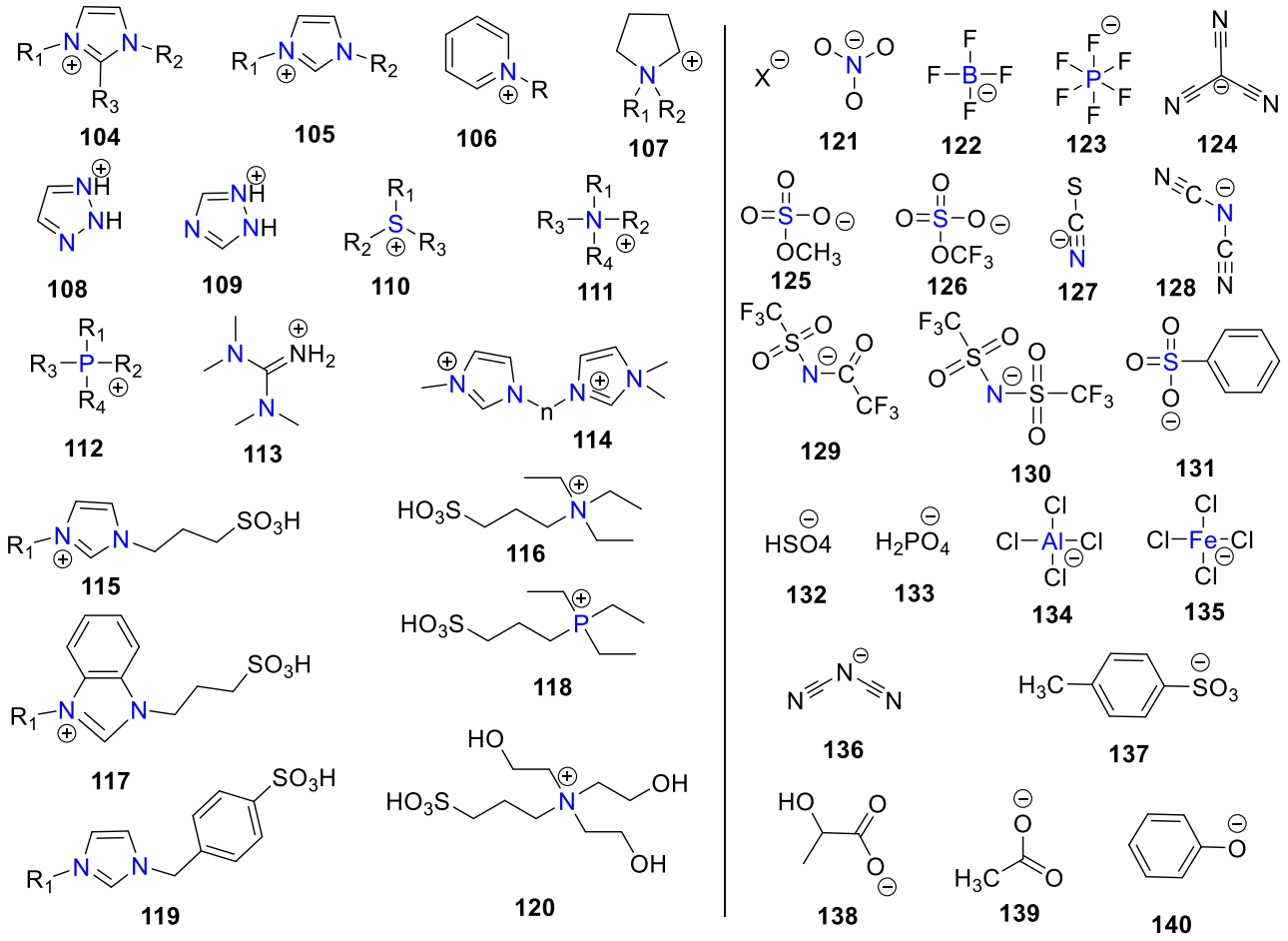


Figure 12. Chemical structures of typically used IL anions **121-140** and cations **104-120**.[60]

One of the biggest challenges in homogeneous catalysis has been the separation, recovery, and recycling of valuable homogeneous catalysts. The use of biphasic ILs has been considered as one of the most promising strategies to overcome this challenge, since ILs have many attractive properties, such as good stability, strong conductivity, low vapor pressure, non-flammability, and very good solubility towards transition metal catalysts. An additional attractive feature of ILs is that they can be readily modified by structure, and therefore a special functionality can be included, depending on particular needs. Moreover, ILs can well dissolve organic substrates, and therefore, increase the reaction rates. Many substrates have been tested in ILs – based hydroformylation reaction, such as styrene, methyl acrylate, norbornene, vinyl acetate, and vinyl naphthalene. Importantly, some alkenes among substrates tested, produce not only aldehydes but also heterocycles or alcohols when cyclization or hydrogenation occurs subsequently to hydroformylation reaction.[61,62]

Some important ILs **141-155** applied in hydroformylation reaction are presented in Figure 13. For example, high viscous ionic compounds **155a** and **155b**, which belong to the family of triazine-based

polyfluorinated triquarternary liquid salts, give almost full conversion in hydroformylation reaction of 1-octene. Importantly, the solubility of hydroformylation reaction substrates in ionic liquid media, such as CO, CO_2, H_2, and C_2-C_4 alkenes must be well understood, for the successful catalysis to be performed. Some trends in solubility can be outlined, based on the experimental data collected so far. In general, CO and H_2 gases are more soluble in common organic solvents, compared to ILs. When [bmim] -containing ILs are used, the solubility of H_2 is increased in the order $[PF_6] < [BF_4] < [SbF_6] \approx [CF_3CO_2] < Tf_2N$.[61] For ILs which contain pyridinium, H_2 is slightly better soluble, than with ILs which contain imidazolium.[61] Then, for [bmim] based ILs, the CO solubility increases in the order $[BF_4] < [PF_6] < [SbF_6] < [CF_3CO_2] < Tf_2N$, and in the order [mmim] < [emim] < [bmim] < [hmim] < [omim] for cations with the same anion, which show that alkyl chain length and anion are depended on each other.[61] When the alkene chain length increases in the order $C_2H_4 < C_3H_6 < C_4H_8$, the solubility of gaseous unsaturated hydrocarbons in ILs is improved.[61] When it comes to the influence of IL anions, alkene solubility increases in the order $[BF_4] < [PF_6] < [SbF_6] < [CF_3CO_2] < Tf_2N$, and also when the alkyl chain length in imidazolium cations is increased. [61]

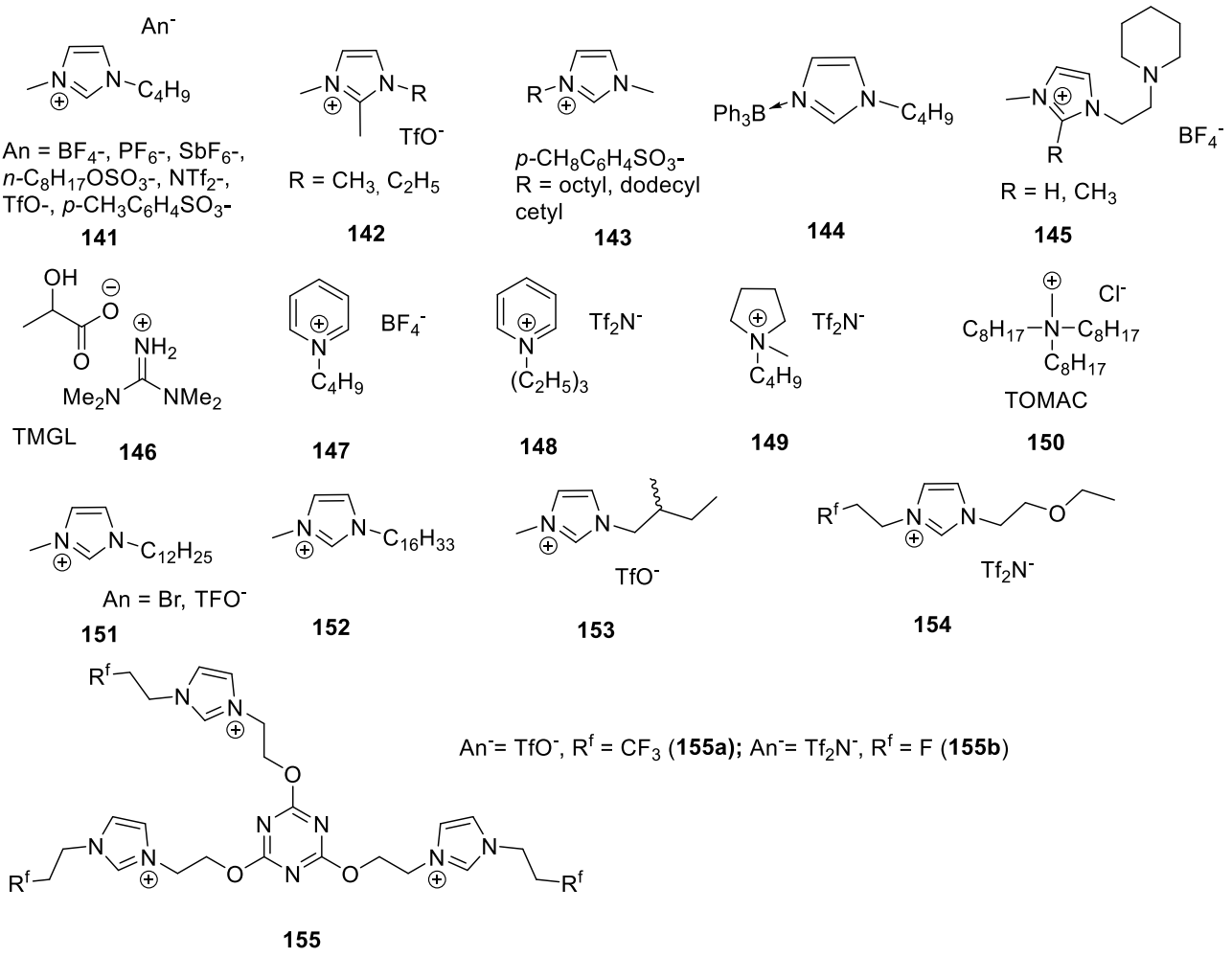


Figure 13. Common examples of ILs **141-155** used in hydroformylation reaction. [61]

4.1 Effects of ionic liquids on the ligand effects

The ligand design has largely led to the success of biphasic hydroformylation reaction. The structure of the ligand used in ionic liquid supported hydroformylation reaction strongly affects main catalyst properties, such as stability, selectivity, solubility, and activity. [61] In the last decades, a wide range of different ligands has been studied, to find more effective and selective catalysts. [61] Different ligands can be classified in various ways, for example by their physicochemical properties, such as solubility in water, organic solvents, or both, by their ionic character (nonionic and ionic) and by their mode of complexation, which can be mono – or bidentate (Figure 14). [61]

Neutral phosphine ligands, such as PPh_3, have been the first widely used class of ligands in biphasic ionic liquid hydroformylation reaction, due to their availability, moderate *l/b* selectivity, and decent reaction rates. [63] However, the big problem was the loss of the catalysts during product separation, which was caused by the catalyst passing into the organic layer during the reaction. When the PPh_3

was functionalized with ionic groups, catalyst leaching decreased, when the catalysts were better immobilized into the ionic liquid layer. There are several examples of the use of monodentate sulfonated PPh_3 ligands (Figure 14, top), such as TPPS and TPPOTS **162**, and commercially available NaTPPTS **161**, which are soluble in both IL and water. Moreover, NR_3^+-fragments have been introduced, such as guanidinium **163-164, 169**, and charged metallocenes **166-167**. However, especially monodentate NaTPPTS showed quite poor *l/b* ratios in ionic liquids, and for that reason, other ligands were required to obtain a larger number of linear products. [63]

Apart from monodentate phosphite ligand TPPOTS, good l/b selectivities are only obtained with the use of bidentate ligands (Figure 14, downside), especially with the Xantphos family of ligands. Leeuwen and co-workers introduced the use of phenoxaphosphino-modified POP-Xantphos ligand **170**, which afforded linear products with selectivity up to 98 %.[64] This is achieved because the dynamic equilibrium is shifted to *ee*-isomer by the large bite angle of the ligand (110˚). Besides, guanidinium-modified Xantphos **169** gave good l/b selectivity (20/1) and low catalyst leaching in hydroformylation reaction of 1-octene in [bmim][PF6]. [64] The success of a ligand is determined by the correct interplay of electronic and steric effects. This is shown when comparing bidentate ligands DPP-cobaltocene **166** and DPPiPr-cobaltocene **167**. DPP-cobaltocene **166** shows bigger activity and *l/b* selectivity, because the space between the phosphine and cationic metallocene is bigger, and thus the charge is not separated from the phosphorous atom. [61,63]

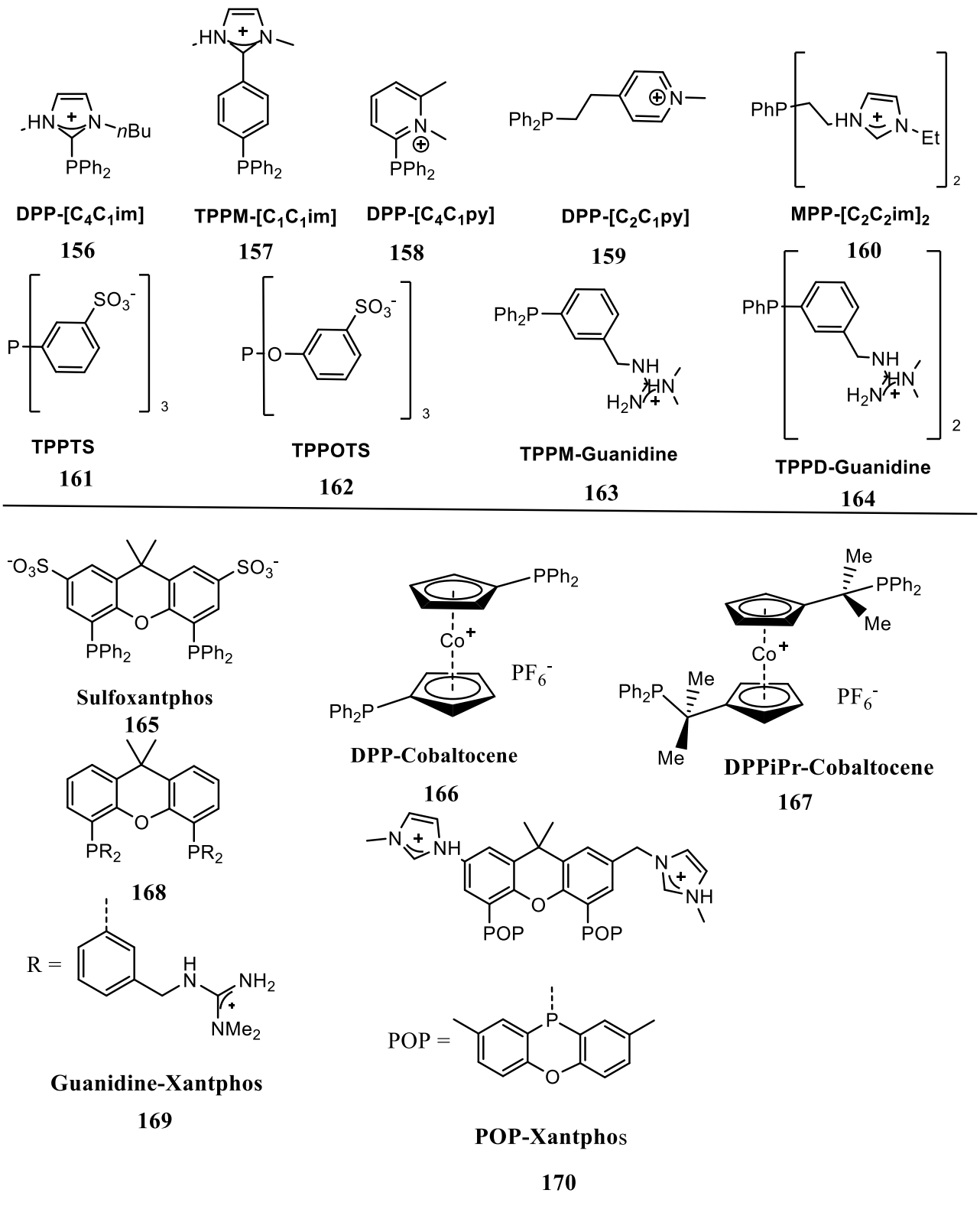
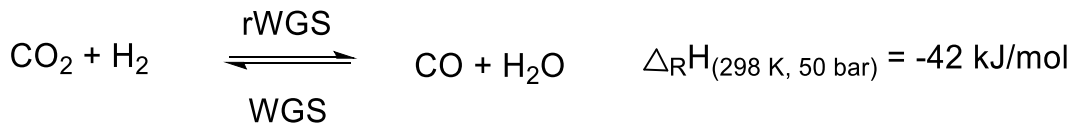


Figure 14. Monodentate (top) **156-164** and bidentate (downside) **165-170** ligands used in ionic liquid-based hydroformylation reaction.[63]

5. Reverse water-gas shift reaction converts CO_2 to CO.

Reverse water gas shift reaction (RWGSR) is a key reaction in the conversion of CO_2 to CO (Scheme 16), and it has thus gained much attention, because it offers a great possibility for using the resulting CO in the production of different chemicals and liquid fuels, while, avoiding the direct handling of CO, which can be problematic due to the toxicity of CO, for instance. [65]

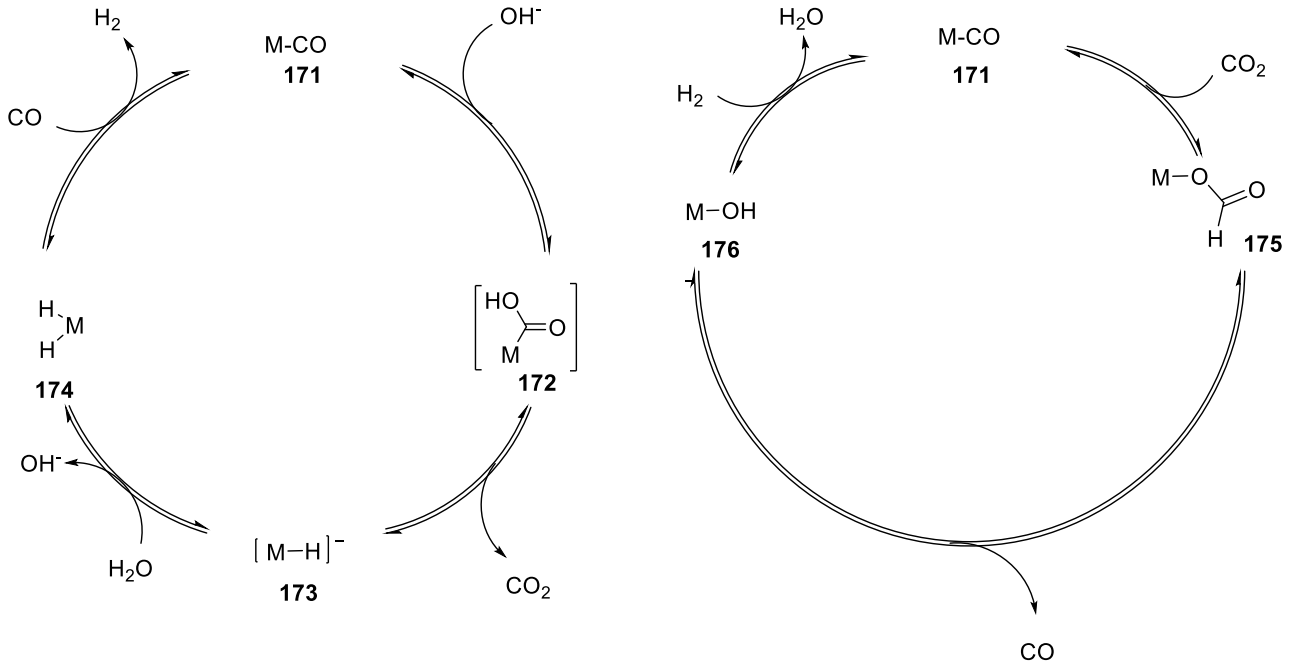


Scheme 16. Reverse water-gas shift reaction (RWGSR) and water-gas shift reaction (WGSR)[9]

Many processes have been reported in which RWGSR is used in producing important compounds with CO_2 as the source of C1. For example, CO_2 can be hydrogenated to chemical fuels, when it is reduced to CO through the RWGSR, then the CO is hydrogenated to alkenes or higher hydrocarbons, which process is called Fischer-Tropsch synthesis. Furthermore, the RWGSR can be effectively used in hydroformylation reaction, when CO_2 is used instead of CO. The back reaction for the RWGSR is, naturally, the water-gas shift reaction (WGS), which is similarly widely used in various industrial processes. [9,65]

There are two different mechanisms for the interconversions of CO/H_2O to CO_2/H_2 with homogenous catalysts (Scheme 17). [9] The mechanism shown on the left is the most probable mechanism for the WGSR, and in the right, there is the reverse pathway for the RWGSR. [9] When a metal carboxylate intermediate **175** forms in the RWGSR mechanism (right), the electron-rich metal centers of the catalyst attacks the carbon center of the CO_2, which has some electrophilicity. Alternatively, the CO_2 can insert into a metal hydride bond, which forms a formato complex **175**, then CO eliminates, and the metal hydroxyl unit **176** undergoes subsequent hydrogenolysis. One of these two pathways must occur because otherwise, the RWGSR reaction cannot be achieved. [9]

The RWGS reaction is endothermic, and thus favors high temperatures (Scheme 18), in addition to that it is limited by equilibrium. [66] The conversion of CO_2 is also found to be more efficient when an excess of hydrogen is used. [66] Moreover, additional side reactions are possible, such as methanation and the Sabatier reaction, which can though also be called methanation (Scheme 18), which are, compared to the CO_2 conversion reaction, exothermic, and give methane as a product. [66]



Scheme 17. Principal pathways for general reaction mechanisms of homogeneously catalysed RWGS (right) and WGS (left) reactions. [9]

Methanation

$$CO + 3\,H_2 \rightleftharpoons CH_4 + H_2O \quad \triangle_R H_{(298\ K)} = -206{,}5\ kJ/mol$$

Sabatier reaction

$$CO_2 + 4\,H_2 \rightleftharpoons CH_4 + 2\,H_2O \quad \triangle_R H_{(298\ K)} = -165{,}0\ kJ/mol$$

Scheme 18. The side reactions of the RWGS reaction[66]

Carbon dioxide is a very thermodynamically stable compound, which makes its conversion to other useful products quite a challenging task. [65] The reactions of CO_2 for that reason also usually require high temperatures, and/or high pressures, which is an effective way to achieve higher conversions, due to the endothermic nature of the reaction. [65] The required temperature for the reactions involving RWGSR is often above 100 °C, which has led to the need to develop efficient catalysts, which could enable a low-temperature RWGSR process. Thus, it has been found recently, that the $Ru(CO)_{12}$ could catalyse the production of CO at 80 °C, in the presence of ionic liquid $HMimBF_4$, where the BF_4^- anion played a very pivotal role in this low-temperature reaction to success. [65]

5.1 Catalysis

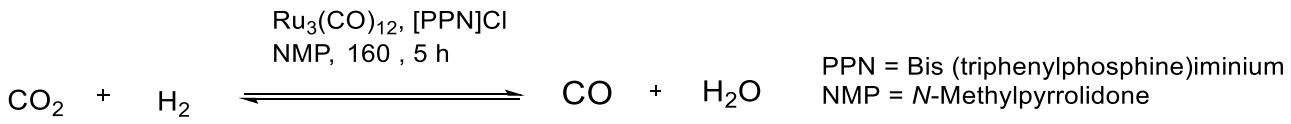
Naturally, catalysts that are active in the WGS reaction are usually also active in the RWGS reaction, as it is a reversible reaction. Those homogenous catalyst complexes, containing transition-metal carbonyl compounds, offer mild conditions for the WGSR, and thus they possess a great theme of interest. Metal complexes of metals, such as Ru, Rh, Fe, Ni, and Os were investigated as potential catalysts for homogenous catalysis of the WGSR.[67,68] Moreover, Ru and Rh have been investigated particularly for the RWGSR, and it was found, that with those metal complexes used for the homogeneous catalysis, the reaction can be carried out with temperatures below 200 °C. [67] The Ru and Fe - based catalysts were also concluded to be more active, than Os-based catalysts. This was found while studying the mechanism of the Fe-catalysed WGSR. [68]

It is notable, that the $Fe(CO)_5$ catalyst has been found to be an active catalyst for the WGSR reaction, and it has been very much used in both theoretical and experimental studies. [67,68] However, compared to the $Ru(CO)_5$ catalyst, the $Fe(CO)_5$ is less efficient for the WGS reaction. In addition to that, $Ru(CO)_5$ was found to be more suitable for homogeneous catalysis, than the $Fe(CO)_5$. Those conclusions were supported by experimental evidence and mechanistic investigations. [67,68]

Some heterogeneous catalysts for the RWGSR, for example, Ni, Pt, Cu/Zn, Au, and Fe, have been widely studied.[67] However, they cannot be used with such mild conditions, as homogenous catalysts, as they have usually required temperatures over 300 °C. Moreover, because of design possibility, homogenous catalysts are more active and selective than heterogeneous catalysts. In spite of these deficiencies, heterogeneous catalysts are still most widely used in the industry for WGS/RWGS reactions. Besides, the attractive features of both catalysts can be combined by using the supported ionic liquid phased (SILP) catalysts, where the homogenous catalyst is dissolved and remains immobile in a thin IL layer. [67]

5.1.1 Ru-catalysed RWGS reaction

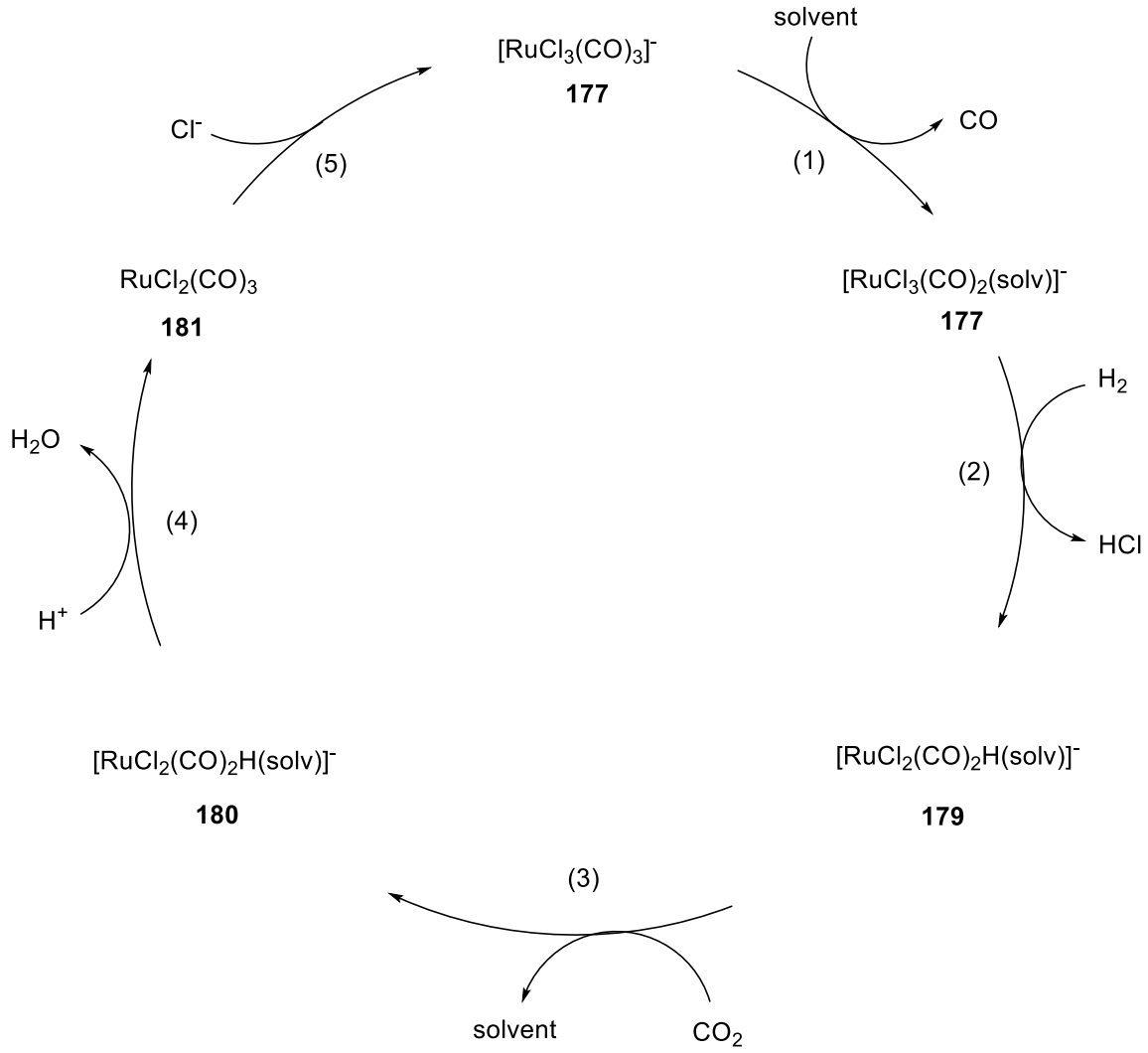
Tominaga and co-workers found already in 1994, that e.g. $Ru_3(CO)_{12}$, which is active also in the hydroformylation reaction, can successfully catalyse the RWGS reaction, where CO_2 is reduced to CO.[5] Based on their investigation, that was possible in the presence of [PPN]Cl, (bis(triphenylphosphine)iminiumchloride), in temperatures above 100 °C and pressure of 78,5 bar (Scheme 19). The most active solvents for that were dimethyl acetamide (DMA) and *N*-methylpyrrolidone (NMP) since they have donating properties. [5,11]



Scheme 19. The formation of CO by the Ru - catalysed RWGS reaction. [5,11]

Homogeneous Ru-based catalyst complexes, such as $Ru_3(CO)_{12}$, $[Ru(bipy)_2(CO)Cl]^-$, $FeH_2Ru_3(CO)_{12}$, K[Ru(H-EDTA)-CO], catalyse the RWGS reaction at relatively low temperatures. Those Ru complexes have shown to be active catalysts. In addition to those, $Ru_3(CO)_{12}$, $Ru_6(CO)_{16}$, $H_4Ru_4(CO)_{12}$, $[Ru(bpy)(CO)_2Cl_2]_2$ (bpy = bipyridine) and $(PPN)Ru(CO)_3Cl_3$ have been widely investigated by Tominaga and Haukka groups. [11,69] They have shown to be quite efficient catalysts for the RWGSR, and significantly, hydroformylation reaction also occurred simultaneously with the RWGSR. Halogen-containing salts also participated in the catalysation of the RWGS reaction, among catalytic complexes.[11,69]

In 2013, Tominaga and co-workers investigated the action of mononuclear Ru halogen compounds in the RWGS reaction, and they showed to have significant catalytic activity. [70] Different Ru complexes were investigated, and the $[PPN][RuCl_3((CO)_3]$ showed to have the best activity for catalysation. They presented a plausible mechanism for the Ru-catalysed reverse water gas shift reaction, which takes into account the effects of the halogen ligand, solvent, and the halogen additives. (Scheme 20). In step 1 marked in the catalytic cycle, a ligand exchange between the starting complex $[RuCl_3(CO)_3]^-$ **177** and the solvent takes place, when CO is released, and $[RuCl_3(CO)_2(solvent)]^-$ **178** is formed. This complex reacts in step 2 with hydrogen, forming hydrido complex $[RuCl_2(CO)_2H(solvent)]^-$ **179**, and releasing HCl. In step 3, CO_2 coordinates with the complex forming **180**, and in step 4, a carbonyl ligand and water are formed, in the reaction between the coordinated CO_2, hydrogen ligand, and the proton. Finally in the last step, the starting catalytic complex **177** is reformed, when $RuCl_2(CO)_3$ **181** undergoes ligand exchange with Cl^-.[70]



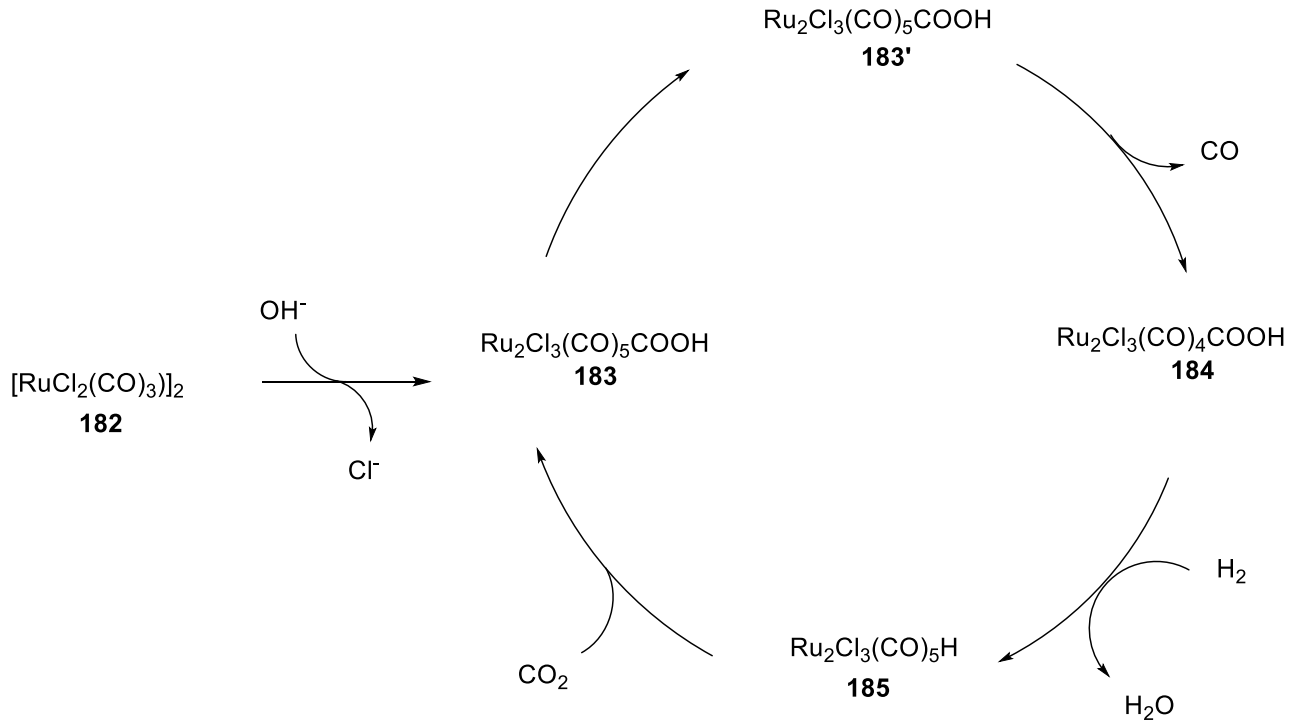
Scheme 20. A plausible reaction mechanism of RWGSR for mononuclear Ru-complexes[70]

Tominaga and co-workers also concluded that the rate-determining step in the catalytic cycle must be step 1 for several reasons, which relate for instance to the effect of the halogen ligand, and to the fact that the solvent affects the reaction rates, which was also one of the results of the investigation. [70] One important result was also that in the studied mononuclear Ru-complex $[RuX_3(CO)_3]^-$, where X = Cl^-, Br^-, I^-, the CO stretching frequency of the complex decreases as following: Cl > Br > I. [70] Thus, it can be concluded, that in the order of Cl^- < Br^- < I^-, the back donation from the metal center to the CO ligands increases. Furthermore, the additive salts have been used in the investigation, [PPN]X, where X = Cl, Br, I, though, the type of salt ligand did not show to affect significantly on the catalyst activity. Nevertheless, the type of halogen in the Ru complex itself affects the catalyst activity, based on the results it decreases as following: Cl > Br > I. [70]

The results of Tominaga and co-workers show that the type of the solvent also affects the catalyst activity, based on ability to donate electrons. [70] Thus, catalytic complexes used with NMP and DMA solvents showed the biggest activity, while catalysts used with THF and dioxane were less active. This same investigation group had also earlier investigated tetranuclear Ru-based catalytic complexes, which also showed good catalytic activity in the RWGS reaction.[71] Though, based on their results with the mononuclear Ru complexes, they concluded, that tetranuclear complexes are not as active in the RWGSR, as convenient mononuclear complexes. [70]

The structure and properties of binuclear catalyst systems, such as $[RuCl_2(CO)_3]_2$, have been widely investigated, but for the optimization of those catalyst systems, it is quite important to have a good mechanistic understanding of their catalytic activity. Thus, Liu and co-workers proposed several possible reaction mechanisms for the $[RuCl_2(CO)_3]_2$ complex, from which the first one is quite similar to the mechanism proposed by Tominaga and co-workers (Scheme 20) for the mononuclear complexes and involves the hydrogen chloride intermediate in its process.[70] The second proposed mechanism involves formic acid intermediate. However, both first and second mechanisms are indirect pathways to form CO and H_2O from CO_2 and H_2. The second mechanism is concluded to be unlikely because the recovery of carbon dioxide by formyl complex is the step, which has the largest energy barrier. The third proposed mechanism is, on the contrary, a direct pathway to form those products, and it can be called an oxidation-reduction mechanism (Scheme 21). That mechanism is proposed to be the most probable mechanism for the reaction of binuclear Ru-complexes. This is based on theoretical studies where the Gibbs free energies for the intermediates, and the transition structures were compared within all three mechanisms. [68]

The mechanism starts with the initial attack of the hydroxyl anion OH^- to the initial complex **182**, with subsequent Cl^- release, leading to metallocarboxylic acid **183**. Then isomerization of this acid takes place (**183** → **183'**), and the forming isomer **184** can release CO. The forming compound can undergo the addition of H_2 and release of H_2O, which leads to an intermediate (**185**). The intermediate can coordinate with CO, and give back the starting complex (**183**). Based on this mechanism, Liu and co-workers concluded, that binuclear halogen carbonyl complexes $[RuCl_2(CO)_3]_2$ ($[Ru(\mu\text{-}Cl)Cl(CO)_3]_2$) are more effective catalysts for the RWGS reaction than the mononuclear $RuCl_2(CO)_3$ complexes. [68] Furthermore, among the binuclear catalyst complexes, $[Ru(\mu\text{-}Cl)Cl(CO)_3]_2$ and $[Ru(\mu\text{-}CO)Cl(CO)_3]_2$, are more active than $[Ru(\mu\text{-}Cl)Cl(CO)_4]_2$ complex, also, $[Ru(\mu\text{-}CO)Cl(CO)_3]_2$ was concluded to be the most active catalyst for the RWGS reaction. [68]



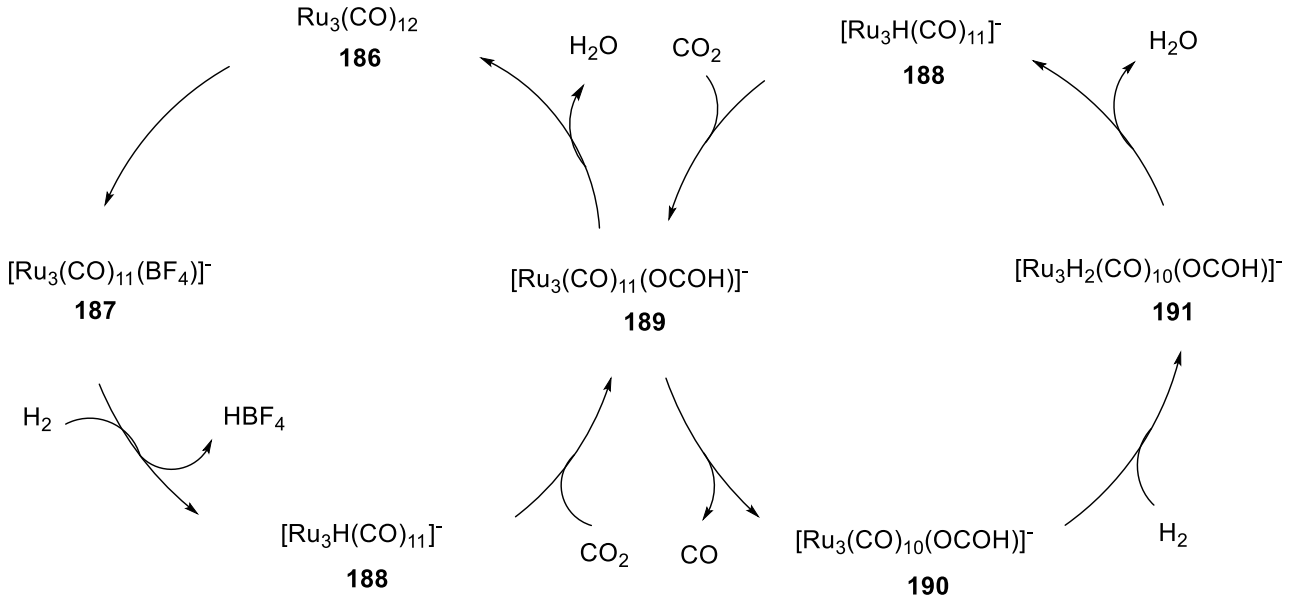
Scheme 21. A plausible reaction mechanism of RWGSR for binuclear Ru-complexes[68]

Ru-based catalyst complexes, which are largely used, and efficient catalysts for the RWGS reaction, have been studied by Han and co-workers. They developed the use of these catalyst complexes at low temperatures, 80 ℃ at the merest. Their catalytic activity was studied using different solvents, such as $HMimBF_4$, HMimCl, and HMimBr. Complexes, such as $Ru_3(CO)_{12}$ and previously described $[RuCl_2(CO)_3]_2$, were found to be very active in 140 ℃, when $HMimBF_4$ was used as solvent. Other investigated Ru complexes, such as $RuH(CO)(PPh_3)Cl$, $RuH_2(CO)(PPh_3)_3$ didn't show any activity in the catalysis. Significantly, when the temperature of the reaction was raised, the amount of produced CO also increased. This can be explained by the endothermic nature of the RWGS reaction; the conversion of CO_2 to CO proceeds better when the temperature is higher. [65] The influence of the solvent was pivotal, and the ionic liquid was the promoter of the reaction. The best yields for CO were achieved with $HMimBF_4$, and among other solvents with the anion part other than BF_4^-, HMimCl and HMimBr showed the lowest yields for CO. It was thus concluded, that the BF_4^- anion has a very significant role in promoting the $Ru_3(CO)_{12}$ catalysed RWGS reaction. [65]

Based on the results of their investigation, and also on the previously described mechanism presented by Tominaga and co-workers for mononuclear Ru complexes[70], Han and co-workers proposed a possible mechanism for the $Ru_3(CO)_{12}$ catalysed RWGS reaction, where BF_4^- anion works as a promoter (Scheme 22). In the mechanism, $[Ru(CO)_{11}(BF_4)]$ (**187**) is formed, when the starting

complex $Ru_3(CO)_{12}$ undergoes ligand exchange with $HMimBF_4$, and releases CO. This complex (**2**) reacts with hydrogen, and the hydride complex, $[Ru_3H(CO)_{11}]^-$ **188** is formed, subsequently HBF_4 is released. This complex **188** reacts with CO_2, and $[Ru_3(CO)_{11}(OCOH)]^-$ **189**, the formato complex, is thus formed. This formato complex further reacts with a proton, which was formed earlier, and the carbonyl ligand in $Ru_3(CO)_{12}$ is formed. [65]

Then, there is also another catalytic cycle, where **189** dissociates, releasing CO and $[Ru_3(CO)_{10}(OCOH)]^-$ **190**, which then reacts with adsorbed H_2, and as a result, the intermediate $[Ru_3H_2(CO)_{10}(OCOH)]^-$ **191** is formed. Subsequently, this intermediate can dissociate into **3** and water H_2O. In the final step, **188** reacts with CO_2 forming **189**, which starts the next cycle. It is notable, that the BF_4^- anion plays a very significant role in forming the active Ru catalyst, which can be seen in this reaction cycle. [65]



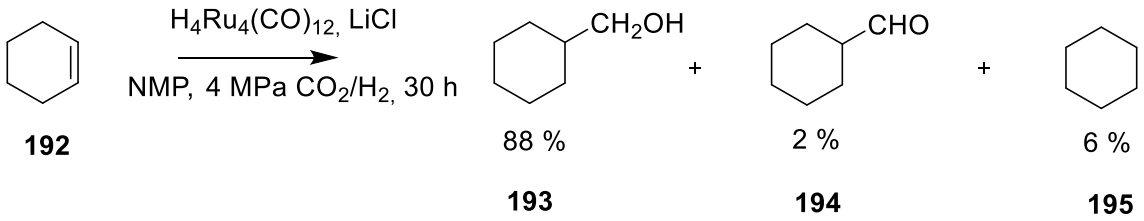
Scheme 22. A possible mechanism for $Ru_3(CO)_{12}$ catalysed RWGS reaction.[65]

The pressure of the CO_2/H_2 mixture also influences the yields of CO produced in the Ru-catalysed RWGS reaction. It is found that the yield of CO increases significantly with the increase of total pressure. At the same time, though, it also increases the yield of an undesired side product of the reaction, methane. The best combination of pressures is found to be 3 MPa for the H_2, and 3 MPa for the CO_2, with a total pressure of 6 MPa for the gas mixture. [65]

6. Combining RWGS and hydroformylation reactions using the same catalyst

6.1 Different Ru-based catalysts with promoters

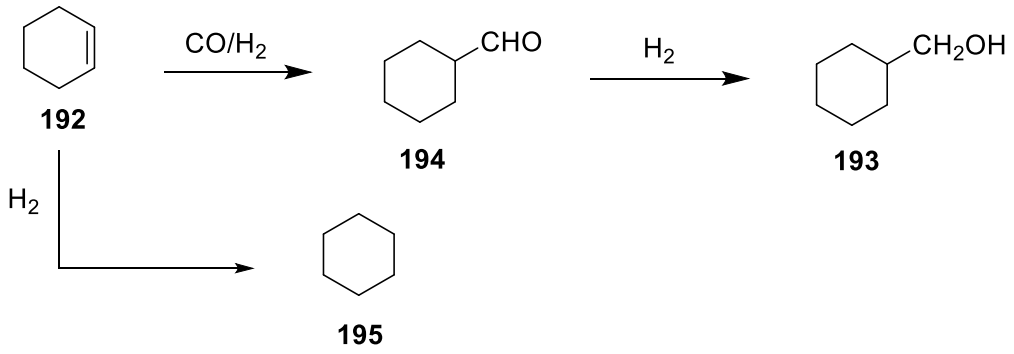
The group of Tominaga and Sasaki in 2000 was the pioneer in performing hydroformylation reaction with concomitant production of carbon monoxide from CO_2 using the RWGS reaction. [72] Previously to this study, the same research group reported that CO_2 can be successfully hydrogenated to CO in the RWGS reaction, with ruthenium cluster complexes, and in presence of halide salts. After that, they found that CO_2 can be hydrogenated in the reaction selectively in the presence of alkenes, in the hydroformylation reaction using Ru-based carbonyl clusters for catalysis and alkaline metal halides. In this study, different alkenes were used in hydroformylation reaction with CO_2, using mainly $H_4Ru_4(CO)_{12}$ as a catalyst, and LiCl as an additive. In the most successful case, cyclohexene **191** was used as a reagent in 140 °C, forming hydroxymethylcyclohexane **193** in 88 % yield, which is a hydrogenated product of cyclohexylcarboxaldehyde **194** (Scheme 23). The formation of those products is strongly depending on the temperature used. The cyclohexylcarboxaldehyde **194** forms already in the temperature of 80 °C, its yield reaches 50 % in 120 °C and starts decreasing above this temperature, where instead, the formation of the alcohol starts. The amount of cyclohexane **195**, the undesired product of alkene **191** hydrogenation, is far less significant than the amount of alcohol **193**, even at high temperatures. [72]



Scheme 23. The hydroformylation reaction of cyclohexene with CO_2, and the products formed.[72]

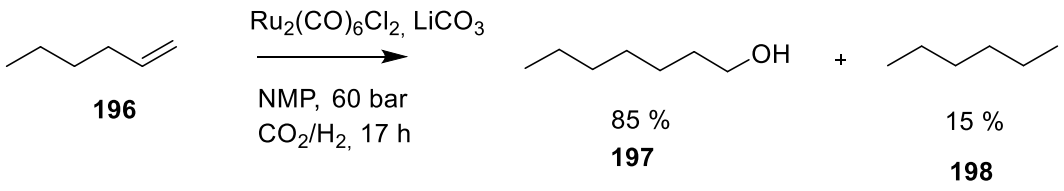
The yield of the alcohol in the CO_2-based hydroformylation reaction was slightly higher (88 %) than the yield of the same product formed in the convenient hydroformylation reaction with CO (82 %). Moreover, significantly, among the salts used in CO_2 based hydroformylation reaction, LiCl was the most effective, and with the absence of salt, only the alkane is formed in the hydrogenation of alkene. Besides, $Ru_3(CO)_{12}$ was also active in CO_2 based hydroformylation reaction, forming alcohol in only a slightly lower yield, 86 %. Instead, $RuCl_2(PPh_3)_3$ showed no activity in hydroformylation reaction, only hydrogenation of alkene proceeded with this catalyst. [72]

With very similar conditions, Fujita and co-workers investigated the influence of the pressures of CO_2 and H_2 on the hydroformylation reaction of cyclohexene **192** (Scheme 24), using $Ru_3(CO)_{12}$ as the catalyst, NMP as a solvent, and LiCl as an additive. They found, that increasing the total pressure of CO_2 and H_2 results in increasing of the yield of cyclohexanecarboxaldehyde **194**, when the RWGS reaction is promoted. When only the H_2 pressure was increased, it promoted the hydrogenation of the aldehyde to hydroxymethylcyclohexane **193**. Instead, when only the pressure of CO_2 was increased, the hydrogenation of the aldehyde to alcohol was repressed. Increasing CO_2 pressure also prevented the formation of cyclohexane **195**, the product of direct hydrogenation of the cyclohexene. [73]



Scheme 24. The conversion of cyclohexene to cyclohexanecarboxaldehyde via hydroformylation reaction, then to hydroxymethylcyclohexane via hydrogenation, and to cyclohexane via direct hydrogenation.[73]

The group of Haukka and Jääskeläinen investigated CO_2 based hydroformylation reaction of 1-hexene **196**, with similar conditions as Tominaga and co-workers, with the idea of investigating the role of catalyst and the promoter.[72] However, they used milder conditions, such as lower pressure (60 bar), and slower reaction times (17 h), with the temperature of 150 °C (Scheme 25).[12,74]



Scheme 25. The hydroformylation reaction of 1-hexene with CO_2 and the products formed.[12]

Several Ru-based catalysts were studied, such as $Ru_3(CO)_{12}$, $H_4Ru_4(CO)_{12}$, $Ru_2(CO)_6Cl_2$, $Ru(bpy)(CO)_2Cl_2$, and the activity of each catalyst was tested with a promoter (LiCl or Li_2CO_3), and also without any promoter. The activity of the two first-mentioned ruthenium carbonyl clusters was very similar to each other. The yield of alcohol **197** with $Ru_3(CO)_{12}$ was 80 %, and with $H_4Ru_4(CO)_{12}$ 75 %, when the promoter was used, and without a promoter, hexane **198** was the main product. A similar effect was observed with $Ru_2(CO)_6Cl_2$ catalyst; with a Li_2CO_3 promoter, the yield of alcohol was 85 %, and when no promoter was used, hexane was again the main product. $Ru(bpy)(CO)_2Cl_2$ catalyst showed no activity in the hydroformylation reaction, even when the promoter was used. [12,74]

However, when $Ru_3(CO)_{12}$ was used without a promoter, the yield of alcohol **197** was still 21 %, which indicates that the hydroformylation reaction still partly occurred. The activity of this catalyst also improved not only with the use of alkaline metal halides but also with the use of alkaline earth metal halides, such as $CaCl_2$ and $SrCl_2$. Significantly, $Ru_3(CO)_{12}$ showed no activity with the $LiCO_3$ promoter, but only with LiCl, however, $LiCO_3$ promoted the reaction catalysed by $Ru_2(CO)_6Cl_2$. Thus, it was concluded, that it is pivotal to have chloride anion in the reaction system. This anion must be present either in the promoter, or within the catalyst itself. [12,74]

6.1.1. Effects of additives

The catalytic activity of tetranuclear ruthenium complexes, for example, $H_4Ru_4(CO)_{12}$, towards the RWGS reaction of CO_2 conversion to CO, seems to depend strongly on the salts used as additives, in particular, on their halide anion species. [71] The activity of these anions, which successfully catalysed this reaction, was studied. [71] The activity was found to affect the reaction rate, where the activity increases as following: $I^- < Br^- < Cl^-$.[71] Interestingly, the proton affinity of those anions increases in the same order. [71]

These effects have been studied for such carbonyl catalysts with different nuclearities, as $H_4Ru_4(CO)_{12}$, $Ru_3(CO)_{12}$, and $[Ru(CO)_3Cl_2]_2$, also for such substrates, as cyclohexene and linear hexene. [71] It seems obvious, that the halide promoter is necessary for high hydroformylation reaction activity. Especially for $H_4Ru_4(CO)_{12}$, when it was used for hydroformylation reaction of 1-hexene to alcohol without the use of promoter, only direct hydrogenation of alkene occurred, forming only 1-hexane. Although some alcohol forming hydroformylation occurred, when $Ru_3(CO)_{12}$ was used as catalyst, the alkane remained the main product. This and previously described investigations[12,75] with several catalytic complexes show, that the role of the promoter is pivotal. [71]

According to the conclusions made by Tominaga and co-workers, the hydrogenation of alkenes (such as cyclohexene) occurred in the absence of salts, when the metal of the ruthenium carbonyl complex was precipitated, which occurred when the complex releases carbonyl ligands. [71] When the salts are added, the ruthenium complex is stabilized, and the precipitation of metal is prevented. In particular, only halide salts show such an effect, other salts are unactive to promote hydroformylation reaction. LiCl is the most active salt, which shows that the Li^+ cation is the most effective. [71]

When Na and K salts were used, the catalytic activity decreased, resulting in comparably small yields for the alcohol, 62 %, and 65 %, respectively. The yield was 80 %, when the Li salt was used. This was explained by the immiscibility of these cations with NMP, the most used solvent. Besides, the activity of the first and second main group metals, such as Li, Na, K, and Cs, was studied, and the hydroformylation activity of these elements used for the production of alcohols was shown to depend on their ionic radii. The yield of the alcohol produced in the hydroformylation reaction decreased, when the ionic radii of the cation increased. Alcohol yields for Li, Na, K and Cs salts were 80 %, 62 %, 65 %, and 55 %, respectively. At the same time, the rate of alkene hydrogenation increased. The alkaline earth metals, such as Mg, Ca, and Sr, were also studied as cations for the additive salts, but the size of ionic radii was not so significant, the yield of oxo-products differentiates only slightly between complexes based on those metals. [12]

Importantly, even the concentrated aqueous HCl (37 %) showed promoting activity in the conversion of CO_2 to CO in hydroformylation reaction. However, the yield of alcohol remained modest (46 %). Besides, as previously mentioned, Li_2CO_3 worked effectively as a reaction promoter (alcohol yield 85 %), only when $[Ru(CO)_3Cl_2]_2$ was used as a catalyst, whereas with the $Ru_3(CO)_{12}$ it does not work. Thus, it can be concluded, that even though the presence of the halide ion is required for the hydroformylation reaction to succeed, it does not have necessarily be originated from a simple salt. The used catalyst precursor can also contain chloride as a ligand, and that is sufficient, the additional chloride is not needed in the reaction system. Therefore, the chlorinated species can be formed from a promoter salt and a catalyst precursor during the catalysis reaction, or the catalyst precursor already contains the chloride ligand, for example $[Ru(CO)_3Cl_2]_2$. [12]

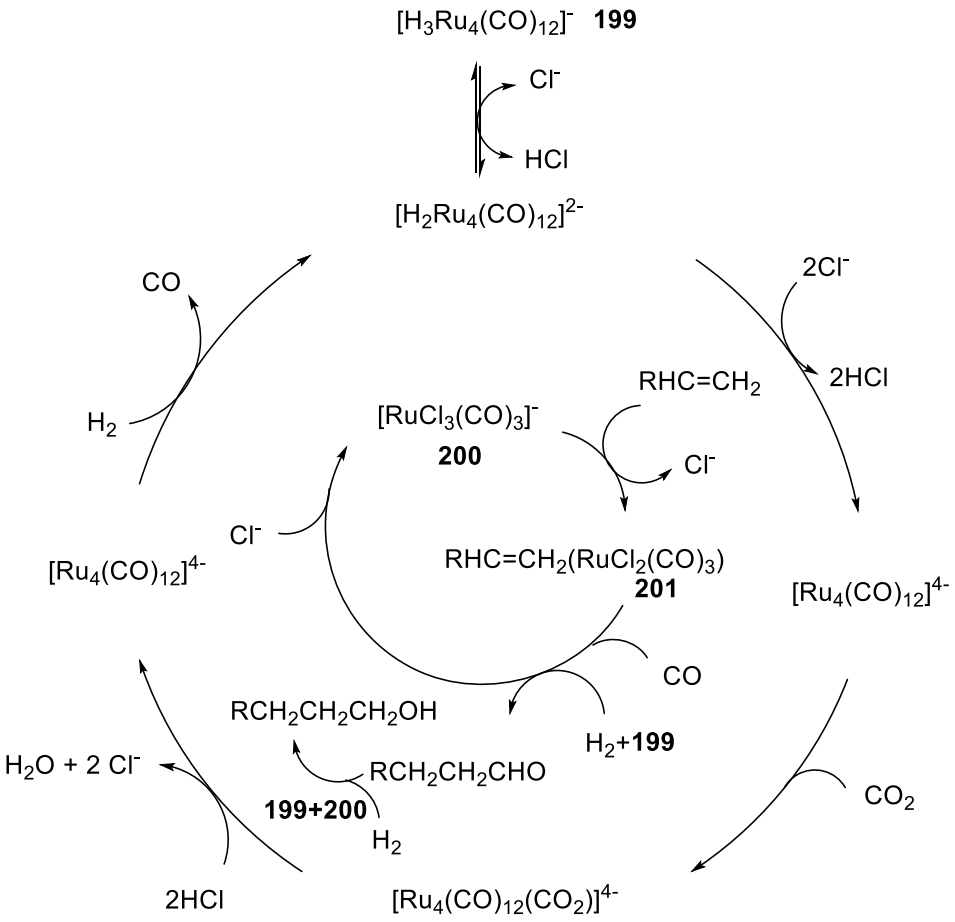
Nevertheless, the removal of chlorides from metal complexes can be enhanced by alkali metal carbonates. [12] It may be possible, that within the hydroformylation process, the same type of dichlorination occurs. [12] Thus, the alkali metal carbonates, and ruthenium carbonyl precursors can introduce chloride anions into the reaction system. Therefore, the chloride may reversibly attach to the metal center as a part of the catalytic cycle. More unclear, however, is the role of the cation, which is still, in addition to halide, needed in the reaction system, for a positive promoting effect.

Nevertheless, it must be taken into account, that the features of separate ions may be less significant in promoting effects, than the solvation properties, and the ionic nature of the additive salt. [12]

6.1.2 Mechanistic considerations

The group of Haukka confirmed using different catalyst complexes, that the reactivity of the catalyst does not depend on its nuclearity, and the catalyst does not have to consist of a cluster core.[12] Importantly, the group of Tominaga investigated the activities of very used catalyst systems, $Ru_3(CO)_{12}$/[PPN]Cl and $H_4Ru_4(CO)_{12}$/[PPN]Cl, within the hydroformylation reaction of cyclohexene. [71,74] They proposed a plausible reaction mechanism (Scheme 26), which involved a halogen-containing promoter, and which was generated by elucidating active catalytic ruthenium species using mass spectrometry. Four active species were detected at the end of the hydroformylation reaction with CO_2, which were the same for both catalytic systems: $[H_3Ru_4(CO)_{12}]^-$ (a tetranuclear complex) (**199**), $[HRu_3(CO)_{10}]^-$ (trinuclear complex), derived from $[HRu_3(CO)_{11}]^-$, also $[RuCl_3(CO)_3]^-$(mononuclear complex) (**200**), and its cyclohexene complex, $[RuCl_3(CO)_3(C_6H_{10})]^-$ (**201**). Interestingly, complex **199** was not observed, but instead all other complexes (**200-201)** could be detected in the reaction solution when hydroformylation reaction with CO was performed. It has been proposed that this explains the difference between hydroformylation reactions with CO and CO_2. [71,74]

The first step of the mechanism within the outer cycle represents the hydrogenation of CO_2 to CO, catalysed by tetranuclear anionic species. The key step for this, according to previous studies of the group of Tominaga, is the formation of a hydrogen-free complex, $[Ru_4(CO)_{12}]^{4-}$, when Cl^- deprotonates hydride complexes, and which can coordinate with CO_2. [71] CO_2 is then converted to CO ligand by the electrophilic attack of the proton of HCl, which also releases water. Then, hydroformylation reaction with CO is shown in the inner cycle, which is catalysed by mononuclear and tetranuclear anionic species. Within this cycle, the substrates coordinate with mononuclear species, then CO is inserted, and the tetranuclear species donates hydrogen. Finally, alcohol is formed by aldehyde hydrogenation, possibly catalysed with a combination of the previous two complexes. [71]



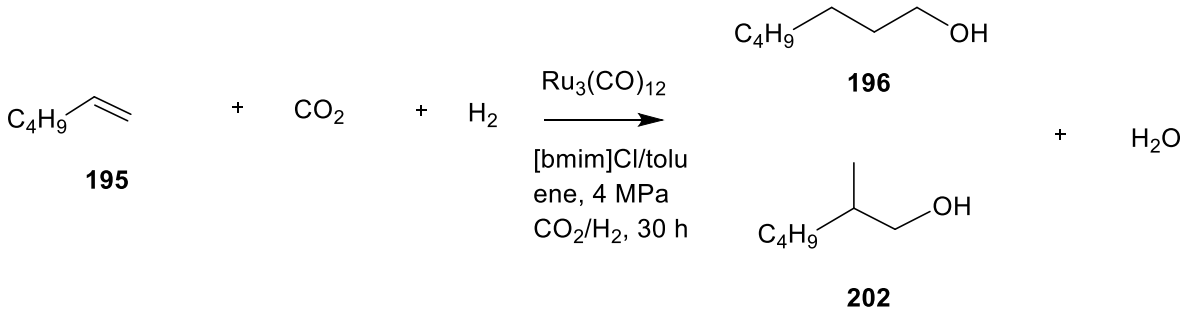
Scheme 26. A plausible reaction mechanism with halogen-containing promoter.[71]

6.2. Involving ionic liquids in the hydroformylation reaction

There were several problems among previously described Ru-based catalytic systems, used in hydroformylation reaction using CO_2. When terminal alkenes were used, they were directly hydrogenated, which proceeded with higher rate, than the hydroformylation reaction.[6,74,76] Furthermore, organic solvents used in the reaction, such as NMP (*N*-methyl-2-pyrolidone), toluene, benzene, dimethoxyethane, and 1,3-dimethylimidazolidinone, had quite high boiling points. This was proposed to cause too much difficulties in their separation from the product, if the reaction would be performed in the industrial practice. [6,74,76] For those reasons, Tominaga and co-workers successfully investigated the possibility to use ionic liquids in performing the hydroformylation reaction. [6,74,76]

6.2.1 Biphasic catalytic systems

In 2003, Tominaga and co-workers were first to report a two-phase catalytic system, which contains ionic liquid and an organic solvent. [76] The system catalyses the CO_2- based hydroformylation reaction, with the ruthenium complex. The use of ionic liquids as an alternative nonaqueous solvent in this kind of system is found attractive, based on their immiscibility with many organic solvents. Nevertheless, the use of ionic liquids does not change the general proceeding of the reaction; CO_2 reacts initially with H_2 forming CO, which serves as a reagent in hydroformylation reaction (Scheme 27). [76]



Scheme 27. The hydroformylation reaction of 1-hexene **195** with CO_2 catalysed by Ru-complex in ionic liquid.[76]

In previous investigations and studies it was concluded, that chloride anions are the most effective additives for the hydroformylation reaction. Based on that, 1,2-dialkylimidazolium salts were used as ionic liquids. Systems, such as [bmim]Cl/toluene (bmim = 1-*n*-butyl-3-methylimidazolium), and [bmim]Cl/THF gave good yields for the alcohols (79-84 %). Moreover, [omim]Cl/toluene (omim = 1-*n*-octyl-3-methylimidazolium cation) and [emim]Cl/toluene (emim= 1-ethyl-3-methylimidazolium cation), showed decent yields for the alcohols, 80 and 60 %, respectively. When the chloride anion in ionic liquids was replaced with PF_4^- or BF_4^-, the yield of alcohols decreased significantly, and at the same time, the yield of alkane, formed as a side product, increased. That was the case especially with PF_4^-, then the yield of the alkane was as high as 86 %.[76]

After the reaction was completed, organic and ionic liquid layers in the mixture were separated spontaneously, and alcohols were found in both layers. Nevertheless, alcohols were easily separated by extraction with diethyl ether. After that, the mixture of the Ru-catalytic complex and ionic liquid could be reused for the second run of the reaction, though their activity is significantly decreased already on the fourth run. Regrettably, the use of ionic liquids did not improve the regioselectivity of the reaction; almost equivalent amounts of linear and branched alcohols were formed. [76]

When biphasic catalytic systems are used with ionic liquids and organic co-solvents, it is very important, that the solvent would be miscible with the ionic liquid within the reaction conditions. [76] Otherwise, the contact of the catalyst to the alkene in the ionic liquid phase would not be possible. The miscibility of those organic solvents depends on their polarity, when it increases, the miscibility also increases. [76] Besides, the aromaticity of the solvent compound also affects miscibility, because aromatic compounds have CH-π or π-π-interactions with ionic liquids, which make them highly miscible with them. [76] Thus, when 1-hexene was converted to alcohol with [bmim]Cl, the miscibility of the solvent affected strongly the conversion; the effectivity of the solvent increased in the order of cyclohexane < Et_2O < THF < toluene. [76]

6.2.2 One-phased catalytic systems

The use of biphasic ionic liquid systems in the catalysis of hydroformylation reaction has a large disadvantage; it still requires the use of volatile organic solvents. [6,74] Therefore, in 2006, Tominaga and co-workers developed a new catalysis system, where a second solvent was not used at all, and the reaction was carried out in the ionic liquid medium only.[6] When only [bmim]Cl was used, the yield of alcohol was only 50,3 %, which is lower, than with the [bmim]Cl/toluene system. But significantly, the yield of the alcohol rose to 82 %, when half of the chloride ions were replaced by NTf_2^- anions, thus the [bmim][Cl + NTf_2] system was the most successful for the reaction.[6,74]

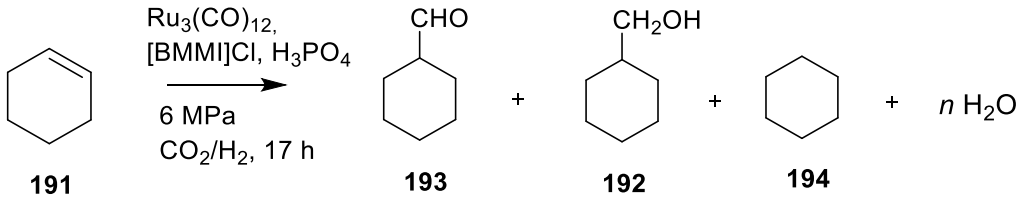
Noteworthy, when the mole fraction of NTf_2^- anions was above 0,5, the yield of the alcohol decreased, which may be caused by aldol condensation of heptanal, the intermediate of the reaction. [6] The replacement of the chloride anions with BF_4^- anions was also quite successful, though the yield of alcohol was slightly smaller (71 %). But on contrast, replacement of the chloride anions with PF_4^- did not lead to an active catalytic system, the yield of heptanol was only 49,5 %. The most reasonable and effective method for separating heptanol from the reaction system was found to be distillation because the ionic liquid is completely miscible with the alcohol.[6]

In 2009, Haukka and co-workers investigated the catalytic activity of polymer complexes of the composition $[Ru(CO)_4]_n$ in CO_2-based hydroformylation reaction of 1-hexene, comparing it to the activity of conventionally used $Ru_3(CO)_{12}$. [75] Those complexes were studied both in the presence of metal halide LiCl and ionic liquid [bmim]Cl, used as reaction promoters, and such solvent systems, as NMP, DMF, and ionic liquids [bmim][Cl+BF_4] and [bmim][Cl+PF_4]. All the main products formed in reactions were alcohols, which are the products of aldehyde hydrogenation, the product of conventional hydroformylation reaction. Moreover, as in previous studies, hexane was formed as a

side product. These results are quite reasonable because Ru-based carbonyl catalysts are known for their high hydrogenation activity, not only for aldehydes but also for alkenes directly. [75]

In particular, linear $[Ru(CO)_4]_n$ complexes showed similar catalytic activity with conventional $Ru_3(CO)_{12}$ catalysts, working as precursors to active catalysts, with selectivity to aldehyde hydrogenation, which forms alcohols.[75] The yields of alcohols varied from 40% to 65 %, the best yield of 65 % was achieved using DMF as a solvent, and LiCl as a promoter. Also [bmim]Cl worked well as a solvent, though the yield of alcohol was slightly lower, 60 % in DMF. But in contrast, when NMP was used as a solvent, [bmim]Cl (60 %) was more active, than LiCl (50 %). Thus, it can be concluded, that [bmim]Cl is a successful alternative to conventional LiCl. When ionic liquid mixtures were used, such as [bmim][Cl+BF_4], yields of alcohol remained close to 40 %, and no significant difference appeared between different mixtures. Similarly to other studies[74], hexane was the main product of the reaction, when the promoter was not used. [75]

In 2014, Ali and co-workers reported the use of a novel ionic liquid for Ru-catalysed CO_2-based hydroformylation reaction producing alcohols, [BMMI]Cl (3-butyl-1,2-dimethylimidazolium chloride), in addition to previously studied [bmim]Cl (Scheme 28). [77] Catalysts, such as $RuCl_3 \times n\ H_2O$, $[RuCl_2(cod)]_n$ and the conventional $Ru_3(CO)_{12}$ were studied, first with no additives at all. The first two mentioned showed no activity in alcohol formation, only hexane was formed. Instead, $Ru_3(CO)_{12}$ showed selectivity for oxo-product (aldehyde and alcohol mixture) up to 83 %, and alcohol selectivity up to 94 %. [BMMI]Cl and [bmim]Cl both showed similar activity for conversion to alcohol, 93 %, and 96 %, respectively. [77]



Scheme 28. The Ru-catalysed hydroformylation reaction of cyclohexene **192** using CO_2 and ionic liquid.[77]

An acid additive, H_3PO_4, was studied with $Ru_3(CO)_{12}$, and it was shown to significantly improve both the catalytic activity and the selectivity for the alcohol. The conversion to oxo-products grew from 51 % to 99 %, when H_3PO_4 was used as an additive. It is found likely, that the acid promotes the addition of hydrogen to carboxylate groups, by facilitating protonolysis and hydride transfer, which are pivotal steps for this addition. [77] It can thus be concluded, that the mechanisms of reaction

processes are known; first, CO_2 hydrogenates to CO, then hydroformylation reaction occurs, and finally, product aldehyde is reduced by Ru-carbene complex. [77]

6.3 Hydroformylation reaction of other alkenes than hexene and cyclohexene

Ali and co-workers also investigated the functionalization of different alkenes to alcohols **203-211** through CO_2-based hydroformylation reaction in [BMMI]Cl ionic liquid. Alkenes, such as cyclic disubstituted alkenes (cyclooctene and norbornene), cyclic disubstituted conjugated dienes (1,3-cyclooctadiene), cyclic disubstituted dienes (1,5-cyclooctadiene), and 2,2'-disubstituted alkenes such as carvone, 1-methylstyrene and *(R)*-(+)-limonene, were effectively converted to alcohols by hydroformylation reaction, with selectivities up to 93 % and conversions up to 99 % (Figure 15). [77]

Among alkenes studied, hindered alkenes, such as 2-methyl-2-butene, underwent quite low conversions to oxo-products (25 %), but with high selectivities (up to 90 %).[77] Terminal alkenes, for example, 1-hexene, were not effectively converted to heptanol, with the selectivity of 38 % maximum. Compounds that are conjugated to aromatic groups showed very low selectivity for oxo-products including alcohols, instead, they were fully hydrogenated. This phenomenon can be rationalized by the fact, that the C=C bond of such compounds is more rapidly hydrogenated, compared to the rate of the RWGS reaction and hydroformylation reaction. [77] This is the case with terminal alkyl-substituted alkenes and compounds where alkenes are conjugated to aromatic groups.[77]

Also, alkenes other than 1-hexene were investigated in the presence of LiCl, CO_2 instead of CO, and Ru-based catalysts. With LiCl, interestingly, the hydroformylation reaction of 2- and 3-hexene did not produce an expected product, 2-ethyl-1-pentanol, instead, a mixture of 1-heptanol and 2-methyl-1-hexanol was obtained. Those are products expected from the hydroformylation reaction of 1-hexene. This was explained by double bond migration from 2- and 3-hexene, occurring before hydroformylation reaction, which produced 1-hexene. Thus, hydroformylation reaction products referring to 1-hexene seem reasonable.[71]

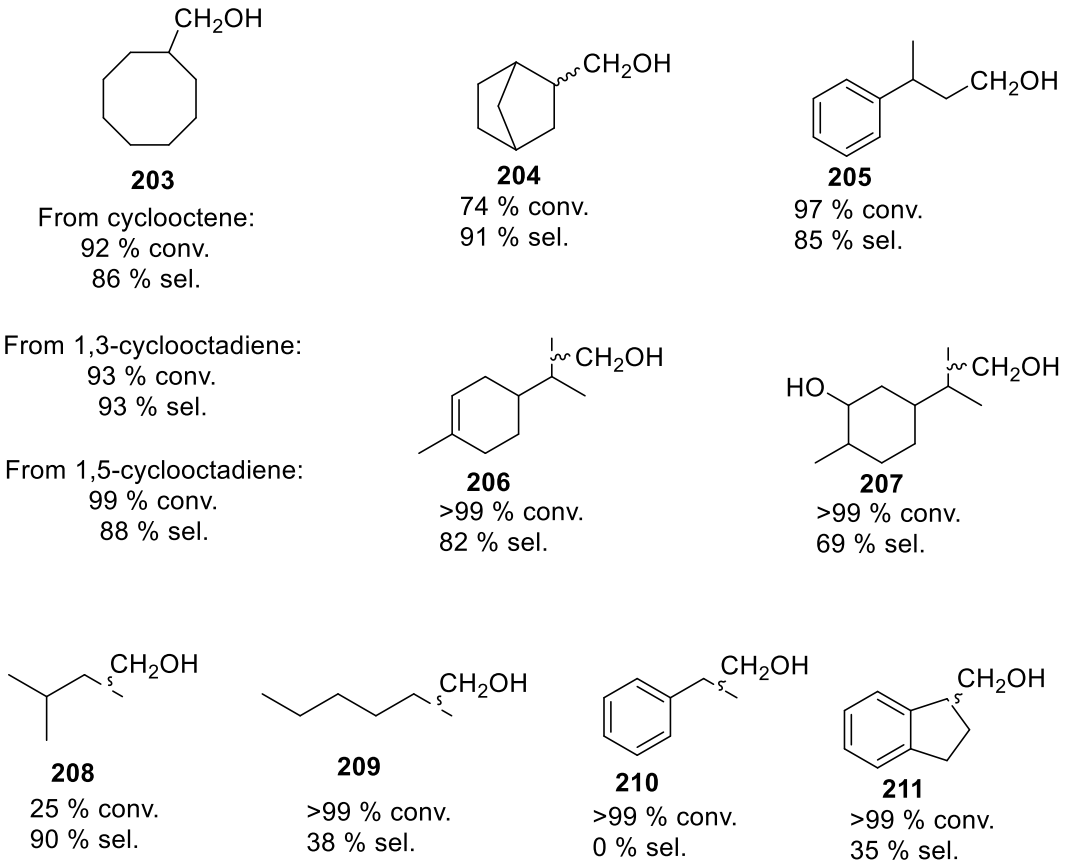


Figure 15. Alcohol **203-211** selectivity and alkene conversion achieved by Ru-catalysed CO_2-based hydroformylation reaction, with [BMMI]Cl as an additive.[77]

6.3.1 Effects of new additives for the hydroformylation reaction of other alkenes than hexene and cyclohexene

As it was previously mentioned, one of the main problems with CO_2-based hydroformylation reaction of alkenes with traditional catalytic systems is the chemoselectivity. [78] In this case, chemoselectivity refers to the selectivity towards the oxo-products formed in hydroformylation reaction, and the alkanes formed in the hydrogenation of starting material. Additional drawbacks are caused also by harsh conditions, such as high pressure and temperature (usually 160 °C). For those reasons, Liu and co-workers developed novel phosphite-based catalyst systems, when different ligands were first tested using 1-octene as a starting material, $Ru_3(CO)_{12}$ as the catalyst, and LiCl as an additive (Scheme 29). [78] The aim was to modify the catalyst with different ligands, to improve its selectivity for hydroformylation reaction instead of direct alkene hydrogenation, and activity for catalysis. Without the use of ligand, the reaction system gave only 33 % of the alcohol. Regrettably, also **L1-L2** showed low selectivity for alcohol, 1-octene was reduced for a great amount. **L3** showed a decent yield for alcohol, though several undesired side products were formed. Ligands **L4-L8** showed very good

improvement in chemoselectivity, where **L5** gave the best yield for the alcohol, 76 %. The *ortho*-substituents on the phenol rings of those ligands strongly affects their activity. Thus, methyl groups in **L6** led to the decreased yield of the alcohol, with the formation of side products. **L9** with methoxy group also gave only moderate yield for the alcohol. In the contrast, ligands **L5** (methyl substituted) and **L7** gave good yields for the alcohol.[78]

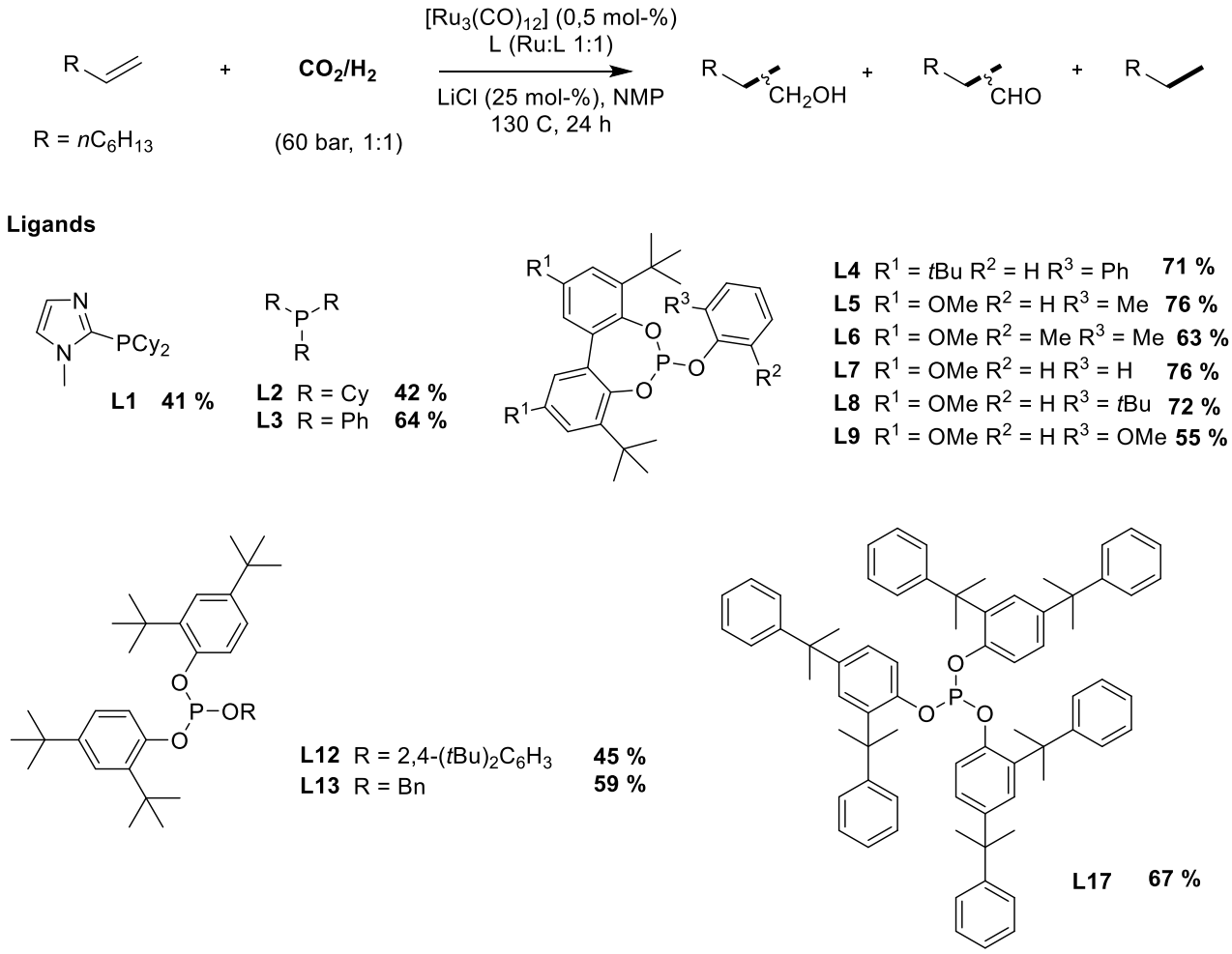
Table 1. Hydroformylation reaction of 1-octene with CO_2: product yields and chemoselectivities.[78]

Ligand	Yield of alcohol (%)	Yield of alkane(%)	*n/iso* selectivity
L1	41	27	49:51
L2	42	34	48:52
L3	64	15	51:49
L4	71	19	54:46
L5	76	15	51:49
L6	63	13	56:44
L7	76	12	53:47
L8	72	12	56:44
L9	55	18	56:44

As a result, ligand **L5** was concluded to be the most proper for the success of the reaction, and it was thus studied more carefully. The influence of pressure on the reaction was studied by increasing partial pressures of CO_2 and H_2. As a result, increasing pressure of CO_2 led to the greater formation of alkane side products. This was proposed to be a result of the lower rate of RWGS reaction, which requires high pressure of H_2. But interestingly, the higher pressure of hydrogen also leads to faster hydrogenation reaction. [78] These results can be compared to the results of the group of Fujita and co-workers, who also investigated the influence of pressures of CO_2 and H_2 on the hydroformylation reaction on cyclohexene, where LiCl was also used as an additive. Increasing the partial pressure of hydrogen promoted the hydrogenation of aldehyde to alcohol in both studies. The group of Fujita concluded, that increasing the total pressure of CO_2 and H_2 resulted in increasing the yield of the aldehyde, while Liu and co-workers showed, on the other hand, that this total pressure did not influence the yield of the alcohol significantly. [73,78]

The effect of the additives LiCl and **L5** on different parts of the reaction, which contains the RWGSR, hydroformylation reaction, and hydrogenation of the aldehyde, as well as direct alkane forming hydrogenation, was studied also with 1-octene as a substrate. The ligand **L5** seemed to not affect the RWGS reaction when on the contrary, LiCl is pivotal for the reaction to succeed. This result is quite the same as the previously described results of Tominaga and Haukka groups, for instance, where the influence of LiCl additive was studied more carefully and was also considered to be necessary for the reaction.[12,76] With the second step of the reaction sequence, the hydroformylation reaction, the effect of ligand was, on the contrary, concluded to be pivotal, promoting the carbonylation.[78] When the ligand was not used, octane was the main product. Still, the LiCl affects this step as well, since when it was absent, the yields of alcohols decreased. Finally, with the hydrogenation step, its activity was decreased, when LiCl was not used, but also when an excess of ligand was used. It was thus proposed, that the LiCl facilitates the reduction of the aldehyde, by acting as a Lewis acid catalyst. Interestingly, the ligand **L5** did not significantly affect the hydrogenation reaction. An important observation was also, that the rates of hydroformylation reaction and aldehyde hydrogenation reactions were lower than of the initial RWGS reaction. This was supported by the fact, that CO and aldehyde were constantly observable during the whole reaction sequence.[78]

The hydroformylation/reduction reaction sequence of different alkenes was also studied, using the **L5** ligand, CO_2/H_2, and LiCl as an additive. [78] Terminal alkenes, such as 1-pentene, showed a decent yield for the alcohol (88 %), though the yield of alcohol from 1-octene was lower, 76 %. Internal alkene, such as 2-octene, showed the yield of alcohol similar to that of the terminal one (75 %). Alcohols generated from cyclic alkenes, such as cyclohexene, *cis*-cyclooctene, and cyclopentene, gave good yields for the alcohols, 90 %, 80 %, and 68 %, respectively. 1,1-Diphenylethylene was previously reported as a difficult substrate to form alcohol with the reaction sequence (only 9 % of the alcohol), but with the phospite ligand, an industrially satisfactory yield was achieved (48 %). The main problem, the regioselectivity for linear and branched products, still remains unsolved. For many substrates, such as terminal and internal alkenes, a mixture of linear and branched products formed. The only exception makes 3,3-dimethylbut-1-ene, which produced 99 % of linear alcohol, though, with a relatively low total yield of the alcohol, 45 %. Nevertheless, the RWGS/hydroformylation/reduction reaction sequence was improved with phosphite modified catalysts. The reaction conditions for alcohol formation were made comparably mild, and the undesired side reaction, hydrogenation of alkene, was succeeded to be slowed down.[78]



Scheme 29. Hydroformylation reaction of 1-octene with CO_2: Ligand examination, and alcohol yields. [78]

7. Conclusions

Converting carbon dioxide to different valuable chemicals has gained large interest among several research groups. The most obvious reason is linked to the CCU theme, which aims to reduce the global impact of carbon dioxide emissions. Particularly, hydroformylation reaction, in tandem with the RWGS reaction, has been indicated to be a very successful and potential way to use carbon dioxide as a raw material. Nevertheless, carbon dioxide is also a very potential alternative to carbon monoxide, which is used conventionally in hydroformylation reaction, since its usage has several problems, such as toxicity and flammability.

The research made especially by Tominaga and Haukka groups has shown, that CO_2 - based hydroformylation reaction can be performed quite successfully, with good yields and selectivities toward the desired product, which can be branched or linear alcohol or aldehyde. Both Ru and Rh – based homogeneous catalytic systems have shown good performance in hydroformylation reaction catalysis, especially when using ionic liquids as solvents. However, the investigations have shown, that hydroformylation reaction requires the presence of chloride anion in the reaction system, either in the catalytic complex itself or in an ionic liquid, otherwise, the yields of oxo-products become very low. There are also other difficulties in reaching good undergoing of the hydroformylation reaction, such as preventing the direct hydrogenation of the alkene, which forms alkane as a side product.

Despite the reached success, the mechanism of CO_2 – based hydroformylation reaction requires much further investigation, for example, which is the rate-determining step in the mechanism. Moreover, the precise kinetics of the reaction has not been investigated yet at all. Also, the potential usage of different metals, other than previously used, for catalytic complexes, needs further investigation. In conclusion, this theme has very much potential and work for future researchers.

EXPERIMENTAL PART

1. Objectives

The aim of the experimental part of this Master's thesis was to further investigate the mechanism of the hydroformylation reaction. The most important part supposed to be the study of kinetic isotope effect (KIE), for which labelled compounds had to be synthesized. Cyclohexene had been chosen as a starting compound for these experiments, monodeuterated **1** and dideuterated **2** versions of it (Figure 1).

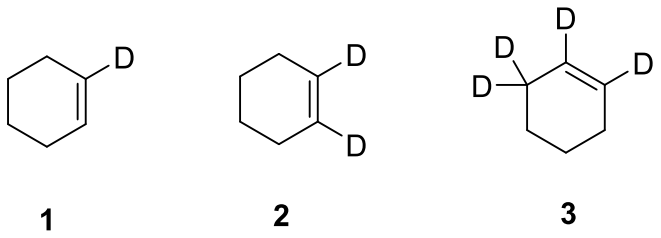


Figure 1. Mono-, di-, and tetradeuterated cyclohexene

We were able to synthesize monodeuterated cyclohexene **1**, and tetradeuterated cyclohexene **3,** but no KIE – experiments were eventually done for the hydroformylation reaction, despite all attempts. 1,2,3,3-Tetradeuterio-cyclohexene **(3)** was synthesized, since many attempts to make **2** were not successful, and it was assumed, that two extra deuterium atoms would not disturb the hydroformylation reaction, which occurs only in the C-C-double bond of the compound. Also, it was thought, that the KIE-experiments would be quite informative also with four deuterium atoms, which may strongly affect the kinetics of the reaction.

2. Synthesis of deuterated compounds and their use in hydroformylation reaction

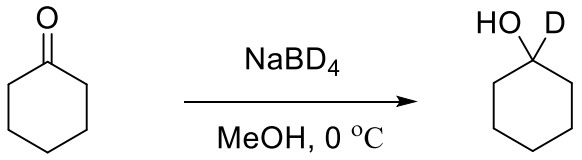
All syntheses of deuterated compounds were performed under ambient pressure. TLC – tests were performed with Merck Silica gel 60 F254 disks. Products were characterized using ^{1}H NMR (Bruker Avance III HD 300 MHz). All solvents and starting reagents were commercially available, used solvents purity is at the level provided by the manufacturer.

Hydroformylation reactions were performed using the pressure reactor (Hastelloy C276, CAT 7), with maximum pressure of 100 bar, and maximum temperature of 250 °C. The reaction mixtures

were made in 7 vessels with Teflon cups (7×10 ml), which were transported into the reactor before pressurizing. The product ratios were estimated using Agilent Technologies 7890A GC system – gas chromatography.

2.1. Synthesis of 1-deuterio-cyclohexene

2.1.1 Synthesis of 1-deuterio-1-cyclohexanol



4 **5**

Scheme 1. Synthesis procedure for deuterated cyclohexanol **5**[79,80]

1-deuterio-1-cyclohexanol **(5)** was synthesized using commercially available cyclohexanone **4.** Sodium borodeuteride (2,00 g, 47,8 mmol, 1,33 equiv) was added to a stirring solution of cyclohexanone (3,7 ml, 50 mmol, 1,0 equiv) and methanol (100 ml) in 0 ℃ using an ice bath. The reaction mixture was stirred for 30 min. The consumption of all cyclohexanone in the reaction was confirmed by TLC. The reaction was then quenched with water (11 ml) and stirred additionally for 10 min. Methanol was evaporated, and the resulting suspension was extracted between water (40 ml) and dichloromethane (3 x 50 ml). The organic layers were combined, dried over Na_2SO_4, and the solvent was removed under reduced pressure. Product (3,60 g, 71,4 %) was obtained as a colorless liquid.

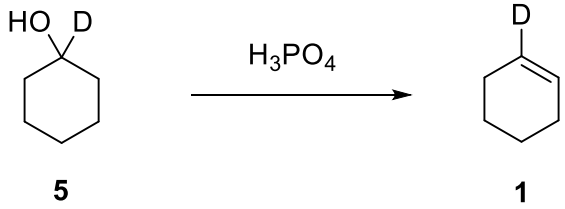
^{1}H NMR (300 MHz, $CDCl_3$): 3,59 (s, 1H), 1,85 (d, J = 9 Hz, 2H), 1,70 (s, 2H), 1,47 (m, 2H), 1,22 (p, J = 10,7 Hz, 4H)

NMR spectrum corresponded to the spectrum found in literature[81]

Level of deuteration: 99 % (the diagnostic peak used was 3,59 (s, 1H), integral 0,01)

R_f (EtOAc/*n*-hexane 20:80): 0,43

2.1.2 Synthesis of 1-deuterio-cyclohexene (method 1)



Scheme 2. Synthesis procedure for 1-deuterio-cyclohexene[82]

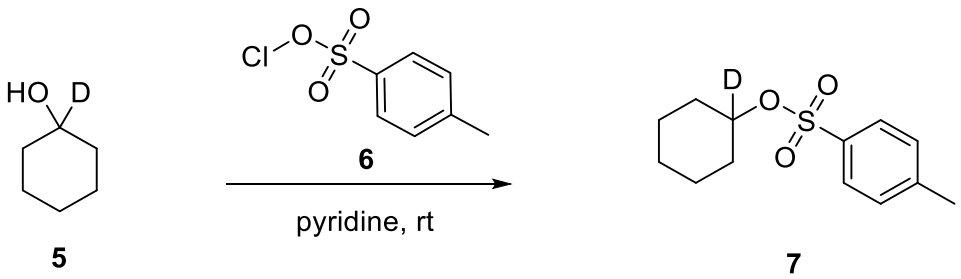
Phosphoric acid (1,20 ml, 23,1 mmol, 2,40 equiv) was added to previously synthesized 1-deuterio-1-cyclohexanol **(5)** (1 ml, 9,6 mmol, 1 equiv), and the mixture was heated to distill under 150 °C for 1,5 h. The product was distilled out at 45 °C, as a colorless liquid (587 mg, 74,4 %). However, NMR characterization and integrals showed, that the product was deuterated with 28 % yield, most of the product was non-deuterated cyclohexene.

^{1}H NMR (300 MHz, $CDCl_3$): 5,67 (t, J = 1,6 Hz, 1H), 2,07-1,94 (m, 4H), 1,68-1,55 (m, 4H)

NMR spectrum corresponded to the spectrum of non-deuterated cyclohexene found in literature[82]

Level of deuteration: 28 % (the diagnostic peak used was 5,67 (t, 1H), integral 1,73)

2.1.3 Synthesis of 1-deuterio-1-(toluene-4-sulfonyloxy)-cyclohexane intermediate



Scheme 3. Synthesis procedure for 1-deuterio-1-(toluene-4-sulfonyloxy)-cyclohexane[83]

1-deuterio-1-cyclohexanol **(5)** (5,20 g, 52,2 mmol, 1,00 equiv) was dissolved in pyridine (75 ml), and *p*-toluenesulfonyl chloride **6** (9,96 g, 52,2 mmol, 1,00 equiv) was added. The reaction mixture was stirred at room temperature for 24 h. The completion of the reaction was confirmed by TLC. The reaction mixture was poured onto ice water (100 ml) and extracted with diethyl ether (50 ml). The organic layer was then washed several times with an aqueous 2 M hydrogen chloride solution, and with water, to remove pyridine. The extract was dried over Na_2SO_4, and concentrated under reduced pressure, to give the product as a yellow oil (7,46 g, 56 %)

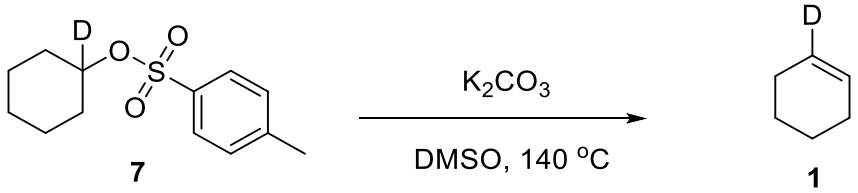
^{1}H NMR (300 MHz, $CDCl_3$): 7,81-7,72 (d, J = 8,3 Hz, 2H), 7,30 (d, J = 7,8 Hz, 2H), 2,42 (s, 3H), 1,81-1,59 (m, 4H), 1,46 (m, 3H), 1,36-1,12 (m, 3H)

NMR spectrum corresponded to the spectrum of non-deuterated **7** found in literature[83]

Level of deuteration: >97 % (no peak was observed at 5,67 ppm)

R_f (EtOAc/*n*-hexane 30:70): 0,25

2.1.4 Synthesis of 1-deuterio-cyclohexene (method 2)



Scheme 4. Synthesis procedure for 1-deuterio-cyclohexene[84]

DMSO (16,7 ml) was added to **7** (5,49 g, 21,6 mmol, 1,00 equiv), and potassium carbonate (3,73 g, 26,9 mmol, 1,25 equiv) to resulting mixture. The reaction mixture was heated to distill at 140 °C for 24 h, the product (1,24 g, 69.6 %) was distilled out as a colorless liquid. NMR characterization showed deuterated cyclohexene with 97 % yield, with a small amount of cyclohexanone as an impurity.

^{1}H NMR (300 MHz, $CDCl_3$): 5,67 (t, J = 3,2 Hz, 1H), 2,0 (m, 4H), 1,62 (p, J = 3,1 Hz, 4H)

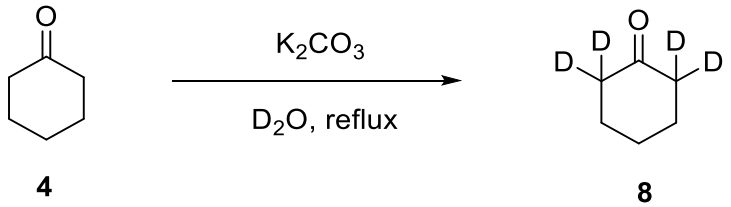
Impurity: ^{1}H NMR (300 MHz, $CDCl_3$): 2,34 (t, J = 6,6 Hz, 4H), 1,86 (m, 4H)

NMR spectrum corresponded to the spectrum of non-deuterated cyclohexene found in literature[82]

Level of deuteration: 97 % (the diagnostic peak used was 5,67 (t, 1H)), integral 1,03)

2.2. Synthesis of 1,2,3,3-tetradeuterio-cyclohexene (3)

2.2.1 Synthesis of 2,2,6,6-tetradeuterated cyclohexanone intermediate



4 8

Scheme 5. Synthesis procedure for 2,2,6,6-tetradeuterated cyclohexanone[85]

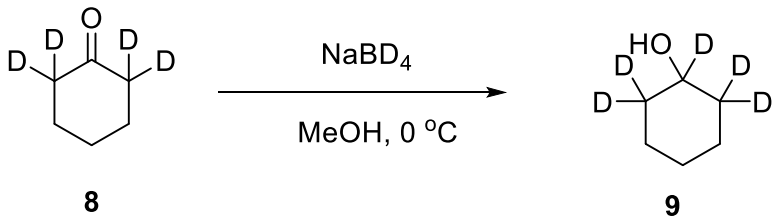
Commercially available cyclohexanone **4** (5,99 ml, 57,9 mmol, 1,00 equiv) was mixed with potassium carbonate (0,6 g) and deuterium oxide (90,0 ml, 4,99 mol, 86,2 equiv). The reaction mixture was heated to reflux for 62 h. After that, the mixture was cooled, extracted with diethyl ether, and the solvent was removed under reduced pressure. The resulting product (4,98 g, 84,1 %) appeared as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$): 1,94-1,76 (m, 4H), 1,77-1,56 (m, 2H)

NMR spectrum corresponded to the spectrum found in literature[85]

Level of deuteration: >97 % (no peaks were observed at 1,85 ppm and 1,70 ppm)

2.2.2 Synthesis of 1,2,2,6,6-pentadeuteriocyclohexanol intermediate



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Scheme 6. Synthesis procedure for 1,2,2,6,6-pentadeuteriocyclohexanol[79,80]

Sodium borodeuteride (2,50 g, 59,7 mmol, 1,33 equiv) was added to a stirring solution of **8** (4,50 g, 44,1 mmol, 1,00 equiv) and methanol (125 ml) in 0 °C using ice bath. The reaction mixture was stirred for 30 min. The lack of the starting material in the reaction was confirmed by TLC. The reaction was then quenched with water (14 ml) and stirred additionally for 1 h. Methanol was evaporated, and the resulting suspension was extracted between water (40 ml) and dichloromethane (3 x 60 ml). Organic layers were combined, dried over Na_2SO_4, and the solvent was removed under reduced pressure. Product (4,25 g, 90,8 %) was obtained as a colorless liquid.

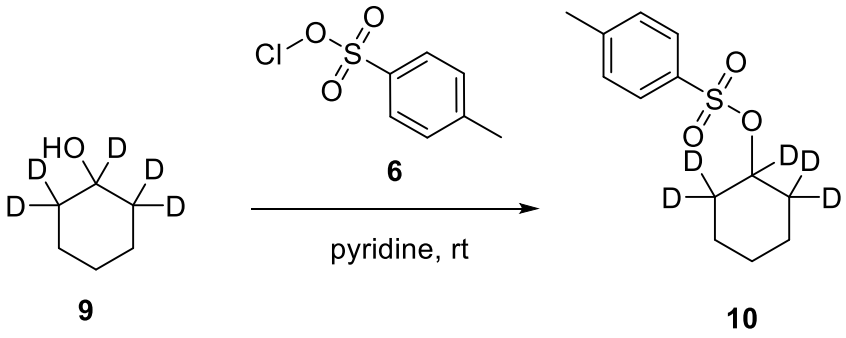
^{1}H NMR (300 MHz, $CDCl_3$): 3,57 (s, 1H) 1,77-1,64 (m, 2H), 1,58-1,46 (m, 1H), 1.32-1,06 (m, 3H)

NMR spectrum corresponded to the spectrum of **5** found in literature[81]

Level of deuteration: 98 % (the diagnostic peak used was 1,77-1,64 (m, 2H) integrals 0,03 for deuterated position, 1,95 for 2H)

R_f (EtOAc/*n*-hexane 20:80): 0,43

2.2.3 Synthesis of 1,2,2,6,6-pentadeuterio-1-(toluene-4-sulfonyloxy)-cyclohexane intermediate



Scheme 7. Synthesis procedure for 1,2,2,6,6-pentadeuterio-1-(toluene-4-sulfonyloxy)-cyclohexane[82]

1,2,2,6,6-pentadeuteriocyclohexanol **(9)** (4,25 g, 40,8 mmol, 1,00 equiv) was dissolved in pyridine (166 ml), and **6** (7,77 g, 40,8 mmol, 1,00 equiv) was added. The reaction mixture was stirred at room temperature for 48 h. The completion of the reaction was confirmed by TLC. The reaction mixture was poured into ice water (100 ml) and extracted with diethyl ether. The organic

layer was then washed several times with an aqueous 2 M hydrogen chloride solution, and with water, to remove pyridine. The extract was dried over Na_2SO_4, and concentrated under reduced pressure, to give the product as a yellow oil (8,15 g, 77,1 %)

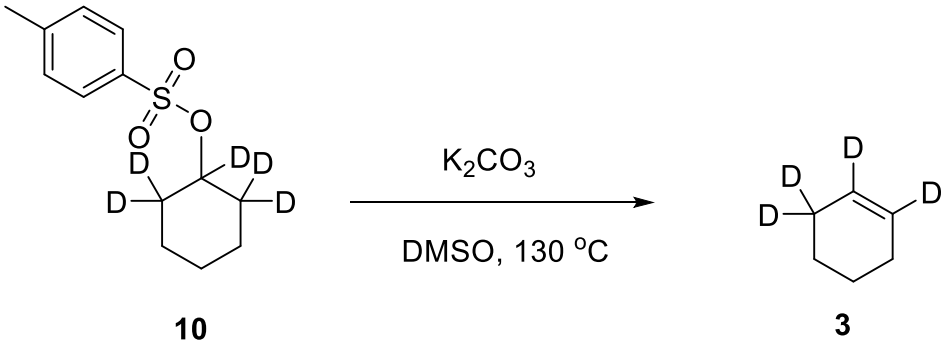
^{1}H NMR (300 MHz, CDCl3): ^{1}H NMR (300 MHz, $CDCl_3$): 7,85-7,67 (m, 2H), 7,39-7,28 (m, 2H), 2,42 (s, 3H), 1,76-1,56 (m, 2H), 1,46 (m, 1H), 1,36-1,12 (m, 3H)

NMR spectrum corresponded to the spectrum of non-deuterated **7** found in literature[83]

Level of deuteration: >97 % (no peaks were observed at 5,67 ppm, 1,85 ppm, and 1,70 ppm)

R_f (EtOAc/*n*-hexane 30:70): 0,25

2.2.4 Synthesis of 1,2,3,3-tetradeuterio-cyclohexene



10 **3**

Scheme 8. Synthesis procedure for 1,2,3,3-tetradeuterio-cyclohexene[83]

DMSO (24,8 ml) was added to **10** (8,15 g, 31,4 mmol, 1,00 equiv), and potassium carbonate was added (5,43 g, 39,3 mmol, 1,25 equiv) to resulting mixture. The reaction mixture was heated to distill at 130 °C for 24 h, the product (1,13 g, 41,2 %) was distilled out as a colorless liquid. NMR characterization showed deuterated cyclohexene with remaining diethyl ether from the previous synthesis of **10**. The solvent was mostly removed with several distillations, which resulted also in reduced yield of the product.

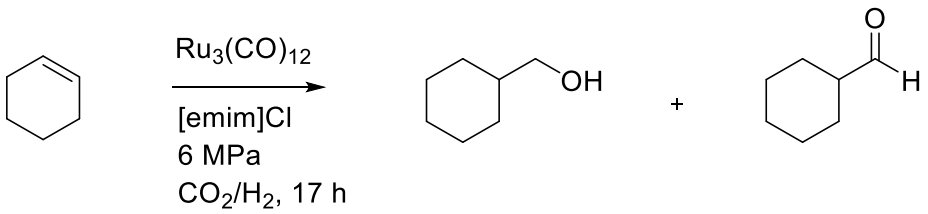
^{1}H NMR (300 MHz, $CDCl_3$): 2,05-1,89 (m, 2H), 1,65-1,49 (m, 4H)

NMR spectrum corresponded to the spectrum of non-deuterated cyclohexene found in literature[82]

Diethyl ether: 3,46 (q, J = 7 Hz, CH_2), 1,19 (t, J = 7 Hz, CH_3)

Level of deuteration: 97 % (the diagnostic peak used was 1,60 (m, 2H) integrals 0,07 for 2H (non-deuterated), 2,02 for diagnostic peak 2H)

3. Attempts at hydroformylation reaction



Scheme 9. Original synthesis procedure for hydroformylation reaction of cyclohexene

Commercially available cyclohexene (100 mg, 1,20 mmol, 1,00 eq) was added to the mixture of catalytic complex (25 mg, 0,039 mmol, 0,032 equiv) and ionic liquid (45,5 mg, 0,310 mmol, 0,255 equiv) in the reaction vessel equipped with a Teflon cup. 6 exactly the same reference reaction mixtures were made in 6 vessels. Vessels were transported into the pressure reactor, then the reactor was flushed with CO_2, then it was pressurized with CO_2 to 30 bar, and finally with H_2 to 60 bar. The reactor was heated in 120 °C for only 5 h, in attempt to only test the operability of the reactor, there was no aim for the reaction to go to the end. The total pressure and temperature were recorded to be 94 bar, and 120 °C, respectively. After 5h, the reactor was left to cool overnight, and then pressures were carefully released. Reaction mixtures was extracted with diethyl ether (15 ml), in order to remove the ionic liquid. The formation of product (possibly cyclohexanemethanol) was approximately confirmed by gas chromatography so that the hydroformylation of deuterated products would be reasonable to perform.

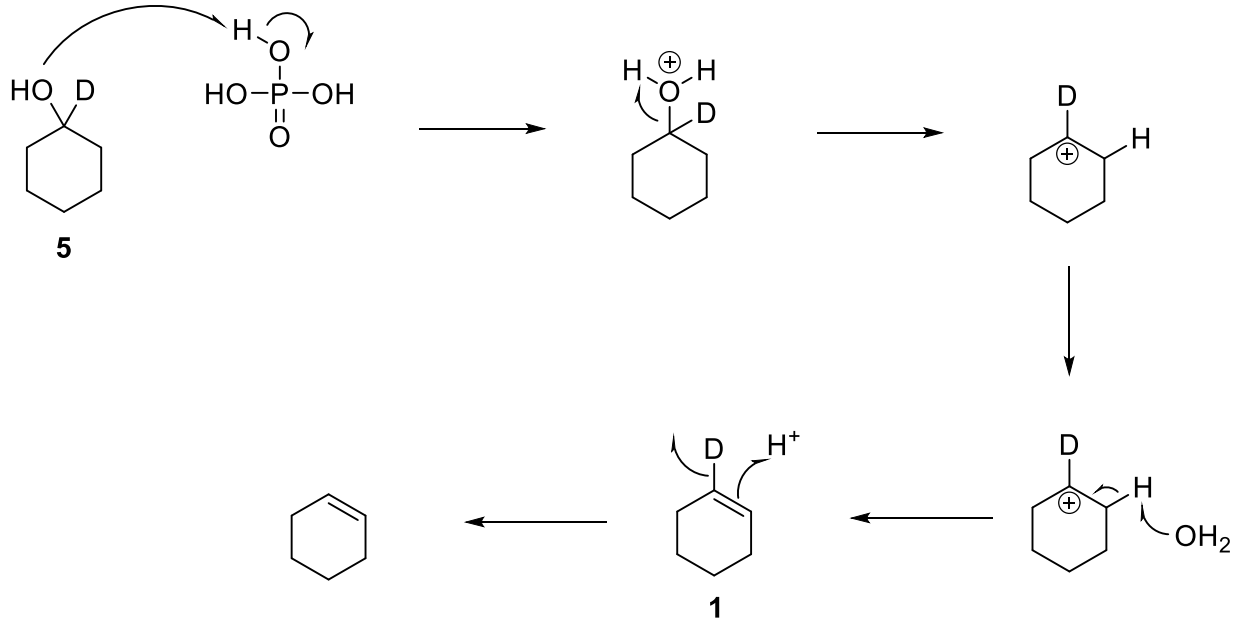
The hydroformylation reaction of 1-deuterio-cyclohexene (**1**) was performed using the same reaction conditions, as previously described for non-deuterated cyclohexene. However, 1 h after the CO_2/H_2 pressures and temperature were set, the total pressure was automatically and quickly released by the reactor, for which the maximum pressure was 100 bar. This happened despite the fact, that the pressure indicator of the reactor showed that the total pressure of the reaction mixture was approximately 95 bar. As a result, all of the possibly formed products evaporated from the reaction mixture.

4. Results and discussion

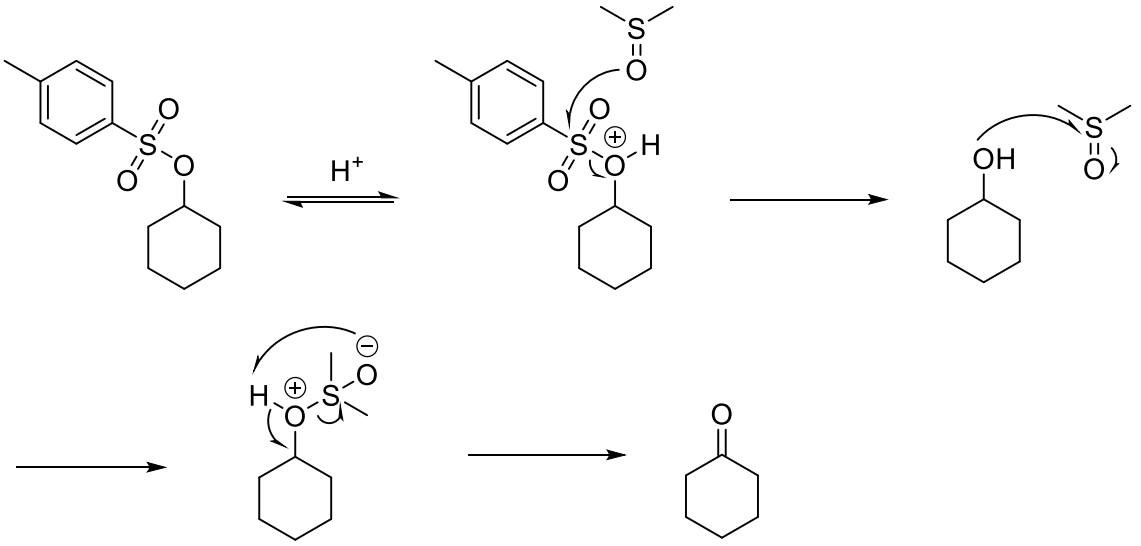
The first attempt to synthesize **1** through reduction of cyclohexanone with sodium borodeuteride followed by elimination of hydroxyl group with phosphoric acid was not successful. The reason for this is likely to be the protonation of the formed **1** followed by removal of the deuterium atom, as shown in Scheme 10.

According to the proton shift mechanism, it is clear, that the use of phosphoric acid for the elimination of the hydroxyl group to form 1-deuterio-cyclohexene (**1)** and 1,2,3,3-tetradeuteriocyclohexene (**3**) is not possible. For that reason, the synthesis of both **1** and **3** was performed by protecting the hydroxyl group with **6**, followed by removal of this group using dimethylsulfoxide and potassium carbonate as a base catalyst. This pathway was not disturbed by the proton shift and was quite successful, according to the integrals of the ^{1}H NMR spectra, which showed good deuteration levels. For both compounds, the synthesis procedures and the results were the same, although both reactions to form **3** proceeded more slowly than the reactions to form **1**. This can be possibly explained by the larger amount of deuterium atoms, which are known to affect the kinetics of a reaction.

Nevertheless, as it can be seen in NMR spectra of **1** and **3**, a very small amount of cyclohexanone was formed in the tosyl group removing reaction, which is confirmed by the NMR shifts. The interesting fact is, that the amount of cyclohexanone is smaller in **3** than in **1**, which is most likely the consequence of using lower temperature in distillation because it is the only difference in reaction procedures. One possible reason for that might be, that when the tosyl group is removed from **7**, corresponding alcohol is formed, which is transformed into cyclohexanone by DMSO by the mechanism, which is like the mechanism of Swern oxidation (Scheme 11). That is likely to be partly caused by the high temperature of the reaction. The occurring of this mechanism is though very unlikely because conventionally the Swern oxidation requires oxalyl chloride and an additional base when alcohol is transformed to a ketone. This may be the reason for the very small amount of formed cyclohexanone. Of course, there can be several more possible mechanisms for the formation of cyclohexanone in this reaction, which can be further investigated by mechanism revealing investigation methods. [86]



Scheme 10. Proposed proton shift mechanism for 1-deuterio-cyclohexene.



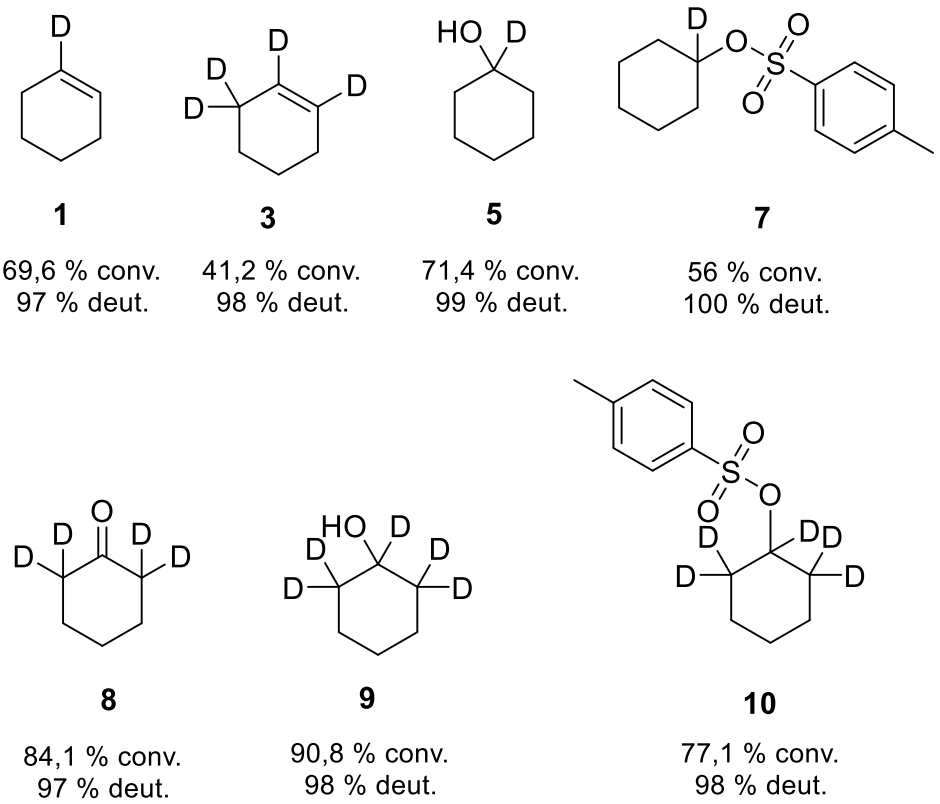
Scheme 11. Proposed mechanism for the formation of cyclohexanone as an impurity

Attempts to perform the KIE-studies at the hydroformylation reaction cannot be considered successful. There might be several possible reasons, why the pressures were released by the reactor. The most probable reason is that the pressure indicator of the reactor did not show the total pressure of the reaction mixture quite accurately, and the real pressure was bigger than 95 bar, and was over 100 bar, which is the maximum pressure allowed for the reactor. The reason for such pressure increase

is probably that the high temperature increased the partial pressures of both H_2 and CO_2, because the vapour pressure of 1-deuterio-cyclohexene (**1**) and possible products also increased.

5. Conclusions

In a conclusion, the procedures used for the synthesis of 1-deuteriocyclohexene (**1**) and 1,2,3,3-tetradeuterio-cyclohexene (**3**) can be considered successful. Yields were mostly decent, the products were mostly pure, and deuteration levels were excellent, as shown in Scheme 12. Nevertheless, the yields could be improved, and to achieve this, for instance, solvent evaporation within the synthesis procedure of **7** and **10** should be done more efficiently. The synthesis procedure for **3** can be also further improved, by changing the reaction temperature, and possibly reducing the reaction time, to avoid producing cyclohexanone as an impurity.



Scheme 12. All synthesized substrates, their levels of deuteration and yields.

There were several reasons, why the attempted KIE-studies for the hydroformylation reaction did not succeed. The synthesis of needed deuterated compounds took a very long time, due to the lack of

practical experience. Therefore, there was not much time left to perform the hydroformylation reaction using the pressure reactor, which usage also needs practical experience. The maximum pressure allowed by the reactor should have been at least 150 bar, so that the pressure and temperature required for the hydroformylation reaction would be possible to achieve, without breaking the reactor. It can be thus concluded, that the type of reactor used in the project was not suitable for the temperature and pressure needed to perform the hydroformylation reaction. In addition, the lack of experience of both the author, and his supervisors in the laboratory, of working with pressurized reactions, made this project quite challenging. The hydroformylation reactions should have been planned more carefully, and supervisors, that have specific experience in performing this kind of reactions, should have been more available. In addition, deuterated compounds should have possibly been ordered from a specific manufacturer, so that the project could have focused only on KIE-studies of the hydroformylation reaction. In the future, the kinetic isotope effect could be investigated, with a more suitable reactor, and possibly using deuterated compounds synthesized during this project. The kinetic isotope effect still needs to be studied in detail, to achieve better knowledge of the mechanism of the hydroformylation reaction, than which has been gained thus far.

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Appendices

APPENDIX 1: ^{1}H NMR spectrum of **5**

APPENDIX 2: ^{1}H NMR spectrum of **1** (partly deuterated)

APPENDIX 3: ^{1}H NMR spectrum of **7**

APPENDIX 4: ^{1}H NMR spectrum of **1 (**deuterated)

APPENDIX 5: ^{1}H NMR spectrum of **8**

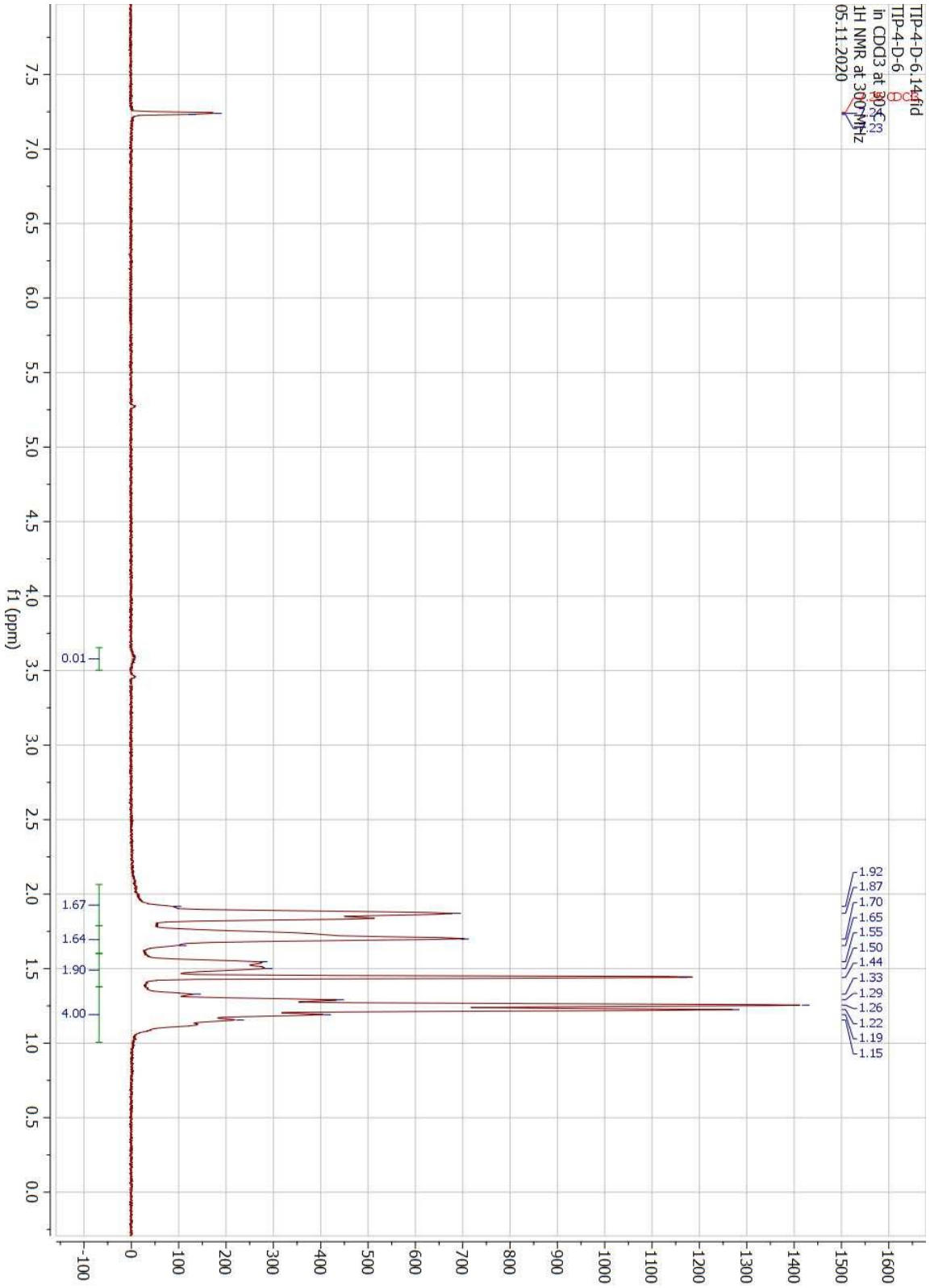
APPENDIX 6: ^{1}H NMR spectrum of **9**

APPENDIX 7: ^{1}H NMR spectrum of **10**

APPENDIX 7: ^{1}H NMR spectrum of **3**

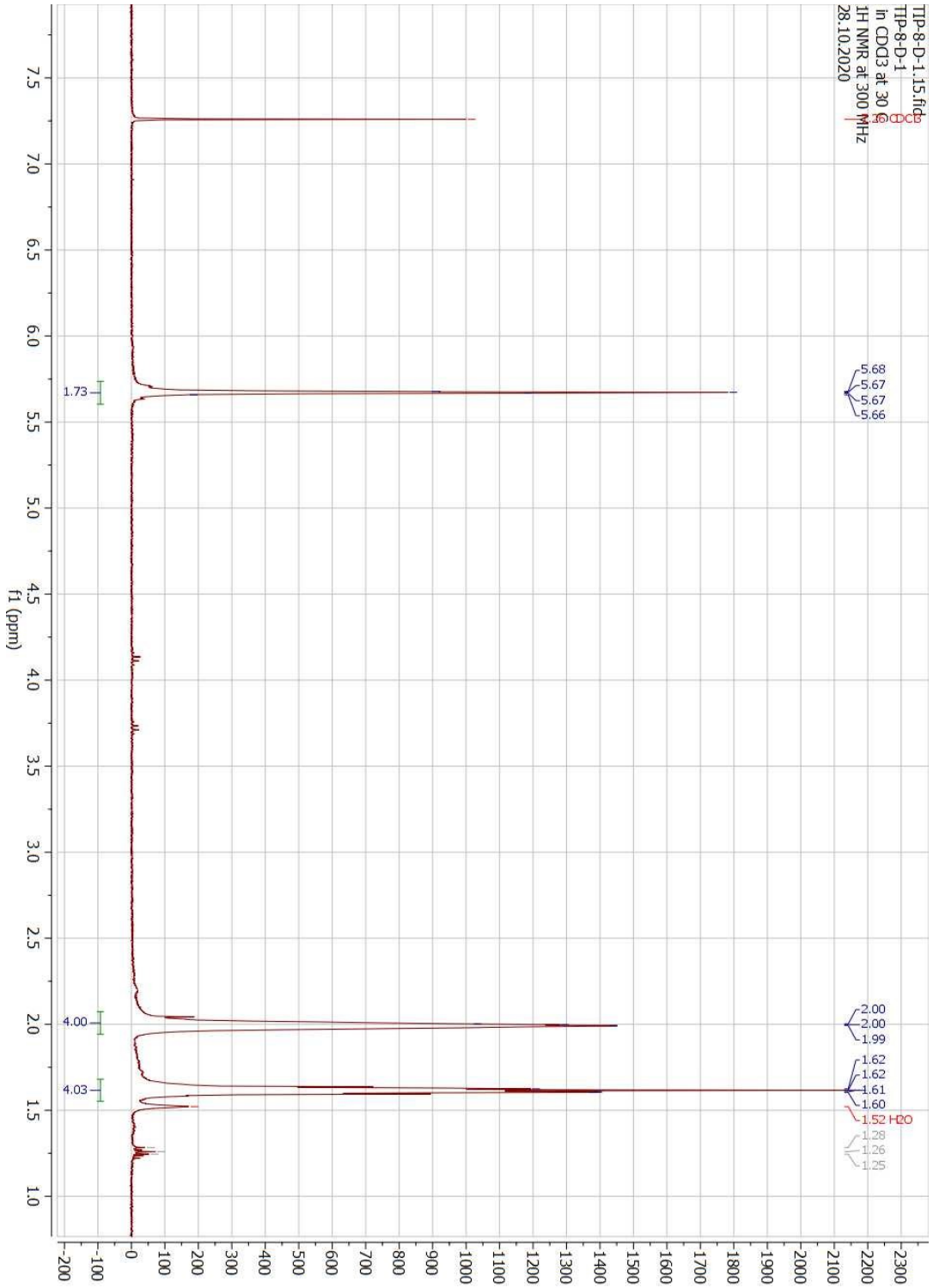
APPENDIX 1:

^{1}H NMR spectrum of monodeuterated cyclohexanol **5**



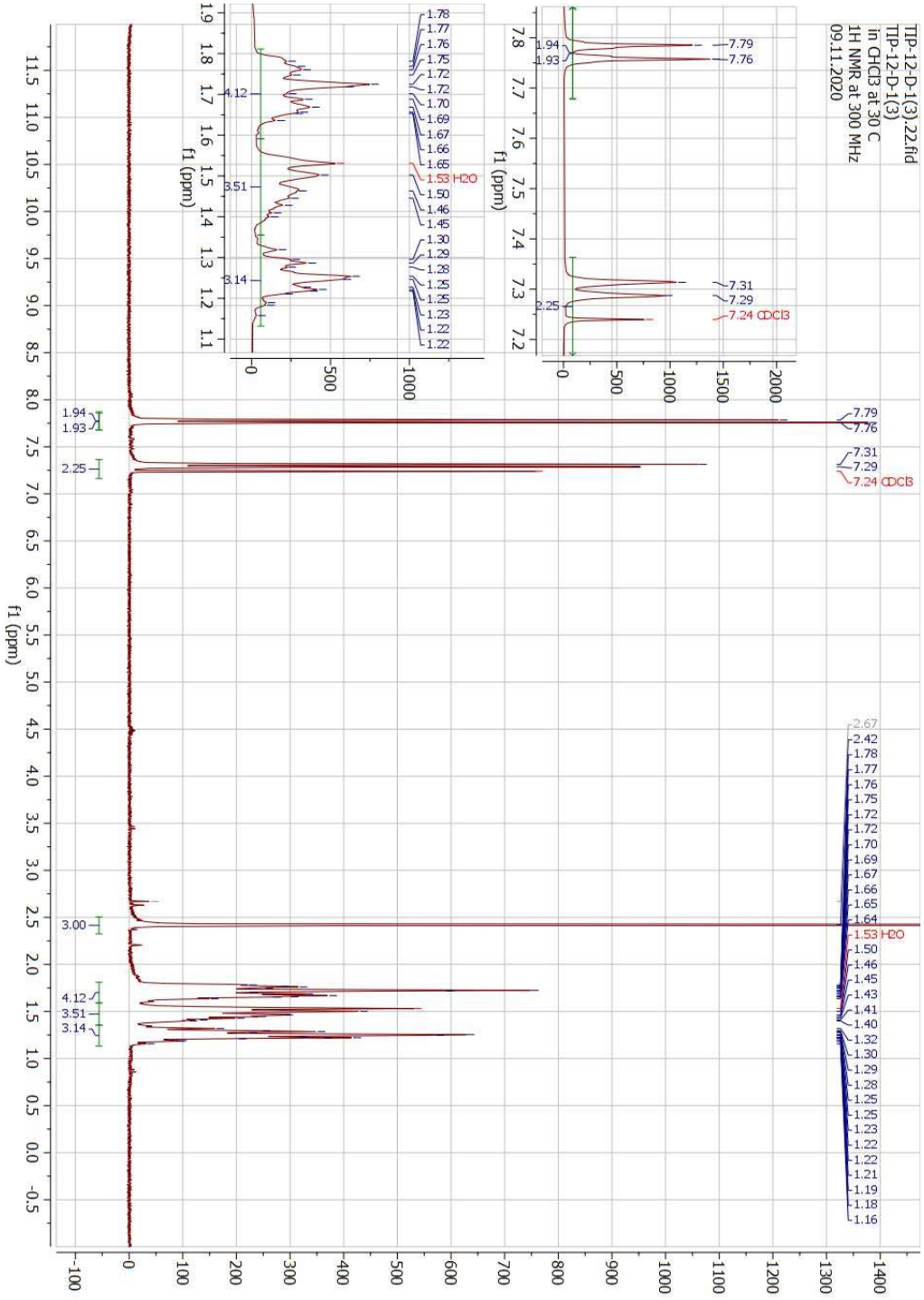
APPENDIX 2:

^{1}H NMR spectrum of partly deuterated **1**



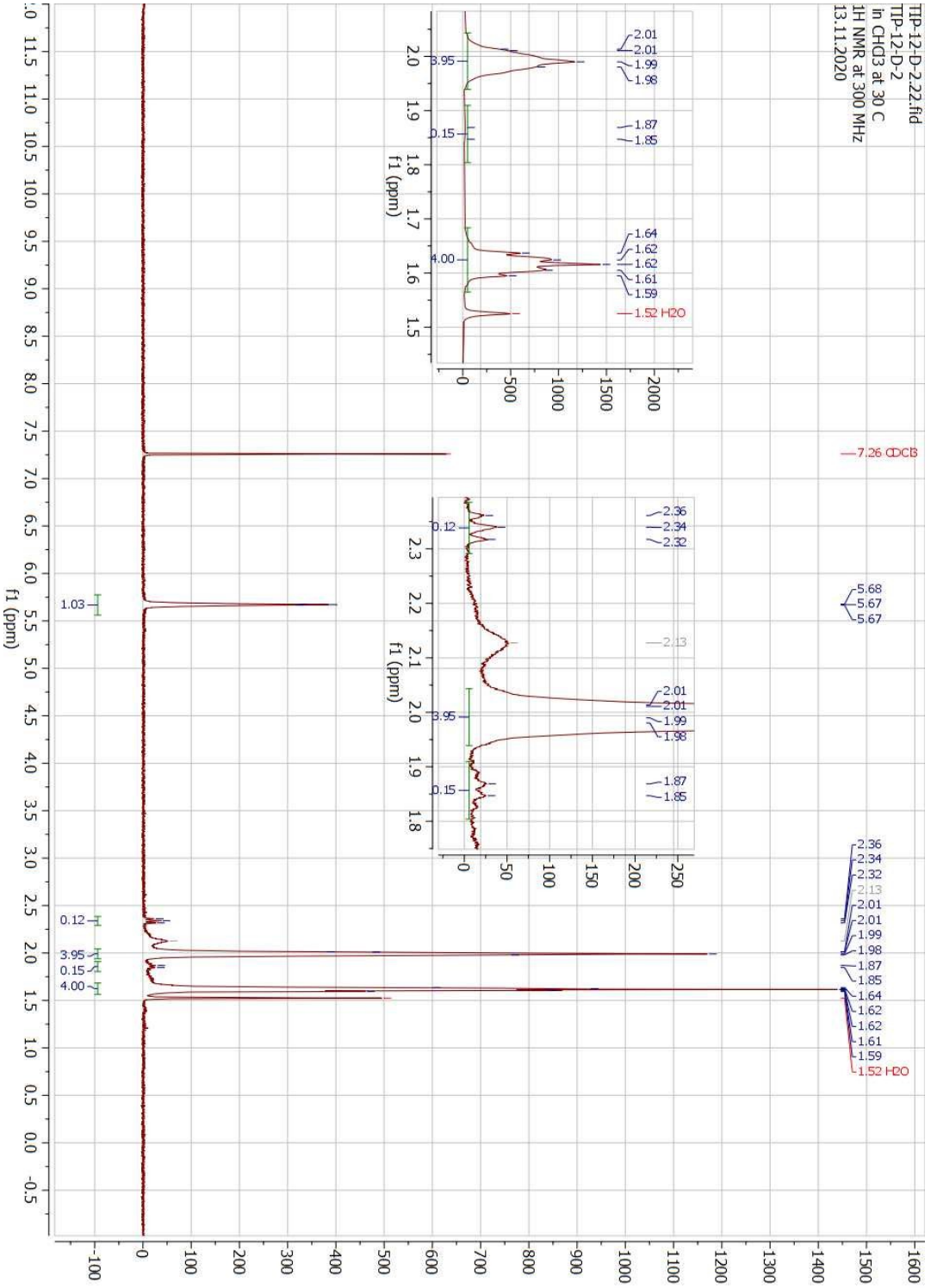
APPENDIX 3:

^{1}H NMR spectrum of **7**



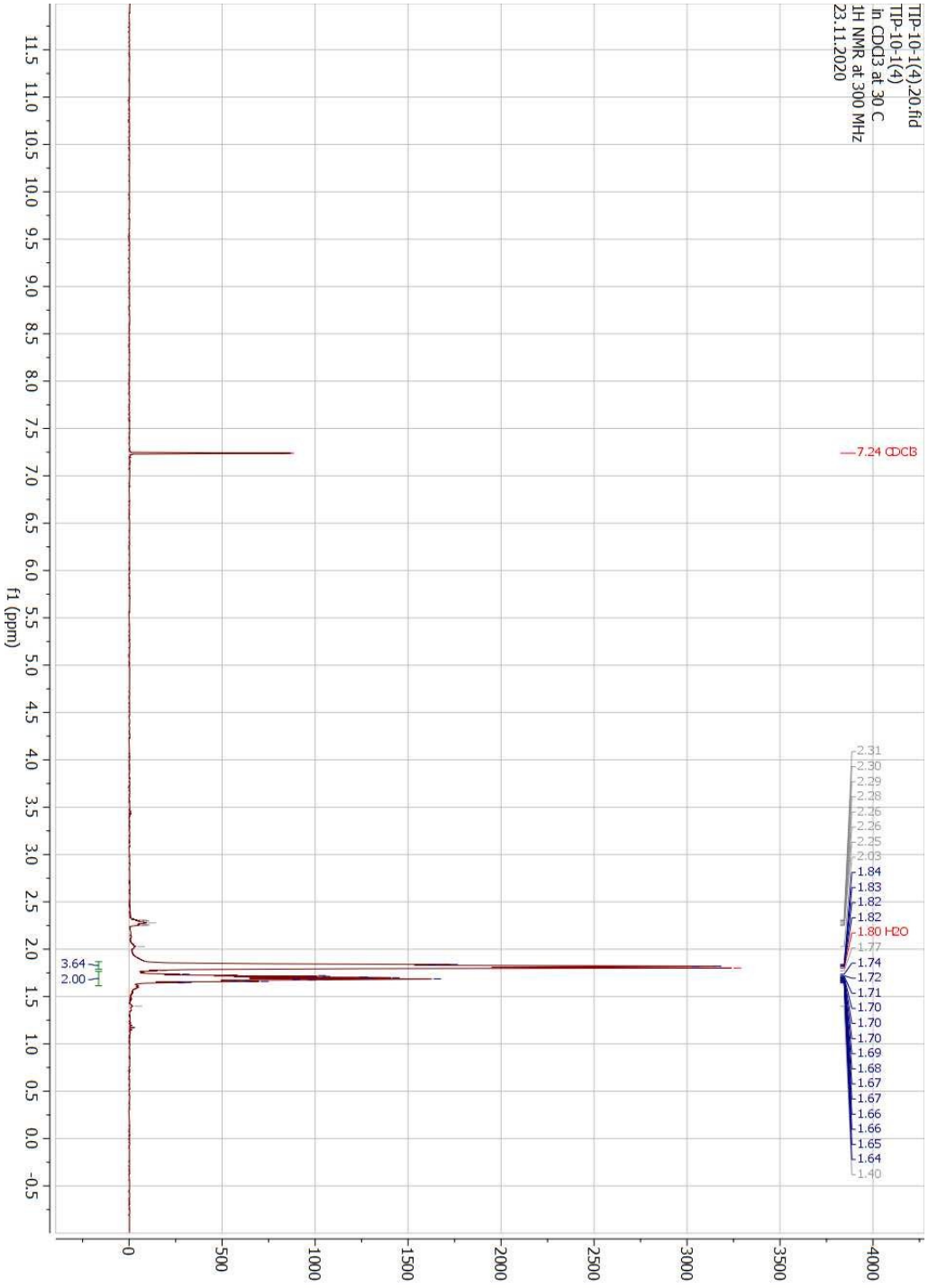
APPENDIX 4:

^{1}H NMR spectrum of deuterated **1**



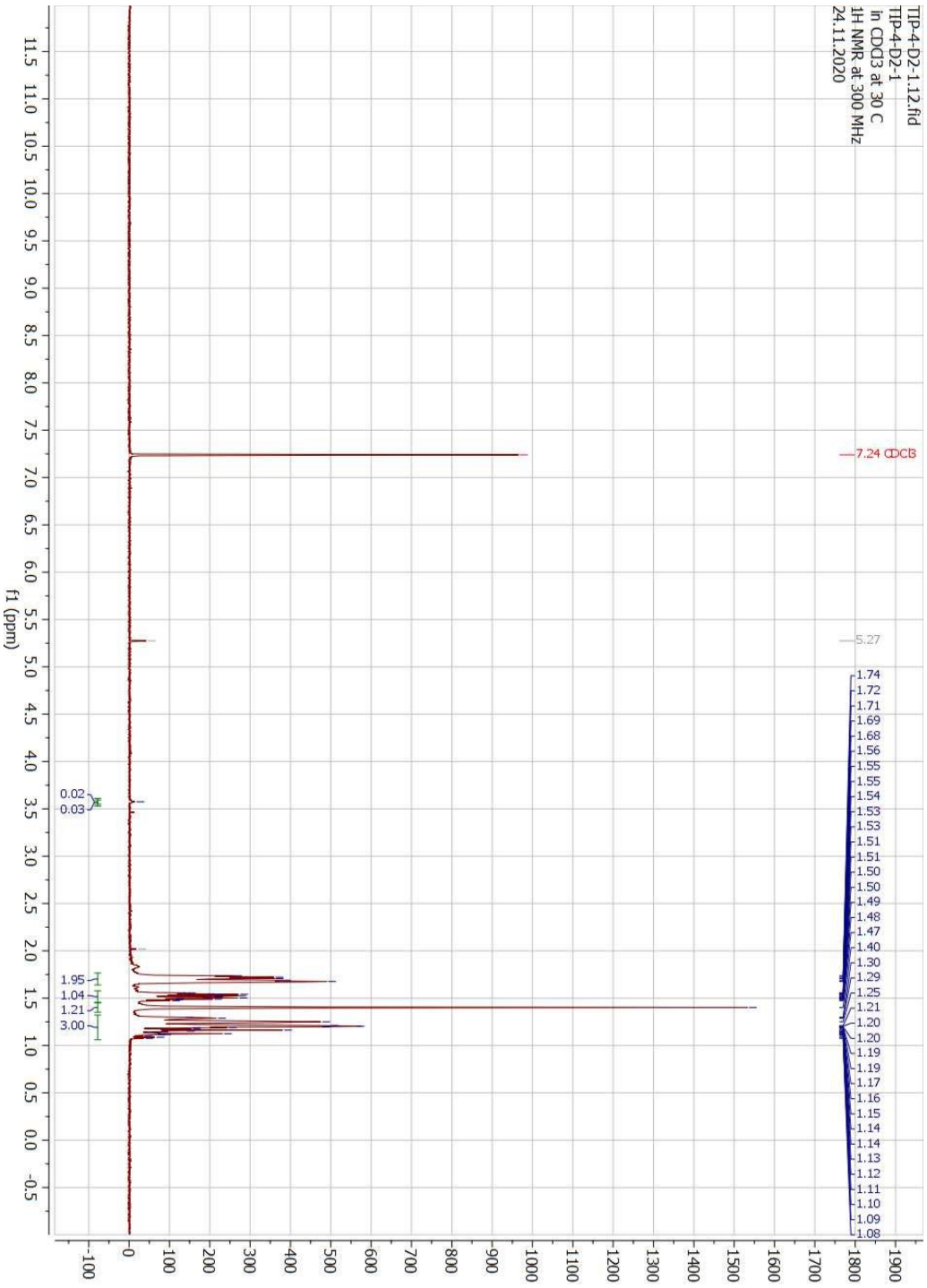
APPENDIX 5:

^{1}H NMR spectrum of **8**



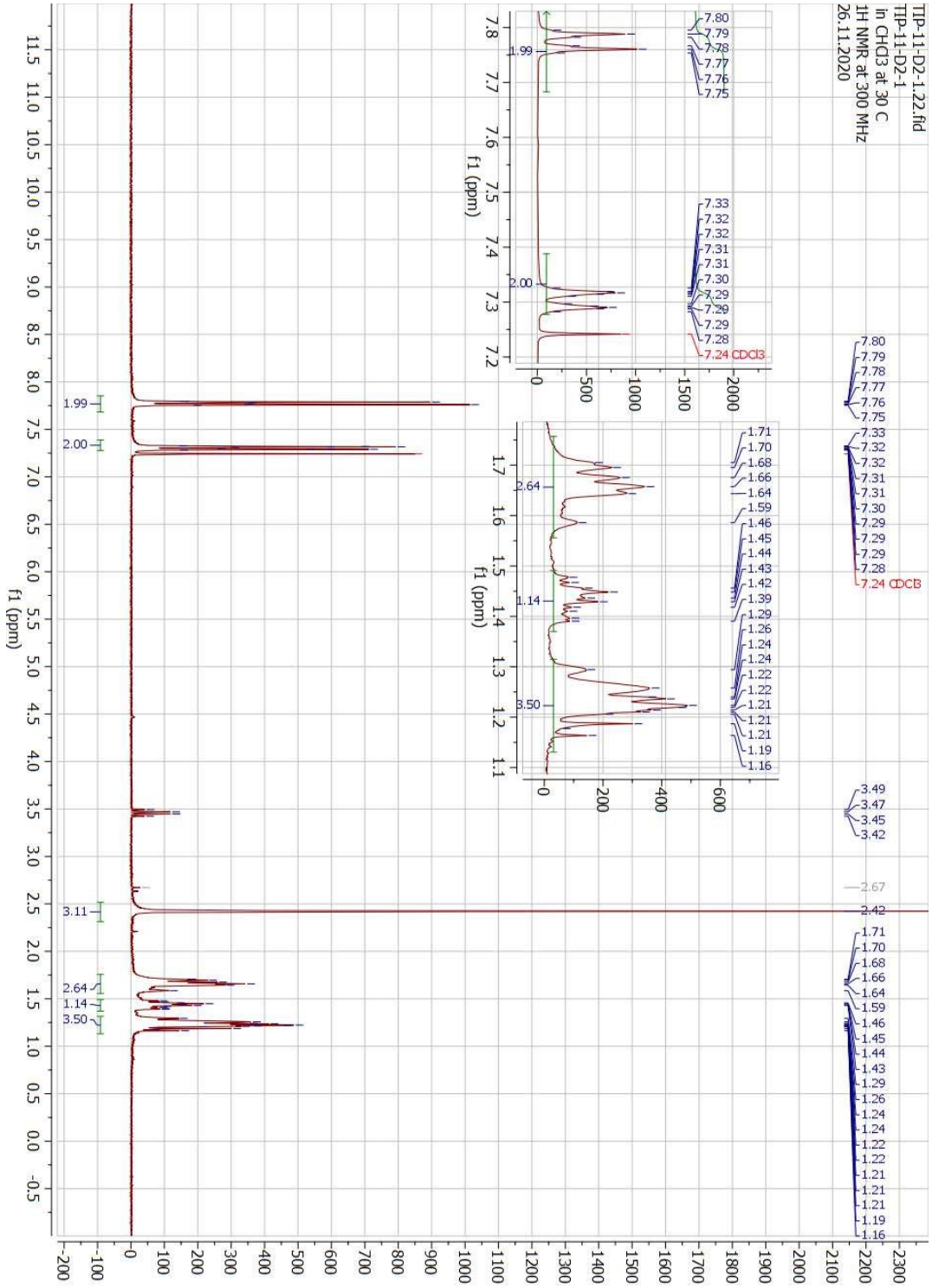
APPENDIX 6:

^{1}H NMR spectrum of **9**



APPENDIX 7:

^{1}H NMR spectrum of **10**



APPENDIX 8:

^{1}H NMR spectrum of **3**