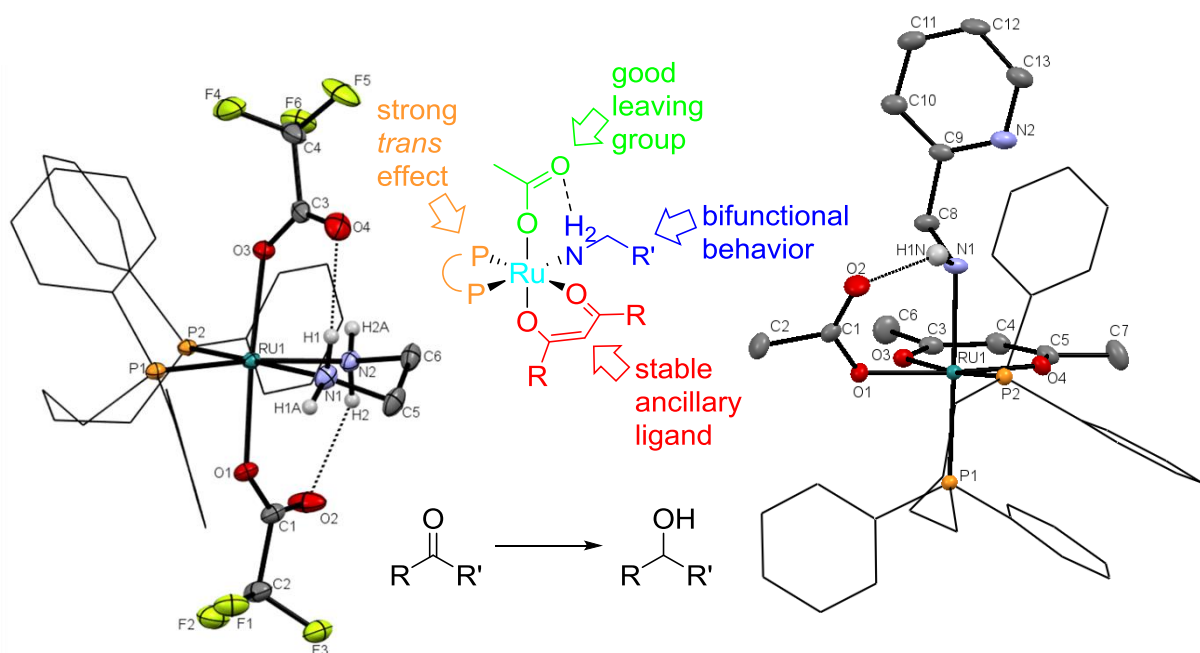**TECHNISCHE UNIVERSITÄT MÜNCHEN**
FAKULTÄT FÜR CHEMIE
PROFESSUR FÜR MOLEKULARE KATALYSE

Ruthenium Diphosphine Complexes bearing Carboxylate Ligands as Active Catalysts for Ketone Transfer Hydrogenation

DANIELA ALEXANDRA HEY

Dissertation

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Vollständiger Abdruck der von der Fakultät für Chemie der Technischen Universität München zur Erlangung des akademischen Grades eines

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Zusammenfassung

Ruthenium(II) Phosphin Komplexe sind bekannt dafür, Hydrierungs- und Transferhydrierungs-reaktionen zu katalysieren. Während im Bereich der Grundlagenforschung meist hochkomplexe Ligandenmotive entwickelt und untersucht werden, welche langwierige und teure Synthesen erfordern, bieten kostengünstige und kommerziell erhältliche Carboxylat-Liganden eine industriell interessante Alternative.

In der vorliegenden Arbeit werden die Synthesen von Ruthenium(II) Diphosphin Komplexen mit Acetat- (OAc), Trifluoracetat- und Acetylacetonat- (acac) Liganden diskutiert und deren Aktivität als Katalysatoren in Transferhydrierungsreaktionen von Ketonen evaluiert.

Der erste Teil der Arbeit beschäftigt sich mit der Darstellung von Ruthenium(II) Diphosphin Komplexen mit labilem Trifluoracetat-Liganden. Die Synthese von $Ru(O_2CCF_3)_2(PPh_3)_2$ aus $RuCl_2(PPh_3)_3$ und $TFA/NaHCO_3$ in *tert*-Butanol oder mit AgO_2CCF_3 in Aceton, wie in der Literatur beschrieben, ist nicht zielführend. Die erstgenannte Vorschrift führt zur Bildung eines dinuklearen Komplexes $Ru_2Cl(O_2CCF_3)_3(PPh_3)_4(\mu\text{-}H_2O)$, nicht nur im Fall von Trifluoressigsäure, sondern auch bei Einsatz der weniger sauren Di- und Monofluoressigsäuren. Die dinuklearen Komplexe, die eigentlich aufgrund der leichten Dissoziation der Fluoracetate äußerst fluktionales Verhalten aufweisen, werden von einem Wassermolekül stabilisiert, welches Wasserstoffbrückenbindungen zu den Carboxylaten ausbildet. Anstelle der literaturbekannten Vorschriften wurde eine verbesserte Syntheseroute zur Herstellung von $Ru(O_2CCF_3)_2(PPh_3)_2$ über die Reaktion von $RuCl_2(PPh_3)_3$ und TlO_2CCF_3 entwickelt.

Der zweite Abschnitt behandelt die Eigenschaften von Ruthenium(II) Diphosphin Komplexen mit OAc- und acac-Liganden. Während Diacetat-, sowie Diacetylacetonat-Komplexe bekannt dafür sind, Hydrierungsreaktionen effizient zu katalysieren, waren gemischte OAc/acac Verbindungen bis dato unbekannt. Die vorliegende Arbeit beschreibt einfache Syntheserouten zur Darstellung von $Ru(OAc)(acac)P_2$-Komplexen, ausgehend von $Ru(OAc)_2P_2$ und Acetylaceton. Diese Komplexe sind aktive Transferhydrierungskatalysatoren, vor allem unter Zugabe von 2-(Aminomethyl)pyridin (ampy). Der isolierte Komplex Ru(OAc)(acac)(ampy)(dppb) zeigt besonders hohe Aktivität in der Transferhydrierung von aromatischen und aliphatischen Ketonen mit *iso*-Propanol, sogar bei geringen Katalysatorbeladungen von 0.01 mol%. SC-XRD-Messungen zeigen, dass Wasserstoffbrückenbindungen zwischen dem OAc- und ampy-Liganden diesen Katalysator stabilisieren.

1

Abstract

This thesis focuses on the synthesis of ruthenium(II) diphosphine complexes bearing carboxylate ligands and their evaluation as catalysts in the transfer hydrogenation (TH) of ketone substrates. Ruthenium complexes are well-known TH catalysts and nowadays a wide variety of sophisticated ligand systems is applied for their preparation, often including several synthetic steps. The synthesis of ruthenium phosphines containing carboxylates ligands, such as acetate (OAc), trifluoroacetate or acetylacetonate (acac), from easily available starting materials offers an alternative to the costly ligand syntheses performed frequently.

The first part of this work concentrates on the synthesis of ruthenium(II) diphosphine complexes with fluoroacetate ligands. Reproduction of the previously described formation of $Ru(O_2CCF_3)_2(PPh_3)_2$ is discussed and prior pathways to obtain this complex via reaction of $RuCl_2(PPh_3)_3$ with TFA/NaHCO$_3$ in *tert*-butanol or with AgO_2CCF_3 in acetone were not successful. The former reaction was found to yield the dinuclear species $Ru_2Cl(O_2CCF_3)_3(PPh_3)_4(\mu\text{-}H_2O)$, as was observed similarly when applying the less acidic di- and monofluoroacetic acid. Instead, the desired complex is synthesized by reaction of $RuCl_2(PPh_3)_3$ with TlO_2CCF_3 in acetone under precipitation of TlCl to yield $Ru(O_2CCF_3)_2(PPh_3)_2$ in solution. The solid-state structures of all obtained fluoroacetate species show hydrogen bonding between the carboxylate moiety and an H_2O molecule, thus stabilizing the otherwise highly fluxional complexes.

In the second part of this thesis, the characterization and catalytic behavior of ruthenium(II) diphosphine complexes with mixed OAc and acac ligands is discussed. While $Ru(OAc)_2P_2$ and $Ru(acac)_2P_2$ complexes have been described as hydrogenation catalysts previously, the mixed OAc/acac species were yet unknown in literature. A straightforward synthesis to obtain $Ru(OAc)(acac)P_2$ (P_2 = 2 PPh$_3$, Ph$_2$P(CH$_2$)$_4$PPh$_2$) complexes from $Ru(OAc)_2P_2$ and acetylacetone is described and the compounds were examined as catalysts in ketone transfer hydrogenation. Addition of 2-(aminomethyl)pyridine (ampy) considerably enhances the catalysts' activity. Especially the isolated Ru(OAc)(acac)(ampy)(dppb), which exhibits hydrogen bonding between the OAc and ampy ligand, efficiently catalyzes the TH of various aromatic and aliphatic ketones, with TOFs up to 125,000 h^{-1} and catalyst loadings as low as 0.01 mol%.

1. Introduction

1.1. Fundamentals of Catalysis

Historical Aspects

> *"[...] some of the greatest scientific advances of the future will depend principally upon this odd faculty of speeding up the rate of chemical reactions [...]"*

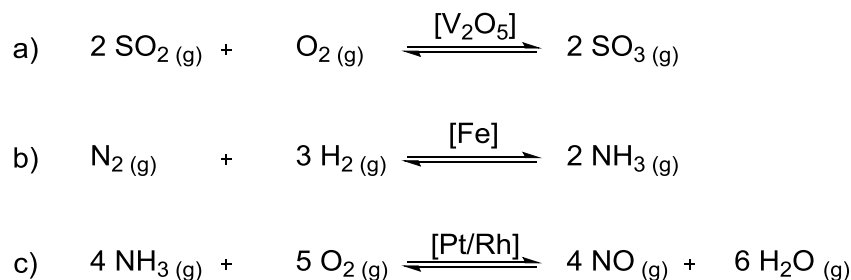<div align="right">The New York Times, June 8, 1923.</div>

Almost a century ago, the *American Chemical Society* referred to catalysis as one of the most important phenomena of science and predicted the crucial need for development in this area of chemistry.[1] At the time, a new catalyst for the combustion of fuel in car engines had been developed by *Edward Sokol* to tackle the increasing problem of oil shortage induced by the recently ended World War I and the rising demand of fuel for cars, trucks and tractors.[2] Although only few principles of catalysis were profoundly understood then, a variety of industrial applications involving catalysts had been known already.

The beginnings of industrial catalysis might be dated back to 1898, when *Rudolf Knietsch* (*BASF*) patented a new method for the synthesis of sulfuric acid.[3] The so-called "contact process" allowed for the large-scale production of sulfuric acid in high concentrations, superseding the previously used lead chamber process, that afforded sulfuric acid at high cost and maximum concentrations of 35%.[4] Although the originally employed platinum catalysts have nowadays been replaced by more efficient vanadium pentoxide,[5] the basic principle of oxidizing sulfur dioxide remains the same until today (Scheme 1, a).

One of the most important inventions in industrial catalysis followed in 1905, when *Fritz Haber* presented an iron-based catalyst for the synthesis of ammonia from gaseous nitrogen and hydrogen (Scheme 1, b).[6] *Haber's* research was rewarded with the Nobel prize in chemistry in 1918 and led to the large-scale production of ammonia, intended to come by the increasing world famine by the production of fertilizers from a now relatively cheap feedstock. As a matter of fact, ammonia found another application that resulted from the expanding armament before and during World War I: the production of nitric acid for explosives. Discovered by *Wilhelm Ostwald* in 1902, nitric acid could be synthesized in large quantities from ammonia and oxygen by passing the gases over a platinum/rhodium catalyst (Scheme 1, c).[7]
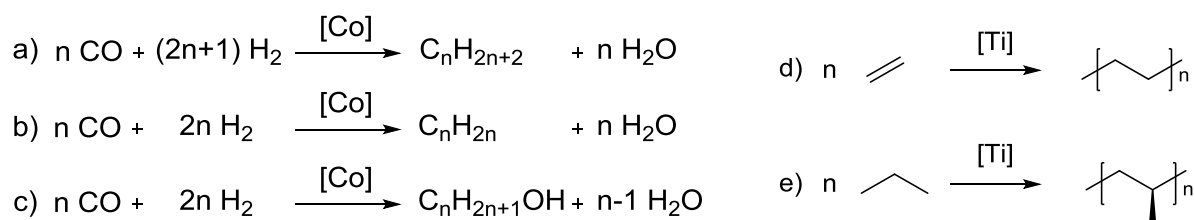
Although the Ostwald process is mostly used for the production of fertilizers today, its beginnings were overshadowed by the use of nitric acid for the weapons industry. Nevertheless, *Ostwald* was awarded with the Nobel prize in chemistry in 1909 "for his work on catalysis, chemical equilibria and reaction velocities", to acknowledge his contribution to a better understanding of catalytic processes in general.

a) $2 \, SO_{2 \, (g)}$ + $O_{2 \, (g)}$ $\xrightarrow{[V_2O_5]}$ $2 \, SO_{3 \, (g)}$

b) $N_{2 \, (g)}$ + $3 \, H_{2 \, (g)}$ $\xrightarrow{[Fe]}$ $2 \, NH_{3 \, (g)}$

c) $4 \, NH_{3 \, (g)}$ + $5 \, O_{2 \, (g)}$ $\xrightarrow{[Pt/Rh]}$ $4 \, NO_{(g)}$ + $6 \, H_2O_{(g)}$

Scheme 1. Milestones of industrial catalysis. a) Principal equation of the contact process for the synthesis of sulfuric acid promoted by a vanadium pentoxide catalyst. b) Ammonia synthesis from gaseous nitrogen and hydrogen catalyzed by an iron catalyst. c) Principal equation of the Ostwald process for the synthesis of nitric acid from ammonia over a platinum/rhodium catalyst.

After World War I, industrial catalytic progress was made mainly in petrochemical industry. The rising need for fuels, outlined among others by the New York Times (*vide supra*), provoked an outburst of catalytic inventions to enhance the availability of combustibles and concurrently reduce their costs. One of the most important processes invented then goes back to 1923, when *Franz Fischer* and *Hans Tropsch* used synthesis gas ($CO + H_2$) for the production of hydrocarbons.[8] Various other developments in petrochemical industry characterized the 1920's and 30's, such as the synthetic methanol production by *DuPont* in 1926,[9] or the catalytic cracking by *Eugène Houdry* in 1936, which will not be addressed in detail within this work.

Named *Fischer-Tropsch-Synthesis* (FTS) after their inventors (Scheme 2, left), this process uses coal to obtain liquid hydrocarbons in two steps.[10] First, coal is converted to synthesis gas in a steam-reforming process. Then, the gas is transformed into liquid or gaseous hydrocarbons over a cobalt catalyst. Depending on the reaction conditions (temperature, pressure), different hydrocarbon products, such as alkanes, alkenes or alcohols (Scheme 2, left), can be obtained, and the outcome of the reaction can thus be modified according to needs.[11] Invented nearly a century ago, this process underlies constant development and adaption and still finds application in industry nowadays. Variation of the starting material from coal to biomass, as well as a change from cobalt- to zeolite-based catalysts still offers new perspectives for FTS.[12]

a) $n\ CO + (2n+1)\ H_2 \xrightarrow{[Co]} C_nH_{2n+2} + n\ H_2O$

b) $n\ CO + 2n\ H_2 \xrightarrow{[Co]} C_nH_{2n} + n\ H_2O$

c) $n\ CO + 2n\ H_2 \xrightarrow{[Co]} C_nH_{2n+1}OH + n\text{-}1\ H_2O$

d) n $\xrightarrow{[Ti]}$

e) n $\xrightarrow{[Ti]}$

Scheme 2. (left) *Franz Fischer* and *Hans Tropsch* invented the *Fischer-Tropsch-Synthesis* for a) alkanes b) alkenes and c) alcohols. (right) *Giuglio Natta* and *Karl Ziegler* developed the (stereoselective) polymerization of d) ethylene and e) propylene.

Another important step in the history of catalysis was achieved in 1953, when *Karl Ziegler* found that the polymerization of ethylene to polyethylene can be carried out at low temperatures and pressures with the help of a transition metal catalyst.[13] Together with *Giuglio Natta*, whose research focused on the stereoselective polymerization of propylene, *Ziegler* received the Nobel prize in chemistry in 1963 for his studies of polymers and polymerization catalysis (Scheme 2, right).[14] In the beginning, catalysts for the polymerization of ethylene consisted of triethyl aluminum and titanium tetrachloride as homogeneous transition metal compounds, and it was not clear how this mixture operated and promoted the reaction. As reaction mechanisms were elucidated, catalysts developed to heterogeneous systems with a high surface, where titanium tetrachloride is still used together with magnesium chloride.[13]

In the same period, multiple catalytic processes for the large scale production of chemicals were invented, for instance the synthesis of acetaldehyde from ethylene at *Wacker Chemie*, the hydration of benzene to cyclohexene (*Universal Oil Products, UOP*) and the first plant for acetonitrile fabrication (*Standard Oil of Ohio, SOHIO*).

Soon after the discovery of the first transition metal catalyst for ethylene polymerization, other catalytic applications of transition metal compounds emerged. In 1965, *Sir Geoffrey Wilkinson* explored the use of rhodium complexes for the hydrogenation of olefins (Figure 1, left).[15] In contrast to several previous reactions in which transition metal catalysts were involved, *Wilkinson* already proposed an operating mechanism for his catalyst via metal hydrides.[16] His profound understanding of metal organic compounds was rewarded with the Nobel prize in chemistry in 1973, together with *Ernst Otto Fischer* for their research of so-called "sandwich"

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complexes (Figure 1, middle).[17-19] Henceforth, catalysis was no longer a matter of trial-and-error, but of explicit comprehension of the processes involved. Catalyst structures, especially in homogeneous processes, were aimed to be clarified, as organometallic chemists defined certain classes of coordination compounds, for example the *Fischer* carbene, named after *Ernst Otto Fischer*, who also discovered the sandwich complexes (Figure 1).[20, 21]

*Wilkinson's* catalyst   *Sandwich* complex   *Fischer* carbene
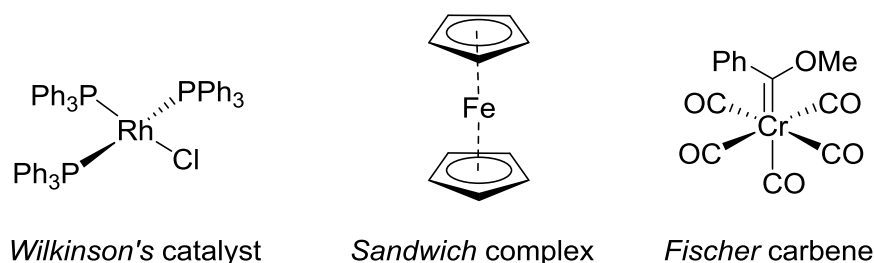
Figure 1. *Wilkinson's* catalyst for the hydrogenation of olefins (left), the first *Sandwich* complex (middle), and an example for a *Fischer* carbene (right).

Nowadays, catalysis is ubiquitous and industry exploits catalysts for a variety of different applications. The spectrum ranges from exhaust gas catalysts to control the output of harmful gases from automobiles to the production of pharmaceuticals and fine chemicals.[22] Implementations also include the usage of the *Selective Catalytic Reduction* (SCR) to lower NO_x exhausts from nitric acid production, power plants, ships and trucks.[23] Development thereby often focuses on the environmental aspect of reactions in order to minimize possibly toxic by-products and to reduce production costs by decreasing energy input. A principal phenomenon of catalysis is approached by the latter aspect, since the definition of a catalyst states the decrease of activation energy barrier of a reaction. In the following, definitions of some basic concepts of catalysis are given.

Definitions

With the evolution of catalytic reactions from laboratory setups to chemical industry, and from the production of basic inorganic compounds to environmentally friendly processes, different definitions of the term "catalyst" emerged. At first, catalysts were considered to break bonds and form new ones without being themselves involved in the structure of the created compound.[24] This assumption, made by *Jöns Jakob Berzelius* in 1835, is nowadays only partially considered true. A catalyst, as it is defined today, lowers the activation energy barrier E_A of a reaction by enabling an alternative reaction pathway (Figure 2).[25]
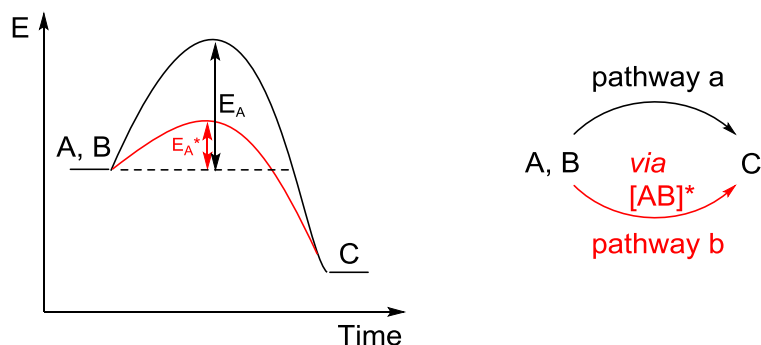
Figure 2. Lowering the activation energy barrier: pathway a (black) without catalyst has a high activation energy E_A, pathway b (red) with catalyst has a lower activation energy E_A^*.

Upon decreasing the activation energy, the reaction rate and thus its velocity is enhanced. As a consequence, reactions that otherwise require harsh conditions, such as elevated temperatures and pressures, can take place under mild circumstances, for instance at room temperature and ambient pressure. Thereby, the catalyst itself does not affect the outcome or the position of equilibrium of a reaction.[8]

Ideally, catalysts are not consumed during a reaction. In reality however they show a limited lifetime due to undesired decomposition processes. Catalyst deactivation refers to the process of a catalyst losing activity or selectivity over time and indeed represents a major problem in catalyst research and industry.[26] Deactivation can be retarded by modifications of the catalyst itself, in heterogeneous catalysis by improving its fabrication to yield more impeccable catalysts,[27] and in homogeneous catalysis by ligand design to afford highly robust metal complexes.[28]

A method to indicate the robustness of a homogeneous catalyst is given by its turnover number (TON).[29] The TON is defined as the molarity of converted substrate per molarity of catalyst before its deactivation (Eq. 1).

$$TON = \frac{moles \ [substrate]}{moles \ [catalyst]} \tag{1}$$

Although the calculation of a TON can be an adequate means for the characterization of homogeneous catalysts, this definition falls short in heterogeneous reactions, since the exact number of active catalyst molecules is often unknown and has to be determined experimentally prior to the calculation of the TON.

A common characteristic for both, homogeneous and heterogeneous catalysts, on the other hand, is the rate of a catalytic reaction, usually called turnover frequency (TOF) in homogeneous catalysis. The rate determines the activity of a catalyst for a certain substrate and is defined as the amount of converted substrate per amount of catalyst over time.

Accordingly, the TOF is calculated by the number of converted substrate molecules per catalyst molecules over time (Eq. 2).[29]

$$TOF = \frac{moles\ [substrate]}{moles\ [catalyst]\ *\ time} \qquad (2)$$

The TOF value can be determined in various ways, the most common possibilities being its calculation at 50% substrate conversion (TOF^{50}) or during the initial reaction stage (TOF^{init}). A calculation of the TOF from the steepest slope of the kinetic plot can also be found in literature.[29] For a better comparison of reported values, the TOF^{50} will be used throughout this work, since it represents a valuably intermediate between the rapid initiation phase regarded with TOFs^{init} and the eventual deactivation when full substrate conversion is approached.

Besides a high activity, catalysts that find application in industry usually reach high selectivity, meaning that one product is observed nearly exclusively from the starting materials without considerable formation of side products. This is usually referred to as chemoselectivity. A specific case is the stereoselectivity that *Giuglio Natta* discovered for the polymerization of propylene with an ethyl aluminum chloride/vanadium tetrachloride catalyst, where one single stereoisomer is formed (*vide supra*).

As mentioned, a distinction between homogeneous and heterogeneous catalysis is vital for the application of certain key figures and for the characterization of catalyst features. In homogeneous systems, the reactants and the catalyst are in the same phase, usually either both in the liquid or the gaseous phase. Heterogeneous catalysis takes place on a surface and thus two phases are involved. Most often the catalyst is solid, while the reactants are liquid or gaseous. A mixed form is also possible, known as supported or immobilized catalysts.[30] These catalysts consist of homogeneous compounds, e.g. transition metal complexes, bound to a solid support, for example a resin.

In industry, most catalytic processes are performed heterogeneously due to the easy separation of the products from the catalyst after the reaction. However, a profound knowledge about the processes taking place on the catalyst surface is often difficult to obtain, though important for catalyst optimization. Therefore, an improvement of these systems cannot be targeted as specifically compared to homogeneous systems. Due to the limited possibility for directed catalyst modifications, selectivity in heterogeneous catalysis might be low, while homogeneous catalysts can be designed to fit a certain substrate or reaction via tailoring the ligands or metals and their oxidation states.

In contrast to homogeneous catalysis, heterogeneous processes frequently apply higher catalyst concentrations and harsh conditions, such as higher temperatures and pressures, while in homogeneous catalysis low catalyst loadings and mild conditions are often sufficient.

On the other hand, homogeneous catalysts are usually less stable under harsh conditions, like an increased temperature, compared to heterogeneous systems.[8] Nevertheless, several examples for the use of homogeneous catalysts in large-scale processes are known, such as the *Shell Higher Olefin Process (SHOP)*, the oxo synthesis, also known as hydroformylation, patented by *Ruhrchemie* or the polymerization of ethylene to low density polyethylene (LDPE).[31] Manifold examples for the application of heterogeneous catalysts in industry can be stated, among which the catalytic cracking of gas oil, the naphtha reforming process or the synthesis of ammonia, which dates back to its beginnings before World War I.[32] A comprehensive representation of the mentioned characteristics of homogeneous vs. heterogeneous catalysis is shown in Table 1.

Table 1. Selected characteristics of homogeneous and heterogeneous catalysis.

Characteristic	Homogeneous catalysis	Heterogeneous catalysis
Catalyst separation	x difficult	✓ easy
Catalyst tailoring	✓ targeted	x random
Selectivity	✓ high	x moderate
Catalyst concentration	✓ low	x high
Reaction conditions	✓ mild	x harsh
Thermal catalyst stability	x low	✓ high
Applicability	x limited	✓ extensive
Examples in industry	*Shell* Higher Olefin Process, *Ruhrchemie* oxo synthesis, olefin polymerization	Ammonia synthesis, Catalytic oil cracking, Naphtha reforming

Despite the extensive implementation of heterogeneous catalysts in large-scale industrial processes, homogeneous catalysis is still important for the synthesis of a variety of chemical compounds, such as aldehydes (hydroformylation), polymers and plastics (olefin polymerization), fine chemicals and pharmaceuticals.[33]

Besides acids and bases, transition metal complexes find catalytic application in the synthesis of these compounds by exploiting diverse reaction pathways. Important reaction types catalyzed by transition metal compounds are hydroformylation, hydrosilylation, coupling, metathesis and hydrogenation reactions (Scheme 3).[34, 35] The hydroformylation and hydrosilylation of olefins (Scheme 3, a and b) are important processes in industry for the synthesis of aldehydes and synthetic rubber precursors, respectively. Coupling reactions are known for various substrates and with different metal catalysts (Scheme 3, c). Some examples for these reactions are the *Negishi* coupling carried out with aryl zinc reagents, the *Suzuki-*

Miyaura coupling with aryl boron compounds, or the *Buchwald-Hartwig* coupling with alkyl amine precursors.[36] Metathesis reactions (Scheme 3, d) describe the rearrangement of alkene moieties. Due to its simplicity, this reaction type is used in industry, among others, for the synthesis of pharmaceutical drugs. This work focuses on hydrogenation reactions (Scheme 3, e), the transformation of a substrate bearing an unsaturated bond with hydrogen. Substrates go beyond olefins to carbonyls, ester, nitriles or arenes.
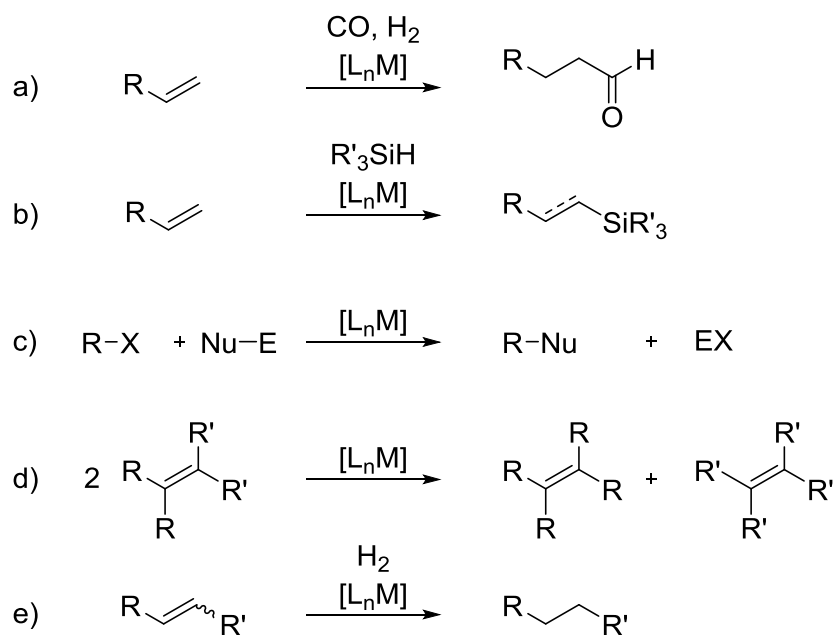
Scheme 3. Transition metal catalyzed reactions. a) Hydroformylation, b) Hydrosilylation, c) Coupling reaction, d) Olefin metathesis, e) Hydrogenation.

1.2. Catalytic Transfer Hydrogenation

The following chapter will discuss catalytic hydrogenation reactions, predominantly the transfer hydrogenation of carbonyl compounds. A detailed insight into the possible mechanisms of this reaction will be given with particular regard to ruthenium(II) complexes as catalysts.

Hydrogenation reactions are the transformation of a substrate bearing an unsaturated double or triple bond with hydrogen. Usually, direct hydrogenation (HY) is carried out with molecular hydrogen, but nowadays ever more alternative hydrogen donors are known, for instance isopropanol, formic acid or glycerol (Figure 3).[37]
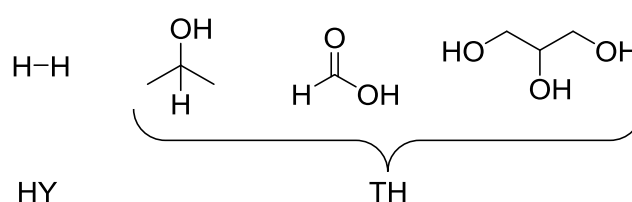
Figure 3. Hydrogen donors for catalytic hydrogenation reactions. HY = Direct Hydrogenation, TH = Transfer hydrogenation.

The transfer of a formal hydrogen from these donor molecules is called transfer hydrogenation (TH) and in comparison to classic HY it offers several advantages for application on laboratory scale:[38]

- safe handling and storage of reagents instead of hazardous hydrogen gas
- operational simplicity rather than pressure valves and other precautions
- readily available and cheap donor molecules
- easy recycling or evaporation of side products formed by the hydrogen donor.

In most cases, isopropanol is applied as hydrogen donor, since it offers an abundant and cheap alternative to hydrogen gas. It converts to acetone upon transferring the formal hydrogen to the substrate. A disadvantage is the reversibility of the reaction with this donor, which is minimized by using isopropanol in high excess or as solvent, or by distilling the formed acetone. Formic acid constitutes another option, decomposing to carbon dioxide gas during the reaction, which is easily removed from the reaction mixture. However, formic acid often reacts with the catalyst to induce side reactions or even catalyst decomposition.[39] Glycerol only emerged recently as hydrogen donor, decomposing to 2-hydroxypropanoic acid upon hydrogen transfer. It represents an economically friendly, "green" choice in comparison with other donor molecules.[40]

A variety of transition metal complexes are known to catalyze HY and TH reactions, converting a wide range of substrates to their saturated products (Scheme 4).[39, 41] The functions being reduced include C=C double and triple bonds, as well as C=O and C=N double bonds. The substrate scope therefore comprises the HY of olefins to alkanes (Scheme 4, a), carbonyls and carboxylic acid esters to alcohols (Scheme 4, b and c), amides to alcohols or amines (Scheme 4, d), as well as imines and nitriles to amines (Scheme 4, e and f).
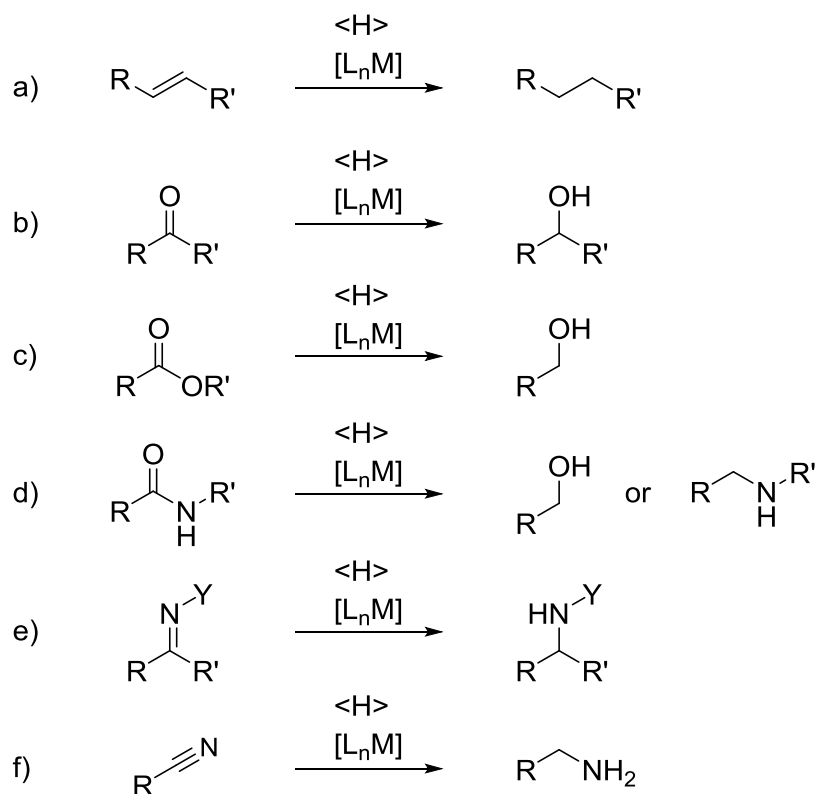
Scheme 4. Substrate scope of transition metal catalyzed HY and TH. <H> = hydrogen donor.

This work focuses on the TH of ketones to their respective alcohols, an important reaction for the synthesis of (chiral) secondary alcohol precursors for pharmacy and agrochemistry.[42] The history of ketone TH dates back to the 1920's, when *Hans Meerwein*, *Wolfgang Ponndorf* and *Albert Verley* discovered simultaneously, but seemingly independently, a new method for the reduction of aldehydes and ketones.[43] While *Meerwein* claimed to have found a new procedure for the reduction of aldehydes and ketones catalyzed by activated metallic magnesium,[44] *Ponndorf* disagreed with the assumption that magnesium acts as a catalyst in this reaction. He and *Verley* rather proposed that alcoholates induce the "exchange of oxidation numbers",[45] or the "exchange of functional groups",[46] of aldehydes and alcohols. They further recognized the reversibility of this reaction that enables the formation of alcohols from carbonyl compounds and *vice versa* (Scheme 5).
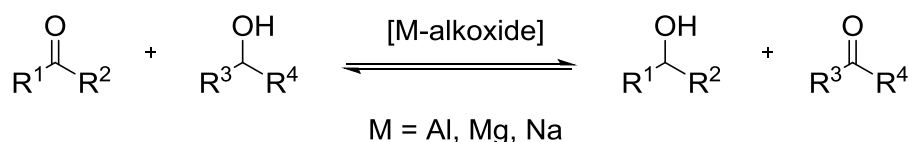
Scheme 5. *Meerwein-Ponndorf-Verley* reduction to transform ketones to alcohols and *vice versa*.

Although each of the three scientists claimed to have made the discovery of this equilibrium reaction first, it is now named *Meerwein-Ponndorf-Verley (MPV)* reduction.

While MPV reduction initially employed stoichiometric amounts of metal alkoxide, mainly aluminum isopropoxide, the usage of rare earth metal catalysts pushed the development towards the catalytic exploitation of the reaction[47] and gradually late transition metal catalysts were employed in combination with small amounts of base. The reaction was then referred to as "transfer hydrogenation" and the catalytic mechanism of TH with transition metal catalysts was elucidated. Since this work focuses on the TH of ketones from isopropanol in isopropoxide as base, an exemplary mechanism is depicted for these conditions (Scheme 6).[48]
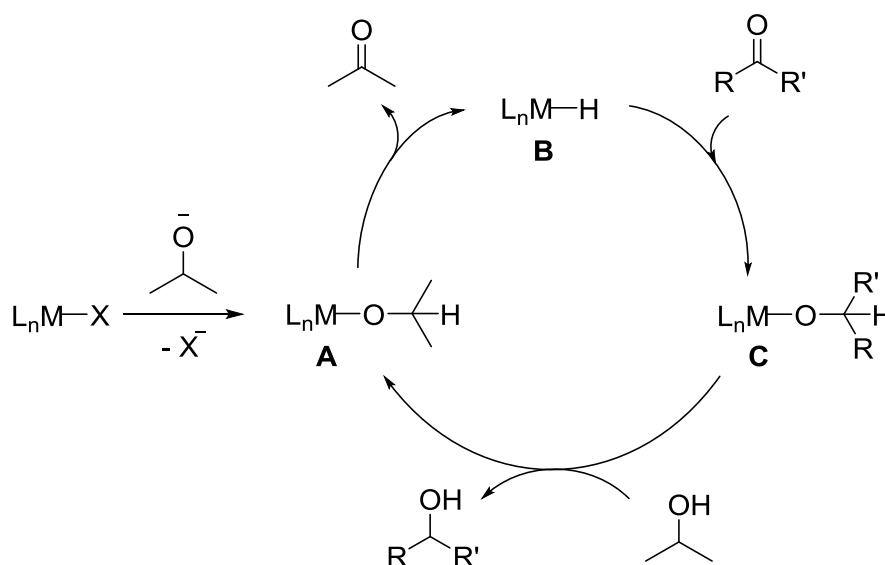

Scheme 6. Monohydride inner sphere mechanism for transition metal catalyzed TH in isopropanol.

In the first step, a labile ligand X dissociates from the transition metal complex L_nM-X to form the isopropoxide complex **A** in isopropanol/isopropoxide. It is crucial that the metal complex bears a labile ligand to obtain a free coordination site for the hydrogen donor. Upon β-hydride elimination from the coordinated isopropoxide in **A** and liberation of acetone, the metal hydride complex **B** is then formed through reductive elimination. In this step, a free coordination site for hydride formation is likewise pivotal. Oxidative addition of the ketone substrate to **B** results in the formation of **C** by hydride transfer from the metal to the substrate. The release of the

hydrogenated substrate and coordination of another isopropoxide molecule to L_nM regenerates the initial species **A**.

The mentioned mechanism is called inner sphere mechanism, since the isopropoxide and the substrate directly coordinate to the metal and these compounds are therefore situated in the inner coordination sphere of the metal. It is further described as "monohydridic" due to the formation of the metal hydride **B**, whereas another mechanism was discovered including the formation of a dihydride (Scheme 7).[49]
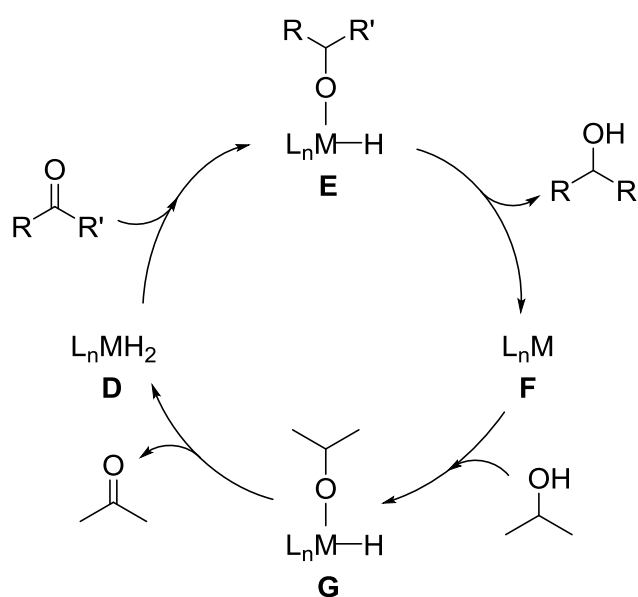
Scheme 7. Dihydride mechanism for the transition metal catalyzed TH in isopropanol.

The starting point for the dihydride mechanism is the transition metal dihydride complex **D**. Upon oxidative addition of the substrate to **D**, one of the hydrides is transferred to the ketone to form the metal hydride alkoxide **E**. Reductive elimination and release of the alcohol product results in the formation of the ruthenium(0) species **F**. Oxidative addition of isopropanol to **F** and subsequent β-hydride elimination from the hydrogen donor leads to the formation of **G** which, under reductive elimination, rebuilds the dihydride complex **D**.

To establish the mechanism according to which a certain catalyst operates, *Jan-E. Bäckvall* introduced a deuteration experiment.[49] Upon deuteration of the hydrogen donor, for instance by using isopropanol-d_1, the position of hydrogen and deuterium should remain equal in the product alcohol when a monohydride mechanism is involved (Scheme 8, a). By pursuing a dihydride pathway, hydrogen scrambling is observed in the product and two different deuterium constitutions can be found for the alcohol (Scheme 8, b). It has to be mentioned however that H-D-scrambling might also lead to an unambiguous determination of the actual mechanism.
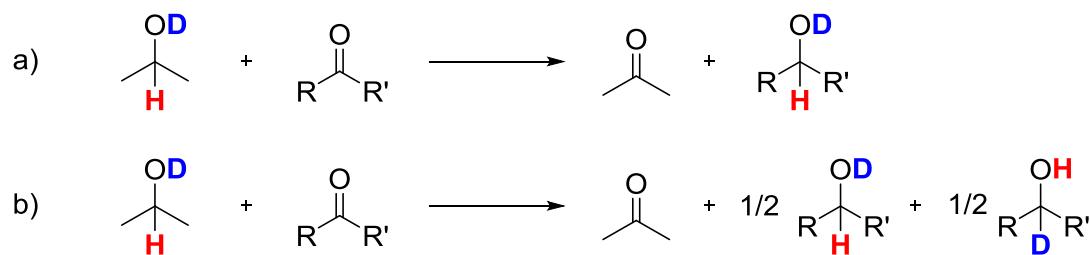
Scheme 8. Experimental proof for mono- and dihydride mechanism. a) Monohydride mechanism, b) Dihydride mechanism.

In the beginning, mono- and dihydride inner sphere mechanism were considered generally valid for the TH of ketones by transition metal catalysts. Only in 1995, *Ryõji Noyori* discovered that additives and ligands with certain functional groups, such as an NH moiety, enhance the rate of catalytic TH considerably.[50] *Noyori* revealed that another mechanism operates when primary or secondary amines are present, namely the bifunctional outer sphere mechanism (Scheme 9).[51]
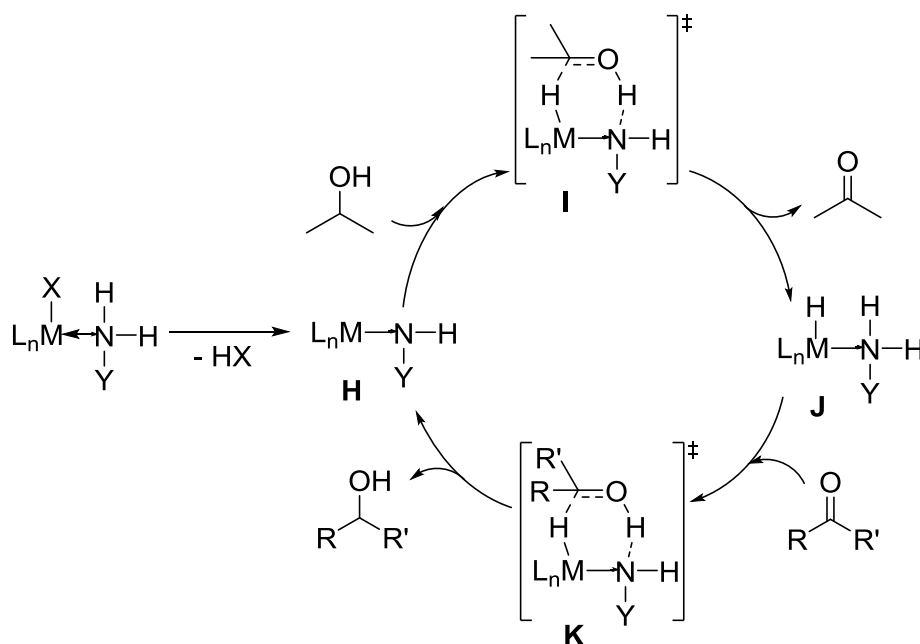
**Scheme 9.** Bifunctional outer sphere mechanism for NH-functionalized transition metal catalyzed TH in isopropanol.

In the first step of the bifunctional mechanism, a labile ligand X dissociates from the transition metal complex L_nM and the coordinated amine ligand is deprotonated due to the employed basic reaction medium. The resulting 16 e$^-$ complex **H** interacts with isopropanol to form a

six-membered pericyclic transition state **I**, in which metal complex and substrate interact through hydrogen bonding. Elimination of acetone from **I** leads to the formation of the hydridic species **J** which can interact with the ketone substrate. Hydrogen bonding from metal to substrate results in the formation of a similar pericyclic transition state **K**. Release of the alcohol product is accomplished by hydrogen transfer from the metal and the ligand to regenerate the initial species **H**.

Metal-ligand bifunctional catalysis proceeds via a 16 e$^-$ ruthenium amide. Most notably, no direct interaction between the metal center and the substrate or isopropoxide is established for the bifunctional route. The ligand, in this case an amine, is responsible for the activation of the substrate by hydrogen bonding to the carbonyl oxygen and rendering the carbon atom more nucleophilic. It further serves as a proton source for the substrate, contemporarily with the hydride transfer from the metal. Additionally, the functional ligand can attract the ketone towards of the metal.[52] This attraction is not only important for a fast reaction rate, it also steers the product conformation in case of asymmetric TH reactions with prochiral substrates.[53]

TH catalysts that operate via a bifunctional mechanism usually show high efficiency, often above the ones lacking this additional ligand feature.[54] The superior performance is partly due to attractions between ligand, substrate and the solvent isopropanol. While the early mechanistic proposal of *Noyori* depicts the basic processes occurring during TH, *Walter Baratta* examined the detailed role of isopropanol in the reaction. Mechanistic considerations including neutron diffraction studies, DFT calculations and the isolation of catalytic intermediates elucidate the crucial role of the alcohol.[55] Besides a shift of the equilibrium to the product side and interaction of one molecule isopropanol with Ru-NH as hydrogen shuttle, the solvent plays a more extensive role. In addition to the single isopropanol molecule depicted in structure **I** (Scheme 9), an additional solvent molecule stabilizes the intermediate species via hydrogen bonding (Figure 4). This leads to a decrease of the energy of the transition states forming the cascade from metal hydride to metal amide. The alcohol thus serves not only as hydrogen donor, but also to establish important interactions between the involved species in order to reduce the reaction energy barrier.
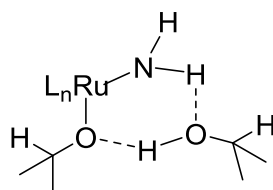
Figure 4. Ru-NH$_2$ isopropoxide formed consecutively from Ru-NH$_2$ hydride in basic isopropanol solution.

Concluding from further evolved mechanistic studies, the mechanism depicted in Scheme 9 can be regarded as general illustration of the processes in metal-ligand assisted TH with transition metal complexes. To exactly determine the intermediates for a certain catalyst, considerations have to include the specific structure of the complex.

1.3. Ruthenium Complexes for Catalytic Transfer Hydrogenation

The following chapter provides an overview of homogeneous ruthenium complexes that serve as catalysts for ketone TH reactions, operating via either inner or outer sphere mechanism.

From the first discovery of catalytic transfer hydrogenation reactions by *Meerwein*, *Ponndorf* and *Verley* to the wide variety of catalysts employed for this transformation nowadays, several evolutionary steps had to be taken over nearly a century (Figure 5).[38] The range of catalysts developed from alkoxides of main group metals (Al, Mg, Na) used in the beginning, over metal complexes of the platinum metals (Ru, Os, Rh, Ir) and heterogeneous rare earth metal supported catalysts (Zr, La, Ce, Sm, Yb), to metal complexes of "abundant" metals like iron and manganese. A detailed insight into the development of homogeneous ketone TH catalysts will be given in the following. The focus will be on transition metal complexes, with particular emphasize on ruthenium(II) compounds.

main group metal alkoxides: **Al**, Mg, Na	Pt metal complexes: **Ru**, Os, Rh, Ir	supported rare earth metals: **Zr**, La, Ce, Sm, Yb	„abundant" metal complexes **Fe**, Mn

Year 1925	1960	1980	2020
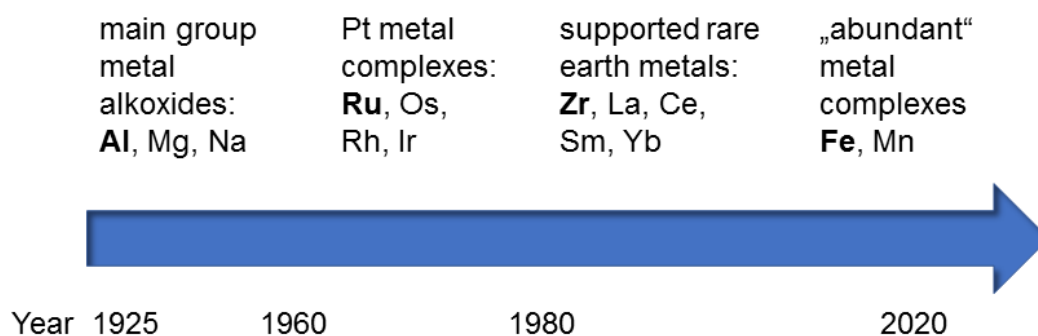
Figure 5. Development of catalysts for the TH of ketones.

When catalytic TH reactions were discovered in 1925, alkoxyl aluminum, alkoxyl magnesium or alkoxyl sodium reagents were applied in stoichiometric amounts to perform the so-called *Meerwein-Ponndorf-Verley* reduction.[44-46] Due to the inconvenience of these compounds, leading to a relatively high amount of by-products, research was directed towards the catalytic use of late transition metal complexes.

Soon after the invention of the *Wilkinson* catalyst $RhCl(PPh_3)_3$ for the HY of olefins,[16] the first late transition metal complex for the catalytic TH of ketones emerged. In 1964, *H. Bernhard Henbest* and *T. R. B. Mitchell* discovered that the iridium hydride complex $IrH(Cl)_2(DMSO)_3$ (Figure 6, left) catalyzes the transformation of cyclohexanone and acetophenone derivatives to their respective alcohols.[56]

Instead of the previously applied stoichiometric amounts of metal alkoxide for *MPV* reductions, the iridium complex was added catalytically (5 mol% Ir with respect to the substrate), and the ketone substrates were converted quantitatively within 12 hours.[57] A structure elucidation revealed important intermediates of the reaction.[58]

Less than a decade later, *Yoel Sasson* and *Jochanan Blum* showed that the ruthenium(II) dichloride complex $RuCl_2(PPh_3)_3$ (Figure 6, middle) promotes the reduction of benzalacetone in benzaldehyde in an even smaller molar amount of 2 mol% Ru with respect to the substrate.[59] Quantitative conversion was achieved within 2 hours, although at high temperatures of up to 200 °C. The subsequent investigation of the catalytic mechanism hints on coordination of both substrate and hydrogen donor to ruthenium, involving a ruthenium hydride species.[60] A following examination of the analogue rhodium and iridium catalysts $RhCl(PPh_3)_3$ and $IrCl(CO)(PPh_3)_2$ showed that the ruthenium species is the most active catalyst in the row for the TH of several considered ketones.[61]

Henbest & Mitchell
1964

Sasson & Blum
1971

Shvo
1985
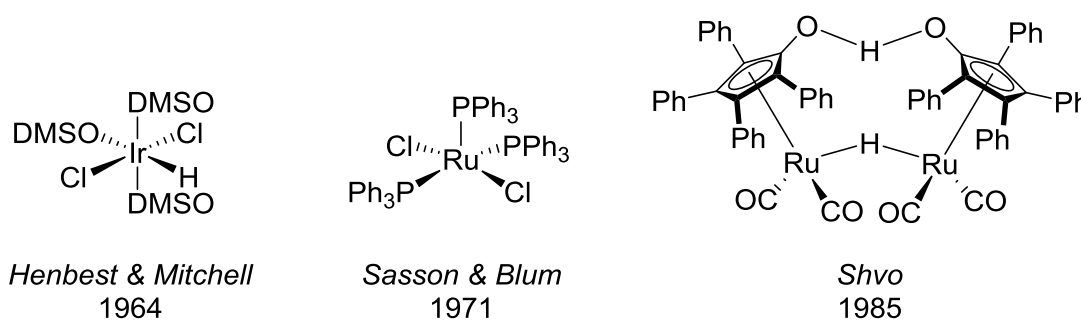
Figure 6. First transition metal catalysts for ketone TH.

Studies of *Ratan L. Chowdhury* and *Jan-E. Bäckvall* revealed that base addition to the lead catalyst $RuCl_2(PPh_3)_3$ considerably increases the reaction rate, resulting in the possibility to carry out the TH of ketone substrates at lower temperatures.[62] These findings established an experimental reaction protocol which is still used similarly up to date. Thus, reactions were carried out in degassed refluxing isopropanol at 82 °C, with 2.4 mol% NaOH as base and 0.1 mol% catalyst. The additional use of base led to 89% conversion within 1 hour even at the lowered temperature, resulting in a TOF of 900 h^{-1}. With the observation that base addition promotes the velocity of the reaction and allows for milder reaction conditions, the way was paved for the discovery of a multitude of transition metal complexes for the catalytic TH of ketones.

In line with previous investigations, *Youval Shvo* presented a dinuclear ruthenium carbonyl complex that had initially been employed for the HY of several unsaturated substrates under hydrogen pressure (Figure 6, right).[63]

This so-called *Shvo* catalyst, whose structure was revealed to contain a bridging ruthenium hydride,[64] catalyzes the TH of several aliphatic and aromatic ketones in a formate/water mixture.[65] It is one of the first examples of TH catalysts where the ligands exhibit a bifunctional behavior, thus facilitating hydrogen transfer from the donor to the substrate through redox activity of the hydroxy cyclopentadienyl ligand.[66] At that time, the term "bifunctional catalysis" was not yet established and only with the findings of *Ryōji Noyori* in 1995, important steps towards this ligand-assisted pathway were pursued explicitly.[50]

In the meantime, another important branch of ketone TH developed, namely the asymmetric TH of ketones by chiral transition metal complexes. Although the idea to enantioselectively transform ketones to chiral alcohols is as old as *MPV* reduction itself,[67] the tailoring of transition metal catalysts to obtain decent enantiomeric excess (*ee*) of chiral alcohols showed success only from 1976 onwards. Then, a ruthenium catalyst was developed for the enantioselective dehydrogenation of 1-phenylethanol.[68] The catalytic system consisted of the previously established TH catalyst $RuCl_2(PPh_3)_3$ and a chiral phosphine, neomenthyl diphenylphosphine NMDP (Figure 7, left). It was found that, depending on the nature of the hydrogen donor/acceptor couple, the reaction proceeded in both directions, thus giving moderate *ee* in the TH of selected ketones.[69] Due to the mediocre enantioselectivity of the ruthenium NMDP system, another catalyst emerged soon afterwards, changing the chiral phosphine reagent from NMDP to 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) (Figure 7, middle) and employing the isolated ruthenium complex $Ru_4H_4(CO)_8[(-)-DIOP]_2$ instead of performing the *in-situ* addition of phosphine to $RuCl_2(PPh_3)_3$.[70]

(+)-NMDP   (-)-DIOP   (*S*)-BINAP
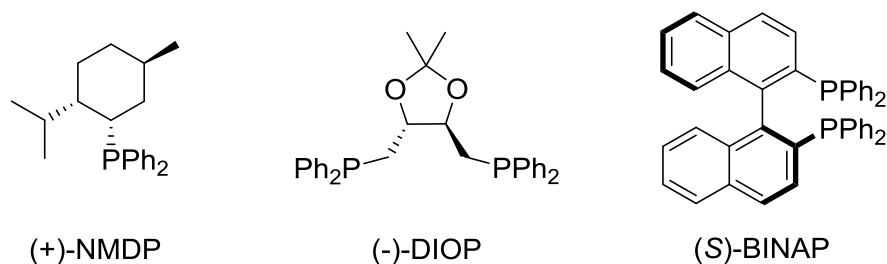
Figure 7. Chiral phosphine ligands for asymmetric TH of ketones with ruthenium complexes.

With these systems paving the way for the enantioselective synthesis of chiral alcohols by TH reactions, a large number of ruthenium complexes with chiral phosphine ligands emerged, one of the most famous phosphines being (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) (BINAP) (Figure 7, right). When *Ryōji Noyori* first published the synthesis of Ru(OAc)$_2$[(*S*)-BINAP], the use of this complex was directed towards HY reactions by molecular hydrogen.[71]

In fact, the reaction worked very efficiently and *Noyori* won the Nobel prize in 2001 together with *William S. Knowles* and *K. Barry Sharpless* for their contribution to catalytic asymmetric synthesis by hydrogenation and oxidation reactions, respectively. However, the application of ruthenium BINAP complexes in ketone TH emerged only later, when the versatility of this complex for various substrates in different hydrogen carrying reactions was realized.[72] Thus, acetophenone substrates could be transformed to their respective alcohols in quantitative yield and *ee* > 87%, an unprecedented enantioselectivity.[73] BINAP complexes are still important catalysts for asymmetric transformations in industry nowadays, used for instance for the production of (*R*)-1,2-propanediole as precursor for the synthesis of the antibiotic levofloxacin, or the isolation of the fragrance compound menthol.[74]

Since the invention of BINAP catalysts, a multitude of chiral and non-chiral phosphines appeared as ligands for transition metal catalyzed TH reactions. Popular examples are (*S*)-P-Phos, (*S*)-PhanePhos, (*R*,*S*)-JosiPhos, (+)-SkewPhos and the non-chiral bis(diphenylphosphino)alkanes (Figure 8).[75-78]
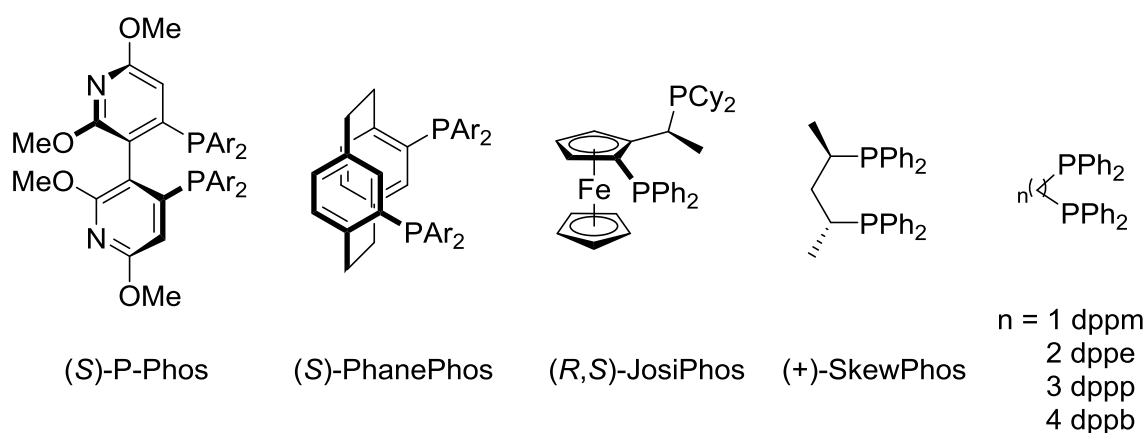
Figure 8. Popular phosphine ligands for (asymmetric) TH reactions.

Apart from phosphines, several other chiral ligands for the asymmetric TH of ketones were known from early years on, for example phenantrolines,[79] tetrahydrobi(oxazoles),[80] and diamine ligands.[50] Despite their potential for oxidation to form phosphine oxides, phosphines offer some advantages over the other ligands,[35] such as their straightforward steric tunability by substitution of the aryl moieties with bulkier or less bulky substituents. The cone angle α (Figure 9), *i.e.* the angle that describes the steric bulk on the metal by a ligand, can be increased or decreased in this way. Electronic properties can also be changed by variation of the moieties, e.g. by introducing alkyl substituents that exhibit an electron-donating effect or halogenated moieties with electron-withdrawing effect.

Diphosphines can further be modified by changing their bite angle β (Figure 9), meaning the angle that is enclosed by the coordinated atoms of a bidentate ligand, upon changing the linking alkyl chain between the phosphorus atoms. Bidentate phosphines also coordinate stronger to the metal than monodentate phosphines, such as triphenylphosphine, due to their chelating effect, providing more stable metal complexes.
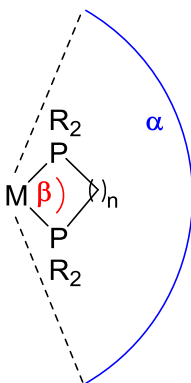
Figure 9. Properties of (di)phosphine ligands. α = cone angle, β = bite angle.

Another important property of phosphines is their considerable *trans* effect, leading to the labilization of the ligand in their *trans* position and thus facilitating its dissociation. This effect can cause the faster liberation of a free coordination site in the catalytic cycle (see chapter 1.2) and therefore enhance the velocity of the generation of the active catalytic species.

Already from the beginning, ruthenium was the most examined metal for homogeneous TH catalysts, especially in combination with diphosphine ligands. Diphosphine complexes with other transition metals, such as rhodium,[81] iridium[82] and osmium[83] were also applied (Figure 10, top) even for asymmetric ketone TH,[84] but proved less effective. Nowadays, the trend develops towards metals that are considered to be more economically friendly. Especially iron pincer complexes developed by *Robert H. Morris* as a forerunner on the topic are considered promising innovative catalysts,[85] but also manganese pincer derivatives designed by *Matthias Beller* or *Karl Kirchner* contribute to the enormous number of novel TH catalysts up to date (Figure 10, bottom).[86] Even though these compounds are considered more environmentally benign, ruthenium complexes are still the most abundant compounds for ketone TH due to their high activity.
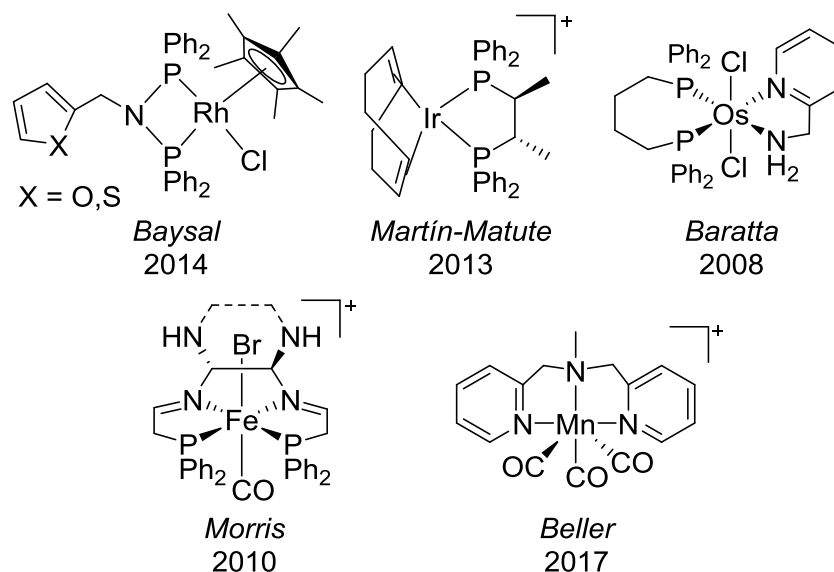
Figure 10. Transition metal complexes for catalytic ketone TH. Rhodium, iridium and osmium diphosphine complexes (top), iron and manganese pincer complexes (bottom).

While in the beginning only a limited number of ligand types, such as the mentioned phosphines, was investigated in combination with ruthenium, today manifold ligands and coordination modes are known. Besides monodentate ligands, a lot of ruthenium pincer complexes can be found for ketone TH, mainly exhibiting bi- or tridentate coordination.[87] Tetradentate ligands are further known, but their application in TH in combination with ruthenium is scarce due to the lack of two *cis* free coordination sites to enable hydrogen transfer from the metal to the substrate, which renders them suitable for TH only when comprising a bifunctional ligand. The coordination of (pincer) ligands to ruthenium is manifold, including C, N and P binding to the metal to afford PCP and NCP,[88] CNN,[55] NNN[89] and CNC[90] ruthenium pincer complexes (Figure 11). S and O pincer binding to ruthenium is also known, but less common.[91]
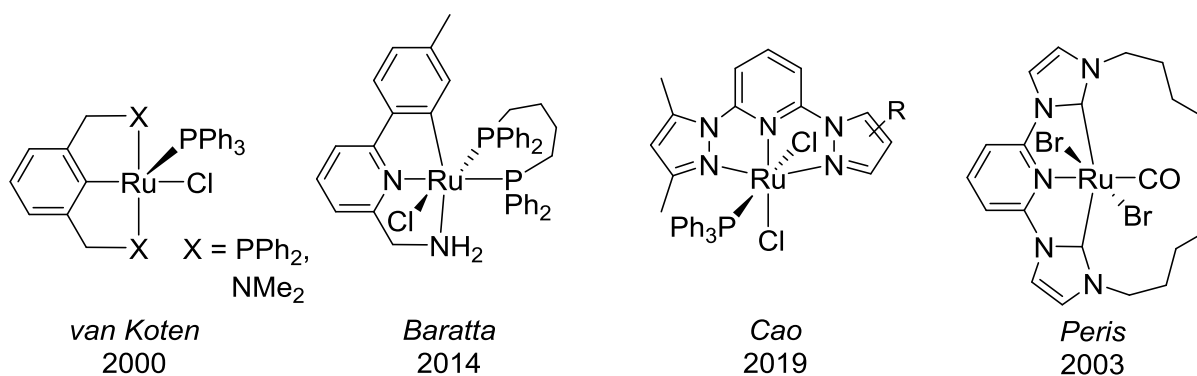
Figure 11. Ruthenium pincer complexes for catalytic ketone TH.

Even though binding of oxygen to ruthenium in pincer ligands is unusual, it finds implementation in other ligand types. A widely spread oxygen donor ligand class are carboxylates, where O can bind in a mono- or bidentate fashion. Carboxylates are labile ligands that can dissociate easily to offer a free site for substrate coordination and formation of the catalytically active species in TH. Especially acetate (OAc) ligands are implemented for ruthenium TH catalysts, such as in the previously mentioned Ru(OAc)$_2$[(*S*)-BINAP] complex[71] or in combination with *N*-heterocyclic carbene (NHC), phosphine and nitrogen donor ligands.[92, 93]

Within the group of ruthenium phosphine complexes, a variation from acetate to other carboxylate ligands has been performed to obtain active hydrogenation catalysts.[94-96] It was observed that bulkier moieties on the carboxylate ligand result in a superior performance when used in the HY of aldehydes under otherwise identic conditions.[97] In addition to a modification of the steric bulk, carboxylate ligands can be tuned upon changing their electronic properties (Figure 12). Application of trifluoroacetate instead of OAc leads to a higher electron withdrawing effect resulting in a more acidic ligand which is charge-stabilized by electron delocalization over the O-C-O bond.
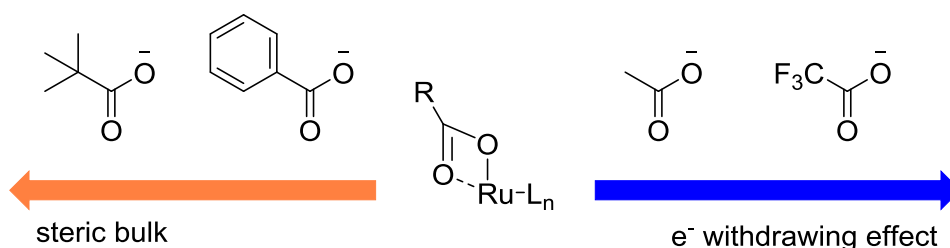

Figure 12. Modifying steric and electronic properties of carboxylate ligands.

The properties of ruthenium phosphine complexes with trifluoroacetate ligands have been explored mainly in the 1980's and 90's, when these compounds were introduced as efficient HY catalysts for aldehydes and ketones.[98-104] While multiple structures containing ancillary ligands, such as carbenes or hydrides, were synthesized, only a limited number of complexes exhibiting the formula Ru(O$_2$CCF$_3$)$_2$P$_2$, where P$_2$ = BINAP, PhanePhos, are known as catalysts for HY reactions.[105-107]

Due to the lability of the Ru-trifluoroacetate bond, an easy dissociation of the anionic ligand is anticipated, allowing for a fast generation of a free coordination site in catalysis. However, this property renders the complexes sensitive towards possibly coordinating solvents, such as methanol and ethanol,[108] oxygen and moisture,[109] and their preparation can be problematic. This constitutes a possible reason for the neglected examination of these compounds nowadays.

A comprehensive study of the preparation and catalytic properties of ruthenium diphosphine complexes with fluoroacetate ligands in ketone TH is provided in this work, illustrating the difficulties faced in their synthesis and the rare application of the catalysts these days.

While trifluoroacetate and carboxylate ligands in general easily dissociate from their ruthenium complexes, other O donor ligands exhibit strong coordination to the ruthenium metal center. Acetylacetonate (acac) offers the possibility of bidentate coordination to ruthenium via two oxygen atoms, affording relatively stable chelate complexes. As one of the most familiar ruthenium acac complexes, $Ru(acac)_3$ catalyzes the reduction of a wide variety of substrates with different functions, most commonly upon addition of 1,1,1-tris(diphenylphosphino-methyl)ethane (triphos) and in the presence of a *Brönsted* or *Lewis* acid.[110, 111] Isolated ruthenium(II) acac catalyst precursors with phosphine ancillary ligands are further known, mostly exhibiting the general structure $Ru(acac)_2L_2$ (Figure 13).
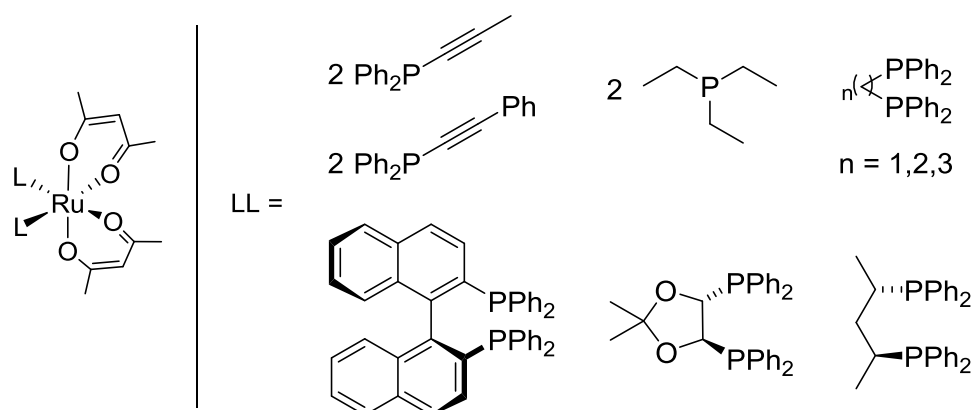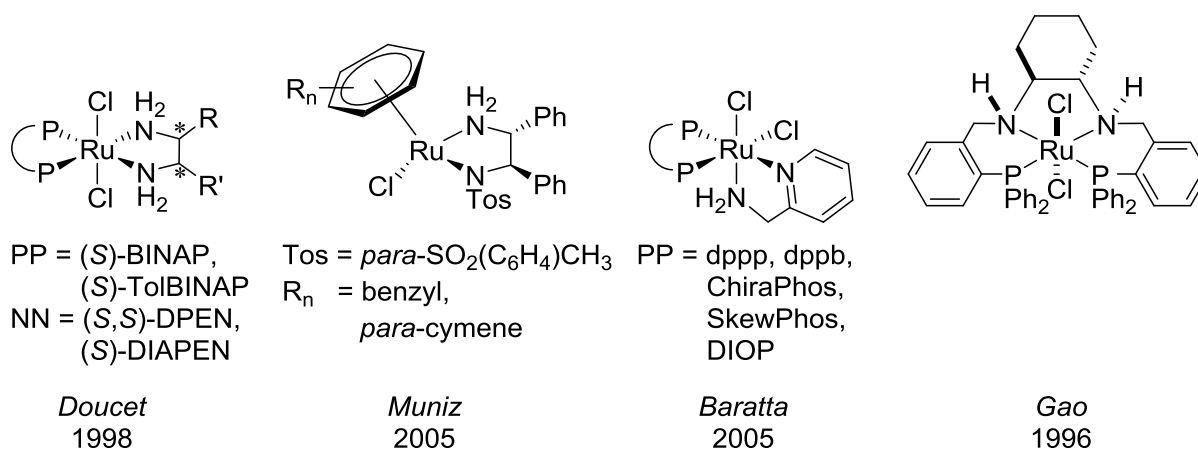

Figure 13. Phosphine ligands used for $Ru(acac)_2L_2$ complexes.

While monodentate phosphine ligands (Figure 13, top left and middle) served to elucidate the structure and coordination modes of their respective ruthenium acac complexes, they have not been examined as catalysts in hydrogenation reactions.[112, 113] Bidentate alkyl bridged diphosphines (Figure 13, top right) led up to the use of these complexes in catalysis.[114] The first bidentate phosphine ruthenium acac species for HY reactions (Figure 13, bottom) were prepared *in-situ* from $Ru(acac)_3$ and the respective chiral phosphine to yield active catalysts for the asymmetric HY of olefins.[115] Although these catalyst precursors were claimed to be as reactive as $Ru(OAc)_2[(S)-BINAP]$ when prepared *in-situ*, their isolation and use in HY reactions without pre-treatment led to practically inert species in the case of the BINAP derivative.[116]

Based on the concluded stability of the $Ru(acac)_2L_2$ complexes and on the easy dissociation of OAc from ruthenium, this work includes a straightforward route towards $Ru(OAc)(acac)L_2$ complexes. These compounds are active TH catalysts due to the facile dissociation of OAc to

liberate a coordination site for the generation of the active catalytic species, resisting deactivation due to their stable ancillary ligands acac and bidentate phosphine.

While most of the above-mentioned catalysts presumably operate via a "classical" inner sphere mechanism (chapter 1.2), several ruthenium complexes were found to take advantage of the outer sphere mechanism. In 1995, *Noyori* observed that primary and secondary amines serve as rate-accelerating additives to increase the activity of ruthenium BINAP complexes in the enantioselective HY of ketones.[73] Whereas in the beginning the amine was added to the reaction mixture *in-situ*, soon a plethora of isolated ruthenium compounds featuring ligands with NH functionality emerged.[117] Ruthenium bifunctional catalysts for the TH of ketones known nowadays feature the general formulae $RuCl_2(NN)(PP)$,[118, 119] $RuCl(arene)(NN)$,[120] $RuCl_2(PNNP)$[121] and many more (Figure 14).

PP = (*S*)-BINAP,
     (*S*)-TolBINAP
NN = (*S,S*)-DPEN,
     (*S*)-DIAPEN

Tos = *para*-$SO_2(C_6H_4)CH_3$
R_n = benzyl,
    para-cymene

PP = dppp, dppb,
    ChiraPhos,
    SkewPhos,
    DIOP

Doucet
1998

Muniz
2005

Baratta
2005

Gao
1996

Figure 14. Selected examples for metal-ligand bifunctional Ru-NH TH catalysts.

Established structural motives displaying functional behavior in ketone TH include ethylenediamine (en), benzylamine (bza) and 2-(aminomethyl)pyridine (ampy) derivatives.[53] These additives were used in combination with ruthenium phosphine carboxylate complexes in this work to yield efficient TH catalysts for the reduction of aromatic and aliphatic ketones, and an insight of the results is given in the following chapters.

2. Objective

Ruthenium(II) diphosphine complexes with carboxylate ligands are efficient catalysts for the transfer hydrogenation of ketones. Among other approaches, the catalytic performance of these complexes can be tuned by appropriate choice of the anionic ligands. In particular, two strategies can be addressed to improve the catalytic properties of the complexes. On the one hand, increasing the activity of a catalyst leads to the faster transformation of substrates. On the other hand, enhancing the robustness of a complex yields catalysts that retard deactivation and show better resistance.

An increase of the catalyst's activity by modification of the anionic ligands can be affected through choice of labile ligands that dissociate easily to generate a free coordination site for formation of the active species. This step can be rate-determining and the use of chloride or acetate often guaranties fast dissociation of a ligand under catalytic conditions. According to the higher acidity of trifluoroacetic acid with respect to acetic acid, trifluoroacetate was envisioned to dissociate even faster than OAc and the respective catalysts might accordingly be more active in ketone TH reactions. In this work, the synthesis of ruthenium(II) diphosphine trifluoroacetate complexes is approached and their application in ketone TH is examined. The isolation of $Ru(O_2CCF_3)_2(PPh_3)_2$ is encountered starting from $RuCl_2(PPh_3)_3$, at first by attempts to reproduce literature procedures and consequently through an improved pathway using TlO_2CCF_3. Stabilization of the synthesized trifluoroacetate complexes is implemented by ligands offering possibility for hydrogen bond formation to the carboxylate.

To promote the robustness of a catalyst, a stable backbone is required and ligands with a strong coordinating ability can be employed. Compounds that allow chelation to ruthenium offer an alternative to complicated ligand scaffolds, avoiding costly multi-step ligand synthesis, as it is frequently carried out for pincer type ligands, for instance. Acetylacetone coordinates to ruthenium(II) via two oxygen atoms, forming a stable six-membered ring structure. Even though ruthenium acac complexes are known as active HY catalysts, the strong coordination of this anionic ligand inhibits the fast generation of a free coordination site under mild conditions. Ruthenium(II) diphosphine complexes featuring both an acetate and an acetylacetonate ligand were expected to yield highly active, but at the same time very robust catalysts. This work comprises the isolation of mixed OAc/acac ruthenium complexes and their examination in the TH of aromatic and aliphatic ketones. The influence of the rate-accelerating additive ampy on the catalyst precursors is investigated and a study of the catalytic activity of the isolated ampy complexes is conducted.

3. Results – Publication Summaries

3.1. Ru(O₂CCF₃)₂(PPh₃)₂ and ruthenium phosphine complexes bearing fluoroacetate ligands: synthesis, characterization and catalytic activity

Daniela A. Hey,[‡] Pauline J. Fischer,[‡] Walter Baratta* and Fritz E. Kühn*

[‡]These authors contributed equally to this work.

This article describes the synthesis of the very reactive ruthenium(II) diphosphine complex $Ru(O_2CCF_3)_2(PPh_3)_2$ with labile trifluoroacetate ligands. Attempts to reproduce literature procedures for synthesizing the complex from $RuCl_2(PPh_3)_3$ with AgO_2CCF_3 in acetone failed, leading to uncharacterized species, while the reaction of $RuCl_2(PPh_3)_3$ with TFA/NaHCO₃ in *tert*-butanol described by *Wilkinson et al.* afforded the dinuclear complex $Ru_2Cl(O_2CCF_3)_3(PPh_3)_4(\mu\text{-}H_2O)$ instead of the previously claimed $Ru(O_2CCF_3)_2(PPh_3)_2$ (Scheme 10).
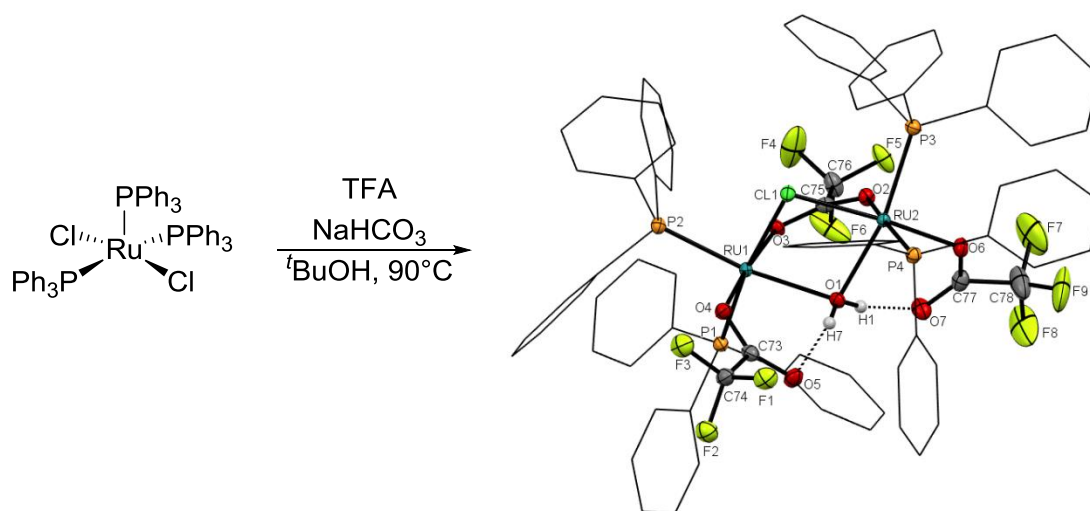
Scheme 10. Synthesis of $Ru_2Cl(O_2CCF_3)_3(PPh_3)_4(\mu\text{-}H_2O)$ from $RuCl_2(PPh_3)_3$ and TFA/NaHCO₃ in *tert*-butanol.

Due to the high acidity of trifluoroacetic acid and the fluxionality of the respective complexes, less acidic difluoroacetic acid (DFA) and monofluoroacetic acid (MFA) were employed with the goal to achieve $Ru(O_2CCHF_2)_2(PPh_3)_2$ and $Ru(O_2CCH_2F)_2(PPh_3)_2$, respectively. However, their behavior led to complexes with similar dinuclear structures that are stabilized by hydrogen bonding of the included H₂O molecule to the fluoroacetate ligands.

The synthesis of $Ru(O_2CCF_3)_2(PPh_3)_2$ was achieved by another pathway, thus starting from either $Ru_2Cl(O_2CCF_3)_3(PPh_3)_4(\mu-H_2O)$ or $RuCl_2(PPh_3)_3$ and reaction with TlO_2CCF_3 in acetone to precipitate TlCl. Although the product exhibits the formula $Ru(O_2CCF_3)_2(PPh_3)_2$ in solution, SC-XRD analysis shows dinuclear species that are bridged by H_2O (Figure 15) or dimerize by inclusion of excess TlO_2CCF_3. Hydrogen bonding of H_2O and trifluoroacetate plays a crucial role also in the stabilization of the former species.
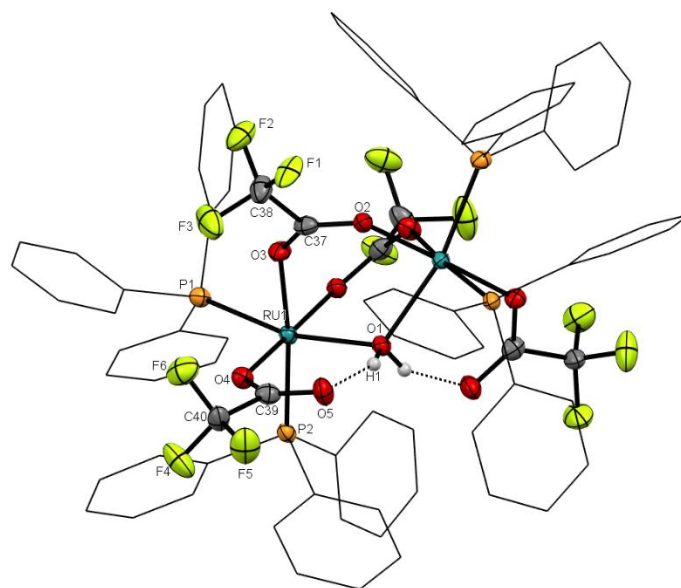
**Figure 15.** Solid state dinuclear structure obtained upon crystallization of $Ru(O_2CCF_3)_2(PPh_3)_2$.

The difficulties to isolate $Ru(O_2CCF_3)_2(PPh_3)_2$ show the lability of trifluoroacetate as ligand and the resulting fluxional behavior of its complexes, often leading to the formation of hydrogen bonded dinuclear species.

3.2. Acetate acetylacetonate ampy ruthenium(II) complexes as efficient catalysts for ketone transfer hydrogenation

Daniela A. Hey, Michael J. Sauer, Pauline J. Fischer, Eva-Maria H. J. Esslinger, Fritz E. Kühn* and Walter Baratta*

Ruthenium complexes with acetate and acetylacetonate ligands are known to efficiently catalyze HY reactions. Here, the synthesis and characterization of ruthenium(II) diphosphine complexes with OAc and acac ligands is elucidated (Figure 16). While diacetate complexes with structures similar to **1** and **2**, and diacetylacetonate species of type **5**, are acquainted in literature, mixed acetate/acetylacetonate derivatives **3** and **4** have not been described previously.
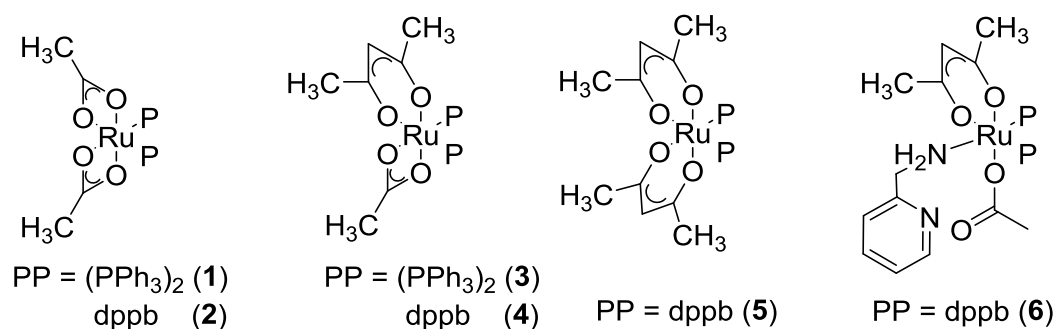
Figure 16. Ruthenium(II) diphosphine complexes with acetate and acetylacetonate ligands.

Complexes **3** and **4** are active catalysts for the TH of acetophenone, exhibiting superior performance with respect to their di-OAc and -acac analogues (Table 2). Especially **4**, containing a bidentate phosphine, displays robustness, although its catalytic activity is mediocre compared to state-of-the-art ruthenium TH catalysts.

Addition of amines, in particular ampy, to **4** increases the catalytic activity of the system considerably, leading to TOFs of 100,000 h^{-1} for the transformation of acetophenone to 1-phenylethanol. The isolation of catalyst precursor **6** (Figure 16), containing an OAc, acac and ampy ligand, offers an alternative to the *in-situ* formation of the catalyst system by **4** and ampy. Complex **6** is achieved easily from **4** and ampy in dichloromethane at room temperature. The SC-XRD structure of **6** shows that ampy NH and OAc C=O form hydrogen bonds, thus stabilizing the complex.

The ampy complex **6** is highly active in ketone TH, showing TOFs of up to 125,000 h^{-1} for the reduction of acetophenone and catalyst loadings as low as 0.01 mol% (Table 2). Besides acetophenone, various aromatic and aliphatic ketones can be transformed to their respective alcohols with **6**.

Table 2. Transfer hydrogenation of acetophenone with complexes **1** - **6**.[a]
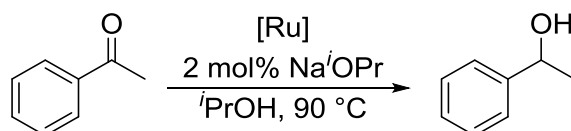
Entry	Catalyst	Catalyst loading [mol%]	Conversion[b] [%]	Time [min]	TOF[c] [h^{-1}]
1	**1**	0.1	38	480	n.d.
2	**2**	0.1	53	480	100
3	**3**	0.1	28	480	n.d.
4	**4**	0.1	75	480	930
5	**5**	0.1	1	480	n.d.
6	**4** + 2 equiv. ampy	0.03	96	10	100,000
7	**6**	0.03	99	5	125,000
8	**6**	0.01	87	10	105,000

[a] Conditions: ^{i}PrOH, 1 mmol acetophenone, 2 mol% NaO^{i}Pr, S/B = 100/2. [b] Maximum conversion, determined by GC; conversion corresponds to yield of 1-phenylethanol. [c] Calculated at 50% conversion.

4. Conclusions and Outlook

In this work, the synthesis of ruthenium(II) diphosphine complexes with carboxylate ligands was accomplished and the isolated compounds were evaluated as catalysts for the transfer hydrogenation of ketones.

The first part of the thesis concentrates on the description of ruthenium trifluoroacetate complexes, bearing fluxional anionic ligands. It was discovered that the formation of $Ru(O_2CCF_3)_2(PPh_3)_2$ from $RuCl_2(PPh_3)_3$ cannot be obtained according to literature procedures, *i.e.* with AgO_2CCF_3 or with TFA/NaHCO$_3$, the former leading to uncharacterized species. The latter synthesis results in the formation of the dinuclear species $Ru_2Cl(O_2CCF_3)_3(PPh_3)_4(\mu\text{-}H_2O)$, which is stabilized by hydrogen bonding between H$_2$O and trifluoroacetate. A change from trifluoroacetic to di- and monofluoroacetic acid yields similar dinuclear complexes. The synthesis of $Ru(O_2CCF_3)_2(PPh_3)_2$ was accomplished from $RuCl_2(PPh_3)_3$ using TlO_2CCF_3 through precipitation of TlCl in acetone. While the monomeric structure is evidenced in solution, SC-XRD measurements show a dinuclear H$_2$O-bridged species also for $Ru(O_2CCF_3)_2(PPh_3)_2$. These results show the high fluxionality of ruthenium(II) phosphine trifluoroacetate complexes, leading to hydrogen bonding of trifluoroacetate to prevent a dissociation of this ligand.

In the second part of the thesis, the synthesis and characterization of mixed acetate/acetylacetonate complexes is described. The isolation of $Ru(OAc)_2P_2$, $Ru(acac)_2P_2$ and $Ru(OAc)(acac)P_2$ complexes with $P_2 = 2$ PPh$_3$, dppb was accomplished and the activity of all precursors in the transfer hydrogenation of ketones was evaluated. Studies show that the most efficient catalyst Ru(OAc)(acac)(dppb) is highly active in combination with ampy, reaching TOFs of 100,000 h^{-1} in the TH of acetophenone. The isolation of the ampy derivative Ru(OAc)(acac)(ampy)(dppb) shows hydrogen bonding of the acetate and ampy ligand, the latter being coordinated to ruthenium via amine NH$_2$. Ru(OAc)(acac)(ampy)(dppb) was examined in the TH of several aromatic and aliphatic ketones yielding TOFs up to 125,000 h^{-1} with catalyst loadings as low as 0.01 mol%.

5. Appendix

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Ich erkläre an Eides statt, dass ich die bei der promotionsführenden Einrichtung **Fakultät für Chemie** der TUM zur Promotionsprüfung vorgelegte Arbeit mit dem Titel:

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5.2. Abbreviations

acac	acetylacetonate
ampy	2-(aminomethyl)pyridine
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
bza	benzylamine
DFA	difluoroacetic acid
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane, $Ph_2P(CH_2)_4PPh_2$
dppe	1,2-bis(diphenylphosphino)ethane, $Ph_2P(CH_2)_2PPh_2$
dppm	1,1-bis(diphenylphosphino)methane, $Ph_2P(CH_2)PPh_2$
dppp	1,3-bis(diphenylphosphino)propane, $Ph_2P(CH_2)_3PPh_2$
E_A	activation energy
ee	enantiomeric excess
en	ethylenediamine
FTS	*Fischer-Tropsch-Synthesis*
GC	gas chromatography
HY	hydrogenation
^{i}PrOH	isopropanol
LDPE	low density polyethylene
MFA	monofluoroacetic acid
MPV	*Meerwein-Ponndorf-Verley*
NaO^{i}Pr	sodium isopropoxide
NHC	*N*-heterocyclic carbene
NMDP	neomenthyl diphenylphosphine
OAc	acetate
Ph	phenyl
SCR	*Selective Catalytic Reduction*
SC-XRD	single crystal x-ray diffraction
SHOP	*Shell* Higher Olefin Process
^{t}BuOH	*tert*-butanol
TFA	trifluoroacetic acid
TH	transfer hydrogenation
TOF	turnover frequency
TON	turnover number
triphos	1,1,1-tris(diphenylphosphinomethyl)ethane

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5.3.1. Ru(O$_2$CCF$_3$)$_2$(PPh$_3$)$_2$ and ruthenium phosphine complexes bearing fluoroacetate ligands: synthesis, characterization and catalytic activity

Published in *Dalton Trans.* **2019**, *48*, 4625-4635.

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5.3.2. Acetate acetylacetonate ampy ruthenium(II) complexes as efficient catalysts for ketone transfer hydrogenation

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5.4. Bibliographic Data of Complete Publications

5.4.1. Ru(O₂CCF₃)₂(PPh₃)₂ and ruthenium phosphine complexes bearing fluoroacetate ligands: synthesis, characterization and catalytic activity

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5.4.2. Acetate acetylacetonate ampy ruthenium(II) complexes as efficient catalysts for ketone transfer hydrogenation

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5.6. Complete List of Publications

[1] *"Current advances on ruthenium(II) N-heterocyclic carbenes in hydrogenation reactions"*
D. A. Hey, R. M. Reich, W. Baratta, F. E. Kühn, *Coord. Chem. Rev.* **2018**, *374*, 114-132.

[2] *"Hydrogen-Bonded Siloxane Liquid Crystals for Hybrid Nanomaterials"*
K. Nickmans, S. O. Jansma, **D. Hey**, G. Velpula, J. Teyssandier, S. De Feyter, A. P. H. J. Schenning, *Helv. Chim. Acta* **2018**, *101*, e1800130.

[3] *"Ru(O$_2$CCF$_3$)$_2$(PPh$_3$)$_2$ and ruthenium phosphine complexes bearing fluoroacetate ligands: synthesis, characterization and catalytic activity"*
D. A. Hey, P. J. Fischer, W. Baratta, F. E. Kühn, *Dalton Trans.* **2019**, *48*, 4625-4635.

[4] *"Acetate Acetylacetonate Ampy Ruthenium(II) Complexes as Efficient Catalysts for Ketone Transfer Hydrogenation"*
D. A. Hey, M. J. Sauer, P. J. Fischer, E.-M. H. J. Esslinger, W. Baratta, F. E. Kühn, *ChemCatChem* **2020**, *12*, 3537-3544*.

[5] *"Highly efficient transfer hydrogenation catalysis with tailored pyridylidene amide pincer ruthenium complexes"*
P. Melle, J. Thiede, **D. A. Hey**, M. Albrecht, *Chem. Eur. J.* **2020**, *26*, 1-10.

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